THE STRUCTURES AND CONFORMATIONS OF SOME CYCLIC O-BENZYLIDENE ACETALS OF HEXITOLS

by

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ABSTRACT

The structure of the previously reported di-O-benzylidene acetal of allitol has been established as that of 2,4;3,5-di-O-benzylidene allitol. An infrared spectroscopic study in carbon tetrachloride solution of the intramolecular hydrogen bonding existing in this compound and the related diacetal, 1,3;4,6-di-O-benzylidene dulcitol was made to determine the preferred molecular conformations. An intraring, bifurcated hydrogen bonded conformation was assigned to the dulcitol derivative. For the allitol derivative no final decision could be made on the basis of existing evidence between the two possible intramolecularly hydrogen bonded conformations.

A spectroscopic method for the determination of the number of cyclic O-benzylidene groups present per mole of parent alcohol has been developed.
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GENERAL INTRODUCTION

The main objective of this research was to establish the structure and if possible the preferred conformation of di-O-benzylidene allitol. This compound was first synthesized in 1932 and no previous attempt appears to have been made to elucidate its molecular structure. From conformational analysis two possible structures, 1,3;4,6-di-O-benzylidene allitol and 2,4;3,5-di-O-benzylidene allitol, are favored for this compound. Both are capable of existing in two nearly equally probable conformations which would be stabilized by intramolecular hydrogen bonds.

Of the ten isomeric hexitols only allitol and dulcitol fail to form tri-O-benzylidene acetals when condensed directly with benzaldehyde. An infrared spectroscopic study of these two di-O-benzylidene acetals in carbon tetrachloride solution was undertaken to determine the nature of the intramolecular hydrogen bonding in these compounds and, if possible, to assign the molecular conformations.

In the course of this research a spectroscopic technique for the determination of the number of benzylidene groups in cyclic O-benzylidene acetals was developed.
I. PREPARATION AND PROPERTIES OF CYCLIC-\(\alpha\)-BENZYLIDENE ACETALS OF GLYCITOLS.

Acetals are a general class of organic compounds formed by the condensation of alcohols with the carbonyl group of aldehydes in the presence of acidic catalysts.

Cyclic \(\alpha\)-benzylidene acetals will be formed from the condensation reaction of benzaldehyde with polyhydroxy alcohols having suitably oriented hydroxyl groups. The reaction is believed to first form the hemiacetal (II) which exists as an unstable intermediate before proceeding to the acetal (III).

\[
\begin{align*}
\text{RHG-OH} + \text{PhCHO} + (\text{CHOH})_n & \rightleftharpoons \text{RHG-OH} + (\text{CHOH})_n \rightarrow \text{RHG-OH} \rightarrow \text{RHG-O} \rightleftharpoons \text{CHPh} + \text{H}_2\text{O} \\
\text{I} & \text{II} & \text{III}
\end{align*}
\]

The condensation reaction is acid catalyzed, the postulated mechanism involving protonation of the hydroxyl oxygen, and, as the reaction is reversible, it is also facilitated by dehydrating agents. The standard catalysts employed are concentrated sulfuric, hydrochloric and hydrobromic acids, gaseous hydrogen chloride, zinc chloride, cupric sulfate and phosphorus pentoxide. In the absence of an acidic catalyst the reaction may proceed only as far as the hemiacetal formation; it continues to the complete acetal only if water is removed from the reaction mixture. The nature of the derived acetal is usually independent of the acidic catalyst employed, however, a few exceptions have been observed. In one case it was
reported that at room temperature hydrogen chloride catalyzed the formation of a 2,3,4,5-di-O^-benzylidene derivative of 1,6-dibenzoyl dulcitol whereas zinc chloride as catalyst yielded at room temperature an isomeric dibenzylidene compound, which when subjected to zinc chloride and benzaldehyde at 60°C reverted into the former isomer (1).

Cyclic O^-benzylidene acetals generally form crystalline, high-melting derivatives of polyols and hence are useful for characterization purposes. These acetals are readily hydrolysed back to the parent alcohol by aqueous acid as their acid catalyzed formation is reversible. Under mild conditions acetals are stable to bases such as hydroxides, alkoxides, ammonia and pyridine. This characteristic of acid lability and base stability makes cyclic acetals extremely useful as intermediates in the synthesis of partially substituted polyhydric alcohols.

As protective substituents cyclic acetal linkages may be employed to block pairs of hydroxyl groups with a high degree of specificity. Furthermore, they possess the nature that they can be placed and removed under mild conditions without causing inversion of configuration at asymmetric centers.

Acetals are generally stable toward the common oxidising agents employed in carbohydrate chemistry such as lead tetraacetate and the periodates. Similarly acetals appear to be stable toward reducing agents. An example is the preparation of 2,4-O^-benzylidene-D-xylitol by reduction of 2,4-O^-benzylidene-D-xylose with hydrogen and Raney nickel under neutral conditions (2). Most acetals of polyhydric alcohols will remain stable in basic solution during
acylation, sulfonation, methylation, benzylation, and tritylation providing the customary mild conditions are employed. However, an exception to basic stability has been noted by Hann, Maclay and Hudson (3) who observed that ketal migration occurred when 2,3,5,6-diisopropylidene-D,L-galactitol was subjected to benzoylation in quinoline at elevated temperatures and yielded 1,6-dibenzoyl-2,3,4,5-diisopropylidene dulcitol. Barker and Bourne (4) accordingly state that although treatment of an acetal or ketal with a basic reagent is unlikely to cause structural rearrangements, this possibility should not be ignored.

Interest in cyclic acetal formation has up to the present been concerned mainly with either stereochemical studies in the determination of the most stable structures of these compounds or with their use as intermediates in the synthesis of partially substituted polyhydric alcohols. Very little industrial use has so far been found for these compounds. Since this research has been mainly concerned with the stereochemistry of the cyclic acetals this aspect will be considered in detail.

The formation of cyclic acetals from polyhydric alcohols will theoretically produce many isomeric products that will differ in structures, configuration, and conformation. The effect of configuration of the reactants on the course of the reaction depends considerably on whether the reaction is reversible or irreversible. Cyclic acetal formations are examples of reversible reactions where, providing a true equilibrium is attained, the composition of the products is independent of mechanism and determined by the relative thermodynamic stabilities of the constituents. The conversion of benzylidene (5) and
ethylidene acetals (6) into the corresponding methylene analogues gives evidence for the reversible nature of the reaction. However, it is not always possible to assess whether a true equilibrium has been reached for as Hann and Hudson (7) point out, the condensation of an aldehyde with a polyhydric alcohol will constitute a series of competitive reactions and a state of reversible equilibrium involving several acetals will be reached. Should one of these acetals crystallize during the reaction then the equilibrium conditions may cause this solid phase to be the principal product.

In predicting the most probable structures and conformations of cyclic acetals several important factors should be considered. The major considerations will be:

(1) The configuration of the hydroxyl groups in the polyhydric alcohol.

(2) The structure of the carbonyl component.

(3) The conditions under which the acetalation occurs.

Although it appears that many variable factors directing acetal formation exist, it has been possible to predict with considerable accuracy the course of the reaction.

In 1946 Hann and Hudson (2) from studies of the known structures of the methylene acetals of sorbitol, mannitol and dulcitol derived a set of rules which predicted the most favored structure of the product in cyclic acetal formation. Although these rules were empirical at the time, stereochemical theory has since placed them on a firm basis. These rules have been regarded as a major contribution to the stereochemistry of acyclic molecules.

The system of nomenclature followed here is that employed by
Barker and Bourne (4,8).

$\alpha$, $\beta$, $\gamma$ rings are rings formed by the engagement of hydroxyl groups attached to carbon atoms which are adjacent, separated by one atom and separated by two atoms respectively. For secondary hydroxyl groups, C (cis) refers to rings formed by the closure at hydroxyl groups on the same side of the Fischer projection formula; similarly T (trans) will refer to ring closure at hydroxyl groups on opposite sides of the Fischer projection formula. The parts of the polyol carbon chain not involved in the formation of the acetal ring are referred to as residues. Fused rings refer to rings in which two carbon atoms are in common.

Barker and Bourne (4) in 1952 modified the original Hann and Hudson rules to include all of the cases of benzylidnation, ethylidnation and methylenation known to that date. The modified rules are:

1. The most favored structure is a $\beta$-C ring.
2. The second most favored structure is for a $\beta$ ring.
3. The third most favored structure is for an $\alpha$, $\alpha$-T, $\beta$-T or $\gamma$-T ring.
4. In methylenation a $\beta$-T ring takes precedence over an $\alpha$-T or $\gamma$-T ring.
5. In benzylidnation and ethylidnation an $\alpha$-T ring takes precedence over a $\beta$-T or $\gamma$-T ring.
6. Rules (4) and (5) may not apply when one or both of the carbon atoms carrying the hydroxyl groups concerned is already part of a ring system.

Of interest is the fact that these rules do not apply to the isopropylidene ketals which exist predominantly as five-membered rings.

Hann and Haskins (2) pointed out that the $\alpha$-benzylidene acetals
would be expected to be more complicated than the methylene acetals as in each O-benzylidene acetal ring there is the possibility of an asymmetric carbon atom which would give rise to stereoisomerism.

