THE FORMATION AND FISSION OF CYCLIC ACETALS

A Thesis submitted by

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CONTENTS

A B S T R A C T

Acetal condensations of a number of aldehydes with D-glucitol in dilute aqueous and non-aqueous acid media have been followed polarimetrically. Those involving acetaldehyde, propionaldehyde, n- and iso-butyraldehyde and benzaldehyde apparently proceed via a kinetically controlled intermediate, with a comparatively large negative optical rotation, before attaining an equilibrium in which the 2,4-monoacetal is the major product. Similar behaviour has not been observed with either formaldehyde or trichloroacetaldehyde.

For the reactions of D-glucitol with n-butyraldehyde and benzaldehyde the intermediate compounds have been isolated, characterized and shown to be the 2,3-O-butylidene and 2,3-O-benzylidene-D-glucitols respectively, which were previously unknown. Proton magnetic resonance (PMR) spectroscopic studies have been carried out on both compounds and these results, together with melting point and specific rotation data, indicated the 2,3-O-benzylidene compound, as isolated, to be a mixture of diastereoisomers.

Work on the hydrolyses of these two acetals suggested that they are considerably more labile than the corresponding 2,4-monoacetals. Moreover, 2,3-O-benzylidene-D-glucitol was hydrolysed much more rapidly than the butylidene compound.

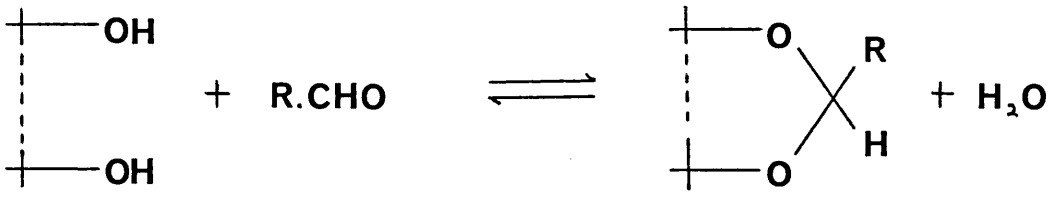
In non-aqueous media, both compounds underwent ring migrations in which the 2,4-monoacetals appeared to be the principal products.

The reactions of n-butyraldehyde with various derivatives of D-glucitol in dilute aqueous acid have been studied in a similar manner, and four new acetals have been isolated and identified. 1-Deoxy-D-glucitol reacted in the same way as D-glucitol, forming 2,3-O-butylidene-1-deoxy-D-glucitol under kinetic control which subsequently passed to 2,4-O-butylidene-1-deoxy-D-glucitol. With 2-deoxy-D-glucitol, the kinetically controlled product was 1,3-O-butylidene-2-deoxy-D-glucitol. No kinetically controlled products could be observed with 3-O-methyl-D-glucitol, but the main product appeared most likely to be 2,4-O-butylidene-3-O-methyl-D-glucitol.

I N T R O D U C T I O N

The Formation of Cyclic Acetals

Cyclic acetals are five, six or seven membered saturated heterocyclic rings containing oxygen atoms in positions 1 and 3, and are products of acid-catalysed condensations of aldehydes with polyhydric alcohols. (Fig. 1)



The equilibrium situations of many such reactions are well documented.[1] Although the variety of possible products increases with the number of hydroxyl groups in the alcohol, it had long been recognised that the configuration of the hydroxyl groups had considerable influence on the type of cyclic acetal that was found in the final products. Certain ring forms appeared to be more favourable than others.

The first attempt to correlate these observations was made by Hann and Hudson[2,3] who drew up a set of empirical rules based upon data available from the methylene acetals of D-glucitol, D-mannitol and dulcitol. Barker and Bourne[4] later modified and extended these rules to cover data for benzylidene, ethylidene and methylene acetals of a wide range of polyhydric

alcohols, and to facilitate discussion they introduced a nomenclature for distinguishing the different types of rings.

The Greek letters α, β and γ were used to signify the relative positions along the carbon chain of the polyhydric alcohol, of the two hydroxyl groups engaged in cyclisation, and C and T indicated the relative configurations (cis or trans) of these two groups as they appeared in the usual Fischer projection formula. C and T were not required if a primary hydroxyl group was involved. Thus, for example, in D-glucitol (Fig. ii) a ring involving hydroxyl groups at positions 1 and 2 was described as an α-ring, a 2,3 ring would be αT, 4,5-, αC, 1,3-, β, 3,5-, βT, 2,4-, βC etc.

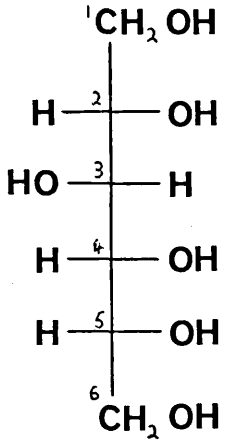


Fig. ii

According to the modified Hann-Hudson rules, the order of preference for the formation of cyclic acetal rings was firstly a βC ring, then a β-ring, followed by an α-, αT, βT- or γT-ring. The order in the latter group was dependent upon such factors as the nature of the aldehyde, and whether part of the polyhydric alcohol was already involved in a ring system. With the aid of these rules the products of a given condensation could be predicted with considerable confidence.

Mills[5] has shown that the existence of cyclic acetals in an equilibrium mixture, in certain preferential ring forms, can be explained by application of the principles of conformational analysis; the most favoured ring forms being conformationally the most stable.

Fig. iii

The five membered (α-) or 1,3-dioxolane ring is not quite planar. Proton magnetic resonance (NMR) spectroscopic studies[6] have shown that the ring is puckered such that the cis-neighbouring substituents define a small dihedral angle. In Fig.iii R' and R" represent the residues of the polyhydric alcohol chain, and their most favourable positions are in a trans-relationship in which interaction is a minimum.[5] Hence an αT-ring is generally expected to be more stable than an αC-ring. Stereoisomerism is possible at the acetal carbon atom (C_2) provided that, in the case of the trans-ring, R' and R" are different.

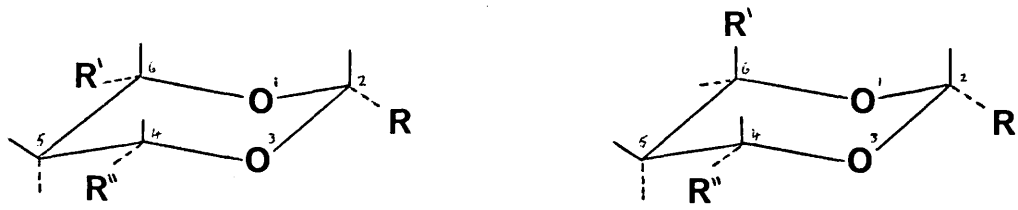


Fig. iv

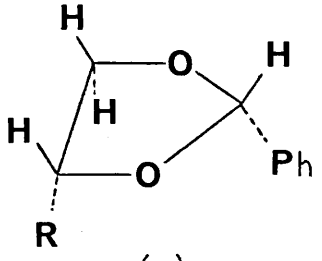
The six membered (β-), or 1,3-dioxane ring (Fig. iv) preferentially adopts the 'chair' conformation. In the most favourable (βC-) ring the residues R' and R" are in equatorial positions, whereas for the alternative (βT-) ring one residue must be axial and the other equatorial. Theoretically stereoisomerism is possible at the acetal carbon atom (C_2) but in practice only one diastereoisomer is normally found since a second would require the substituent R in an unfavourable, axial position.

The seven membered (γ-), or 1,3-dioxepan ring is far less common among the cyclic acetals of polyhydric alcohols than are the other two rings. It is by comparison a very flexible structure.

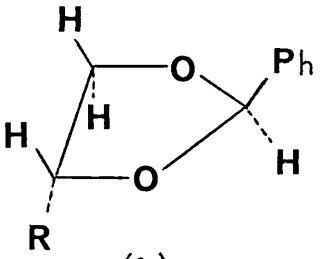
One of the most useful tools for studying the formation, structure and reactivity of cyclic acetals is proton magnetic resonance spectroscopy (PMR). Baggett et al.[7] have examined

the spectra of a great many substituted 1,3-dioxanes and 1,3-dioxolanes, and have observed that the signal for the proton on the acetal carbon atom (C_2) of 2-phenyl derivatives is unsplit and occurs in a region of the spectrum which is usually free from other signals.

The magnitude of the chemical shift of this signal is dependent to some extent on the proximity of the proton to other substituents on the ring. For example, in a series of 4-alkyl-2-phenyl-1,3-dioxolanes, in p-dioxan solutions, acetal proton signals were found in the ranges τ 4.62 - 4.67 and 4.46-4.52 and were assigned to the isomers (a) and (b) respectively (Fig. v).



(a)



(b)

The displacement of the acetal proton signal to lower field in the (b) isomers was attributed to deshielding arising from the expansion of the electron clouds of the acetal proton and the 4-substituent because of their proximity.

Benzylidene acetal protons on 1,3-dioxolane rings usually resonate at lower fields than those on 1,3-dioxane rings.

It has been suggested[8] that this may be explained by the deshielding effect, on the acetal proton, of the unshared electrons on the adjacent oxygen atoms, which are held, in the 1,3-dioxolane ring, in orbitals eclipsed with the C_2-H bond.

From correlations between stereochemical environments and chemical shifts of acetal proton signals ring sizes, conformations and absolute configurations have been determined for many Benzylidene[7,9,10,11,12] and some Furfurylidene[13] acetals. Moreover observation of these signals during reactions can provide information concerning the formation or decay of particular acetals.[11,14,15]

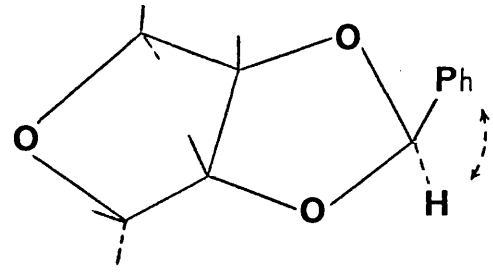
The course of acid catalysed acetalation of polyhydric alcohols has received comparatively little study. Hann and Hudson[2] envisaged that such condensations would entail a succession of reactions, some perhaps in competition, and that a state of reversible equilibrium in the acid reaction mixture, involving a number of acetals, would finally be attained. The kinetic phase of the reaction is controlled by the energies of activation which can depend on factors other than the stability of the final products.

Polyhydric alcohols are assumed to preferentially adopt a planar zig-zag conformation of the carbon chain.[16] However,

it is not certain that this conformation necessarily persists in solution. Interactions with solvent molecules may cause distortions and it is possible that formation of the most stable products could thus be hindered.

A consequence of kinetic control is often the rapid formation of an intermediate product requiring a low energy of activation, which then slowly passes to the more thermodynamically stable product.

By means of PMR spectroscopy, Al-Jeboury et al.[14] have followed the benzylidenation of 1,4-anhydroerythritol in nitromethane at 25-30° in the presence of toluene-p-sulphonic acid. They noticed that there was a rapid development of an acetal proton signal at relatively high field followed by the slow appearance of a signal at lower field, paralleled by diminution in intensity of the first signal. At equilibrium, the integrated areas of the two signals were comparable. The two signals were attributed to the isomers of the acetal with phenyl groups in the endo- and exo-positions respectively (Fig. vi).



The same effect was found to take place during the benzylidenation of cyclohexane-cis-1,2-diol. The selective formation of the endo-isomer reflected an initial kinetic control that was attributed to the fact that a substantial rotational energy barrier retarded the formation of the exo-isomer.

The operation of kinetic control has been demonstrated in the early stages of the acid catalysed benzylidenation of methyl-α-D-galactopyranoside in N,N-dimethylformamide (DMF)[11] where small amounts of the diastereoisomers of 3,4-O-benzylidene derivatives were detected. At equilibrium, the only apparent product was the 4,6-acetal.

The Fission of Cyclic Acetals

Fission of cyclic acetals is generally brought about by the attack of an electrophilic species (X) on one of the ring oxygen atoms, followed by rupture of the adjacent bond with the acetal carbon atom, to form an oxocarbonium ion intermediate (Fig. vii). The oxocarbonium ion can then undergo further reaction.

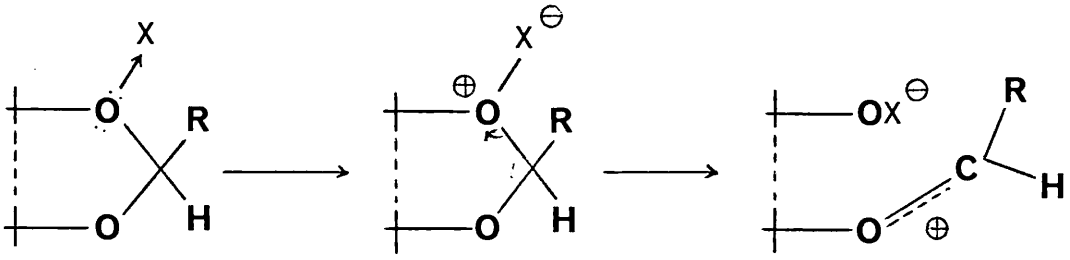


Fig. vii

Electrophilic reagents that have been used for this purpose include Lewis acids (e.g. Boron trichloride[17,18] and Aluminium trichloride[19,20,21,22]), cations of the type $RC^{O}O$ as in acetolysis[23,24,25,26], hydroxonium ions as in hydrolysis, and protons.

Hydrolysis of the acetal products opposes the acid catalysed condensation of aldehydes with polyhydric alcohols. In contrast with the latter reaction, acid catalysed hydrolyses

of both linear and cyclic acetals have been considerably explored and a mechanism (Fig. viii) is now well established, the principal evidence for which has been reviewed by Fife and Jao.[27]

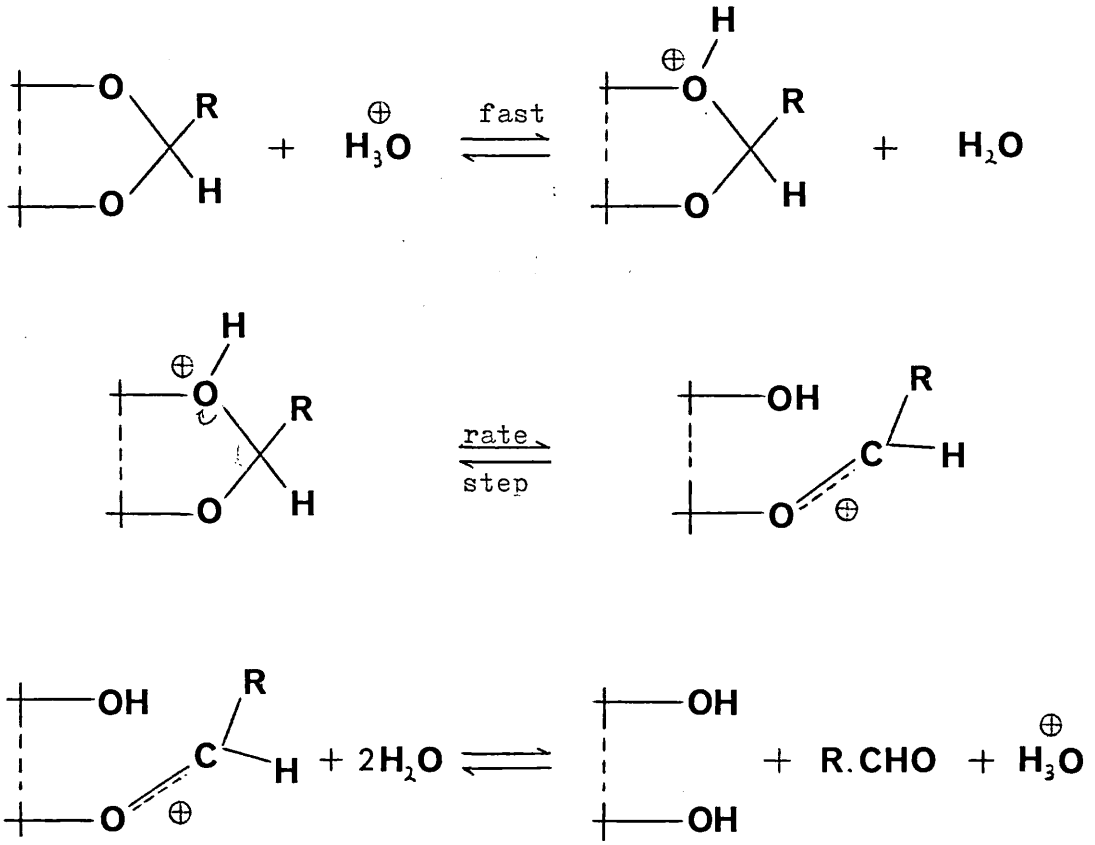


Fig. viii

The reaction shows specific acid catalysis and the rate determining step involves the formation of an oxocarbonium ion by the unimolecular breakdown of the protonated acetal

(an A-1 mechanism). In common with this mechanism is the marked effect of the substituent R, on the acetal carbon atom, on the reaction rate. An electron-donating group enhances the reaction by assisting protonation and stabilizing the oxocarbonium ion transition state, whilst an electron-withdrawing group has the opposite effect. If the substituent can interact with the oxocarbonium ion through resonance then the effect on the reaction rate is even more marked.

Most of the work on the hydrolysis of cyclic acetals has been carried out with the more simple substituted 1,3-dioxanes and 1,3-dioxolanes. Of the hexitol cyclic acetals, Hockett et al.[28] have studied the hydrolysis of 4,6-O-ethylidene-D-glucitol in aqueous sulphuric acid, by following the change in optical rotation of the reaction mixture with time.

By a similar method, S.E. Harwood[29] investigated the kinetics of hydrolysis of some butylidene and but-2-enylidene acetals of D-glucitol in aqueous hydrochloric acid. She found that the reactions were of first order with respect to the acetals, and concluded that the mechanism for the 2,4-O-butylidene acetal was A-1, since the logarithm of the rate constant varied linearly with the acidity function, $-H_0$, giving a line of unit slope.[30] Somewhat surprisingly, there was little

significant difference in the rates of hydrolysis of the 2,4- 4,6- and 3,4-O-butylidene-D-glucitols, as might have been expected from the predicted order of stability of the rings ($\beta C > \beta > \alpha T$)[4]. However, the unsaturated 2,4-O-but-2'-enylidene-D-glucitol was hydrolysed much faster than the corresponding saturated acetal a fact which is consistent with the formation of a resonance stabilised transition state.

The reductive cleavage of 1,3-dioxanes and 1,3-dioxolanes in ether solution with aluminium chloride and lithium aluminium hydride has been extensively studied by Leggetter and his co-workers,[19,20,21,22] and their observations have indicated that the formation of the oxocarbonium ion is the rate controlling stage. They have pointed out that oxocarbonium ion formation requires that a C-O-C group attain coplanarity for optimum stabilisation.[20] This is more readily achieved in the 1,3-dioxolane ring because it is more nearly complanar initially,[6] than is the 1,3-dioxane ring whose ideal conformation approaches that of the chair form of cyclohexane. On this basis, five membered acetal rings would be expected to cleave more readily than six membered rings.

If an oxocarbonium ion recyclises, by reacting with another hydroxyl group of the same polyhydric alcohol, the net result is a ring migration. An example of this was discovered

by Reeves[31] who found that in glacial acetic acid 3,5-O-benzylidene-1,4-anhydro-D-mannitol underwent a rearrangement to the 2,3-O-benzylidene compound (Fig. ix). More recently, Al-Jeboury et al.[14] have shown that this reaction also takes place at 25-30° in DMF containing toluene-p-sulphonic acid.