Conformational analysis of the cyclic acetal rings is necessary to provide a theoretical basis for these empirical rules and to enable one to answer the following questions:

(1) What is the most probable ring structure of an O-benzylidene acetal formed from a polyhydroxy alcohol of known configuration?

(2) How many conformations are likely to be favored for the acetal and which of these is likely to be the more stable?

II. STEREOCHEMISTRY OF CYCLIC ACETALS.

Recent advances in the stereochemistry of carbohydrates and their cyclic derivatives are reviewed by Mills (9), Ferrier and Overend (10), and Isbell and Tipson (11).

Condensation of benzaldehyde with a polyhydric alcohol generally results in the formation of a six-membered cyclic acetal ring although five and seven membered rings are known.

A. STEREOCHEMISTRY OF SIX-MEMBERED ACETAL RINGS.

A considerable amount of information is now available about the stereochemistry of six-membered rings from studies with cyclohexane and cyclohexane derivatives (12). The chair form (I) is invariably the preferred conformation having minimized non-bonded repulsions. Other possible six-membered ring conformations include the boat (II), planar (III), sofa (IV), half chair (V) and skewed (VI) forms. Substituents will tend to occupy equatorial rather than axial positions to minimize diaxial repulsions.
The substitution of two oxygen atoms in the cyclohexane ring to form a 1,3-dioxane ring as found in cyclic acetals does not appear to alter these rules substantially. However, the possibility of slight distortions from the cyclohexane conformations exists since C-O will give a shorter bond distance than C-C and replacement of two hydrogen atoms by lone pairs of electrons on oxygen might be expected to decrease non-bonded ring interactions. Thus the 1,3-dioxane ring (VII) is probably less strained and somewhat more distorted than the cyclohexane ring.

Examining the $\beta$-C ring (VIII) both $R_1$ and $R_2$ may be in equatorial positions while in a $\beta$-T ring (IX) if $R_1$ is equatorial $R_2$ must be axial. Since the equatorial positions are energetically favored over axial positions then it is reasonable that $\beta$-C rings will be favored over $\beta$-T rings. Examining the acetal carbon atom, the favored position for the bulky phenyl group of a cyclic O-benzylidene acetal will be in the equatorial (e) position. Thus (VIII) ($R_3$ = phenyl) will represent the predicted most stable six-membered O-benzylidene acetal where the two residues and the bulky phenyl group are all on the same side of the ring. Assuming that the repulsive forces from the unshared electrons of the ring oxygen in the 1,3-dioxane ring are less than those from a hydrogen atom, then the equatorial position at the acetal carbon atom will be favored over the axial position much more in a 1,3-dioxane ring than in a cyclohexane ring. It is therefore highly unlikely that the isomer of a $\beta$-C O-benzylidene acetal having the phenyl group in an axial position would be stable enough to isolate. This is in agreement
with experimental results indicating only one diastereoisomer is formed in most benzylidenation reactions affording six-membered rings.

Comparing the positions of groups $R_5$ and $R_6$ of (VIII), one sees that although both $R_5$ and $R_6$ suffer repulsions from $R_1$ and $R_2$, only $R_5$ suffers repulsions from two hydrogen atoms. The repulsion between $R_6$ and the oxygen atoms cannot be accurately assessed but is assumed to be less than repulsions from two hydrogen atoms. The probability is thus seen that the axial group $R_6$ will be more favored than the equatorial group $R_5$ and hence axial hydroxyl groups in O-benzylidene acetal rings may readily occur. From conformational considerations alone Mills (9) predicted that 2,4-O-methylene-D-glucitol, 1,3;4,6-di-O-methylene dulcitol and the related ethylidene and benzylidene derivatives were stable acetals with axial hydroxyl groups.

As previously stated only one diastereoisomer is obtained from most benzylidenation reactions which produce six-membered rings. However, in certain cases two products have been isolated and cited as being diastereoisomers. Gluco-gulo-heptitol reportedly yielded a mono O-benzylidene acetal which could be converted to 3,5-O-benzylidene-gluco-gulo-heptitol on recrystallization from ethanol (13). Similarly D-perseitol (D-manno-D-gala-heptitol) has been reported to yield two 1,3;5,7-di-O-benzylidene acetals (14). However, both of these compounds gave indistinguishable infrared spectra in nujol mulls and potassium bromide disks, had optical rotations differing by only 0.1°, and one form could be converted
into the other by repeated recrystallizations from ethanol-pyridine (15). This evidence indicates that the latter reported pair of diastereoisomers probably exist as polymorphic forms.

Of considerable interest is the isomerism encountered in the benzylidene acetals of glycerol. Fischer in 1894 (16) was the first to describe a definite condensation product from glycerol and benzaldehyde which he suggested was either the 1,3- or 1,2-\(\alpha\)-benzylidene derivative. However, Fischer's product was probably a mixture of both derivatives for Hibbert and Hill (17) and Verkade and van Roon (18) later isolated two separate 1,3-\(\alpha\)-benzylidene acetals as well as the predominant 1,2-\(\alpha\)-benzylidene acetal. The two 1,3-\(\alpha\)-benzylidene glyceritols possess a cis-trans relationship but it should be pointed out that in these acetals (X and XI) the acetal carbon atom is not asymmetric.

Brimacombe, Foster and Stacey (19) have examined the isomeric 1,3-\(\alpha\)-benzylidene-glyceritols (2-phenyl-5-hydroxy-1,3-dioxanes) spectrophotometrically in carbon tetrachloride solutions \(<0.005\text{M}\) at which concentrations intermolecular hydrogen bonding is eliminated (20). From the infrared stretching frequency in the hydroxyl region they have been able to assign cis and trans configurations to the two isomers by examining the extent of intramolecular hydrogen bonding. Brimacombe, Foster et al. (21) first examined the extent of hydrogen bonding between hydroxyl groups and ring oxygen in a series of monohydroxy derivatives of tetrahydropyran, tetrahydrofuran and 1,3-dioxanes under similar conditions. Absorptions near \(3630 \text{ cm}^{-1}\) and \(3590 \text{ cm}^{-1}\) were associated with free and intramolecularly bonded hydroxyl groups respectively.
Examination of the infrared spectra of 1,3-dioxane-5-ol showed absorptions at 3635 cm\(^{-1}\) and 3594 cm\(^{-1}\) with relative extinction coefficients of 21 and 100 respectively. The relative extinction coefficients indicate that an equilibrium of chair conformations exist (XII and XIII) which favors the conformation (XIII) having an intramolecularly hydrogen bonded axial hydroxyl group. From this evidence it would appear that an equatorial substituent on C\(_2\) in conformation (XIII) of 1,3-dioxane-5-ol would effectively fix this conformation thus causing complete intramolecular hydrogen bonding.

Spectroscopic examination of the two 1,3-O-benzylidene-glyceritol isomers showed that the isomer of m.p. 84°C gave only one hydroxyl stretching absorption at 3590 cm\(^{-1}\) indicating conformation (X) while the other isomer (m.p. 63° - 64°C) gave two hydroxyl stretching frequencies at 3633 cm\(^{-1}\) (\(\varepsilon = 79\)) and 3601 cm\(^{-1}\) (\(\varepsilon = 26\)) indicating an equilibrium between the bonded (XIV) and non-bonded (XV) conformations. From this spectroscopic examination the isomer of m.p. 84°C was allocated the cis configuration and the other isomer (m.p. 63° - 64°C) the trans configuration.

The conformation (XIV) contains the phenyl group in the sterically unfavorable axial position and the observation that a proportion of the molecules exist in this conformation reflects the strength of the intramolecular hydrogen bond. The non-bonded interactions associated with the axial phenyl group in conformation (XIV) could possibly result in some deformation of the chair structure but the extent would probably be slight and would adversely affect the intramolecular hydrogen bond.
In the hydrogen bonds the hydroxyl groups are shown bonded to both ring oxygens forming a bifurcated bond. Experimental evidence suggests that bifurcated bonds are present but does not confirm their existence. Brimacombe, Foster et al. (21) have shown the importance of both ring oxygens in 5-hydroxy-1,3-dioxane structures as intramolecular hydrogen bonding between the hydroxyl group and the ring oxygen in tetrahydropyran-3-ol occurs to the extent of approximately 50% (Δν = 40 and 50 for free and bonded hydroxyl groups respectively) whereas the introduction of a second ring oxygen giving 1,3-dioxane-5-ol gives more extensive intramolecular hydrogen bonding (Δν = 21 and 100 for free and bonded hydroxyl groups respectively).

Dobinson and Foster (22) have compared the hydrogen bonding effects in derivatives of trans-cyclohexane-1,2-diol (XVI) and 5-hydroxy-1,3-dioxane (XIII). Intramolecular hydrogen bonding in both of these compounds involves five-membered rings and as their Δν values (arithmetical difference between free and bonded hydroxyl absorption frequencies) were found to be similar it appears that these bonds are of equal strength. However, the bulk of the isopropyl group in trans-1-isopropylcyclohexane-1,2-diol was found to be sufficient to anchor the molecule exclusively in the chair conformation with the isopropyl group equatorial and the hydroxyl groups axial. The bulk of the phenyl group appears somewhat less than that of the isopropyl group as it has been shown by Brimacombe, Foster et al. (21) that it is not sufficient to anchor trans-5-hydroxy-2-phenyl-1,3-dioxane in conformation (XV). Dobinson and Foster are currently attempting the synthesis of trans-5-hydroxy-2-t-butyl-
1,3-dioxane to determine if the bulky t-butyl group will exist only in an equatorial position.

The spectroscopic observations made by Brimacombe, Foster et al. (21,22,23,24) have thus pointed out the significance of intramolecular hydrogen bonding in stabilizing conformations which otherwise would be considered unfavorable.

The condensation of aldehydes with glycerol significantly differs from the pattern observed with higher polyhydric alcohols as the proportion of five-membered ring cyclic acetalts of glycerol always markedly exceeds the proportion of six-membered ring acetals providing the reaction mixture remains liquid. One noted exception is the \( \text{O}-\text{methylene} \) glycerol which when acid equilibrated, produced the six-membered cyclic acetal in greater yield. Thus, although intramolecular hydrogen bonding undoubtedly influences the reaction behaviour of certain higher polyhydric alcohols with aldehydes, it is probably not the determining influence with glycerol. If this was so, \text{cis-1,3-benzylidene} \text{glycerol} \((X)\) would be expected to be the major condensation product of benzaldehyde with glycerol.

Plantadosi et al. (25) have shown that in catalytic amounts of acid an equilibrium exists between the \(1,2-\) and \(1,3-\) \text{benzylidene} glycerols and have calculated an equilibrium constant. Their results indicate an equilibrium ratio of approximately 9:1 favoring the \(1,2-\) \text{benzylidene-glycerol} thus indicating the preference for the five-membered ring configuration.

An example where the empirical rules regarding cyclic acetal formation fail to differentiate a preferred structure is the formation of \(1,3-\text{benzylidene-(XVII)}\) and \(1,3-\text{methylen}e\) acetal
of D and L arabitol in preference to the corresponding 3,5-
substituted acetals (XVIII). Since both the 1,3- and 3,5- struc-
tures have β rings the acetal formation rules will not differen-
tiate between them. From an examination of the stereochemistry
of both structures it is seen that the possibilities of intra-
molecular hydrogen bonding are greater in the 1,3- than the 3,5-
derivative since the former contains an axial hydroxyl group
which can intramolecularly bond with the ring oxygens.

B. STEREOCHEMISTRY OF FIVE-MEMBERED ACETAL RINGS.

The possibilities of isomerism in five-membered rings are
shown in the Mills projection formulae (XIX) and (XX). As the
five-membered ring is nearly planar the α-T ring will be
favored over the α-C ring which will have R₁ and R₂ in eclipsed
positions. The α-T ring, being more symmetrical, should be more
stable than a terminal α ring. Evidence for this is the rearrange-
ment of 1,2;4,5-di-0-isopropylidene-D,L-galactitol to 2,3;4,5-di-0-
isopropylidene dulcitol when catalyzed by pyridinium chloride or
quinolinium chloride (26).

Stereoisomerism at the acetal carbon atom will be impossible
if R₃=R₄ and impossible in an α-T ring if R₁=R₂. In all other
cases isomerism is possible and it is difficult to predict a favored
isomer. This is especially so in an α-T ring where R₁ and R₂ are
closely similar. Stereoisomerism in the five-membered ring is
probably the reason for variable melting points being reported for
1,3;2,4;5,6-tri-0-benzylidene-D-glucitol (26,27).
XVII

XVIII

XIX

XX

XXI

XXII
C. STEREOCHEMISTRY OF FUSED RING ACETALS.

Fused bi- and tri-cyclic rings are quite common in acetals of higher polyhydric alcohols. The most common fusion is with two six-membered rings, however, examples of six and seven membered fused rings are known.

Fusion of two m-dioxane rings as found in \(1,3;2,4\) and \(2,4;3,5\)-diacetals of hexitols will give either a trans (XXI) or cis (XXII) ring junction. These ring fusions will be analogous with either cis or trans decalin.

Trans decalin has a rigid conformation with sharply defined axial and equatorial positions.

It would be expected that a fused trans bicyclic m-dioxane ring system having both residues \(R_1\) and \(R_2\) equatorial (XXIII) would be a favorable conformation. Thus if di-\(\alpha\)-benzylidene allitol has a \(2,4;3,5\)-acetal ring structure it should exist in a stable symmetrical configuration.

Trans fused bicyclic acetals having one residue equatorial should be slightly less favorable. An example of such a conformation is \(1,3;2,4\)-D,L-ribitol (XXIV).

Trans fused bicyclic acetals having an axial residue will be less stable. Evidence of this is the failure to isolate the \(1,3\) \(2,4\)-diacetal of mannitol or the \(3,5;4,6\)-diacetal of glucitol.

Trans fused bicyclic acetals having both residues axial would be expected to be extremely unstable and are probably not formed since under these conditions, more stable acetal rings could be produced.
Fused six-membered bicyclic acetals with a cis ring junction can produce two possible conformations (XXV) and (XXVI). (XXV) is the "O-inside" conformation while (XXVI) is the "H-inside" conformation. Evidence indicates that the O-inside conformation is the more favorable as the repulsive forces caused by the close approach of the four endo hydrogen atoms in the H-inside conformation appears quite unfavorable. The possibility of an inside axial substituent can be dismissed as it would be extremely unfavorable compared to other conformations.

III. STEREOCHEMISTRY OF KNOWN O-BENZYLIDENE ACETALS OF HEXITOLS.

Ten possible stereoisomeric hexitols can exist and all have been synthesized.

A. O-BENZYLIDENE ACETALS OF SORBITOL.

In 1935 Vargha (28) isolated a mono-O-benzylidene acetal of sorbitol which was identified as the 2,4-derivative. Wolfe, Hann and Hudson (29) in 1942 isolated a di-O-benzylidene derivative which they identified only as a 1,2,3,4-O-benzylidene acetal.
Angyal and Lawler (26) in 1944 carefully hydrolysed this acetal and isolated a mono-O-benzylidene acetal identical to Vargha's, thus showing the di-O-benzylidene acetal to be 1,3;2,4-di-O-benzylidene sorbitol. In a similar manner they obtained an identical di-O-benzylidene acetal from controlled hydrolysis of a tri-O-benzylidene sorbitol. Variations for the melting point of this compound have been reported with values ranging from 191°C to 204°C. A 4,6-O-benzylidene derivative has also been synthesized but from the reduction of 4,6-O-benzylidene-D-glucose so it cannot be stated that this is a more favorable configuration of mono-O-benzylidene sorbitol (30).

The mono-O-benzylidene sorbitol identified as a 2,4-derivative should possess a very stable conformation (XXVII) having a β-C ring with both residues equatorial and an axial hydroxyl group in a position to intramolecularly hydrogen bond to the ring oxygens.

The 1,3;2,4-O-benzylidene sorbitol will be a fused ring diacetal with cis ring junction and should possess the preferred 0-inside conformation having the residues C₅ and C₆ equatorial (XXVIII).

1,3;2,4;5,6-tri-O-benzylidene sorbitol should exist in a similar conformation to that of 1,3;2,4-di-O-benzylidene sorbitol that except it will have a five-membered acetal ring in an equatorial position to the fused cis diacetal rings (XXIX).

As mentioned previously, the possibility of isomerism at the acetal carbon atom of the five-membered ring may account for the variation in reported melting point of the tri-O-benzylidene acetal.
B. O-BENZYLIDENE ACETALS OF MANNITOL.

Direct condensation of mannitol with benzaldehyde yields a tri-$\alpha$-benzylidene acetal. Tri-$\alpha$-benzylidene-$\alpha$-mannitol was first synthesized in 1888 by Meunier (31) and this was the first reported synthesis of an $\alpha$-benzylidene acetal. The analysis of Meunier's acetal indicated that the triacetal was contaminated with a diacetal and later workers have reported a higher melting point (32,33). The structure of tri-$\alpha$-benzylidene mannitol has not as yet been elucidated but tri-$\alpha$-methylene-$\alpha$-mannitol is known to possess a 1,3;2,5;4,6- structure which is also the probable structure for the tri-$\alpha$-benzylidene acetal. This would consist of two six-membered rings fused trans-anti-trans to a seven-membered ring (XXX). The trans-anti-trans configuration is known to be a stable structure with three cyclohexane rings. A 1,3;2,4;5,6- or 1,2;3,5;4,6- structure (XXXI) would lead to a conformation having a five-membered acetal ring axial in a fused bicyclic six-membered acetal ring system with a trans ring junction which is not expected to be favorable. Similarly a 1,2;3,4;5,6- structure would not be expected to be favorable as six-membered rings generally take precedence over five-membered rings when both are possible.