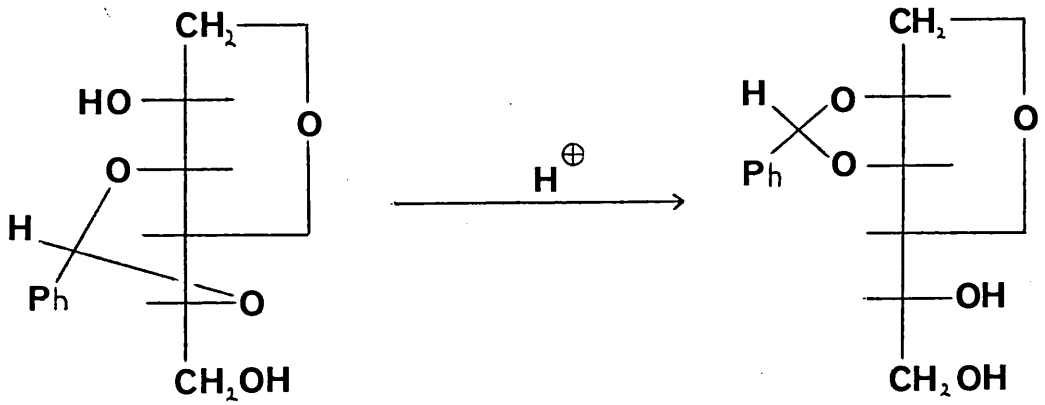


Fig. ix

Owing to the competition from hydrolysis and resynthesis reactions, ring migration in aqueous acid media is not often easy to detect. However, it has been shown[32] that, in dilute aqueous acetic acid, 2,4:3,5-di-O-furfurylidene- and 2,4:3,5-di-O-benzylidene-D-glucitols rearrange by ring migration to the corresponding 1,3:2,4-diacetals (Fig. x).

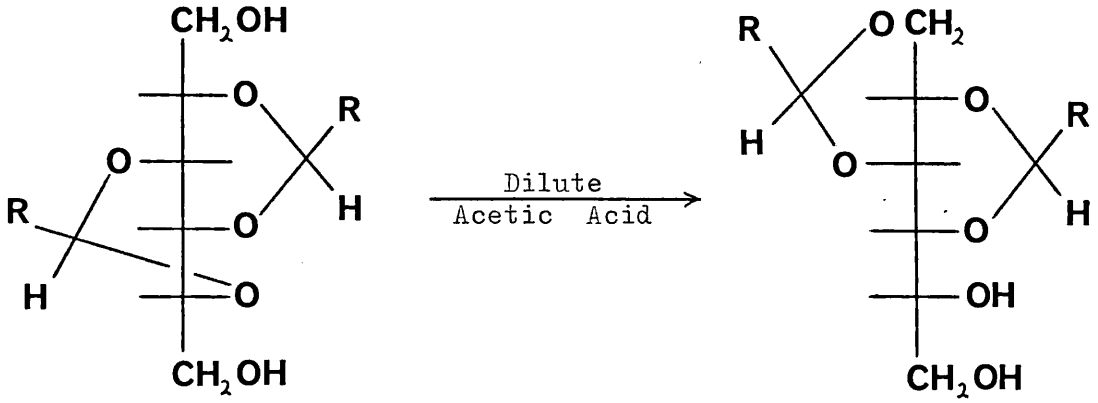

CH2OH
O
R
O
H
R
O
O
H
O
CH2OH
Dilute
Acetic Acid
R
O CH2
H
O
O
R
O
H
OH
CH2OH

Fig. x

Cyclic Acetals of D-Glucitol

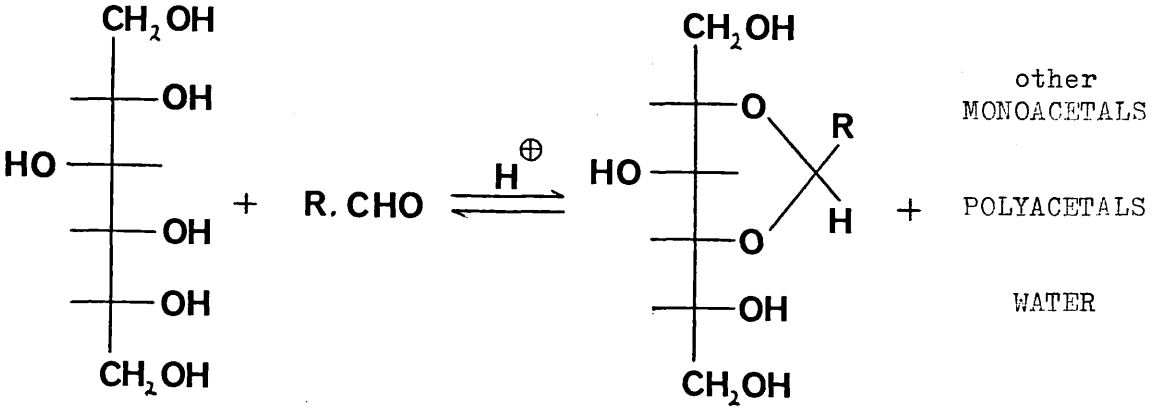


Fig. xi

When equimolar quantities of D-glucitol and an aldehyde are dissolved to form a concentrated solution in aqueous sulphuric acid (c.3N) and left to stand at room temperature for some time, the principal product obtained from the reaction mixture is the 2,4-monoacetal (Fig. xi). Formation of this particular monoacetal is predictable since it is a βC-ring[4] and is thermodynamically the most stable.[5,20] The reaction has been found to be applicable to furfuraldehyde,[33] crotonaldehyde,[34] n-butyraldehyde,[35] iso-butyraldehyde, propionaldehyde and benzaldehyde,[29] and in every case the 2,4-monoacetal crystallizes out of solution, thus discouraging further condensation with the aldehyde to form polyacetals. 2,4-O-Ethylidene-D-glucitol could not be obtained by this method, presumably due to its greater solubility in the reaction mixture, and this

would probably apply also to 2,4-O-methylene-D-glucitol.[29]

The formation of polyacetals in substantial yield is assisted by the removal of water from the system. For example, tri-O-furfurylidene, tri-O-n-butylidene-, tri-O-iso-butylidene[29] and tri-O-but-2-enylidene-D-glucitols[34] have been prepared by azeotropic distillation of the reactants in the presence of toluene-p-sulphonic acid.

The aforementioned reactions have all involved reactants in very highly concentrated solutions. There are few reports of such reactions being conducted in dilute ($< M$) aqueous solutions. Under these conditions, monoacetal products would remain in solution and the reverse reaction should play an important role in governing the constitution of the final mixture. It also seems reasonable to assume that the formation of polyacetals would be retarded in the presence of a large excess of water.

The subject of this thesis arose as a result of an observation by Dr. S.E. Harwood.[29] Taking an equimolar mixture (c.0.1M) of n-butyraldehyde and D-glucitol in 2N aqueous acid solution she followed the reaction polarimetrically, at 30°. The variation in the optical rotation of the system with time is shown below (Fig. xii).

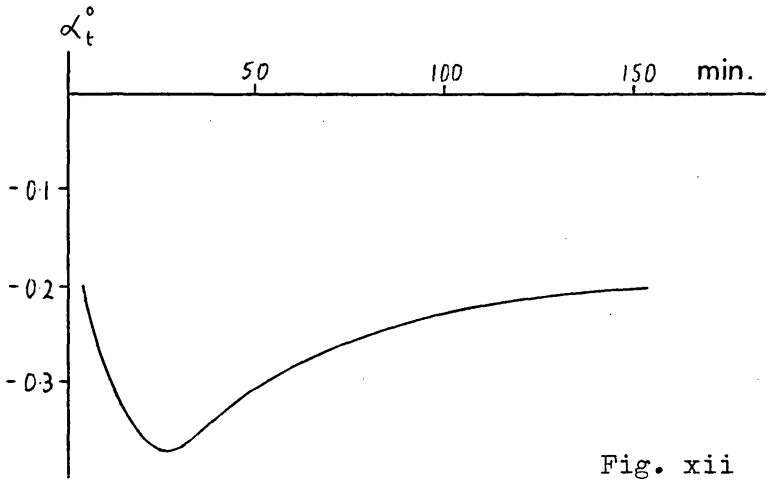


Fig. xii

Polarimetric curves of similar form were obtained in the presence of both hydrochloric acid, and sulphuric acid catalysts and later the same result was obtained with 2,5-dichlorobenzene-sulphonic acid, thus eliminating the possibility that the shape of the curve was associated with the acid radical.

Dr. Harwood pointed out that the rapid attainment of such a minimum, followed by the increase to the equilibrium rotation, was characteristic of a kinetically controlled first stage, followed by a thermodynamically controlled second and final stage. The kinetically controlled product was detectable on account of its relatively large negative optical rotation.

For the reasons already outlined, the final reaction mixture would be expected to contain a high proportion of 2,4-O-butylidene-D-glucitol ($[\alpha]_D^{24}$-9.6 in water)[35]. At the time, the only known compound of n-butyraldehyde and D-glucitol having

a larger negative rotation was 4,6-O-butylidene-D-glucitol. ($[\alpha]_D^{20}$ -26.8° in water)[36] and this could have accounted for the results. It was therefore suggested that initial attack took place at a primary hydroxyl group and hence the formation of the 4,6-monoacetal (β-ring). This compound could then rearrange, perhaps by ring migration, to give the more stable 2,4-monoacetal (βC-ring). In a scheme of this sort there would be good reason to expect the formation of the 1,3-monoacetal in almost equivalent amounts, since the two primary hydroxyl groups of D-glucitol should show similar reactivity.

These ideas provided a hypothesis, the validity of which was now to be tested by further investigation.

D I S C U S S I O N

I. PRELIMINARY INVESTIGATION

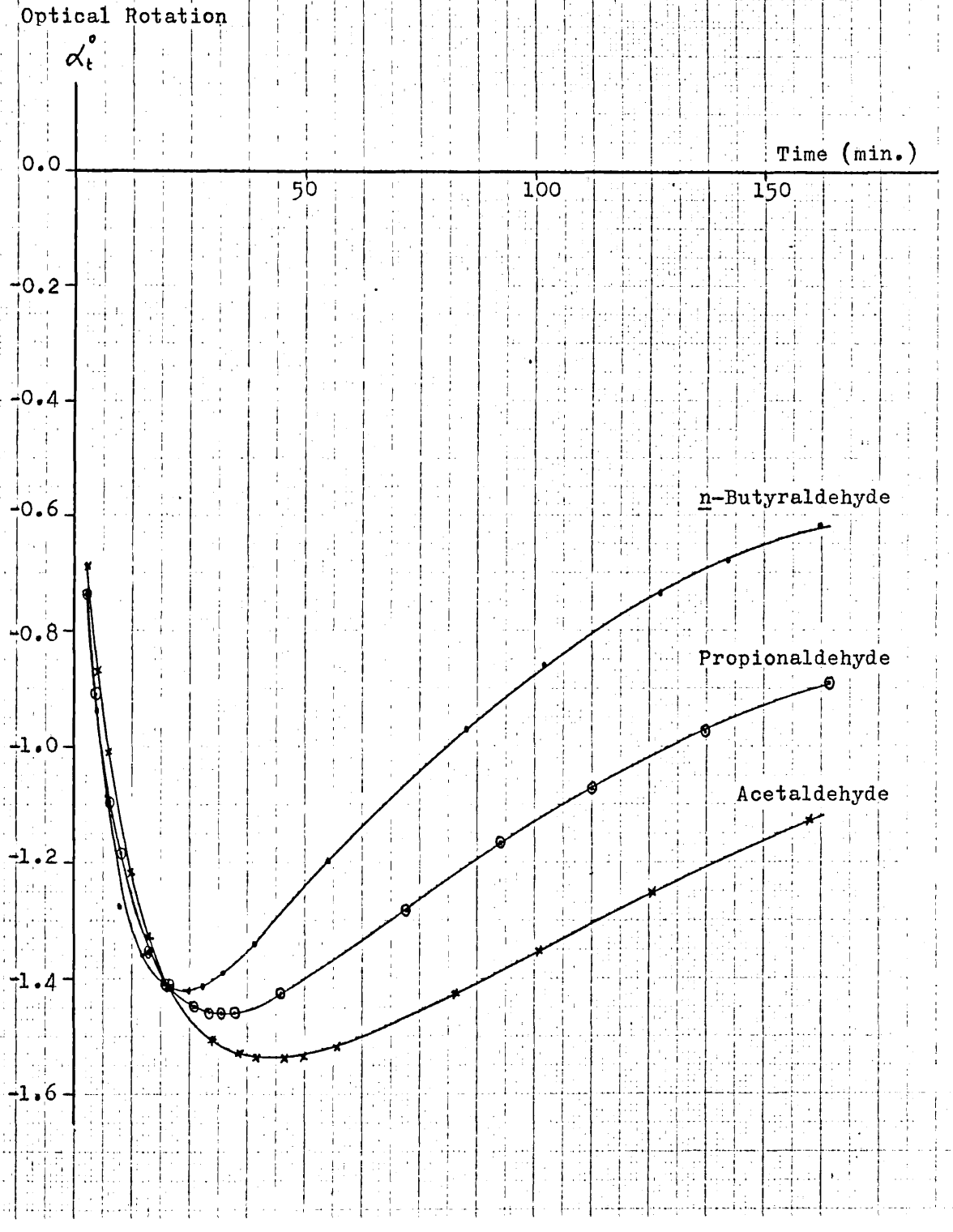
Reaction of Aldehydes with D-Glucitol in Aqueous Media

Having regard to the observation of Dr. S.E. Harwood[29] that the reaction of n-butyraldehyde with D-glucitol in aqueous acid appeared to proceed via a kinetically controlled intermediate, with a relatively large negative optical rotation, the reactions of a number of aldehydes with D-glucitol were investigated, in order to establish whether or not the phenomenon was general.

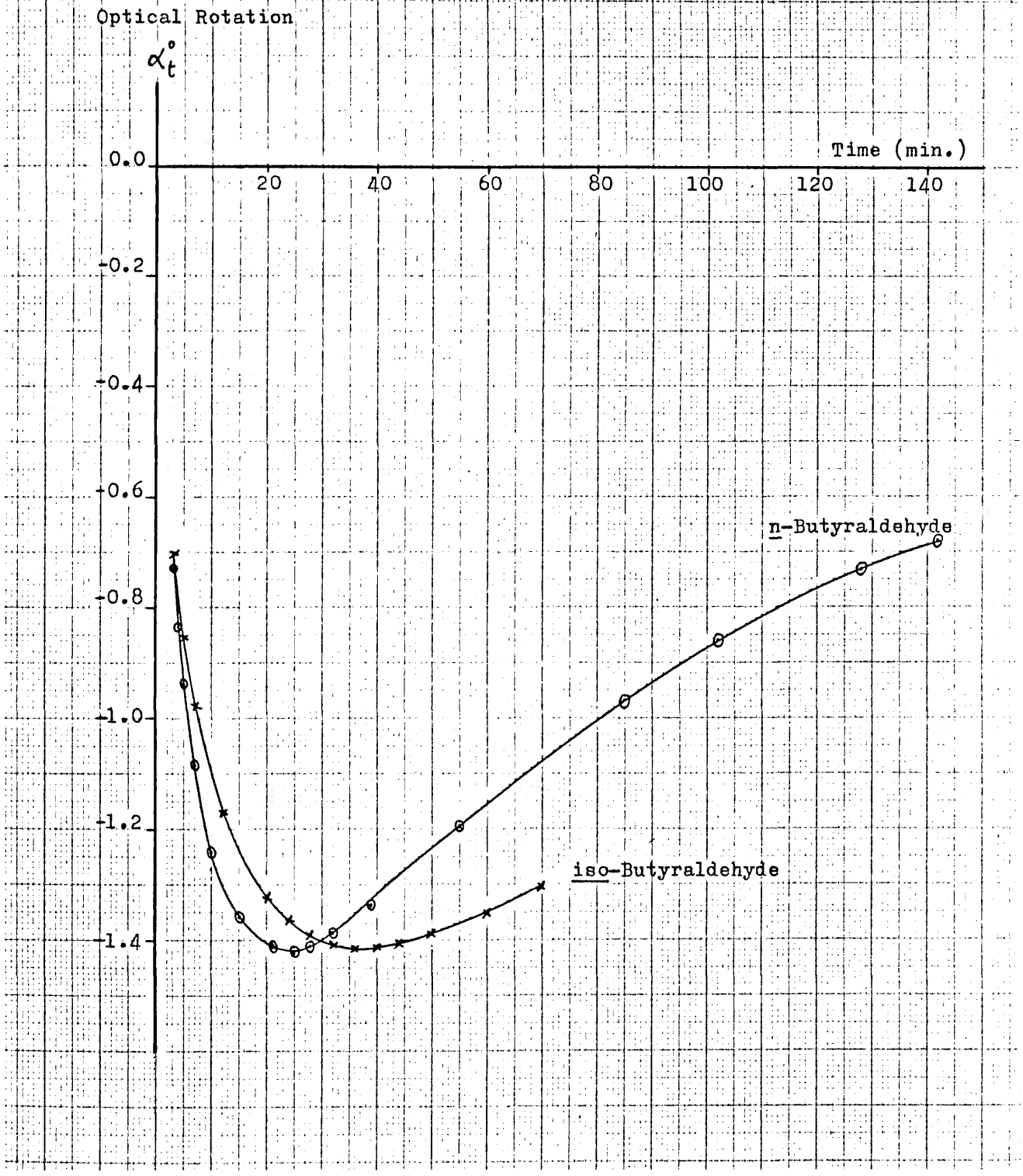
n-Butyraldehyde, acetaldehyde, propionaldehyde, iso-butyraldehyde, formaldehyde, benzaldehyde and trichloroacetaldehyde were each allowed to react with equimolar quantities (0.25M) of D-glucitol in aqueous hydrochloric acid at 25° (Expt. 1, p.136). The reactions were followed polarimetrically and the results have been summarized in Graphs 1-5 (pp.25-29). Since this work has often involved optical rotation data of both signs, the optical rotation has been described throughout as increasing in the positive direction and decreasing in the negative direction, in order to avoid confusion.

The graphs indicated that n-butyraldehyde was far from being an isolated case. Acetaldehyde, propionaldehyde and benzaldehyde all presented similarly shaped polarimetric curves, although, in the case of benzaldehyde, DMF was included to facilitate solubility. Polymerisation of iso-butyraldehyde eventually

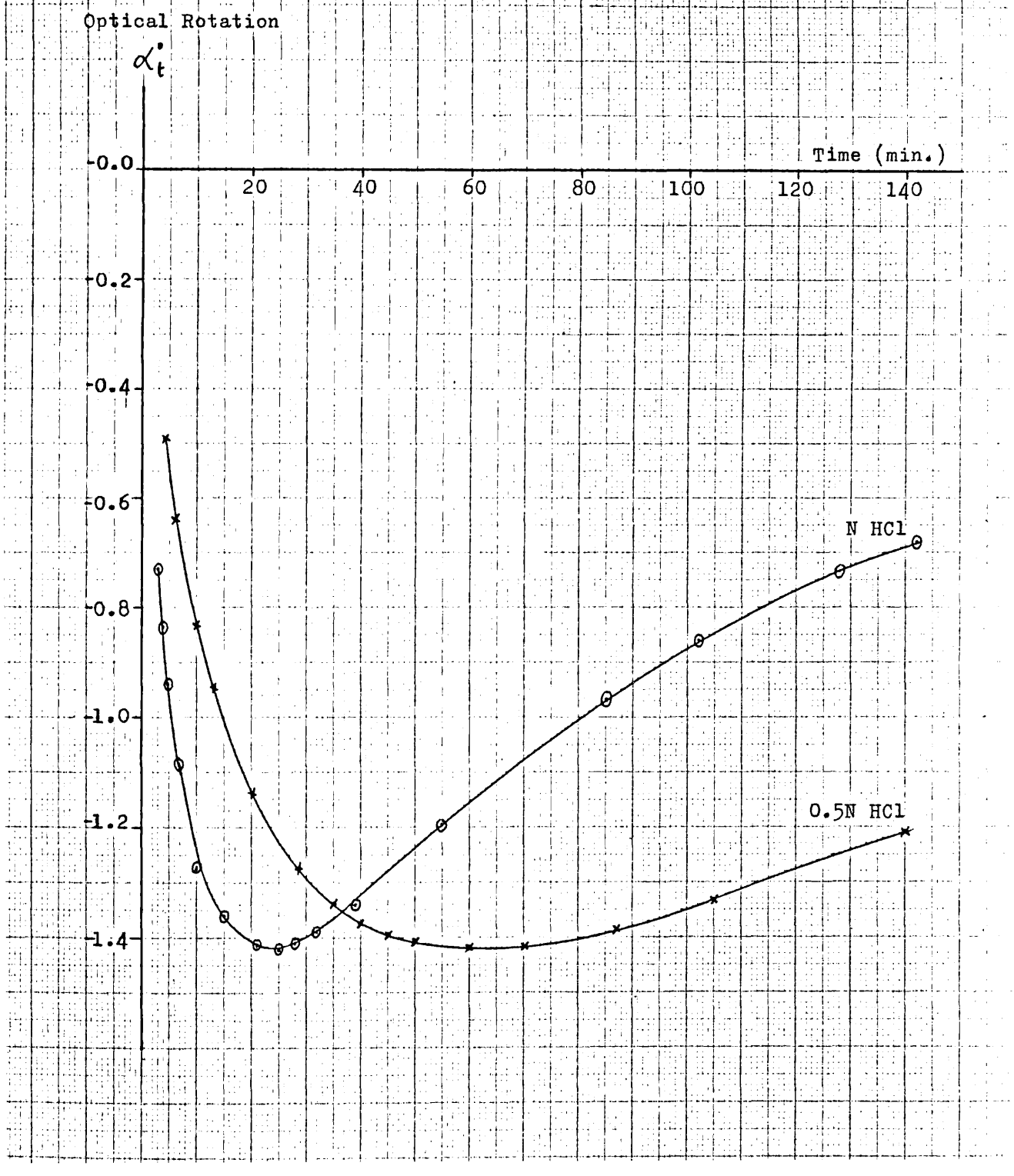
GRAPH 1. Reactions of some Aliphatic Aldehydes (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°.



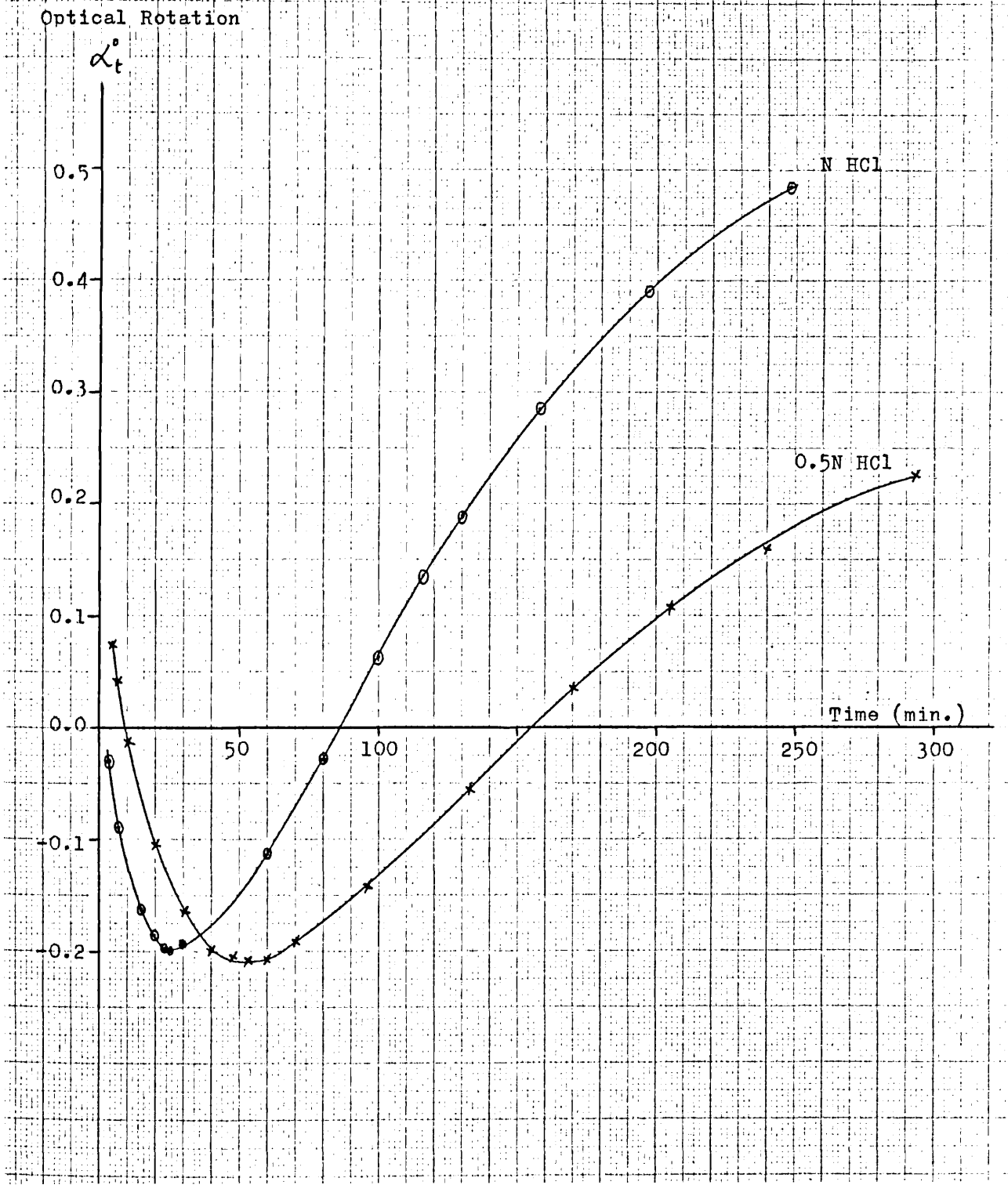
GRAPH 2. Reactions of n- and iso-Butyraldehydes (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°.



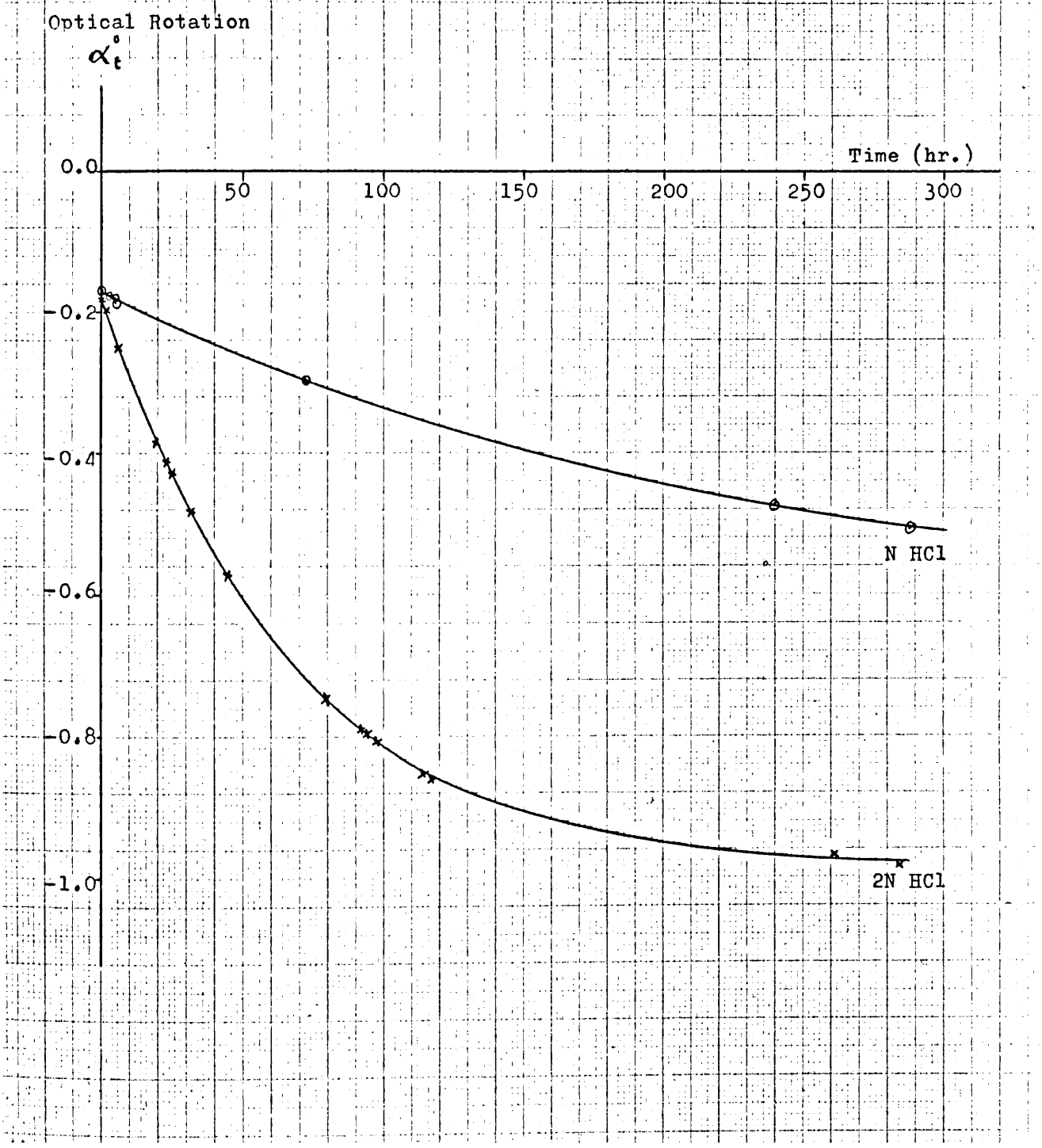
GRAPH 3. Reactions of n-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in N and 0.5N Aqueous Hydrochloric Acid at 25°.



GRAPH 4. Reactions of Benzaldehyde (0.25M) with D-Glucitol (0.25M) in DMF containing Water (20% v/v) and Hydrochloric Acid at 25°.



GRAPH 5. Reactions of Formaldehyde (0.25M) with D-Glucitol (0.25M) in N and 2N Aqueous Hydrochloric Acid at 25°.



rendered that solution opaque, so that the reaction was unable to be followed for its full duration, but this appeared also to conform to the general pattern.

Formaldehyde was an exception. Optical rotation did decrease as the reaction proceeded, but, by comparison with the other reactions, this decrease was very slow. The curve, with 2N hydrochloric acid, showed no sign of turning after 42 days.

With trichloroacetaldehyde in N hydrochloric acid, no significant change in optical rotation was observed over a period of 216 hours (see Table 13, p.217). Since acetal formation is likely to be accompanied by some change in rotation, it must be concluded that this reaction did not take place under these conditions. However, the possibility of hemiacetal formation cannot be entirely ignored.

The similarity of the polarimetric curves for the reactions of acetaldehyde, propionaldehyde, n-butyraldehyde, iso-butyraldehyde and benzaldehyde suggested that these reactions had a common mechanistic pattern. The fact that formaldehyde had a different type of curve did not itself imply a difference in mechanism, since nothing was known of the relative optical rotation values of the individual components in the mixture.

Variation of the acid concentration affected the reaction rates, but the characteristic shapes of the polarimetric curves were maintained. (Graph 3, p.27).

It was not without possibility that the observed intermediate in these reactions might be a hemiacetal. However, change in optical rotation was only observed on addition of acid, and hemiacetal formation is normally regarded as being independent of acid or base. The work of Adkins and Broderick[37] has indicated that hemiacetals of simple, monohydric alcohols, are generally unstable, even in the presence of the water produced during acetal condensation. The accumulation of a large quantity of a hemiacetal in these cases, in dilute aqueous solution, would therefore seem unlikely.

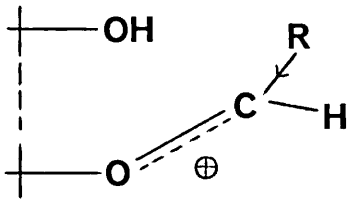
The rate of initial reaction (Graph 1, p. 25) appeared to increase in the order,

MeCHO < Et CHO < n Pr CHO

which is the order of increasing electron donating power of the alkyl groups. Furthermore formaldehyde, with no alkyl groups, had a very slow reaction, whilst trichloroacetaldehyde, with a strong electron-withdrawing group was apparently unreactive. Neglecting possible steric effects, these results would imply that, in general, this reaction is favoured for aldehydes with electron-donating substituents.

The exact mechanism for acetal formation has still to be elucidated, but if, as Bell and his coworkers[38] suggest, the rate determining step involves the formation of an oxocarbonium

ion, then the above observation would lend support to this idea, since electron donating substituents would tend to stabilize an oxocarbonium ion intermediate. (Fig. xiii).



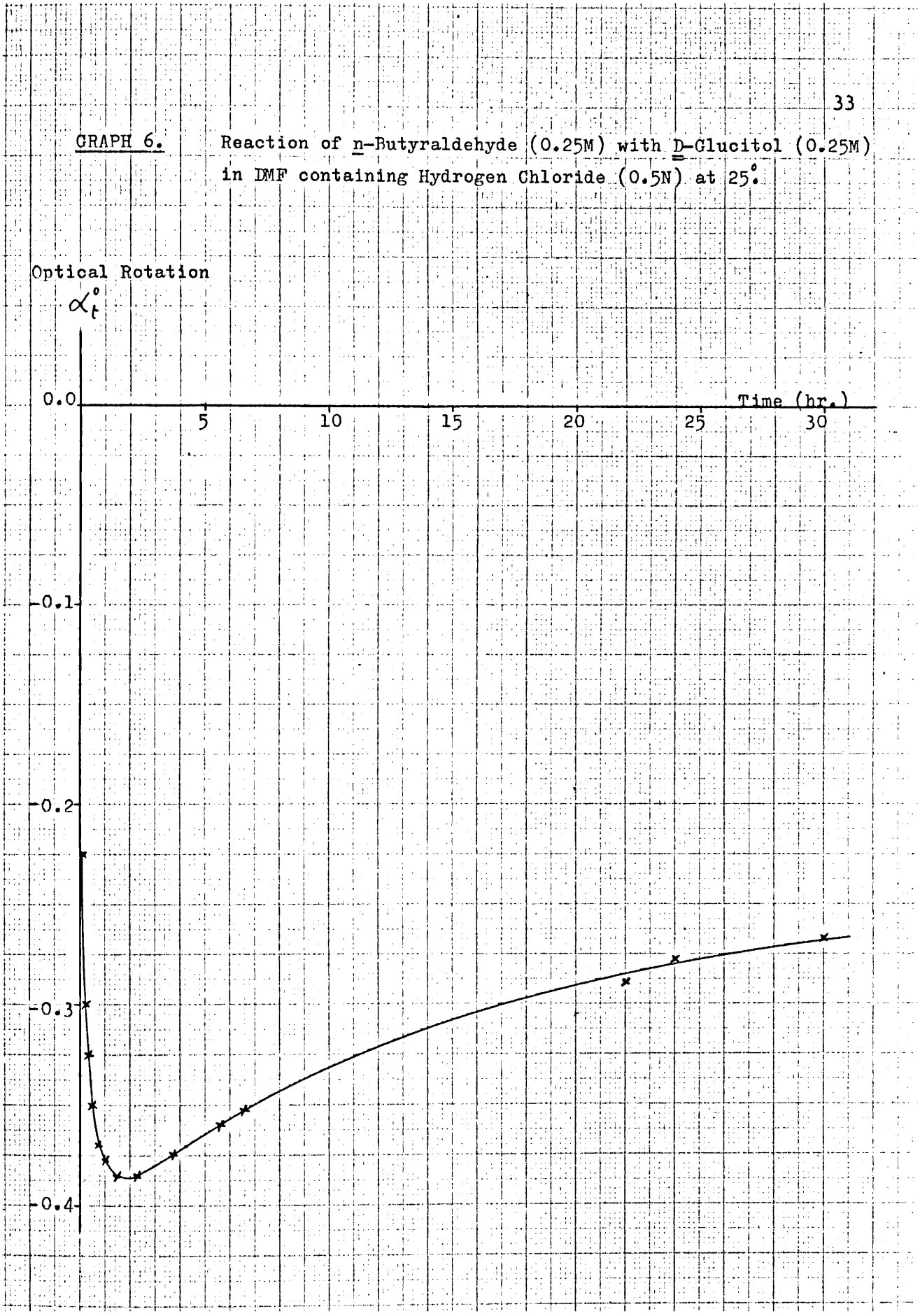
The reaction of benzaldehyde with D-glucitol must be excluded from these speculations, as no allowance can be made for the effects of the different solvent system. In addition, resonance interaction would be expected between an oxocarbonium ion and the benzene ring.

Reaction of Aldehydes with D-Glucitol in Non-aqueous Media

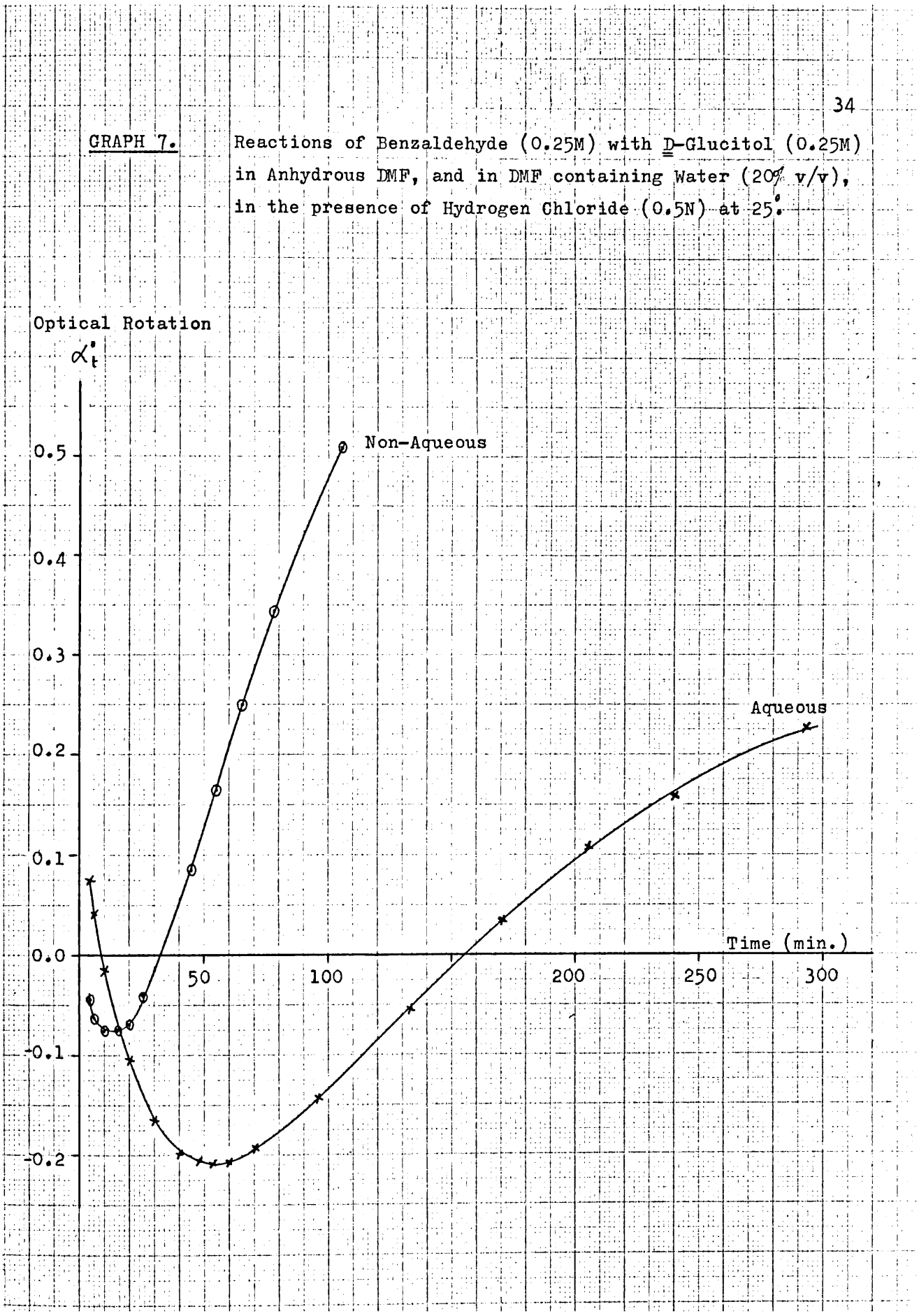
The effect of the solvent was investigated in Expt. 2 (p.138) where the reactions of n-butyraldehyde and benzaldehyde with D-glucitol were conducted in DMF containing dissolved hydrogen chloride (0.5N). Graphs 6 & 7 (pp.33-34) show that the characteristic shape of the polarimetric curves presented by these reactions in aqueous media was also common to the reactions in DMF.