C. O-BENZYLIDENE ACETALS OF TALITOL.

Direct condensation of benzaldehyde and talitol yields a tri-$\alpha$-benzylidene acetal. E. Fischer in 1894 (34) first synthesized a tri-$\alpha$-benzylidene acetal of D-talitol but was unable to obtain a product having a sharp melting point after several recrystallizations. Lobry de Bruyn and Alberda van Ekenstein in 1899 (35) and Bertrand
and Bruneau (36) in 1908 also synthesized the triacetal and obtained a melting point of 210°C. No attempt has as yet been made to determine the structure of this compound. The most probable structure appears to be the 1,2;3,5;4,6-\(\alpha\)-benzylidene acetal (XXXII) which will consist of two fused six-membered rings with a trans ring junction and a five-membered acetal ring in an equatorial position. If this is the conformation then possible isomerism exists at the acetal carbon atom of the five-membered ring. Another possible structure would be 1,3;2,5;4,6-\(\alpha\)-benzylidene talitol (XXXIII). This structure would have two six-membered rings fused to a seven-membered ring with both a cis and a trans ring junction.

D. \(\alpha\)-BENZYLIDENE ACETALS OF IDITOL.

D- and L-iditol have both been reported to form a tri-\(\alpha\)-benzylidene acetal when condensed with benzaldehyde in the presence of either hydrochloric or sulfuric acid. The structure of this acetal is not known. A di-\(\alpha\)-benzylidene acetal has also been prepared and has been found to be the major product in the condensation of L-iditol with benzaldehyde (37). The diacetal was shown to have the 2,3,4,5- structure and thus undoubtedly is 2,4;3,5-di-\(\alpha\)-benzylidene iditol. This molecule would have two fused six-membered rings with a cis ring junction and equatorial residues (XXXIV). It is of interest to compare the conformation of this acetal with a proposed 1,3;4,6-di-\(\alpha\)-benzylidene iditol (XXXV) which should also be a stable structure, being similar to the stable conformation of the di-\(\alpha\)-benzylidene acetal of dulcitol. Such a conformation would have two
separate six-membered rings with an equatorial-equatorial ring
junction and with axial hydroxyl groups capable of intramolecularly
hydrogen bonding with the ring oxygens. The preference for the
2,4;3,5- structure seems to indicate that fused rings are favored
over isolated rings.

The tri-\(\text{O}\)-benzylidene iditol will probably have either the
1,3;2,4;5,6- or the 1,3;2,5;4,6- configuration. A 1,3;2,4;5,6-
configuration would have as the most favorable conformation two
fused six-membered rings, \(\text{O}\)-inside conformation, \(\text{cis}\) ring junction
and an equatorial five-membered ring (XXXVI).

A 1,3;2,5;4,6- structure (XXXVII) would consist of two
six-membered rings fused \(\text{cis-anti-cis}\) to a seven-membered ring.

E. \(\text{O}\)-BENZYLIDENE ACETALS OF DULCITOL.

Direct condensation of dulcitol with benzaldehyde in the
presence of acidic catalysts yields a di-\(\text{O}\)-benzylidene acetal
(38). There has not been any reported synthesis of the tri-\(\text{O}\-
benzylidene dulcitol, although a tri-\(\text{O}\)-(o-nitrobenzylidene)
acetal has been reported (39). The di-\(\text{O}\)-benzylidene dulcitol
has the 1,3;4,6- structure of which D. Livingstone (40) has made
a conformational study and predicted the most stable conformation
to be (XXXVIII). This conformation, as mentioned when discussing
the di-\(\text{O}\)-benzylidene acetals of iditol, should be quite favorable
having two isolated six-membered rings with an equatorial-equatorial
trans ring junction and also having axial hydroxyl groups capable
of intramolecularly hydrogen bonding to the ring oxygens.

Livingstone confirmed the reported failure of dulcitol to form
a tri-\(\text{O}\)-benzylidene derivative under forcing conditions with a variety of catalysts and recorded the ultraviolet and infra-red spectra of the 1,4;3,6-di-\(\text{O}\)-benzylidene dulcitol.

F. \(\text{O}\)-BENZYLIDENE ACETALS OF ALLITOL.

Direct condensation of allitol with benzaldehyde in the presence of concentrated hydrochloric acid, as in the case of dulcitol, leads to the formation of a di-\(\text{O}\)-benzylidene and not a tri-\(\text{O}\)-benzylidene acetal (41). A conformational study of this compound was made in the present research as it was thought that the preferred structure was possibly the 1,3;4,6- since this could lead to a conformation analogous to that of 1,3;4,6-di-\(\text{O}\)-benzylidene dulcitol (XXXVIII) but having equatorial hydroxyl groups. The other possibility is the 2,4;3,5- structure which is predicted from the established rules for acetal formation.

IV. HYDROLYSIS OF CYCLIC-\(\text{O}\)-BENZYLIDENE ACETALS.

The hydrolysis of cyclic \(\text{O}\)-benzylidene acetals is believed to proceed via the mechanism outlined in FIGURE 1.

Few workers have been concerned with rate determination studies of the hydrolysis of these acetals and in most cases forcing conditions are employed for rapid and complete hydrolysis. With hot N-hydrochloric acid the hydrolysis is usually complete within one hour. The acid stability of such acetals will depend upon such factors as:

1. Size and position of ring.

2. Solubility of the acetal and hydrolysed products in the acidic medium.
MECHANISM OF CYCLIC ACETAL HYDROLYSIS

\[
\begin{align*}
\text{RHC} - O - (\text{CHOH})_n - \text{CHPh} + H^+ & \rightleftharpoons \text{RHC} - O - (\text{CHOH})_n - \text{CHPh} \\
\text{RHC} - O - (\text{CHOH})_n - \text{CHPh} & \rightleftharpoons \text{SLOW} \text{RHC} - O - \text{H} \\
\text{RHC} - O - (\text{CHOH})_n - \text{CHPh} & \rightleftharpoons \text{SLOW} \text{RHC} - O - \text{H} \\
\text{RHC} - O - (\text{CHOH})_n - \text{OH} + H^+ & \rightleftharpoons \text{RHC} - O - (\text{CHOH})_n - \text{CHPh} \\
\text{RHC} - O - (\text{CHOH})_n - \text{OH} & \rightleftharpoons \text{RHC} - O - (\text{CHOH})_n - \text{CHPh} + \text{PhCHO}
\end{align*}
\]

FIGURE 1
3. Volatility of the carbonyl compound.

From thermodynamic considerations the difference in activation energies necessary for the synthesis of acetal rings of different types will be the energy required to distort the zig-zag carbon chain which controls the energy differences in the products. Acetal rings which are most readily formed should be those that are most stable to hydrolysis. TABLE I shows cyclic acetals which have been subjected to graded acidic hydrolysis:

TABLE I

<table>
<thead>
<tr>
<th>Parent Acetal</th>
<th>Order of Ring Scission</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3;2,4;5,6-tri-O-benzylidene sorbitol</td>
<td>α</td>
<td>β</td>
<td>βC</td>
<td></td>
</tr>
<tr>
<td>1,3;2,4;5,6-tri-O-methylene sorbitol</td>
<td>α</td>
<td>β</td>
<td>βC</td>
<td></td>
</tr>
<tr>
<td>1,3;2,4-di-O-ethylidene sorbitol</td>
<td>β</td>
<td>βC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3;2,5;4,6-tri-O-ethylidene mannitol</td>
<td>γ-T</td>
<td>β</td>
<td>β</td>
<td></td>
</tr>
</tbody>
</table>

These data indicate that of the benzylidene, ethylidene and methylene acetals of the two hexitols the order of ring hydrolysis is $\alpha$, $\gamma$-T $> \beta > \beta$-C which is in the order of decreased ring stability.

The only studies on rates of hydrolysis of cyclic O-benzylidene acetals appear to be those recently reported by Brimacombe, Foster and Haines (45) who followed the hydrolysis of 1,2- and 1,3-O-methylene glycerol and cis- and trans- 1,3-O-benzylidene glycerol. These workers hydrolysed a 1% solution
of 1,2- and 1,3-O-methylene glycerol in N-sulfuric acid at 89°C and observed t1/2 values of 42 and 129 minutes respectively, indicating the preferred stability of the six-membered over the five-membered ring. They also observed that both cis- and trans-1,3-O-benzylidene glycerol hydrolysed extremely rapidly having t1/2 values of 17 minutes in 0.02N sulfuric acid at 35°C. The 1,3-O-methylene and 1,3-O-benzylidene acetals appear to reflect extremes of acid lability and stability among cyclic acetals.

The hydrolysis was followed at time intervals by neutralizing aliquot samples of the reaction mixture, oxidizing with sodium meta-periodate and determining periodate consumption by addition of standard arsenite and back titrating with iodine.

V. SPECTRA OF O-BENZYLIDENE ACETALS.

A. INFRARED SPECTRA

As mentioned previously, Brimacombe, Foster, et al. (21) have examined the infrared spectra in carbon tetrachloride solution of several cyclic acetals of glycerol. These spectra were in solutions less than 0.005M and were only concerned with the hydroxyl stretching frequency region.

Isbell, Stewart and Tipson (46) have examined the infrared spectra of a series of 1-methoxyethylidene and isopropylidene cyclic acetals to determine if it was possible to unequivocally detect the 1,3-dioxane ring. They also reviewed related spectra obtained by other workers to determine if other correlations existed. They found that the absorption bands were not highly characteristic
of the type of ring present and that there were no readily
distinguishable bands suitable for the assignment of ring struc-
ture or for the study of ring conformations in these compounds.

TABLE II lists the absorption bands assigned to the 1,3-
dioxane ring by Isbell et/ al. and related workers.

TABLE II
ABSORPTION BANDS ASSIGNED TO 1,3-DIOXANE RING

<table>
<thead>
<tr>
<th>WAVENUMBER (CM$^{-1}$) OF SPECTRAL REGION OF ABSORPTION BANDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
<tr>
<td>1190-1151</td>
</tr>
<tr>
<td>1190-1158</td>
</tr>
<tr>
<td>1173-1151</td>
</tr>
<tr>
<td>DOUBLET BETWEEN 1160 and 1120</td>
</tr>
<tr>
<td>1181-1153</td>
</tr>
</tbody>
</table>

B. NMR SPECTRA

Foster et/ al. (50) have reported the NMR spectra of 5-
hydroxy-1,3-dioxane and some related compounds. These spectra
were obtained at 34°C from ca. M solutions of these compounds
in chloroform with tetramethylsilane as the internal reference.
They published the spectra of cis- (XXXIX) and trans- (XL)
5-acetoxy-2-phenyl-1,3-dioxane. With the trans acetal the
axial and equatorial protons on C4 and C6 are not equivalent
and were found to couple together and with H5 giving a complex
pattern. With the cis acetal no coupling was observed and a single broad peak was formed from the protons on C₄ and C₆ which indicated that these pairs had lost their axial-equatorial character and that the cis form rapidly interconverts between two conformations. No further NMR spectra of cyclic-O-benzylidene acetals have been reported. The low solubility of acetals of higher polyhydric alcohols will make it difficult to obtain solutions of sufficient concentration to obtain their NMR spectrum with present day equipment.
RESULTS AND DISCUSSION

I. THE STRUCTURE OF DI-Ω-BENZYLIDENE ALLITOL.

As previously mentioned, conformational analysis indicated two probable structures for di-Ω-benzylidene allitol. These structures were 1,3;4,6-di-Ω-benzylidene allitol (XLII) and 2,4;3,5-di-Ω-benzylidene allitol (XLI) and no decision between them could be made on conformational grounds alone.

FIGURE 2 indicates the steps followed in the structural elucidation. Hydrolysis of methylated 2,4;3,5-di-Ω-benzylidene allitol (XLIII) would yield 1,6-di-Ω-methyl allitol (XLIV) while hydrolysis of methylated 1,3;4,6-di-Ω-benzylidene allitol would yield the 2,5-di-Ω-methyl isomer (XLV). 1,6-Di-Ω-methyl allitol (XLIV) has four vicinal hydroxyl groups while 2,5-di-Ω-methyl allitol (XLV) has only two. Since lead tetraacetate is a selective oxidising agent for the cleavage of the carbon chain between pairs of vicinal hydroxyl groups and one mole of lead tetraacetate is consumed per pair of such groups then (XLIV) would consume three moles of oxidising agent per mole while (XLV) would consume only one mole.

Experimentally a maximum value of 3.05 moles of lead tetraacetate per mole of di-Ω-methyl allitol was consumed during 18 hours (FIGURE 3). Since the conditions of methylation and hydrolysis were selected to rule out migration of either the Ω-benzylidene or methyl ether groups, this result may be taken as proof of the 2,4;3,5-di-Ω-benzylidene allitol structure (XLI).
STRUCTURAL ELUCIDATION OF DI-α-BENZYLDENE ALLITOL.

FIGURE 2
FIGURE 3 - LEAD TETRAACETATE OXIDATION OF D(-)-METHYL ALLITOL
II. INTRAMOLECULAR HYDROGEN BONDING.

The examination of the infrared spectra of $2,4;3,5$-$\alpha$-benzylidene allitol (XLI) and $1,3;4,6$-$\alpha$-benzylidene dulcitol (XXXVIII) in the region $3500 \text{ cm}^{-1}$ to $3700 \text{ cm}^{-1}$ was conducted to determine the type and extent of intramolecular hydrogen bonding existing in these compounds. The following solutions in carbon tetrachloride were prepared: $3.1 \times 10^{-4}$ M cyclohexanol, $2.0 \times 10^{-4}$ M $2,4;3,5$-$\alpha$-benzylidene allitol and $1.0 \times 10^{-4}$ M $1,3;4,6$-$\alpha$-benzylidene dulcitol. From the plot of the difference in percentage transmittance of solution and solvent against wave length the hydroxyl stretching absorption frequency of these compounds was determined (FIGURE 4). The following absorption maxima were determined: cyclohexanol ($\nu=3624 \pm 2 \text{ cm}^{-1}$), $2,4;3,5$-$\alpha$-benzylidene allitol ($\nu=3603 \pm 2 \text{ cm}^{-1}$), $1,3;4,6$-$\alpha$-benzylidene dulcitol ($\nu=3579 \pm 2 \text{ cm}^{-1}$).

The appearance of single absorption peaks for both $2,4;3,5$-$\alpha$-benzylidene allitol and $1,3;4,6$-$\alpha$-benzylidene dulcitol indicated unique conformations for these compounds and the frequencies of maximum absorption indicated that relatively strong intramolecular hydrogen bonds are present in both compounds.

III. THE PREFERRED CONFORMATIONS OF DI-$\alpha$-BENZYLIDENE ACETALS OF THE HEXITOLS.

From the known structures of the di-$\alpha$-benzylidene acetals of allitol, dulcitol and iditol it appears that several factors operate to favor one structure and conformation over others which have approximately equal non-bonded interactions. These factors appear to include:
1. Preference for 6- over 5-membered rings.
2. Preference for a symmetrical structure.
3. Preference for fused rings over isolated rings.

The conformation of 2,4;3,5-di-O-benzylidene allitol (XLI) appears to be very favorable, being symmetrical with a trans-fused 6-membered ring system and equatorial hydroxymethyl groups which are intramolecularly hydrogen bonded to the oxygen atom of the meta-dioxane rings (XLIa or b).

Examination of molecular models indicated that hydrogen bonding could occur between the primary hydroxyl groups and the oxygen atom of the same ring (XLIa) or the oxygen atom of the adjacent ring (XLIb). In the former case a 5-membered hydrogen bonded ring resulted and in the latter case a 6-membered hydrogen bonded ring. Hydrogen bond lengths calculated from accepted bond distances and bond angles (51) agreed with those measured directly on Cenco-Pfizersen scale models and were r(OH···O) = 1.80Å for conformation (XLIa) and r(OH···O) = 1.35Å for conformation (XLIb).

The infrared spectral data compiled by Brimacombe et al. (21) and Kuhn (20) (TABLE III) indicates that both 6- and 5-membered ring hydrogen bonds of this type occur. Of interest is the observation that 2-hydroxymethyl-tetrahydropyran and 2-hydroxymethyl-tetrahydrofuran exist in completely hydrogen bonded 5-membered ring conformations while the 1,2-O-acetals of glycerol which can take up similar 5-membered ring hydrogen
<table>
<thead>
<tr>
<th>ALCOHOL</th>
<th>STRUCTURE</th>
<th>INFRA-RED ABSORPTION (CM⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-HYDROXYMETHYL TETRAHYDROPYRAN</td>
<td><img src="image1" alt="Structure" /></td>
<td>3600</td>
</tr>
<tr>
<td>2-HYDROXYMETHYL TETRAHYDROFURAN</td>
<td><img src="image2" alt="Structure" /></td>
<td>3597</td>
</tr>
<tr>
<td>CIS-2-PHENYL-1,3-DIOXAN-5-OL</td>
<td><img src="image3" alt="Structure" /></td>
<td>3633</td>
</tr>
<tr>
<td>TRANS-2-PHENYL-1,3-DIOXAN-5-OL</td>
<td><img src="image4" alt="Structure" /></td>
<td>3593</td>
</tr>
<tr>
<td>1,2-Ω-METHYLENE GLYCERITOL</td>
<td><img src="image5" alt="Structure" /></td>
<td>3646</td>
</tr>
<tr>
<td>1,2-Ω-ISOPROPYLIDENE GLYCERITOL</td>
<td><img src="image6" alt="Structure" /></td>
<td>3647</td>
</tr>
<tr>
<td>CIS-CYCLOHEXANE-1,3-DIOL</td>
<td><img src="image7" alt="Structure" /></td>
<td>3619</td>
</tr>
<tr>
<td>CIS-CYCLOHEXANE-1,2-DIOL</td>
<td><img src="image8" alt="Structure" /></td>
<td>3544</td>
</tr>
<tr>
<td>CIS-CYCLOPENTANE-1,2-DIOL</td>
<td><img src="image9" alt="Structure" /></td>
<td>3626</td>
</tr>
<tr>
<td></td>
<td><img src="image10" alt="Structure" /></td>
<td>3587</td>
</tr>
<tr>
<td></td>
<td><img src="image11" alt="Structure" /></td>
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</tr>
<tr>
<td></td>
<td><img src="image12" alt="Structure" /></td>
<td>3572</td>
</tr>
</tbody>
</table>
bonded conformations actually exist in both free and bonded forms. The hydroxyl stretching frequencies of 2-hydroxymethyl-tetrahydropyran and 2-hydroxymethyl-tetrahydrofuran and the bonded conformations of the 1,2-0-acetals of glycerol range from 3597 cm\(^{-1}\) to 3608 cm\(^{-1}\). The value observed for 2,4;3,5-di-0-benzylidene allitol, (3603 cm\(^{-1}\)) falls precisely in the middle of this range. No data are at present available for 3-hydroxymethyl-tetrahydropyran which would be the model for the 6-membered hydrogen bonded conformation (XLIIb). We are therefore unable to make a final assignment of either (XLIIa) or (XLIIb) as the more preferred conformation for 2,4;3,5-di-0-benzylidene allitol. The predicted conformation for 1,3;4,6-di-0-benzylidene allitol (XLII) shows that it also could be stabilized by intramolecular hydrogen bonding. In this case a 6-membered hydrogen bonded ring with the hydroxyl of one ring bonding to the oxygen atom of the other ring would occur. It thus appears that although both conformations (XII) and (XIII) are symmetrical and can both be stabilized by intramolecular hydrogen bonding the fused bicyclic ring system is a more stable structure than two separate rings.