Optical rotations of the various components involved are not

GRAPH 6. Reaction of n-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in DMF containing Hydrogen Chloride (0.5N) at 25°.



GRAPH 7. Reactions of Benzaldehyde (0.25M) with D-Glucitol (0.25M) in Anhydrous DMF, and in DMF containing Water (20% v/v), in the presence of Hydrogen Chloride (0.5N) at 25°.



necessarily strictly comparable in the two media. Nevertheless, although the n-butyraldehyde reaction showed initially a rapid decrease in optical rotation, the subsequent increase in rotation was much slower in the non-aqueous medium. It could be that the second stage of this reaction is assisted by the presence of an excess of water. The same effect could not, however, be noticed in the reaction with benzaldehyde.

It would be interesting to observe the effects, on these two reactions, of the total absence of water, by removing the water that is produced during condensation. This could probably be done with the aid of molecular sieves as in the synthesis of esters.[39]

II. BUTYLIDENE-D-GLUCITOLS

Of the three aliphatic, straight chain, aldehydes investigated, n-butyraldehyde was selected for a more detailed study. The phenomenon was first encountered with n-butyraldehyde and D-glucitol, and, as a result of previous work by Dr. D. Lewis and Dr. S.D. Harwood,[35,36] a number of butylidene-D-glucitols were readily available. Owing to their higher volatility, acetaldehyde and propionaldehyde were more difficult to weigh accurately for quantitative work. Whereas higher homologues than n-butyraldehyde were very sparingly soluble in aqueous media.

Effects of Dilute Aqueous Acids on n-Butyraldehyde

The ultra-violet spectrum of a dilute aqueous solution of n-butyraldehyde showed a broad band with a maximum at about 281mμ. due to carbonyl absorption. Aldehydes are known to exist in aqueous solution as an equilibrium between the carbonyl and the hydrated forms.

$$R.\,CHO + H_2O \rightleftharpoons R.\,CH(OH)_2$$

Since this equilibrium is very rapidly established,[40] the amount of aldehyde in the carbonyl form, which is that measured spectrometrically, should be directly proportional to the total amount of aldehyde in the system. This was confirmed by the fact that the absorption at 281 mμ. of an aqueous, or aqueous acidic, solution of n-butyraldehyde obeyed Beer's Law.

It was noticed that the absorption at 281 mμ. of an aqueous solution of n-butyraldehyde increased with increasing concentration of hydrochloric acid. The effect of the acid must have been to shift the hydration equilibrium to the left. Gruen and Mc. Tigue[41] have observed a similar effect by the addition of electrolytes (e.g. sodium chloride) to aqueous solutions of a number of aldehydes, including n-butyraldehyde, and have attributed it to the decrease in water activity accompanying the increase in electrolyte concentration.

The spectrum of an aqueous solution of n-butyraldehyde remained unaltered after the solution had been standing for many days. However, on addition of hydrochloric acid, a new absorption band appeared in the spectrum at 238 mμ. after a few hours. The solution also developed a strong and very characteristic odour. It was felt, that, before proceeding with the main work, this effect should be studied with a view to determining its importance as a side reaction.

Whilst studying the aldol condensation of n-butyraldehyde with formaldehyde in aqueous sulphuric acid, Mitsui et al.[42] noticed that n-butyraldehyde also underwent self-condensation to form 2-ethyl-2-hexenal (2-ethyl-3-propylacrolein).

$$2\ Pr.CHO \longrightarrow Pr.CH = C(Et)CHO + H_2O$$

Previous work on the acid catalysed aldol condensation of n-butyraldehyde[43] involved the use of cation exchange resins as catalysts in non-aqueous conditions. Here, both 2-ethyl-2-hexenal and parabutyraldehyde (a cyclic trimer) were produced, depending on the conditions.

When a solution of n-butyraldehyde in 2N aqueous hydrochloric acid was left for several days at 25° (Expt. 3, p.139) an oil separated out. This oil readily formed a 2,4-dinitrophenylhydrazone derivative, which indicated that it was a carbonyl compound.

The base catalysed aldol condensation of n-butyraldehyde (a much faster reaction) has been well explored, and 2-ethyl-2-hexenal is known to be the chief product. An authentic sample was therefore prepared accordingly (Expt. 4, p.140), and a mixture of its 2,4-dinitrophenyl-hydrazone derivative, with the derivative, mentioned above, from the acid catalysed reaction, suffered no depression of melting point. It was thus concluded that 2-ethyl-2-hexenal was formed slowly in a solution of n-butyraldehyde in aqueous hydrochloric acid.

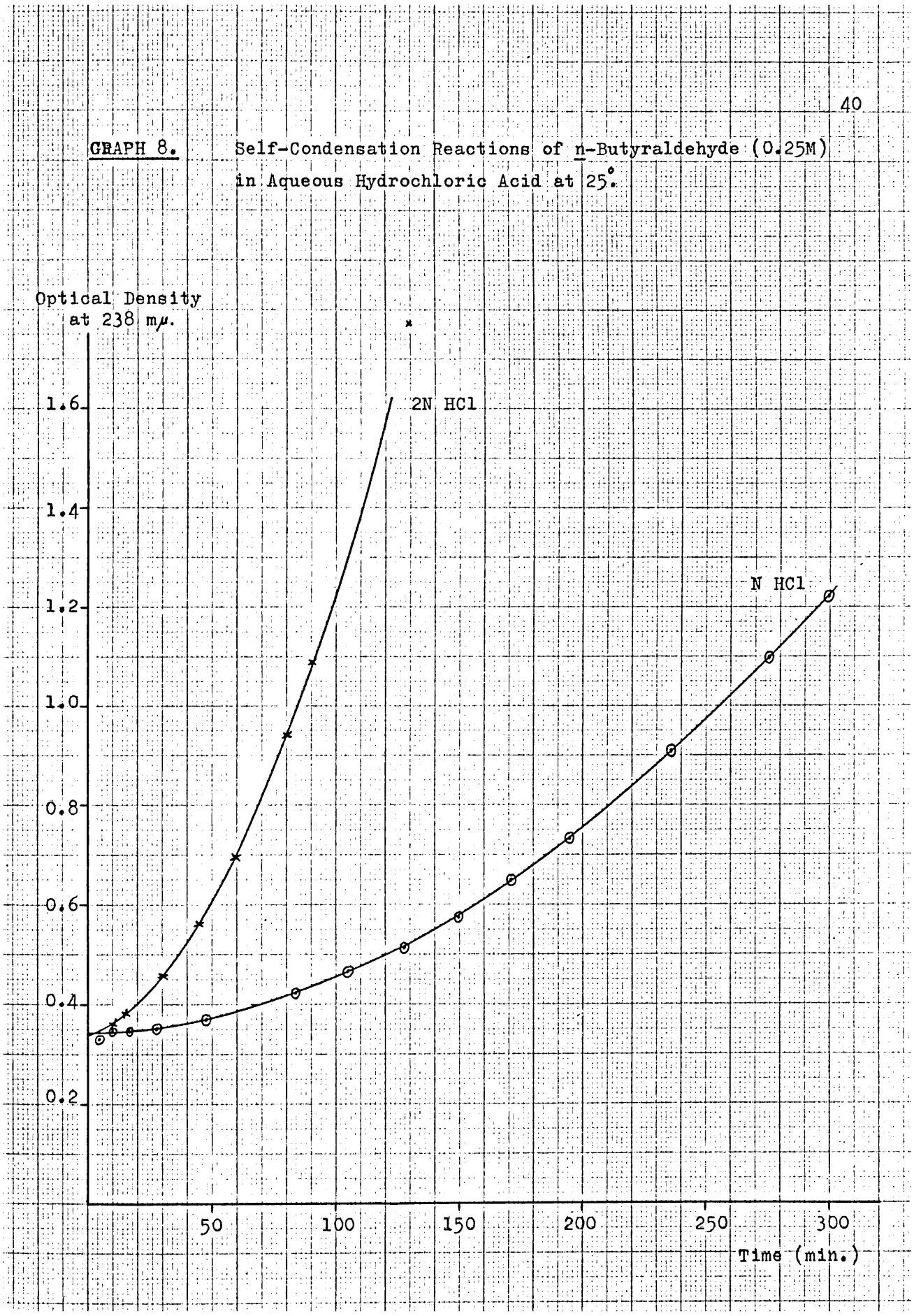
The formation of this compound was followed by measuring the increase in absorption at 238 mμ of solutions of n-butyraldehyde in N and 2N aqueous hydrochloric acid. (Expt. 3, p.139). Having determined the molar extinction coefficient of

2-ethyl-2-hexenal (ε_{233} 1.42 x 10^4 in 2N aqueous HCl), it was estimated that, after 168 minutes in 2N aqueous hydrochloric acid, the concentration was 0.16 x 10^{-3}M. Since the initial concentration of n-butyraldehyde was 0.25M, this represented a very small percentage reaction.

An inspection of the slopes of the optical density/time curves (Graph 8, p. 40) from Expt. 3, suggested that the formation of 2-ethyl-2-hexenal was preceded by that of an intermediate compound. This compound must be the hydrated form, n-butyraldol. The extent of its formation was not determined. However, the dehydration stage is known to be favoured under acidic conditions,[42] and this was supported by the fact that the product only gave the 2,4-dinitrophenylhydrazone derivative of 2-ethyl-2-hexenal. The aldol probably attained a small equilibrium concentration during the reaction.

From these investigations it was concluded that although n-butyraldehyde can undergo self-condensation in dilute aqueous acids, the reaction is very slow. In any event, in the following work, this reaction was competing against the much faster acetal condensation of n-butyraldehyde with polyhydric alcohols.

GRAPH 8. Self-Condensation Reactions of n-Butyraldehyde (0.25M) in Aqueous Hydrochloric Acid at 25°.



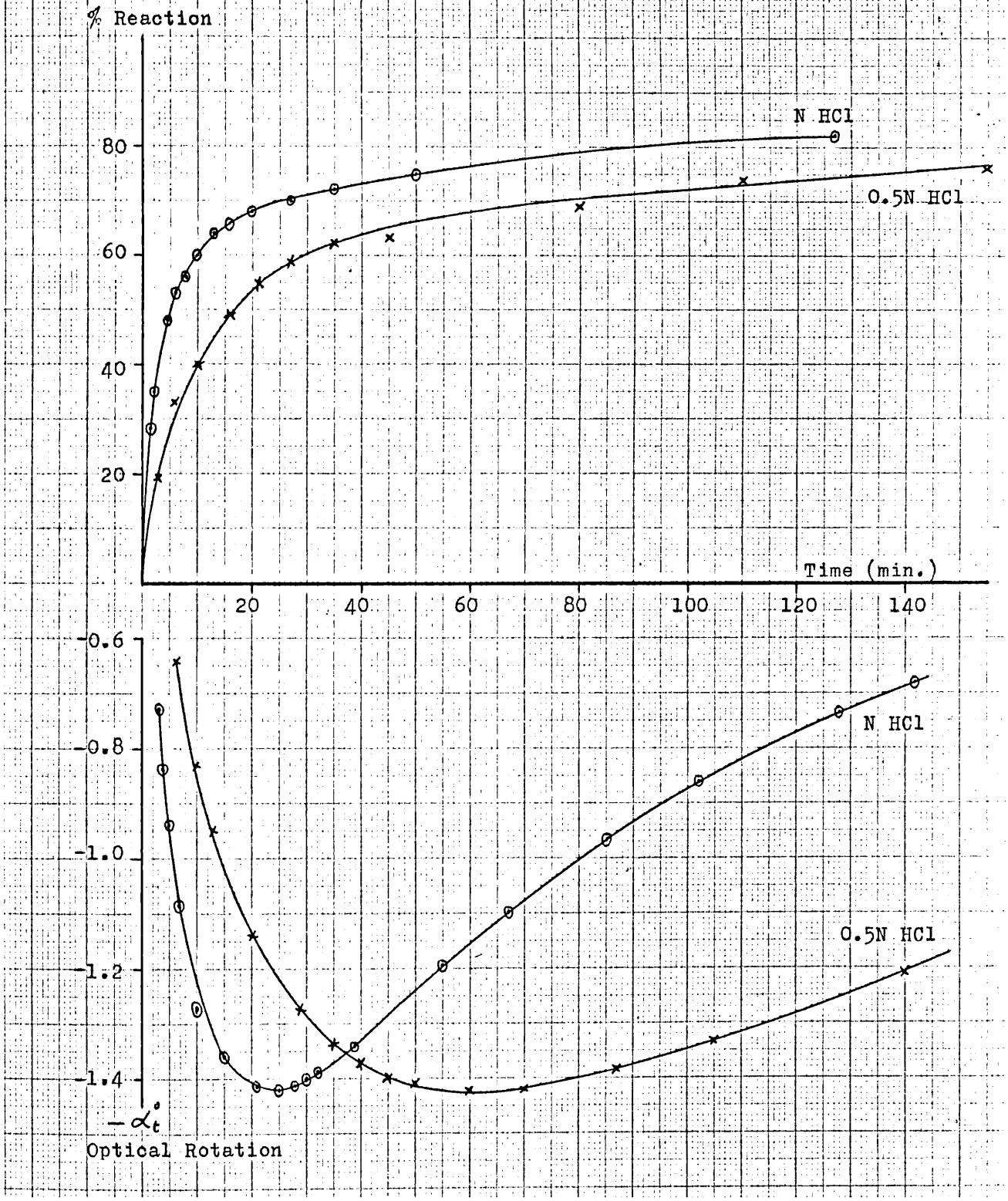
II. (i) Formation of O-Butylidene-D-glucitols

The extent of the reaction of n-butyraldehyde with D-glucitol (0.25M) in aqueous hydrochloric acid was most satisfactorily estimated by following the disappearance of the aldehyde in the system spectrophotometrically. (Expt. 5, p.141). In Graph 9 (p. 42), the consumption of n-butyraldehyde during the reaction has been compared with the corresponding change in optical activity of the system. Minimum optical rotation, in both 1.0N and 0.5N acid media, was attained rapidly after 63-70% of the aldehyde had reacted. Beyond this stage, aldehyde consumption was much slower and an equilibrium value of 89% was finally reached.

Before any information could be gleaned about the various compounds involved, it was necessary to be able to stop the reaction at a chosen stage. This was achieved by rapid neutralisation of the acid catalyst with aqueous sodium hydroxide solution (Expt. 6, p. 141), whereupon the optical rotation remained constant. A figure for this rotation, calculated from the dilution, agreed closely with the observed value.

In Expt. 7 (p.143) aliquots, from the reaction conducted in N aqueous hydrochloric acid, were removed and neutralized after 10 min. (60%) and 30 min. (71%), and at equilibrium (89%). After freeze-drying the samples, the organic portions of the residues were extracted into pyridine.

GRAPH 9. Reactions of n-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in N and 0.5N Aqueous Hydrochloric Acid at 25°.



Analysis of the Reaction Mixtures

A first analysis of the pyridine extracts was carried out by means of paper chromatography. In all three samples, the presence of D-glucitol and several of its mono-O-butylidene acetals was indicated, and the equilibrium mixture contained, in addition, a trace of material with R_F of the same order as that of a diacetal. However, these chromatograms gave little impression of the extents to which the various components occurred in the samples and it became obvious that a more sensitive analytical technique would be required.

For this reason the potential of gas-liquid chromatography (GLC) was investigated. In order to obtain suitably volatile derivatives of D-glucitol and its acetals, they were converted into their trimethylsilyl (TMS) ethers, according to the method of Sweeley et al.[44] TMS derivatives were ideal since they could be stored for several days in dry diethyl ether solutions without noticeable deterioration, and were convenient for use on a micro scale. Of the various columns available, by far the most satisfactory for this work was one with a stationary phase of 10% m-bis(m-phenoxyphenoxy)benzene (PPE) on a celite support.

TMS derivatives of D-glucitol and all its available mono- and di-O-butylidene acetals were prepared and chromatographed, and the retention volumes (RV) were measured relative to that of D-glucitol TMS. This data has been collected, together with

that for some other acetals in Table 19 (p.222). 2,4-O-Butylidene-D-glucitol was well separated from the 3,4- and 4,6-O-butylidene-D-glucitols, which were just resolvable. The 1,3:2,4-diacetal had a very much greater retention volume.

The samples taken from the reaction mixture were likewise converted into TMS derivatives and examined by GLC. As was expected, each sample contained D-glucitol, and the equilibrium sample (Fig. xiv) contained some diacetal, but the variation in the proportions of the individual monoacetals, during the reaction, was most interesting. This variation has been represented diagramatically in Fig. xv (p. 46), in which only the monoacetal sections of the gas chromatograms have been shown.

From Fig. xv it could be seen that the samples taken in the early part of the reaction contained a small amount of 2,4-O-butylidene-D-glucitol, and a much larger quantity of a substance of slightly smaller RV which will be described, for convenience, as Compound A. In the equilibrium mixture, the situation was reversed, and the 2,4-monoacetal appeared to be predominant All three mixtures also contained lesser amounts of other monoacetals which were not resolvable.