The known conformation of 1,3;4,6-di-0-benzylidene dulcitol (XXXVIII) is an example where a structure with two separate rings is favored over one with two fused rings (XLIII). The 2,4;3,5-di-0-benzylidene dulcitol structure (XLIII) is not favored since it would have two axial hydroxymethyl groups. Furthermore, the observed hydroxyl stretching frequency of 3579 cm\(^{-1}\) for 1,3;4,6-di-0-benzylidene dulcitol indicates a strong intramolecular
hydrogen bond which stabilizes this conformation. Calculations show \( r(\text{OH} \cdots \text{O}) = 2.42 \AA \) in (XXXVIII). The reason that this 5-membered ring intramolecular hydrogen bond is unusually strong may possibly be due to its bifurcated nature.

It should be pointed out when discussing intramolecular hydrogen bonds that a linear arrangement of (OH\cdots O) which has been shown to be the energetically favored arrangement in crystals is undoubtedly not obtained; it would be formed only with considerable strain on the conformation. A compromising non-linear minimum energy configuration probably occurs (52).

For di-\( \text{O} \)-benzylidene iditol the occurrence of the 2,4;3,5-structure (XXXIV) rather than the 1,3;4,6- (XXXV) appears to place more importance on the preference for fused bicyclic rings than on stabilization by intramolecular hydrogen bonding, for the 1,3;4,6-di-\( \text{O} \)-benzylidene iditol should possess a favorable bifurcated intramolecular hydrogen bond similar to that in 1,3;4,6-di-\( \text{O} \)-benzylidene dulcitol. However, the greater symmetry of conformation (XXXIV) compared to (XXXV) may also be a contributing factor.

IV. SYNTHESIS OF 2,5-DI-\( \text{O} \)-BENZOYL-1,4;3,6-DIANHYDRO-L-IDITOL.

The conversion of 2,5-di-\( \text{O} \)-(p-toluenesulphonyl)-1,4;3,6-dianhydro-D-mannitol to 2,5-di-\( \text{O} \)-benzoyl-1,4;3,6-dianhydro-L-iditol is a second example of the recently reported \((53,54)\) \(S_N^2\) displacement of a tosyloxy group by a benzoate ion. Reist and Baker (54) successfully displaced with inversion both tosyloxy groups of 2,3-di-\( \text{O} \)-benzoyl-4,6-di-\( \text{O} \)-(p-toluenesulphonyl) -L-D-galactopyranoside by benzoate ion employing sodium benzoate
in N,N-dimethyl formamide. Since the tosyloxy group on carbon 4 was in an axial position this reaction is quite unusual. Few nucleophiles are powerful enough to displace the tosyloxy groups without neighbouring group participation. Sodium iodide generally does not react with isolated secondary tosylates and sodium hydroxide or sodium methoxide upon reaction hydrolysises the tosylate with retention of configuration (55).

The conversion of 2,5-di-O-(p-toluenesulphonyl)-1,4;3,6-dianhydro-D-mannitol (XLIV) to 2,5-di-O-benzoyl-1,4;3,6-dianhydro-L-iditol (XLV) was probably a particularly favorable case since two endo tosyloxy groups were replaced with inversion by benzoyloxy groups which assumed exo positions. This is in agreement with the observation that the tosyloxy groups of 2,5-di-O-(p-toluenesulphonyl)-1,4;3,6-dianhydro-D-mannitol are readily replaceable with sodium iodide (56).

V. ATTEMPTED SYNTHESIS OF 2,5-DI-O-BENZOYL-1,3;4,6-DI-O-BENZYLIDENE ALLITOL.

The attempted replacement of the tosyloxy groups of 2,5-di-O-tosyl-1,3;4,6-di-O-benzylidene dulcitol (XLVI) to form 2,5-di-O-benzoyl-1,3;4,6-di-O-benzylidene allitol (XLVII) would be expected to be a favorable replacement as the axial tosyloxy groups would be replaced by equatorial benzoyl groups. However, on the basis of several experimental attempts this replacement does not appear to take place.

The importance of this reaction is that if this replacement did occur the configuration at carbon atoms 2 and 5 would be
inverted and hence this synthesis would provide a method of preparing the rare hexitol, allitol, from the more common dulcitol.

VI. HYDROLYSIS OF \(\alpha\)-BENZYLIDENE ACETALS.

The hydrolysis of the several cyclic \(\alpha\)-benzylidene acetals (TABLE IV) was followed spectrophotometrically.

### TABLE IV.

**HYDROLYSIS OF \(\alpha\)-BENZYLIDENE ACETALS**

<table>
<thead>
<tr>
<th>(\alpha)-BENZYLIDENE ACETAL</th>
<th>(t_2) (MIN)</th>
<th>OBSERVED MOLES BENZYLIDENE GROUP PER MOLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-(\alpha)-benzylidene-D-mannitol</td>
<td>12</td>
<td>2.97 ± .03</td>
</tr>
<tr>
<td>Tri-(\alpha)-benzylidene-D-talitol</td>
<td>&lt;3</td>
<td>2.93 ± .03</td>
</tr>
<tr>
<td>2,4;3,5-Di-(\alpha)-benzylidene allitol</td>
<td>5</td>
<td>2.01 ± .02</td>
</tr>
<tr>
<td>1,6-Di-(\alpha)-methyl-2,4;3,5-di-(\alpha)-benzylidene allitol</td>
<td>&lt;3</td>
<td>1.95 ± .02</td>
</tr>
<tr>
<td>1,3;4,6-di-(\alpha)-benzylidene dulcitol(a)</td>
<td>&lt;3</td>
<td>2.04 ± .02</td>
</tr>
<tr>
<td>2,5-Di-(\alpha)-methyl-1,3;4,6-di-(\alpha)-benzylidene dulcitol(a)</td>
<td>6.5</td>
<td>1.81 ± .03</td>
</tr>
<tr>
<td>2,5-Di-(\alpha)-benzyl-1,3;4,6-di-(\alpha)-benzylidene dulcitol(a)</td>
<td>8</td>
<td>1.85 ± .03</td>
</tr>
<tr>
<td>Methyl-4,6-(\alpha)-benzylidene-(\beta)-D-glucopyranoside(b)</td>
<td>&lt;3</td>
<td>1.04 ± .01</td>
</tr>
</tbody>
</table>

\(a\) Prepared in this laboratory by E. Premuzic (57).

\(b\) Prepared by G. Creamer (58).

From the rate plots (FIGURES 6 AND 7), values of \(t_2\) were calculated and also the number of moles of benzylidene group per mole of acetal after complete hydrolysis. This value was calculated using a value of 10,200±100 for \(\epsilon\) (FIGURE 5).
Due to the high acid concentration (1.25M hydrochloric acid) the hydrolysis of these compounds was very rapid and the rates may be compared only qualitatively.

The mono-O-benzylidene acetal, methyl-4,6-O-benzylidene-\(\beta\)-D-glucopyranoside, appeared to hydrolyse fastest while tri-O-benzylidene-D-mannitol was the slowest.

Since the concentration of all of these O-benzylidene acetals was approximately the same, and all possess 6-membered acetal rings, the number of rings and the position and type of substituents attached should account for the differences in hydrolysis rates.

The presence of substituents in the acetal ring appears to decrease the ease of hydrolysis (e.g., larger \(t_1\) values for 2,5-di-O-methyl-1,3;4,6-di-O-benzylidene dulcitol and 2,5-di-O-benzyl-1,3;4,6-di-O-benzylidene dulcitol than for 1,3-4,6-di-O-benzylidene dulcitol.

2,4;3,5-Di-O-benzylidene allitol possessing two \(\beta\)-C-rings as expected hydrolysed more slowly than 1,3;4,6-di-O-benzylidene dulcitol which possesses two \(\beta\)-rings.

The reason for the rapid hydrolysis of tri-O-benzylidene-D-talitol compared to tri-O-benzylidene-D-mannitol does not appear to be readily explainable.

As the purpose of this portion of the research was to develop a method for determination of the number of moles of benzyldiene group per mole of hexitol, the acid concentration employed was too high to enable only partial hydrolysis to be
detected and to permit a good comparison of the acid stability of each of the \(Q\)-benzylidene acetals.

It would be of interest to follow the hydrolysis of the tri-\(Q\)-benzylidene acetals at such an acid concentration that graded hydrolysis of the acetal rings could be examined.
FIGURE 5 - CONCENTRATION OF BENZYLIDENE GROUPS VERSUS OPTICAL DENSITY OF CYCLIC O-BENZYLIDENE ACETALS.

SLOPE = 10,200

- TRI-O-BENZYLIDENE-D-MANNITOL
- BENZALDEHYDE
- 1,3,4,6-DI-O-BENZYLIDENE DULCITOL
- 2,5-DI-O-METHYL-1,3; 4,6-DI-O-BENZYLIDENE DULCITOL
- 2,5-DI-O-BENZYL-1,3; 4,6-DI-O-BENZYLIDENE DULCITOL

CONC. (PhCH) X 10^5 M/L
FIGURE 6 - HYDROLYSIS CURVES OF CYCLIC O-PHENYLIDENE ACETALS

- 13:4:6-DI-O-BENZYLIDENE DULCITOL
- 24:3:5-DI-O-BENZYLIDENE ALLITOL

Optical Density

Time (Min.)

0.0  10  20  30  40  50  60  70  80  90  100  110  120  130  140  150  160  170  180  190  200
Figure 7 - Hydrolysis Curves of Cyclic $\alpha$-Benzyllidene Acetals

- Tri-$\alpha$-benzyllidene-D-talitol
- 16-Di-$\alpha$-methyl-2,4,3,5-di-$\alpha$-benzyllidene allitol
- 2,5-Di-$\alpha$-methyl-1,3,4,6-di-$\alpha$-benzyllidene dulcitol
- $\beta$-Methyl-4,6-$\alpha$-benzyllidene-D-glucopyranoside
EXPERIMENTAL

I. MATERIALS AND REAGENTS.

BENZALDEHYDE.

Reagent grade benzaldehyde was purified as recommended by Vogel (59), distilled under nitrogen at reduced pressure and stored in the dark under nitrogen. \( n_D^\circ 1.5470 \) (lit. value \( n_D^\circ 1.5463 \) (60)).

ALLITOL.

The allitol sample was prepared in this laboratory by W. Bowering from D-ribose in a previous research (61). It was recrystallized from ethanol-water and melted at 148°C.

D-MANNITOL.

Reagent grade D-mannitol, (Matheson, Coleman and Bell Co.,) was recrystallized from absolute ethanol, m.p. 165°-165.5°C (lit. value 166°C (62)).

TRI-O-BENZYLIDENE-D-TALITOL.

This compound was prepared in a previous research (63) m.p. of 186.0°-186.5°C (lit. value 210°C (35,36). Analysis: Calcd. for C\(_{27}\)H\(_{26}\)O\(_6\): C, 72.63; H, 5.87%

Found: C, 71.97; H, 5.82%

The infrared spectrum indicated no hydroxyl groups to be present and a chromatoplate run in pyridine and developed with sulfuric acid-nitric acid spray reagent showed only one spot.

CYCLOHEXANOL.

Reagent grade cyclohexanol (Fisher Scientific Co.,) was distilled under reduced pressure and a middle fraction (b.p. 76.5°C)
was collected. $n_D^{22.6} = 1.4649$ (lit. value $n_D^{22} = 1.4650$ (60)).

**CARBON TETRACHLORIDE.**

Analytical reagent carbon tetrachloride was distilled over phosphorus pentoxide. b.p. 76.0°C, $n_D^{15} = 1.4631$ (lit. value $n_D^{15} = 1.46305$ (60)).

**DIOXANE.**

Reagent grade dioxane (British Drug Houses) was purified as recommended by Vogel (59) and stored over sodium in a nitrogen atmosphere (b.p. 100.5–101°C).

**ANHYDROUS PYRIDINE.**

Reagent grade pyridine was distilled from calcium hydride. b.p. 112.0°–112.5°C.

**METHYL IODIDE.**

Methyl iodide (Eastman Kodak Co.,) was dried over phosphorus pentoxide and the middle fraction (b.p. 42.0°C) was collected.

**POWDERED SODIUM.**

Freshly cut sodium was powdered following the procedure of Fieser (64). The xylene was decanted off and the sodium suspension was stored in dry dioxane.

**THIN LAYER CHROMATOGRAPHY.**

Thin layer chromatoplates were prepared on glass plates from a slurry of silicic acid, plaster of paris and water in the proportions (4:1:8) and dried overnight at 100°C as described by Allentoff and Wright (65).

**II. 2,4;3,5-DI-O-BENZYLIDENE ALLITOL.**

Allitol (0.246 g, 0.00135 mole) was dissolved in 0.49 g concentrated hydrochloric acid after mechanically shaking for
10 minutes. Freshly distilled benzaldehyde (0.49 g, 0.0046 mole) was then added dropwise with shaking. The solution became turbid almost immediately and the contents of flask formed a solid white mass after 2-3 minutes. The mixture was shaken vigorously for one hour and then placed in a refrigerator overnight. The crude acetal was washed acid-free with ice water and was further washed with ether followed by ice water and dried overnight in vacuo over phosphorus pentoxide. The crude product (0.448 g, 92.7% yield) was recrystallized from absolute ethanol. m.p. 235.0-236.5° C. (Reported m.p. 249-250° C (41)).

Analysis: Calcd. for C_{20}H_{22}O_6: C, 67.02; H, 6.19%; Found: C, 67.19; H, 6.07%.

A chromatoplate of the recrystallized di-O-benzylidene allitol run in methanol and developed with sodium periodate-potassium permanganate spray reagent showed one long, thin spot near the solvent front. Another chromatoplate run in chloroform showed one spot near the origin (R_f ≈ 0.15) and a trace of another spot just below (R_f ≈ 0.06).

The infrared spectrum of the compound is shown in FIGURE 8.

III. 1,6-DI-O-METHYL-2,4;3,5-DI-O-BENZYLIDENE ALLITOL.

2,4;3,5-Di-O-benzylidene allitol was methylated according to the procedure of Freudenberg (66). Di-O-benzylidene allitol (0.100 g) was dissolved with heating and stirring in 3.0 ml. of dioxane. A large excess of powdered sodium (0.2 g) was added to the cooled solution which was then refluxed and magnetically
stirred. In the first 10 minutes a powdery solid appeared to form in the flask and on the surface of the sodium. After 6 hrs. the contents of the flask were evaporated under reduced pressure to a yellowish residue containing finely divided metallic sodium. Methyl iodide (4 ml.) was added and the mixture refluxed and stirred for a further 6 hrs. Evaporation gave a sodium-free yellowish residue which was extracted 5 times with 8 ml. portions of hot benzene. The filtered extracts were combined and evaporated to a white crystalline residue which was dried overnight in vacuo over phosphorus pentoxide. The crude di-O-methyl-di-O-benzylidene allitol (98% average yield) was recrystallized from absolute ethanol as colorless, needle-like crystals. m.p. 202.0-203.5°C.

Analysis: Calcd. for C_{22}H_{26}O_6: C, 68.37; H, 6.78; OCH_3, 15.57%. Found: C, 68.52; H, 6.90; OCH_3, 16.04%.

The infrared spectrum showed no hydroxyl stretching absorption (FIGURE 8). A chromatoplate showed only one spot when run in chloroform and developed with potassium permanganate-sodium periodate spray reagent.

IV. 1,6-DI-O-METHYL ALLITOL.

1,6-Di-O-methyl-2,4;3,5-di-O-benzylidene allitol, 0.100 g, was dissolved in dioxane, 4.0 ml., and N hydrochloric acid, 1.0 ml., was added. The solution was refluxed for 3 hrs., the hydrochloric acid was neutralized with excess silver carbonate, 10 ml. dioxane was added and the hot solution was filtered through a Celite pad on a sintered glass funnel. The filtrate was evaporated to a
FIGURE 8 - INFRARED SPECTRA OF SOLID SAMPLES.
syrup which crystallized

>in vacuo

over phosphorus pentoxide. The crude product was recrystallized from benzene as colorless plate-like crystals having a m.p. of 103.0-104.5°C.

Analysis: Calcd. for C_{18}H_{38}O_6: C, 45.71; H, 8.63; OCH_3, 29.53%

Found: C, 45.02; H, 8.25; OCH_3, 29.60%

Paper chromatography of the compound in butanol-acetic acid-water (4:1:5) showed one spot corresponding in R_f value to that of other di-0-methyl hexitols when sprayed with potassium permanaganate-sodium periodate reagent.

V. LEAD TETRAACETATE OXIDATION OF 1,6-DI-0-METHYL ALLITOL.

1,6-Di-0-methyl allitol, 0.0100 g, was dissolved in 25.0 ml. of a 0.0738 M solution of lead tetraacetate in glacial acetic acid (mole ratio of lead tetraacetate to di-0-methyl allitol 3.88:1). The reaction mixture was kept at 25.0±1°C in a constant temperature bath and 2.00 ml. aliquots were withdrawn at intervals, excess potassium iodide solution was added, and the liberated iodine was titrated with standard sodium thiosulfate solution with starch indicator. The results are shown in FIGURE 3.