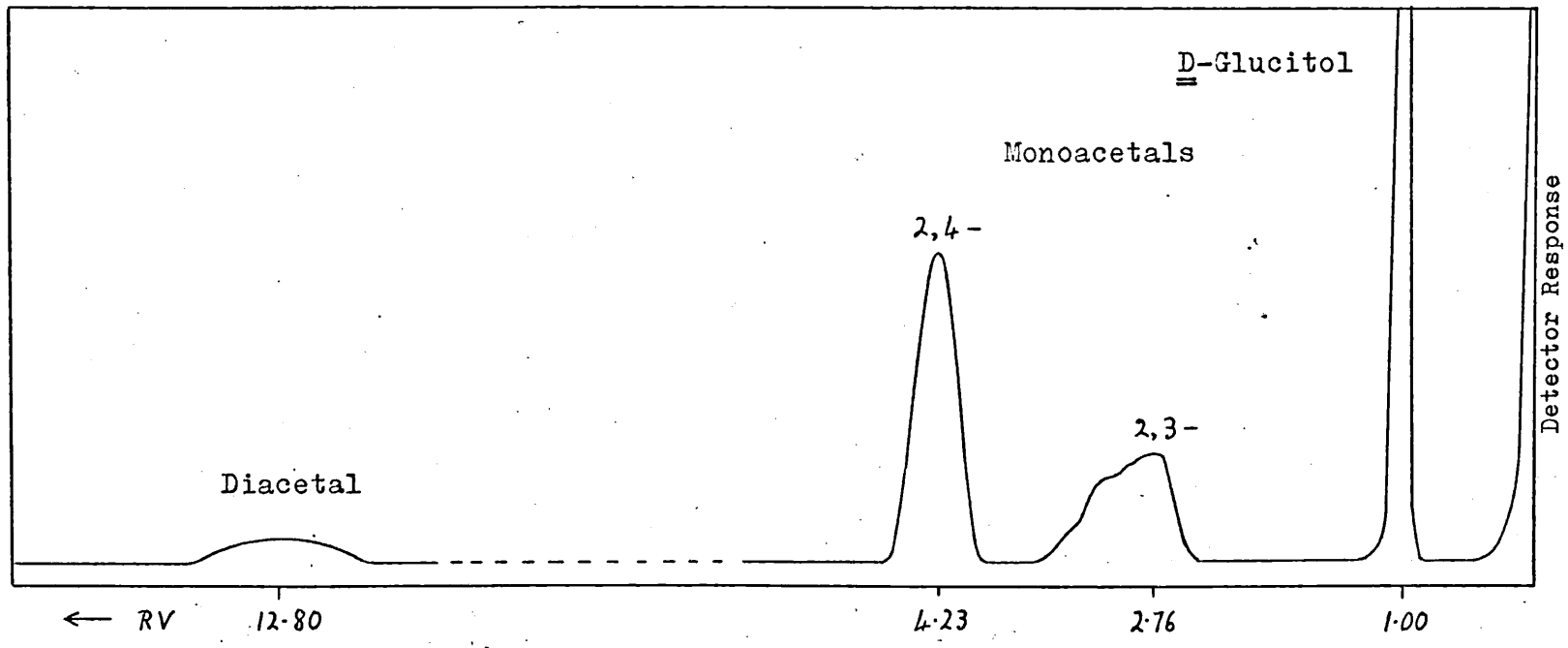
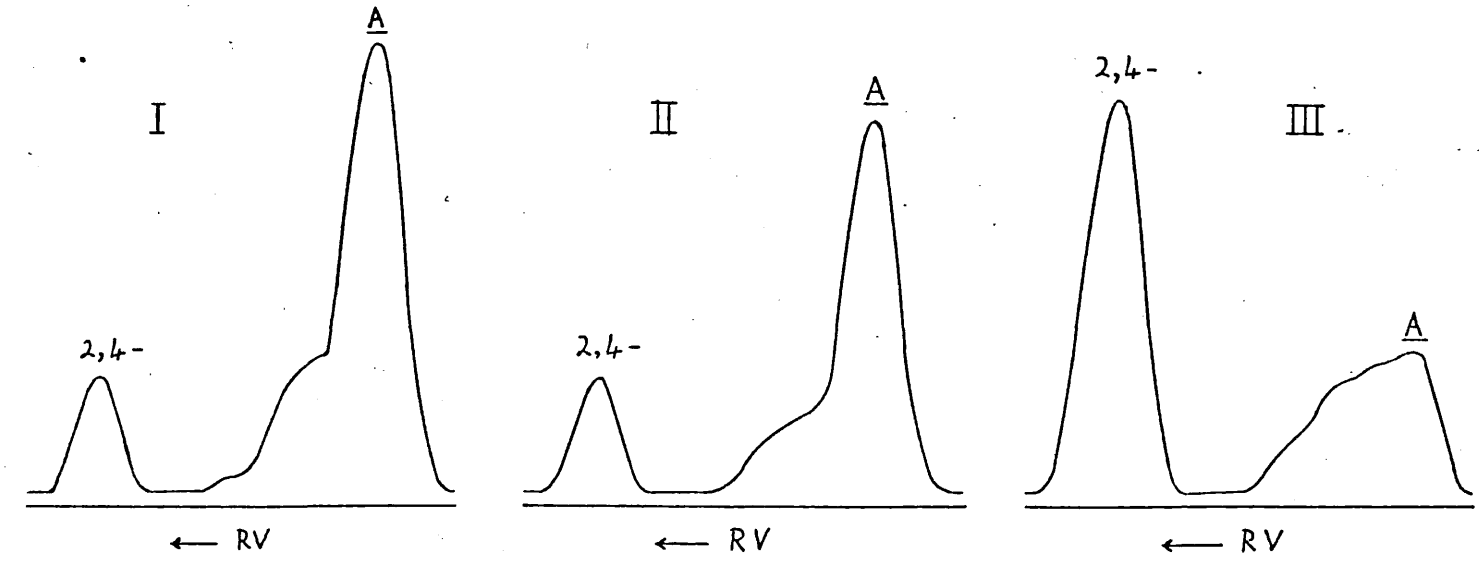


Fig. xiv Gas Chromatogram (TMS Derivatives) of a Reaction Mixture of n-Butyraldehyde (0.25M) and D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid, at Equilibrium.



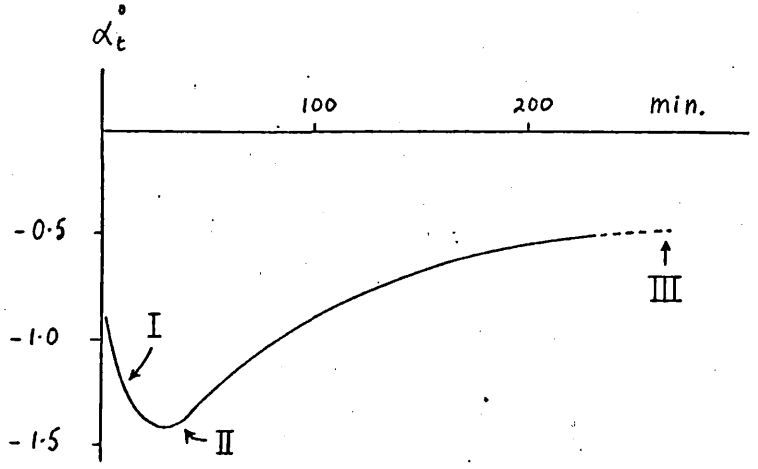


Fig. xv

Gas Chromatograms showing Monoacetal Mixtures during the Reaction of n-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°.

Isolation of Components from the Reaction Mixture

The next stage was the isolation of the more important components of these reaction mixtures, and attention was first concentrated on the diacetal that had been found to be present at equilibrium.

A reaction mixture was allowed to equilibrate for three days (Expt. 8, p.144), and after neutralizing and freeze-drying, the organic material was extracted into warm ethanol and evaporated to a syrup. The diacetal was separated by adsorbtion chromatography with alumina. Having the least affinity for the adsorbent, it was readily eluted from the column with ethanol, and was obtained as a crystalline solid, which was shown, by a mixed melting point determination, to be identical to a sample of 1,3:2,4-di-O-butylidene-D-glucitol.

The appearance of this diacetal in the equilibrium mixture was not surprising, since it would be predicted to be the most stable di-O-butylidene acetal of D-glucitol.[4]

When the column was eluted with 90% ethanol/water a mixture of monoacetals was obtained, but not D-glucitol. Thus a method for at least a partial separation of these compounds had revealed itself.

A mixture, rich in compound A, was prepared (Expt. 9, p.145) from the reaction arrested in its early stages. The mixture was

transferred, in ethanol solution, on to an alumina column and eluted with an ethanol/water mixture of gradually increasing water content. The first solid material to be yielded, on evaporation of the fractions, appeared, from GLC analysis, to be a single compound with RV in the range recorded initially for Compound A. Later fractions were increasingly contaminated with other monoacetals, and could be purified by repetition of the chromatographic separation. It was fortunate that, of all the monoacetals present in the mixture, compound A probably had the least affinity for alumina.

Compound A could be recrystallized from a large volume of chloroform, and was obtained as light fluffy crystals. The lowest melting point recorded was 111-113°, and by repeated recrystallization the melting point could be raised to 117-119°, yet, all specimens within this melting point range behaved chromatographically, and on paper ionophoresis in a borate buffer, as a single substance.

Thus it had been shown that the kinetic phase of the reaction of n-butyraldehyde with D-glucitol in aqueous hydrochloric acid gave rise to a substantial amount of Compound A, which elemental analysis indicated to be a mono-O-butylidene-D-glucitol. A sample of Compound A m.p. 116-118° had a large negative specific

rotation $[\alpha]^{26}_{Hg\ 5461}$ -46° (*c*, 1 in H_2O), which was required to explain the observed minimum in the polarimetric curve. In the latter stage of the reaction Compound A was replaced by 2,4-O-butylidene-D-glucitol, the thermodynamically most favourable product.[4]

II. (ii) Structural Analysis and Characterization of Compound A

The evidence so far presented has suggested that Compound A could be a mono-O-butylidene-D-glucitol. In its physical characteristics, however, it differed markedly from the already known isomers; 2,4- , 3,4- [35] and 4,6-O-butylidene-D-glucitol.[36]

A mono-O-butylidene-D-glucitol should be directly hydrolysable in aqueous acid, into its components:- n-butyraldehyde and D-glucitol. In Expt. 10 (p.147), Compound A was hydrolysed in aqueous hydrochloric acid containing 2,4-dinitrophenylhydrazine. The liberated aldehyde was immediately precipitated as its 2,4-dinitrophenylhydrazone derivative, which was estimated gravimetrically, and the yield corresponded closely to that calculated for a mono-O-butylidene-D-glucitol. The derivative was shown to be that of n-butyraldehyde, by the fact that its melting point, with an authentic specimen was not depressed.

By hydrolysis of another sample of Compound A in aqueous hydrochloric acid, the polyhydric alcohol was obtained, and characterized as its acetate derivative. This was shown to be the hexa-acetate of D-glucitol.

Thus it was confirmed that Compound A resulted from a condensation of n-butyraldehyde and D-glucitol, probably in unimolecular proportions. All calculations for the analysis of

Compound A have been based upon the assumption of a mono-O-butylidene-D-glucitol having a molecular weight of 236.

Free hydroxyl groups in an acetal molecule are susceptible to acetylation when the substance is treated with excess of a reagent containing acetic anhydride in pyridine. In Expt. 11 (p. 148) a known weight of Compound A was boiled under reflux with this reagent, and then the mixture was poured into water. The excess acetic anhydride was titrated, as acetic acid, against standard alkali, and the difference between this titre and that for a control solution, containing no Compound A, was taken to be equivalent to the acetic anhydride used to acetylate the sample. From this information, the number of hydroxyl groups in the molecule was estimated. The average figure, 3.71, was somewhat smaller than that for 2,4-O-butylidene-D-glucitol, upon which the method was checked, but it nevertheless approximated to 4, which is the requirement for a mono-O-butylidene-D-glucitol.

The structural analysis of Compound A involved the determination of the positions of these free hydroxyl groups on the D-glucitol chain, and hence, which pair of oxygen atoms was included in the acetal ring.

Periodate Oxidation of Compound A.

An aqueous solution of sodium metaperiodate is one reagent which will selectively cleave vicinal diol groups in polyhydric

alcohols by oxidation.[1] By measuring the consumption of periodate for a given weight of sample, the number of vicinal diol groupings in the molecule can be deduced. If one of a pair of adjacent hydroxyl groups is primary, then one mol. of formaldehyde is a product of the oxidation. A secondary alcohol group, situated in the centre of a 1,2,3-triol system, is converted into one mol. of formic acid. Both the formaldehyde and formic acid may be estimated quantitatively. Finally, yet more information can be obtained by isolation and identification of the residues after periodate oxidation.

The uptake of periodate was determined (Expt. 12, p.150) by the spectrophotometric method of Aspinall and Ferrier.[45] One mol. of Compound A required two mol. of oxidant, indicating the presence, in the molecule of two pairs of vicinal hydroxyl groups, and, as a result of the oxidation, one mol. of formaldehyde and one mol. of formic acid were liberated. The formaldehyde was detected and estimated colourimetrically with chromotropic acid reagent[46] (Expt. 13, p.153) and formic acid was determined by titration with standard alkali (Expt. 14, p.156) using methyl red as indicator.[47]

These results could only be explained by the presence in the molecule, of a 1,2,3-triol system which included one primary hydroxyl group. Thus the number of possible structures for

Compound A was reduced to the following four: 1,3- , 2,3- , 4,5- or 4,6-O-butylidene-D-glucitol. (Fig. xvi).

The range of possible structures was narrowed still further by examination of the acetal residue after periodate oxidation of Compound A (Expt. 15, p. 156).

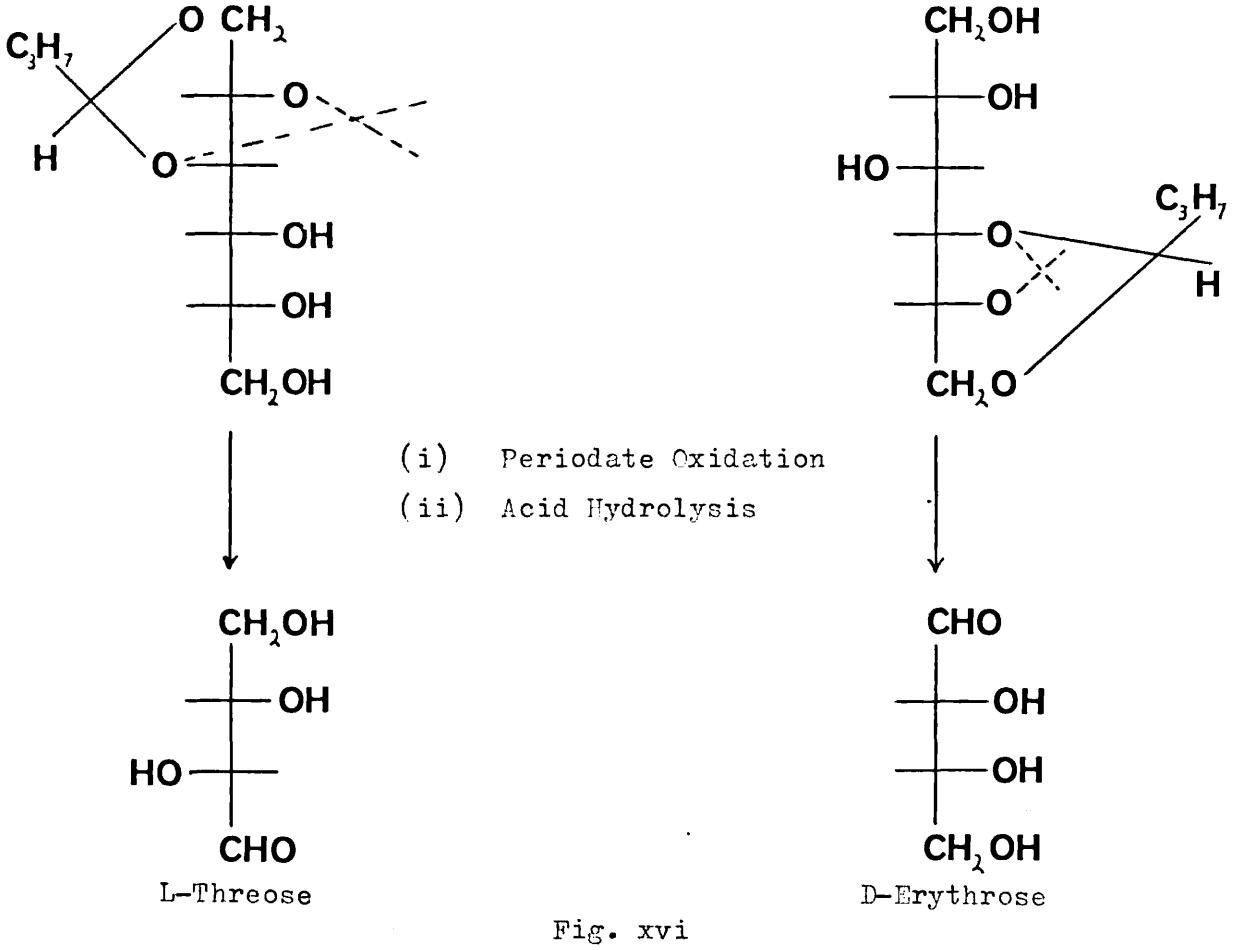


Fig. xvi

All four structures should give rise to tetroses when their respective residues from periodate oxidation are hydrolysed to remove the acetal rings. (Fig. xvi). In the cases of 1,3- or 2,3-O-butylidene-D-glucitol, L-threose, and from 4,5- or

4,6-O-butylidene-D-glucitol D-erythrose should be obtained.

A tetrose was indeed obtained, when Compound A was treated in this manner, and it was characterized by its phenylosazone derivative. Paper ionophoresis of the tetrose sample in Molybdate Buffer indicated that it could not have been D-erythrose, and its R_s value was of the same order as that quoted in the literature for L-Threose.[48]

The tetrose sample was also identified by GLC using the m-bis(m-phenoxyphenoxy) benzene (PPE) stationary phase at 150°. Standard samples of D-erythrose and D-threose were available, and it was found that trimethylsilyl (TMS) derivatives of these sugars, and of the sample, each gave two peaks of very small retention volumes, which were thought to be due to anomeric forms. A mixture of the sample with D-erythrose gave three peaks, whereas, when a mixture of the sample with D-threose was chromatographed, the peaks were entirely superimposed. From this it was concluded that the tetrose was not D-erythrose, and must therefore, be L-threose.

The fact that D-erythrose was not the product of these reactions eliminated 4,5- and 4,6-O-butylidene-D-glucitols as possible identities for Compound A. The 4,5-acetal would, in any case, be an unfavourable structure as it contains an oC-ring.[4] A 4,6-O-butylidene-D-glucitol was already known,[36] and its properties were quite different from those of Compound A.

Methylation of Compound A.

So far it had been shown that Compound A was either 1,3- or 2,3-O-butylidene-D-glucitol. In order to distinguish between these two acetals, it was decided to fully methylate the compound, and then to remove the acetal ring by hydrolysis, to leave two free hydroxyl groups at positions 1 and 3 or 2 and 3. (Fig. xvii). Only if the hydroxyl groups were in the 2 and 3 positions should the resulting compound be subject to periodate oxidation.

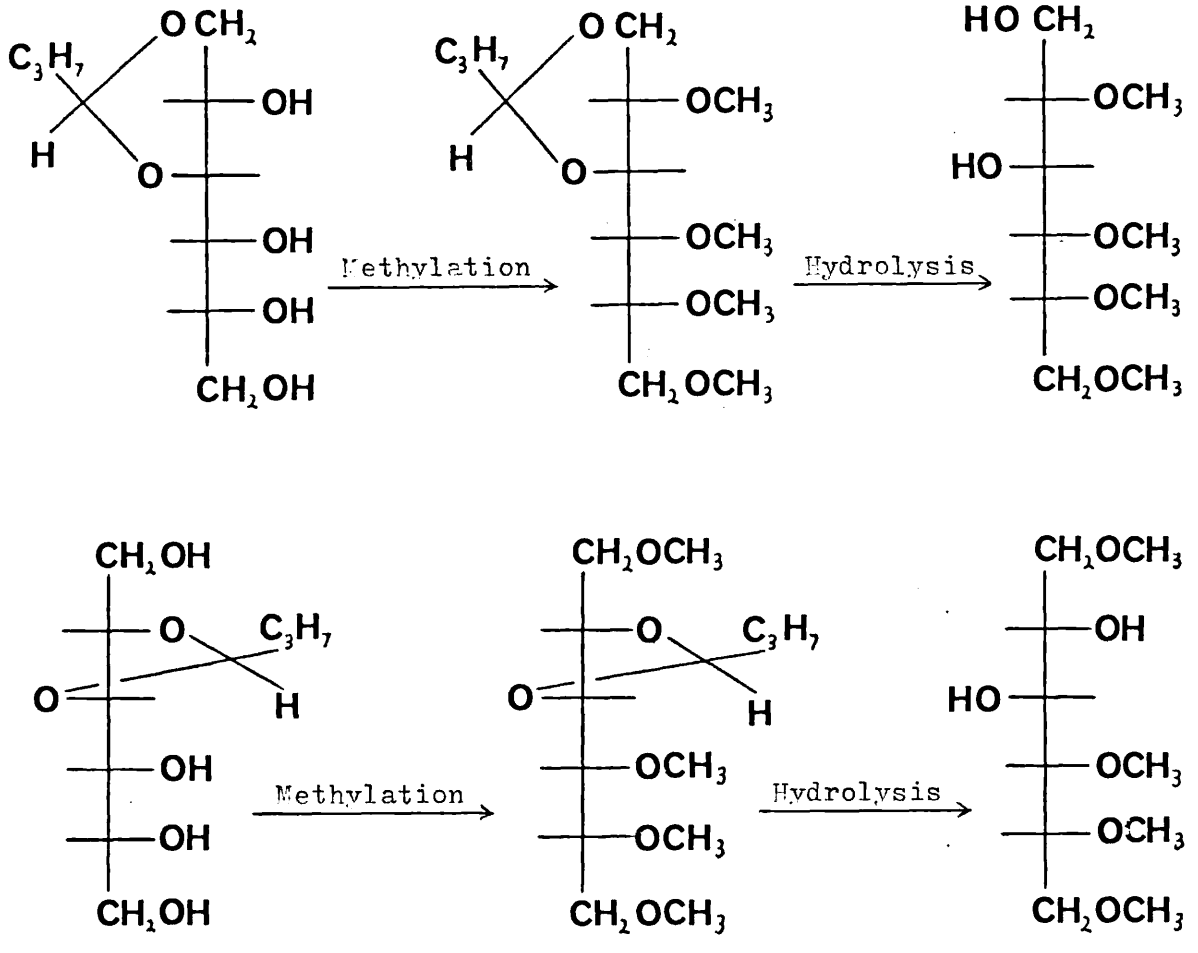


Fig. xvii

In view of the comparative scarcity of Compound A it was considered advisable to test the method of methylation on 2,4-O-butylidene-D-glucitol, which could be more readily prepared.[35] Methylation was carried out in DMF, with methyl iodide and silver oxide. (Expt. 16, p.158),[49] and the product, after vacuum distillation, was collected as a clear colourless syrup. On storage in the deep-freeze the syrup crystallized and had a melting point 13-17° elemental analysis, GLC, and the infrared spectrum, indicated that the compound was virtually fully substituted, after one methylation.

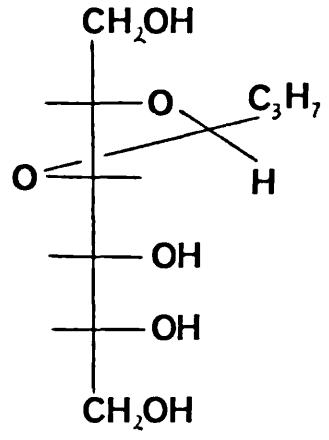
Following the same procedure, Compound A was methylated (Expt. 17, p.159), and the crude product distilled to yield a colourless syrup. This syrup did not solidify on cooling in the deep-freeze. The results of elemental analysis were as for a tetra-O-methyl derivative of a mono-O-butylidene-D-glucitol.

The two methylated acetals were next hydrolysed by heating for some hours with dilute aqueous sulphuric acid (Expt. 18, p.161). The products were obtained as syrups, having similar infrared spectra, and the removal of the acetal rings was confirmed by the fact that the compounds formed trimethylsilyl derivatives, which gave single peaks when analysed by GLC.

Both hydrolysates were subjected to periodate oxidation

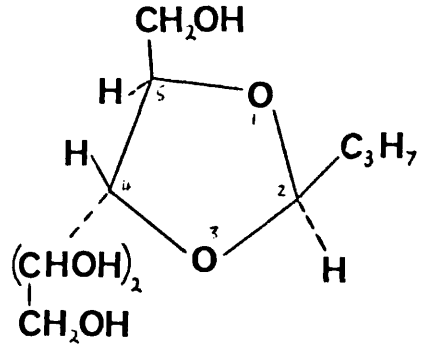
(Expt. 19, p.162), and as expected, the sample prepared from 2,4-O-butylidene-D-glucitol took up practically no periodate. However, that obtained from Compound A required an average of 0.91 mol. of periodate, which approximated to one mol.

The two hydroxyl groups must have been attached to adjacent carbon atoms, and so it followed that the butylidene group in Compound A spanned the 2 and 3 positions. (Fig. xviii).



Proton Magnetic Resonance Spectroscopy

The fact that Compound A contained a five-membered acetal ring raised the question of stereochemistry at the acetal carbon atom C_2, (Fig. xix).



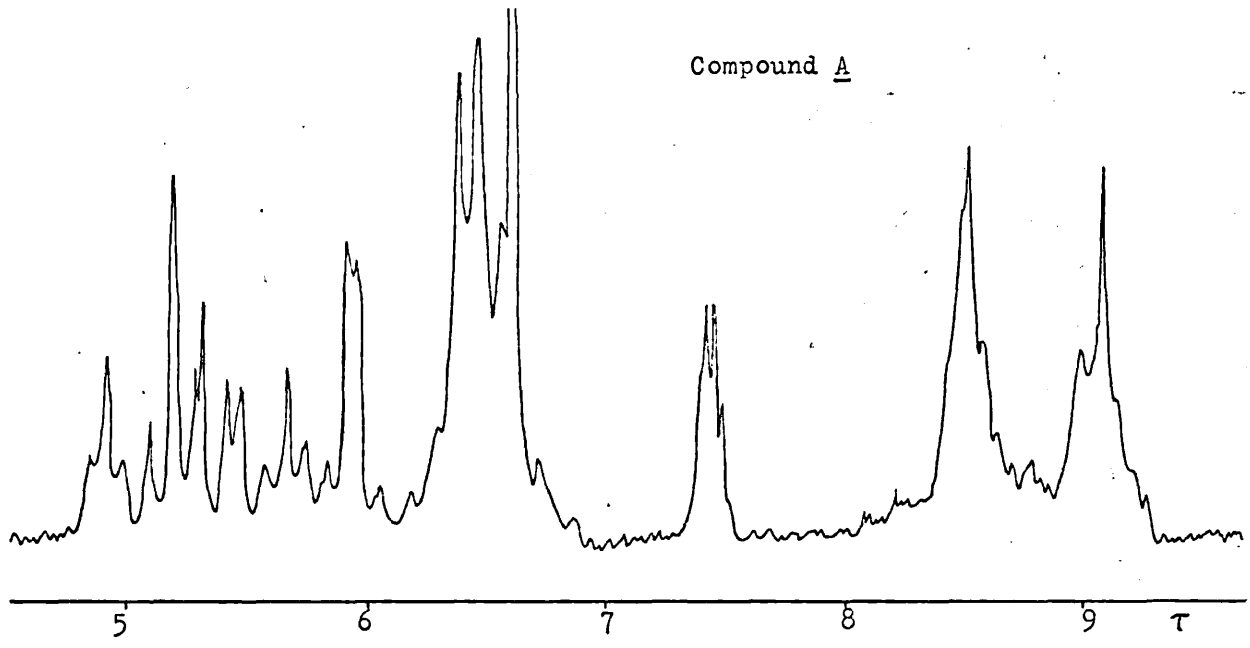
Mills[5] has pointed out that diastereoisomers of a 1,3-dioxolane derivative, having mutually trans-substituents in positions 4 and 5, are likely to be of comparable thermodynamic stability if the substituents are closely similar. Bearing in mind its variable melting point, it was therefore not improbable that Compound A was actually a mixture of diastereoisomers, which were so similar as to be virtually inseparable by chromatographic or ionophoretic methods.

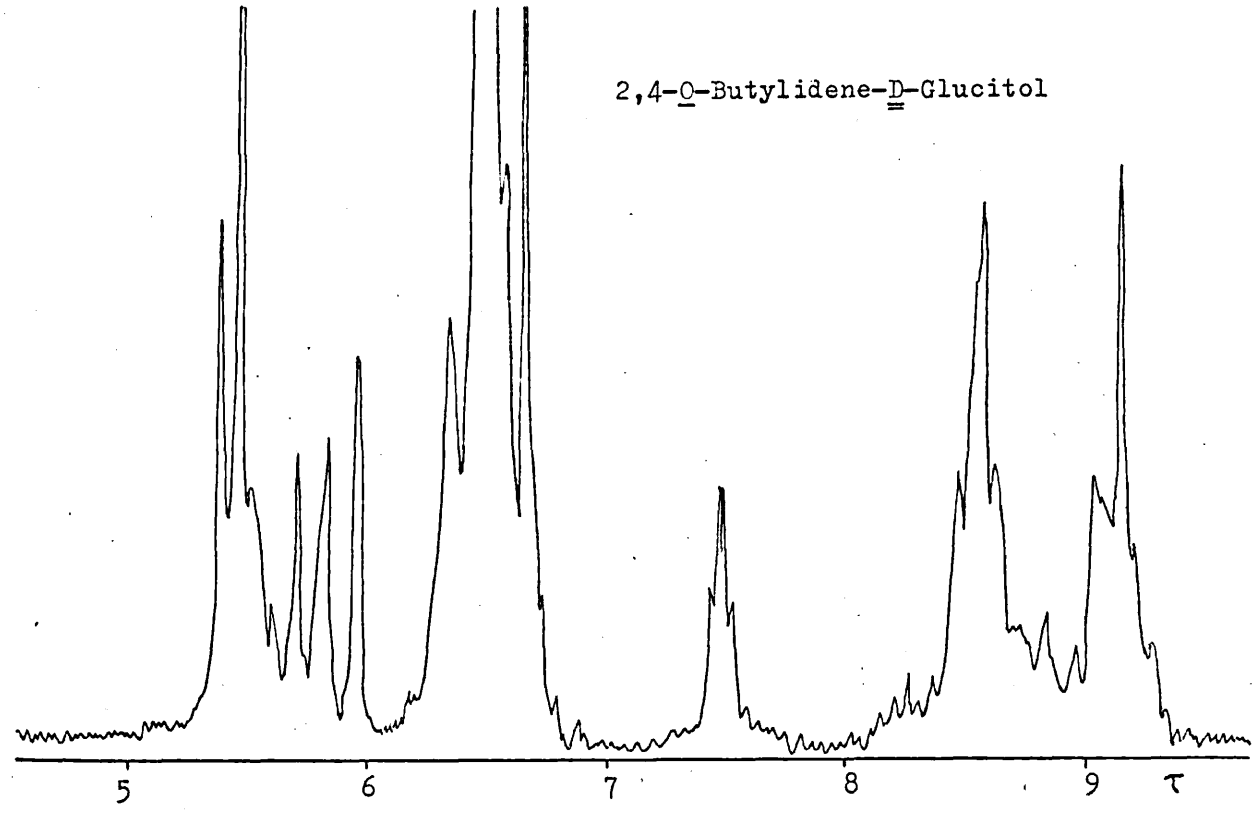
With the hope of gaining additional insight into the structure of Compound A, the proton magnetic resonance PMR spectrum of a solution in deuterated dimethylsulphoxide, was studied and compared with that of 2,4-O-butylidene-D-glucitol. (Fig. xx).

The two complex bands at τ 8.54 and 9.10 in these spectra, did not appear in the PMR spectra of analogous benzylidene compounds (to be discussed later), and since their integrated areas were equivalent to 4 and 3 protons respectively, the signals have been attributed to the protons of the n-propyl chain. The signal at τ 9.10 was probably due to the protons of the terminal methyl group. The shapes of these two signals were characteristic of a system in which the coupling constants are of the same order as the difference in chemical shift.

The signal at lowest field, in the spectrum of Compound A, appeared to be a triplet, τ 4.92, enclosing an area equivalent

Fig. xx PMR Spectra of Mono-O-Butylidene-D-Glucitols in Deuterated Dimethylsulphoxide.





to a single proton. As such a signal could arise through coupling of a single proton with protons of an adjacent methylene group, it was assigned to the proton on C_2 (Fig. xix p.57). This assignment was confirmed by recourse to the technique of double resonance. The application of a second radiofrequency field at the methylene resonances τ 8.54 was observed to collapse the triplet structure at τ 4.92. However, in the reverse procedure, irradiation at 4.92 did not appear to have much effect on the observed structure of the methylene multiplet, probably owing to its complexity.

In the spectrum of 2,4-O-butylidene-D-glucitol the acetal proton signal appeared at higher field, and was, in fact, obscured by other signals. A similar shift has been noticed with the acetal proton signals of benzylidene acetals,[7] where the signals for a series of 2-phenyl-1,3-dioxane derivatives, with equatorial substituents at the 4 and 6 positions (i.e. βC-rings), were found to occur at higher field than those of a series of 4-alkyl-2-phenyl-1,3-dioxolanes (i.e. α-rings). This could be taken as a further indication that Compound A contained a five-membered ring.

Diastereoisomerism in Compound A could manifest itself in the nature of the acetal proton signal. A mixture of diastereoisomers might either show two completely resolved triplets, or a complex signal of the two partially superimposed.

The spectra of samples with melting points 111-113° and 117-118° were therefore compared, but no significant differences were detectable. It appeared that, if diasteroisomerism was responsible for the variable melting point of Compound A, then the isomers were so similar that their acetal proton signals could not be satisfactorily resolved here.

Derivatives of Compound A.

Primary hydroxyl groups are known to react preferentially, in the formation of triphenylmethyl (trityl) ethers of polyhydroxy compounds,[50] and, on this basis, Compound A would be expected to readily yield a bis-triphenylmethyl derivative. Several attempts were made to prepare this derivative (Expt. 20, p.162), but the only crystalline material that was isolated was some triphenylcarbinol, which presumably resulted from hydrolysis of excess triphenylchloromethane, when the reaction mixture was precipitated in cold water.

The syrupy product of this reaction was acetylated (Expt. 21, p.163) with a mixture of acetic anhydride in pyridine, and a crystalline substance was isolated which was found, from infrared analysis, to contain no free hydroxyl groups. The elemental analysis of this substance corresponded most closely with that calculated for a bis-triphenylmethyl-diacetate derivative of Compound A, and differed considerably from the

calculated figures for other possible derivatives. Unfortunately, owing to the poor solubility of the sample in alkaline saponification reagents, the acetyl-content could not be reliably estimated.

No other crystalline derivatives could be prepared from Compound A, although efforts were made to form a dibenzoate, tetra-acetate and phenylboronate. The difficulties encountered in the preparation of crystalline derivatives might well be explicable, if the samples of Compound A, employed, were actually mixtures of the two diastereoisomers.

II. (iii) Fission of O-Butylidene-D-Glucitols

Hydrolysis

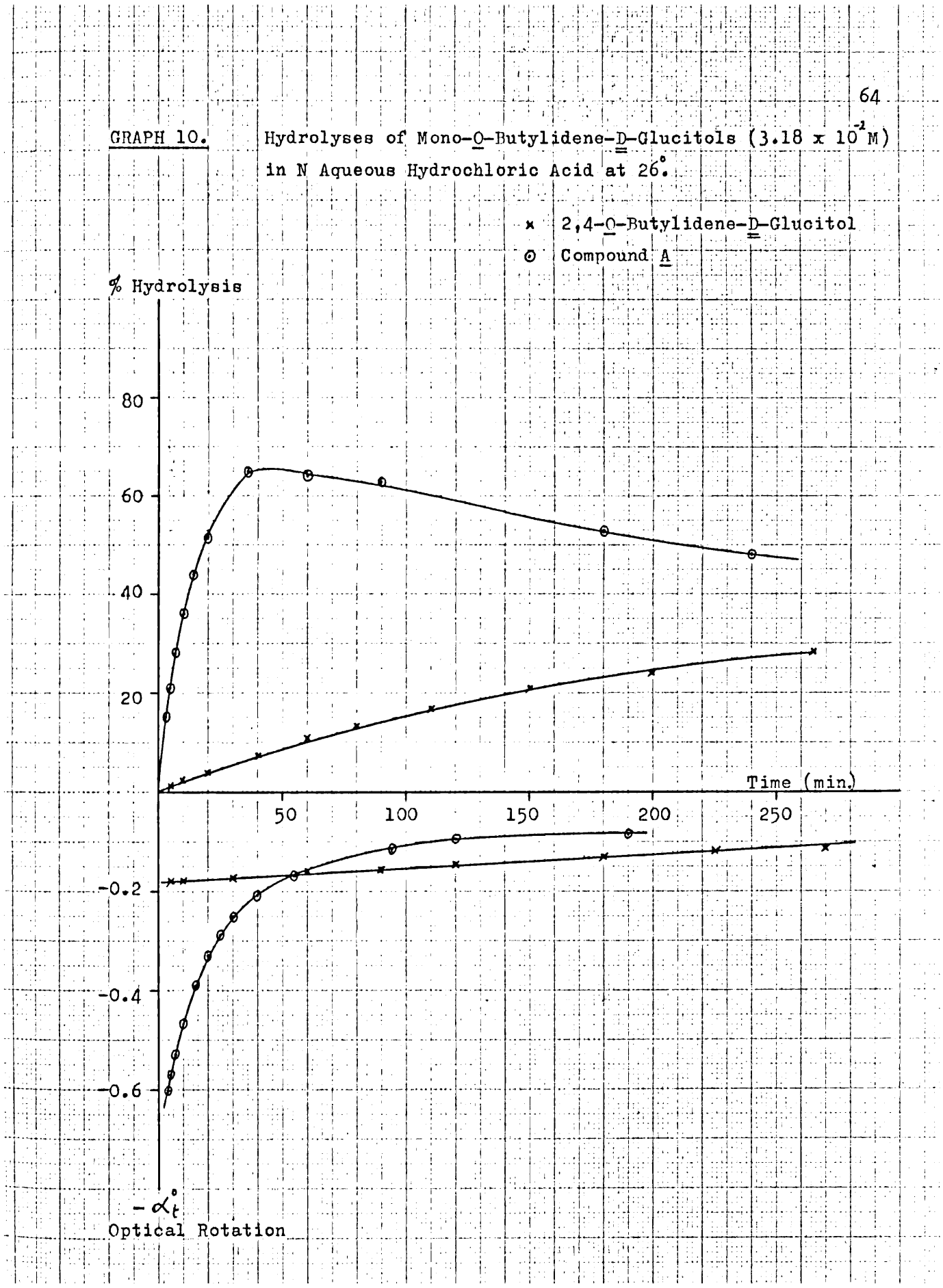
Since Compound A (2,3-O-butylidene-D-glucitol) and 2,4-O-butylidene-D-glucitol had been found to be the most important products, arising out of the kinetic and thermodynamic stages, respectively, of the acid catalysed condensation of D-glucitol and n-butyraldehyde, it was felt that a comparative study of the hydrolytic behaviour of these two acetals would prove profitable.

The hydrolyses were conducted at 26° with dilute solutions of the acetals in N aqueous hydrochloric acid and, in Expt. 22 (p.166) were followed polarimetrically. Graph 10 (p. 64) shows how the optical rotations in both reactions increased with time and approached a common value at equilibrium.

Periodically during these reactions samples were taken and analysed gas chromatographically as TMS derivatives. The hydrolyses were also followed by spectrophotometric estimation of the liberated n-butyraldehyde (Expt. 23, p.167) (Graph 10 p. 64), and by these means a picture was constructed of the changing compositions of the reaction mixtures.

Hydrolysis of 2,4-O-butylidene-D-glucitol slowly released D-glucitol and n-butyraldehyde, and traces of some other mono-acetals, which were probably formed mainly by recombination of

GRAPH 10. Hydrolyses of Mono-O-Butylidene-D-Glucitols (3.18×10^{-2} M) in N Aqueous Hydrochloric Acid at 26°.



the hydrolysis products, soon appeared in the reaction mixture. Equilibrium was attained when 40% of the acetal had hydrolysed and the composition of the mixture was then similar to that obtained from reacting D-glucitol with n-butyraldehyde in aqueous acid (Fig. xiv p.45).