VI. INFRARED SPECTROSCOPY.

The infrared spectra were measured in the 3500 to 3700 cm⁻¹ region on a Perkin-Elmer No. 112-G single beam spectrophotometer in a 9.0 cm. pyrex cell with sodium chloride windows. The concentrations of the solutions were sufficiently low (1.0 x 10⁻⁴ to 3.1 x 10⁻⁴M) that intramolecular hydrogen bonding was excluded (20, 21). Complete spectra of the solid compounds were run on
the Perkin-Elmer No. 21 double-beam spectrophotometer in potassium bromide windows.

VII. 2,5-DI-O-BENZOYL-1,4;3,6-DIANHYDRO-L-IDITOL.

A sample of 2,5-di-O-(p-toluenesulphonyl)-1,4;3,6-dianhydro-D-mannitol (1.00g, 0.00220 mole) previously prepared in this laboratory by M. Jackson (67) was dissolved in 30 ml. of N,N-dimethyl formamide. The solution was magnetically stirred and heated to just below reflux temperature. Sodium benzoate (0.793g, 0.00551 mole) was slowly added to the solution over a period of one hour. The sodium benzoate slowly dissolved and after a few minutes the solution became light yellow in color. After 3 hrs. the solution was cooled to room temperature, whereupon a white, flocculent precipitate settled out of the solution. Distilled water was added dropwise to the reaction mixture until all of the precipitate had dissolved (5 ml.). Further addition of water (30 ml.) produced a colorless crystalline precipitate which was washed with water and dried in vacuo overnight over phosphorus pentoxide. The crude product, 0.718g (92.3%), was recrystallized from absolute ethanol and melted at 109°-110°C. A mixed melting with an authentic sample of 2,5-di-O-benzyol-1,4;3,6-dianhydro-L-iditol was 109°-110°C. The two samples gave indistinguishable infrared spectra.

VIII. ATTEMPTED SYNTHESIS OF 2,5-DI-O-BENZOYL-1,3;4,6-DI-O-BENZYLIDENE ALLITOL.

2,5-Di-O-(p-toluenesulphonyl)-1,3;4,6-di-O-benzylidene dulcitol was prepared according to the procedure of Hann, Haskins and
Hudson (68). Di-Ω-benzylidene dulcitol (1.007g) prepared by E. Premuzic in this laboratory (57) was dissolved in 10 ml. of anhydrous pyridine and 1.3g of p-toluenesulfonyl chloride was slowly added to the ice-cooled solution. The p-toluenesulfonyl chloride readily dissolved with shaking. Upon standing overnight crystals had deposited on the sides of the reaction flask. Distilled water (25 ml.) was added dropwise to the flask. After approximately 5 ml. of water had been added a white powdery precipitate appeared. The contents of the flask were poured into 200 ml. of distilled water and vigorously stirred. The product was recovered on a filter and dried in vacuo over phosphorus pentoxide, (1.704g, 91.3% yield). The crude 2,5-di-Ω-p-toluenesulfonyl)-l,3;4,6-di-Ω-benzylidene dulcitol was recrystallized from 70 parts of pyridine; m.p. 213°-215°C (decomposition). Lit. value 215°C (decomposition). (68).

2,5-Di-Ω-(p-toluenesulfonyl)-l,3;4,6-di-Ω-benzylidene dulcitol (1.00g) was dissolved in 30 ml. of N,N-dimethyl formamide, heated to just below reflux temperature and magnetically stirred. The compound dissolved after 20 minutes heating. Sodium benzoate (0.54g, mole ratio of sodium benzoate to 2,5-di-Ω-(p-toluenesulfonyl)-l,3;4,6-di-Ω-benzylidene dulcitol of 2.5:1) was added slowly to the solution which changed color from colorless to dark orange and then black in a few minutes after the initial sodium benzoate addition. The solution was refluxed for 3 hrs. and cooled to room temperature. Distilled water was added dropwise to initiate crystallization. After 25 ml. of water had been added
a flocculent black precipitate formed. A further 50 ml. of water was added and the product was filtered through a sintered glass funnel. The product was finely divided, dark brown in color and did not appear to be crystalline. Upon redissolving the product in fresh N,N-dimethyl formamide and reprecipitating with water it remained dark brown and did not crystallize. No sharp melting point of product was observed as it appeared to start decomposing ~160°. Three further attempts to prepare 2,5-di-O-benzoyl 1,3;4,6-di-O-benzylidene allitol by this procedure were made with the following modifications: The refluxing temperature was decreased from 148°C to 125°C, the sodium benzoate was first dissolved in N,N-dimethyl formamide before addition of the 2,5-di-O-(p-toluenesulfonyl)-1,3;4,6-di-O-benzylidene dulcitol, the time of refluxing the reaction mixture was varied. In all of these cases the isolated product was brown in color and yields varying from 24% to 68% of original material were recovered. The product when recrystallized from dioxane-water was shown to be 2,5-di-O-(p-toluenesulfonyl)-1,3;4,6-di-O-benzylidene dulcitol by its melting point and thin layer chromatography.

IX. TRI-O-BENZYLIDENE-D-MANNITOL.

The procedure followed for the synthesis was that employed by Patterson and Todd (33).

D-Mannitol (2.995g, 0.0164 mole) was dissolved with shaking in 9.0 ml. of concentrated hydrochloric acid. Freshly distilled
benzaldehyde (6.30g, 0.0594 mole) was added dropwise with shaking. The flask was stoppered and shaken mechanically for 30 minutes. A solid white product appeared to form after approximately one minute of shaking. The reaction vessel was placed in a refrigerator for 12 hrs. after which time the contents of the flask had formed a solid white mass. The product was transferred to a sintered glass funnel and washed with ice water and ether. The washing was continued until the filtrate gave a negative test for chloride ion. The crude product, 6.277g (85.5% yield), was recrystallized from carbon tetrachloride and had a m.p. of 206°C (lit.value 218-219°C) (32);

\[ [\alpha]_{D}^{30} = 16.65 \text{ (CHCl}_3, 1.2.00, c. 3.512) \]

lit. value \[ [\alpha]_{D}^{17} = 16.5 \text{ (CHCl}_3, 1.1.00, c. 7.0192) \] (69)

Analysis calcd for C$_2$H$_6$O: C, 72.63; H, 5.87%

Found: C, 72.35; H, 5.72%

The infrared spectrum indicated the absence of hydroxyl groups and thin layer chromatography showed a single spot when run in pyridine and developed with concentrated sulfuric acid-nitric acid spray reagent.

X. HYDROLYSIS OF O-BENZYLIDENE ACETALS.

Several cyclic O-benzylidene acetals were hydrolyzed with 1.25M hydrochloric acid in ethanol solution and the hydrolysis was followed spectrophotometrically by the appearance of the carbonyl absorption peak in the ultraviolet spectrum. The procedure was as follows: A standard solution of the acetal
(2.94 x 10^{-4}M) in absolute ethanol was prepared. A 6.25M solution of hydrochloric acid was prepared by diluting one volume of hydrochloric acid with an equal volume of absolute ethanol. The solutions were kept in a constant temperature bath at 25.0 ± 0.1°C. The standard acetal solution (1.00 ml.) was pipetted into a 10 ml. volumetric flask, 2.00 ml. of 6.25M hydrochloric acid was added and the volume was made to the mark with absolute ethanol. The final concentration of acetal was 2.94 x 10^{-5} M and of hydrochloric acid was 1.25M. The solution was transferred to a 1.00 cm. stoppered quartz cell which was balanced in a Beckmann D.U. spectrophotometer against a matched cell containing a blank solution of hydrochloric acid in absolute ethanol. Readings of optical density at λ246μm were recorded at regular time intervals. From the plot of time versus optical density (FIGURES 6 and 7), the time required for complete hydrolysis was measured and from the value of optical density maximum and the extinction coefficient (ε), the number of benzylidene groups per acetal molecule could be calculated. The value of was determined by preparing standard solutions of benzaldehyde in 1.25M hydrochloric acid in absolute ethanol and measuring the optical density maximum at λ246μm as well as by measuring the optical density maximum of hydrolysed standard solutions of: tri-O-benzylidene-D-mannitol, 1,3;4,6-di-O-benzylidene dulcitol, 2,5-di-O-methyl-1,3;4,6-di-O-benzylidene dulcitol and 2,5-di-O-benzyl-1,3;4,6-di-O-benzylidene dulcitol. From the plot of optical density versus concentration of benzylidene groups (FIGURE 5) a straight line was drawn having a slope (ε) of 10,200.
SUGGESTIONS FOR FURTHER RESEARCH.

1. The synthesis of 1,3,4,6-di-\(\alpha\)-benzylidene allitol could be carried out under more forcing conditions and with different acidic catalysts to see if a tri-\(\alpha\)-benzylidene acetal could be formed.

2. Graded acidic hydrolysis of tri-\(\alpha\)-benzylidene iditol to di-\(\alpha\)-benzylidene iditol would be of interest as the possibility exists for the isolation of a di-\(\alpha\)-benzylidene derivative which does not possess the most favored structure.

3. The hydrolysis of \(\alpha\)-benzylidene acetals at varying hydrogen ion concentration would be of interest to determine the acid stability of different types and sizes of acetal rings. Graded hydrolysis of the tri-\(\alpha\)-benzylidene acetals of mannitol and talitol could provide a route for their structural elucidation.
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