Compound A, on hydrolysis, presented a most interesting situation, which is illustrated diagrammatically in Fig. xxi. In the initial reaction, the acetal was rapidly broken down into its components, to the extent of 66% and during this period very few traces of any other monoacetals could be detected. The latter stage of the reaction evidently involved the recombination of the hydrolysis products, because the amount of aldehyde in the system diminished, and other monoacetals began to appear in the mixture. At equilibrium, only 38% of the acetals was hydrolysed, and the composition of this mixture was similar to that obtained by hydrolysing the 2,4-O-butylidene-D-glucitol.

It was remarkable that the hydrolysis of Compound A, like its formation, appeared to be an example of a reaction which was kinetically controlled. The fact that very little of any other product could be detected, in the initial reaction, indicated the comparative insignificance of possible ring migration reactions at this stage. Under thermodynamic control, the system slowly equilibrated and came to the same final

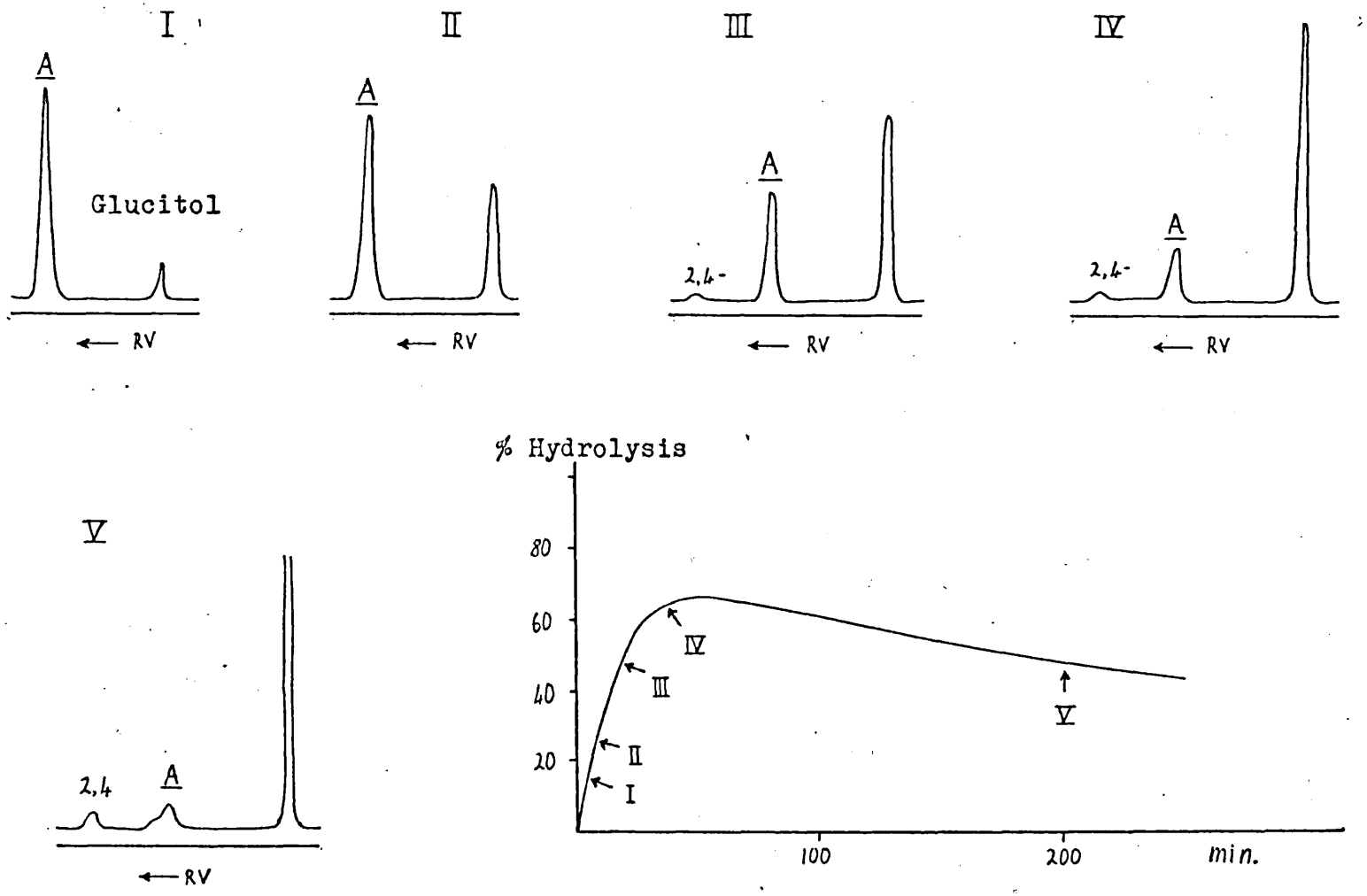


Fig. xxi Hydrolysis of Compound A (3.18×10^{-2}M) in N Aqueous Hydrochloric Acid at 26°.

position as did the hydrolysed 2,4-monoacetal.

Polarimetric data from the hydrolysis of 2,4-O-butylidene-D-glucitol has been applied to the first order kinetic equation[29]

$$\ln. \frac{(a_o - a_\infty)}{(a_t - a_\infty)} = kt$$

where a_o, a_t and a_∞ were the observed optical rotations at times $t = o$, $t = t$ and $t = \infty$ respectively. Good linear graphs of $\log.(a_t - a_\infty)$ against time were obtained.

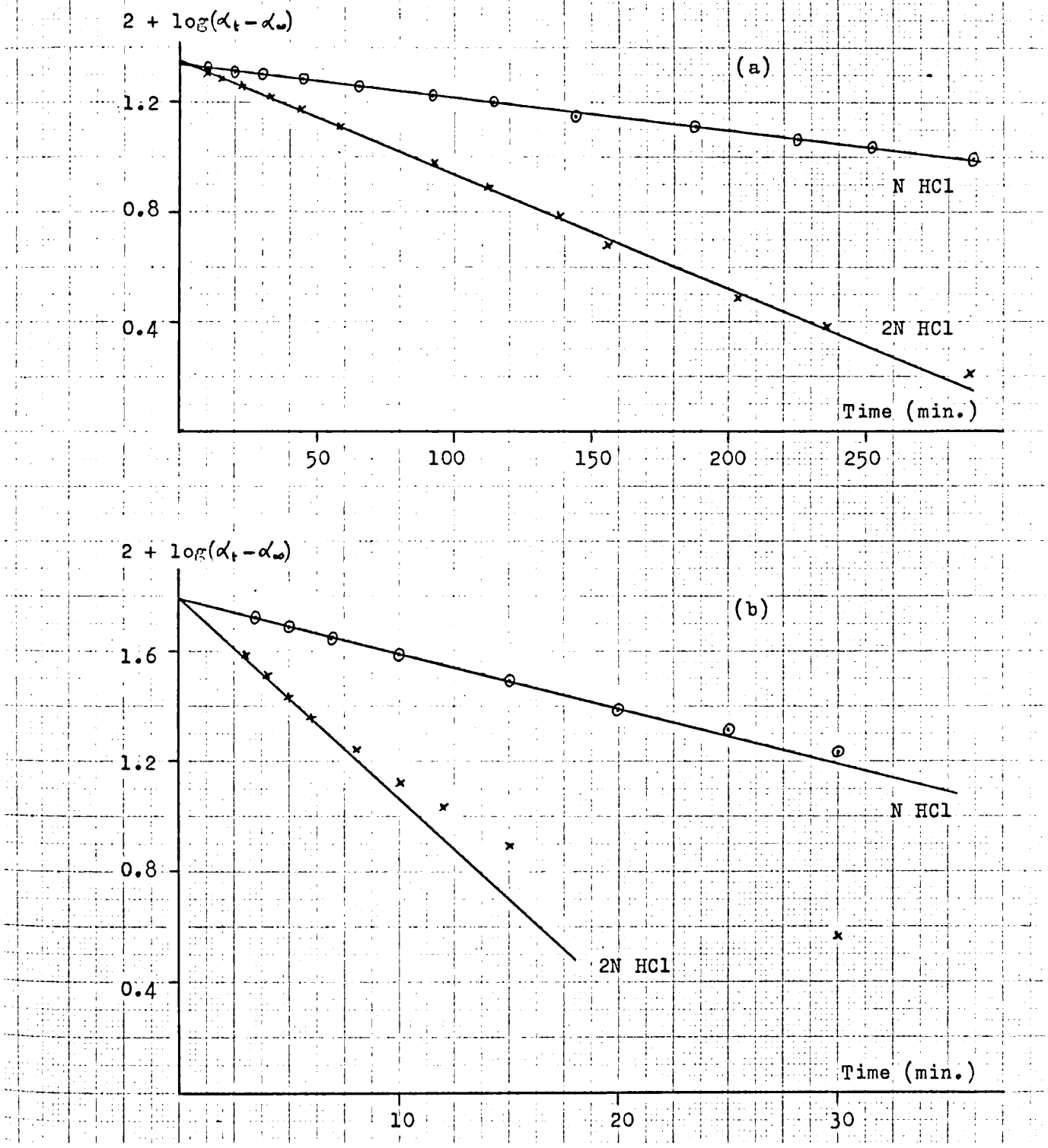
This work was repeated with 2,4-O-butylidene-D-glucitol in N and 2N aqueous hydrochloric acid at 26°, and the simple first order equation was found to be obeyed with remarkable precision. (Graph 11 (a) p. 68).

The reason for this was not altogether clear, since the equation was based on the assumption that the hydrolysis went virtually to completion, with no rotationally significant intermediate, and that D-glucitol was the exclusive optically active product. However, it had been inferred, from the previous discussion, that to represent the system as -

ACETAL ⇌ D-GLUCITOL + n-BUTYRALDEHYDE

was a vast oversimplification of the situation, and the assumption, that the equilibrium favoured the right hand side, was not valid.

GRAPH 11. Plot of $2 + \log(\alpha_t - \alpha_\infty)$ against Time for the Hydrolysis in Aqueous Hydrochloric Acid at 26° of (a) 2,4-O-Butylidene-D-Glucitol and (b) Compound A.



The specific rotation of D-glucitol in aqueous solutions is small ($[\alpha]^{26}_{Hg\ 5461}$ c. - 1.3° in 0.5N aqueous HCl), and so the rotation of D-glucitol in these reaction mixtures would be close to zero. It may, perhaps, be fortuitous that the rotations due to the other compounds in the mixtures were also small, or of opposite signs, and thus to a certain extent self-cancelling.

Polarimetric data from the hydrolysis of Compound A was similarly applied to this equation but, in this case, the linear law was less rigourously obeyed. (Graph 11(b) p. 68)

From spectrophotometric measurements, the molar concentration, (x), of n-butyraldehyde in the system, at any time, (t) could be deduced, and this was equivalent to the amount of monoacetal hydrolysed after time (t). Where (a) represented the initial molar concentration of the acetal, then (a-x) was the concentration of acetal at time (t).

For a straightforward first order reaction,

$$\ln. \frac{a}{(a-x)} = kt$$

$$\text{or } \log (a-x) = \frac{-kt}{2.303} + \log a$$

The initial stages of these hydrolyses were probably more accurately represented by this equation, since a measurement

at equilibrium was not required, although deviations from linearity would occur due to the influence of the opposing reactions.

Graphs of log (a-x) against time were plotted with spectrophotometric data from the hydrolyses of the two butylidene-D-glucitols and, from the initial slopes, rate constants(k) were calculated. The results have been listed in the table below, together with rate constants calculated from polarimetric data.

Pseudo - First Order Rate Constants ($kx10^4 sec.^{-1}$) at 26^o

	Normality of acid	10^4k (Compound A)	10^4k (2,4-O-Butylidene-D-glucitol)
Spectrophotometric	1.0N	6.8	0.3
Polarimetric	"	7.4	0.5
Spectrophotometric	2.0N		1.1
Polarimetric	"	26.9	1.6

There was some difference between the figures obtained from the two methods, and in general those calculated from spectrophotometric data were somewhat smaller. Owing to the complexity of these reactions, which have here been represented as of simple first order, the rate constants must be regarded as being merely approximate.

What nevertheless was remarkable about these figures, was the much greater rate of hydrolysis of Compound A, when compared with that of 2,4-O-butylidene-D-glucitol. The difference in rate can be explained from the theory[20] that the oxocarbonium ion intermediate, formed in the rate-determining step, can be more easily achieved from a nearly coplanar five-membered ring, than from a six-membered ring, which is ideally in a chair conformation. However, 3,4-O-butylidene-D-glucitol does not hydrolyse much faster than the 2,4-isomer; The relative rate constants are 1.3:1 in N hydrochloric acid at 38.6°[29] The reason for the considerable difference in acid lability of Compound A (2,3-) and 3,4-O-butylidene-D-glucitol, which both have α-rings, is not yet apparent.

Ring Migration

Having observed the behaviour of Compound A under hydrolytic conditions, it was decided to investigate its reactivity in a non-aqueous acidic medium. In Expt. 24 (p.168) it was dissolved in a solution of hydrogen chloride in dry DMF and over a period of many hours the optical rotation of the solution was seen to change.

Periodically, samples were taken from the system, and analysed chromatographically. The results, illustrated in Fig. xxii (p.72), indicated that Compound A underwent a slow rearrangement to other monoacetals, in particular to 2,4-O-

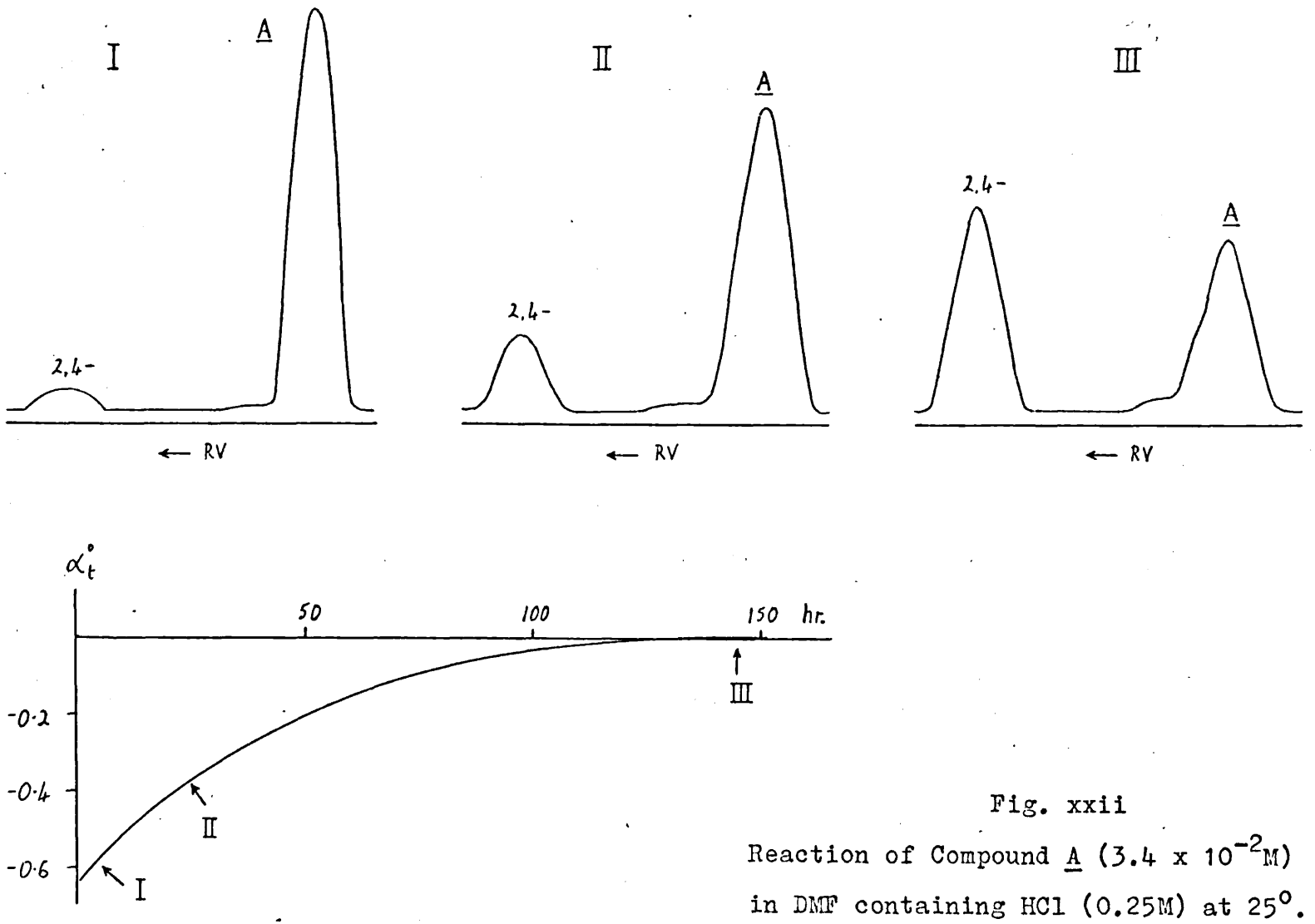


Fig. xxii

Reaction of Compound A (3.4×10^{-2}M) in DMF containing HCl (0.25M) at 25°.

butylidene-D-glucitol, and no D-glucitol was detected in the mixture during the reaction.

The preceding evidence has demonstrated that, in the presence of reagents which cleave acetal rings, Compound A was considerably less stable than 2,4-O-butylidene-D-glucitol to which it tended to revert.

III. BENZYLIDENE-D-GLUCITOLS

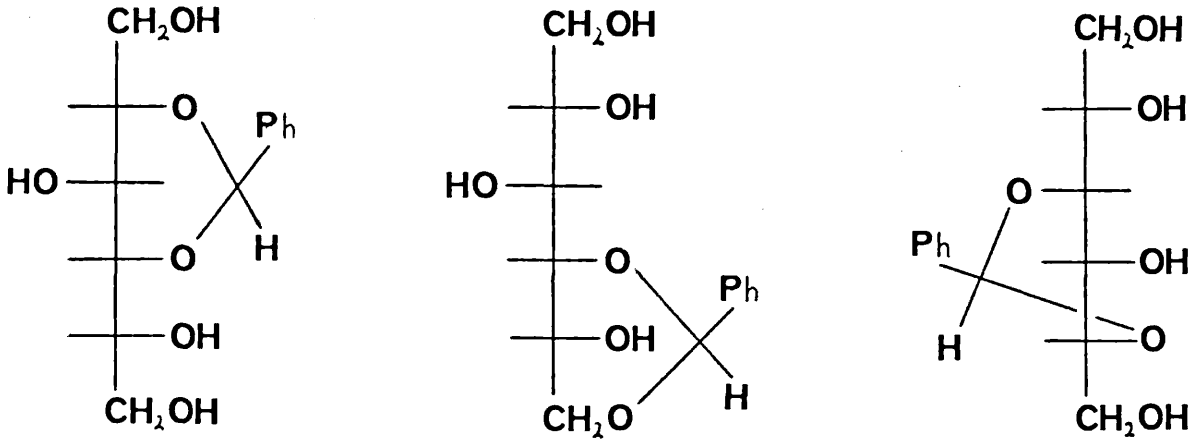


Fig. xxiii

Of the mono-O-benzylidene-D-glucitols (xxiii) the 2,4-acetal has been known for many years. Meunier[51] first prepared it around 1890, by treating D-glucitol with benzaldehyde in hydrochloric acid at room temperature, but it was not until 1935 that it was correctly identified by von Vargha.[52,53]

Up until now no other monoacetals had been synthesized by direct action of benzaldehyde on D-glucitol. However, by hydrogenation of 4,6-O-benzylidene-D-glucose, Sowden[54] prepared 4,6-O-benzylidene-D-glucitol. More recently, Bonner et al.[55] have obtained the 3,5-acetal by partial hydrogenolysis of 2,4:3,5-di-O-benzylidene-D-glucitol. The acetal itself was isolated, after chromatography on alumina, in the form of a glassy solid, but was characterized as its tetra-acetate.

In the Preliminary Investigations (I) it had been found that the reaction of D-glucitol with benzaldehyde in the presence of dilute aqueous hydrochloric acid, like that with n-butyraldehyde, probably proceeded via an intermediate compound with a relatively large negative optical rotation. The only additional factor, in the case of benzaldehyde, was the inclusion of DMF in the system to facilitate solubility. For the purpose of comparison, this reaction has been studied in a similar manner to the reaction with n-butyraldehyde.

III. (i) Formation of O-Benzylidene-D-glucitols

The reaction of benzaldehyde with D-glucitol was conducted with equimolar quantities (0.25 M) of the reactants in aqueous DMF in the presence of hydrochloric acid (Graph 4 p.28). In Expt. 25 (p.169), samples were taken in the early stages of the reaction, when the optical rotation of the mixture was approaching its minimum, and later, when a steady value of optical rotation was being attained. From these samples, TMS derivatives were prepared for analysis with GLC.

Analysis of the Reaction Mixture

The gas chromatography column with a polyphenylether stationary phase, which had been so successfully employed for separation of butylidene-D-glucitols, was unsatisfactory here, owing to the extremely large retention volumes of the mono-O-benzylidene compounds. Of the columns available, the best one for this purpose had a methylsilicone stationary phase, SE-30, on a support of Gas Chrom P. and was used at 175°.

A sample of 2,4-O-benzylidene-D-glucitol TMS derivative gave a single peak with RV 4.51. When the samples, taken from the reaction mixture, were chromatographed, it could be seen that they contained, besides D-glucitol, a number of compounds with RV's in the range 3.5-5.0, which were presumably mono-acetals. Unfortunately, none were completely resolved.

It was, however, plain that in the early stages of reaction, the most prominent compound was not the 2,4-monoacetal, but a compound with smaller RV which has been designated, for the purpose of this work, as Compound B.

The PMR spectra of benzylidene acetals have been studied extensively, and it has been found[7] that the signal for the proton on the acetal carbon atom is unsplit, and occurs in the central part of the spectrum in a region that is usually free from other signals.

The PMR spectrum of 2,4-O-benzylidene-D-glucitol in deuterated dimethylsulphoxide was recorded and has been reproduced in Fig. xxvi (p.86). It was noticed that a singlet, of integrated area equivalent to one proton occurred at τ 4.37, in an otherwise completely clean part of the spectrum, and this has been assigned to the proton on the acetal carbon atom.

For similar solutions of the samples taken from the reaction mixture, PMR spectra were also recorded, and the region τ 3.0 - 5.0 was scrutinized. As expected, the pattern of signals was quite complex, since a number of compounds were known to be present. A sample from the latter part of the reaction showed two distinct sets of multiple signals, of comparable intensity; one with a peak at τ 4.41, which probably arose principally from the 2,4-monoacetal, and another, at slightly lower field, with two peaks τ 4.08 and 4.15. The spectra of samples taken in the early stages of reaction were

of similar form, in this region, but the signal at τ 4.41 was considerably smaller in area, than the two peaks at lower field.

These results confirmed, the observation that 2,4-O-benzylidene-D-glucitol was not, at least initially, the main product of condensation between benzaldehyde and D-glucitol in dilute aqueous hydrochloric acid. But, to Compound B, it was necessary to assign two signals (τ 4.03 and 4.15), which suggested that, so long as only monobenzylidene acetals were involved, the term Compound B may well actually embrace more than one compound.

Isolation of Compound B.

A mixture of D-glucitol and its benzylidene acetals, containing a high proportion of Compound B, was prepared, by stopping the reaction at the stage of minimum optical rotation (Expt. 26, p. 170). This mixture was fractionated on an alumina column, using eluents of aqueous ethanol. The first solid material that was obtained from the column, on evaporation of the fractions, gave a single peak, with RV in the range previously recorded for Compound B, when its TMS derivative was analysed by GLC. The separation was not, by any means, perfect, as subsequent fractions contained increasing amounts of other components, but, by repeating the fractionation process, further purification could be effected.

Compound 3 was recrystallized from ethyl acetate and had m.p. 123-127°. The results of its elemental analysis compared favourably with figures calculated for a mono-O-benzylidene-D-glucitol.

It was found that by recrystallizing the sample many times, from ethyl acetate, the melting point could be raised to 131-133°. Furthermore, when the liquors from recrystallizations were evaporated to dryness, the combined residues, after crystallizing from ethyl acetate had m.p. 118-119°. But, gas chromatographically, all samples melting within the range 118-133°, behaved as a single substance. The samples were also investigated by paper ionophoresis in sodium borate buffer, and they all appeared to be identical.

However, an indication that the melting point variation, among samples of Compound 3, implied differences in composition was provided by a comparison of the specific rotations in aqueous solutions.

m.p.	$[\alpha]^{25}_{Hg\ 5461}$	$[\alpha]^{25}_{D}$
118-119°	-41.3°	-35.5°
123-127°	-38.5°	-33.0°
127-130°	-35.4°	-29.9°
131-133°	-33.6°	-28.3°

The data, listed above, indicated that Compound B must have been a mixture of at least two compounds with differing specific rotations. The component with the smaller negative rotation was slightly less soluble in etnyl acetate, and hence the optical rotation tended to become less negative with recrystallization. A complete separation of these compounds could probably be achieved by a tedious process of fractional crystallization from this solvent.

III. (ii) Structural Analysis of Compound B

The material which had been isolated, and described as Compound B, was believed to consist of some condensation products of D-glucitol and benzaldehyde. When an aqueous solution of the substance was warmed with cation exchange resin ($H^{\oplus}$ form), benzaldehyde was liberated, and was characterized as its phenylhydrazone. (Expt. 27, p.171). The remaining polyhydric alcohol behaved as glucitol, rather than mannitol or dulcitol, when examined by paper ionophoresis in sodium metavanadate buffer.[56,57] It therefore seemed likely that Compound B was composed of benzylidene-D-glucitols.

The proportions of carbon and hydrogen restricted Compound B to a mixture of monoacetals, and its chromatographic and ionophoretic properties, in so far as they had been studied, suggested a considerable similarity in its components. Such similarity could be exhibited by diastereoisomers, if Compound B was directly analogous to Compound A.

The following structural analysis was carried out on a sample of Compound B with m.p. 127-130°, and was based upon the assumption of a molecular weight of 270, as for a mono-O-benzylidene-D-glucitol. It was hoped that, should the sample contain two or more acetals in which the benzylidene groups

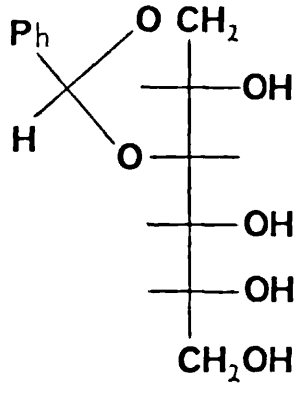
spanned different pairs of oxygen atoms on the glucitol chain, then the inconsistency of the results would reveal this fact.

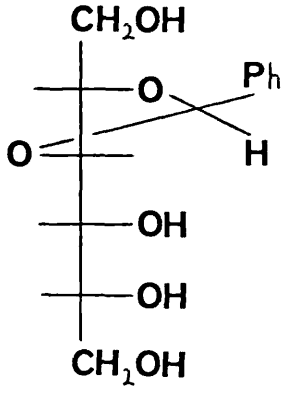
Periodate Oxidation

The experimental figures, for initial periodate oxidation of Compound B, approximated fairly closely to whole numbers (Expts. 28-30, p.172). One mol. of the substance consumed two mol. of periodate and one mol. each of formaldehyde and formic acid were released, thus indicating the presence of a 1,2,3-triol system involving one primary hydroxyl group. Prolonged treatment with the oxidant caused considerable overoxidation, which resulted in an increase in the acid produced. The formic acid, released by the initial periodate oxidation, was probably sufficient to bring about a slow, but noticeable hydrolysis of the acetal residue, exposing further pairs of vicinal hydroxyl groups to oxidation.

In the light of the above results it was concluded that the largest fragment of the initial oxidative scission of Compound B must be the benzylidene acetal of a tetrose. This was obtained, and hydrolysed in dilute acetic acid, to remove the benzylidene group. (Expt. 31, p.174). The syrupy product migrated as a single substance when examined by paper ionophoresis in a sodium molybdate buffer, and its rate of migration was less than that of erythrose, but comparable to that of

threose.[48] In addition, GLC of the product, as its TMS derivative, showed that it had a retention volume identical to the sample of L-Threose obtained, by a similar process from Compound A. Therefore, Compound B could have consisted of either 1,3- or 2,3-O-benzylidene-D-glucitols, or of a mixture of the two. (Fig. xxiv).





Methylation of Compound B.

Methylation of Compound B was accomplished by treatment, in DMF solution, with methyl iodide in the presence of silver oxide (Expt. 32, p.175) and the product was a colourless, viscous syrup, which elemental analysis indicated to be the tetra-O-methyl derivative.

By hydrolysis of this syrup in dilute sulphuric acid, (Expt. 33, p.177) the benzylidene group was detached, and the remaining material, also a syrup, formed a TMS derivative which gave one sharp peak, when analysed by GLC. In both the RV of

its TMS derivative, and its infrared spectrum, the hydrolysate closely resembled the material derived similarly from the methylation, and subsequent hydrolysis of Compound A. It also was oxidised by aqueous sodium metaperiodate (Expt. 34, p.177) and must therefore have contained a pair of vicinal hydroxyl groups.

Thus it followed that the benzylidene group had spanned oxygen atoms attached to adjacent carbon atoms, and so Compound B must have been 2,3-O-benzylidene-D-glucitol. (Fig. xxiv).

Proton Magnetic Resonance Spectroscopy

Now that Compound B had been shown to contain a five-membered ring, its properties characteristic of a mixture (e.g. variable melting point and specific rotation) became explicable through diastereoisomerism. As a further investigation of this, the NMR spectra, of solutions in deuterated dimethylsulphoxide, of a number of samples of Compound B were studied, and compared with that of 2,4-O-benzylidene-D-glucitol. (Figs. xxv and xxvi, pp.85-86).

A signal common to the spectra of both compounds was a multiplet at τ 2.55 with an integrated area equivalent to five protons, which was due to the protons of the benzene nucleus.[58]

The spectrum of 2,4-O-benzylidene-D-glucitol (Fig. xxvi)

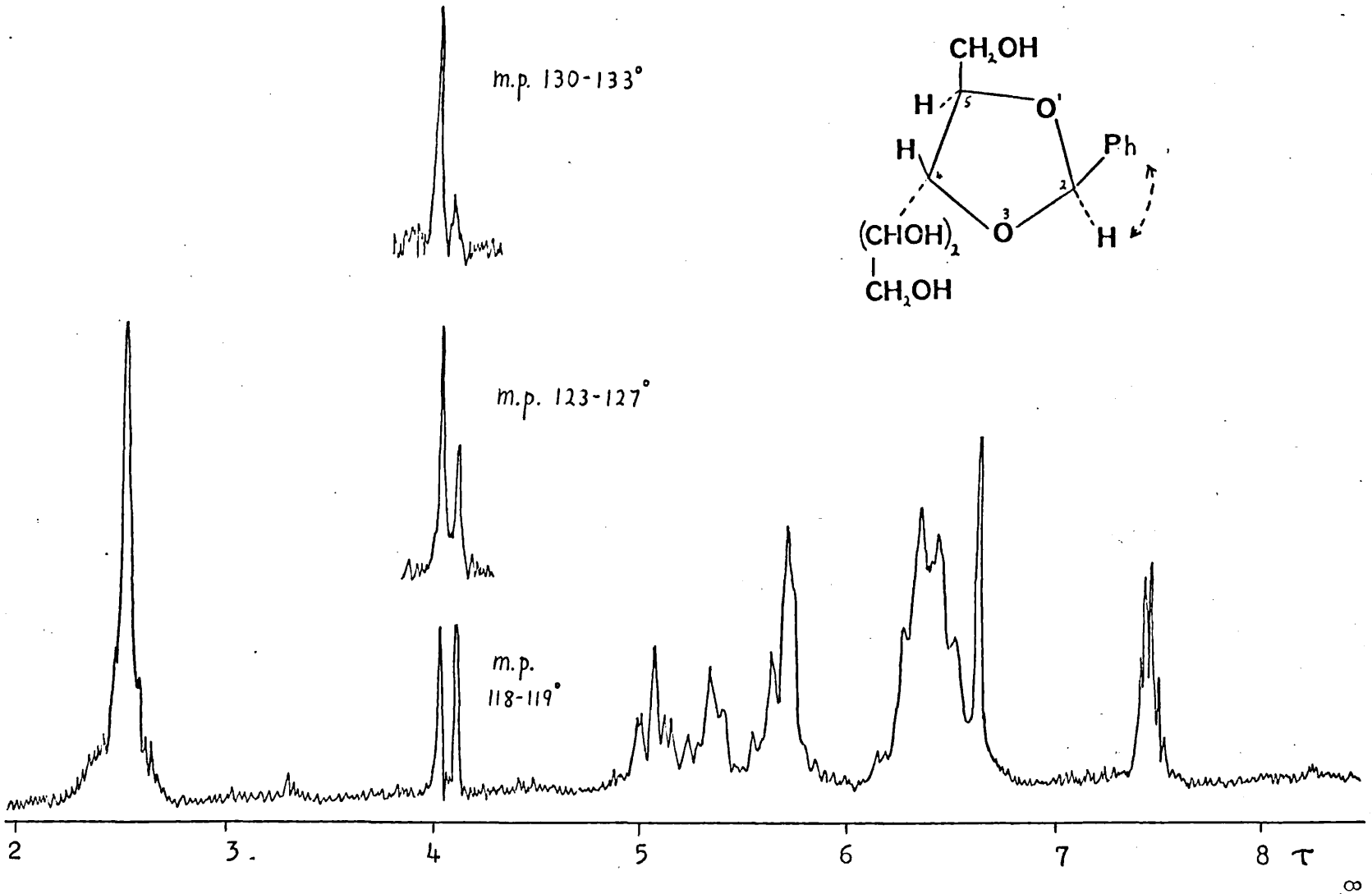


Fig. xxv PMR Spectrum of Compound B in Deuterated Dimethylsulphoxide.

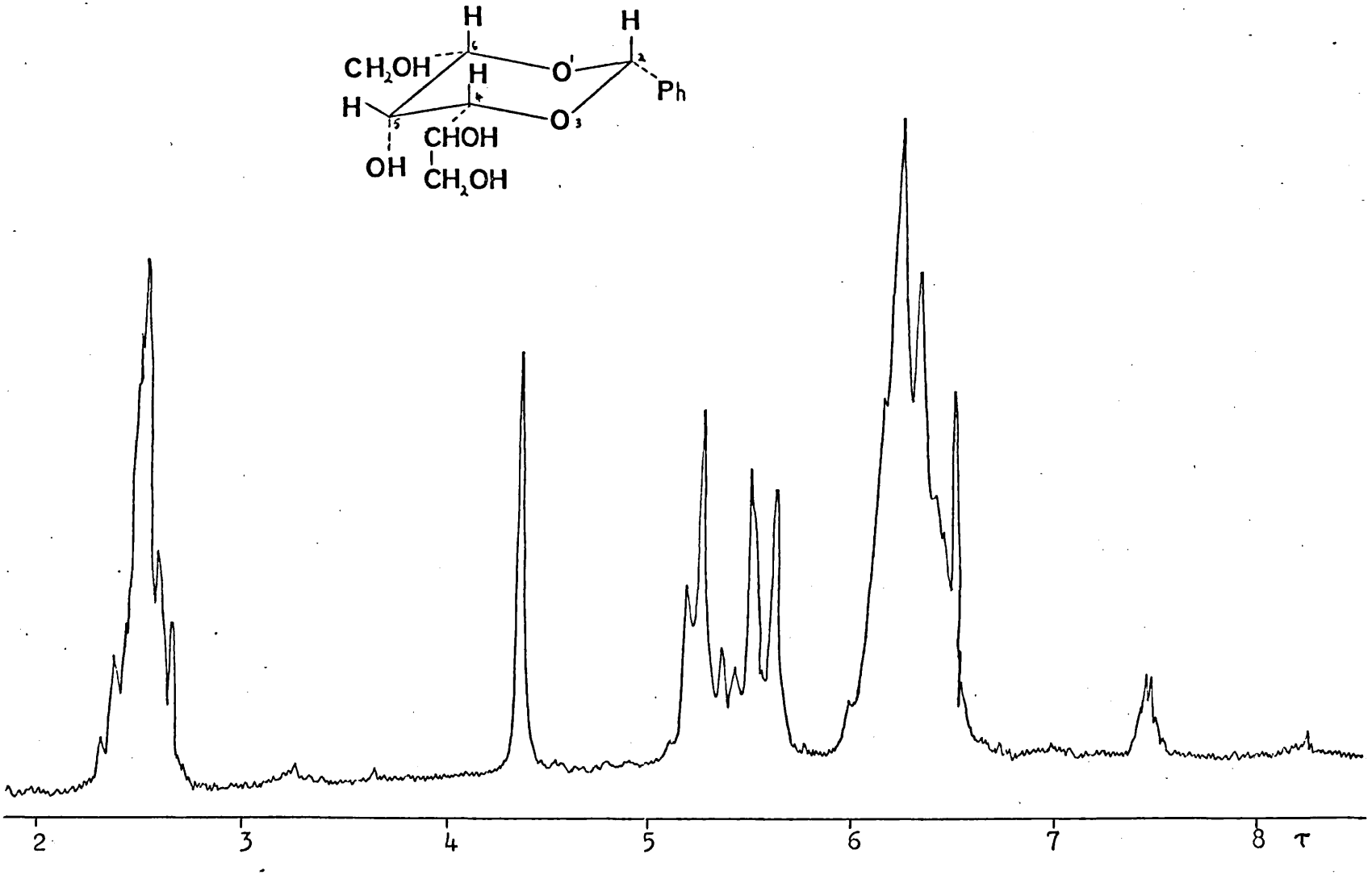


Fig. xxvi PMR Spectrum of 2,4-O-Benzylidene-D-Glucitol in Deuterated Dimethylsulphoxide.

had a sharp signal at τ 4.37, in a region completely devoid of other signals. Since it represented the resonance of a single proton, it was assigned to the proton on the acetal carbon atom (C_2)[7].

In the spectrum of Compound B (Fig. xxv) the region τ 2.7 - 4.9 was likewise free from signals, except for a pair at 4.05 and 4.13, which had a total integrated area equivalent to one proton. For the same reason, this was attributed to the proton on C_2. The fact that these signals occurred at lower field than that for the acetal proton of 2,4-O-benzylidene-D-glucitol was taken as an additional indication that Compound B contained a five-membered ring. Baggett et al.[7] have reported differences in chemical shift, of similar magnitudes, between the acetal proton signals of a series of 2-phenyl-1,3-dioxanes with equatorial substituents at positions 4 and 6, and those of a series of 4-alkyl-2-phenyl-1,3-dioxolanes in p-dioxane solutions.

It was interesting to observe that the signal at τ 4.13 diminished with increasing melting point of the sample, such that when the melting point was 130-133° it was barely discernable. On the other hand, with a sample of melting point 118-119°, the two signals were of comparable intensity.

The presence of two resonances for the proton at C_2 was

undoubted evidence for the existence of both diastereoisomers of Compound 3. This information alone could not justify the assignment of absolute configurations. However, it could be deduced that the sample of Compound 3 with m.p. 130-133° was almost a pure diastereoisomer (τ 4.05), and of the two, it had the less negative specific rotation (see table on p.79).

When samples were taken from the early stages of reaction of benzaldehyde and D-glucitol in aqueous hydrochloric acid, it will be recalled that their NMR spectra showed signals at 4.08 and 4.15 (p.77). These signals can now be assigned probably to the two diastereoisomers of 2,3-O-benzylidene-D-glucitol, and since they were of similar areas, it was likely that the isomers were synthesized in comparable amounts.

III. (iii) Fission of Compound B

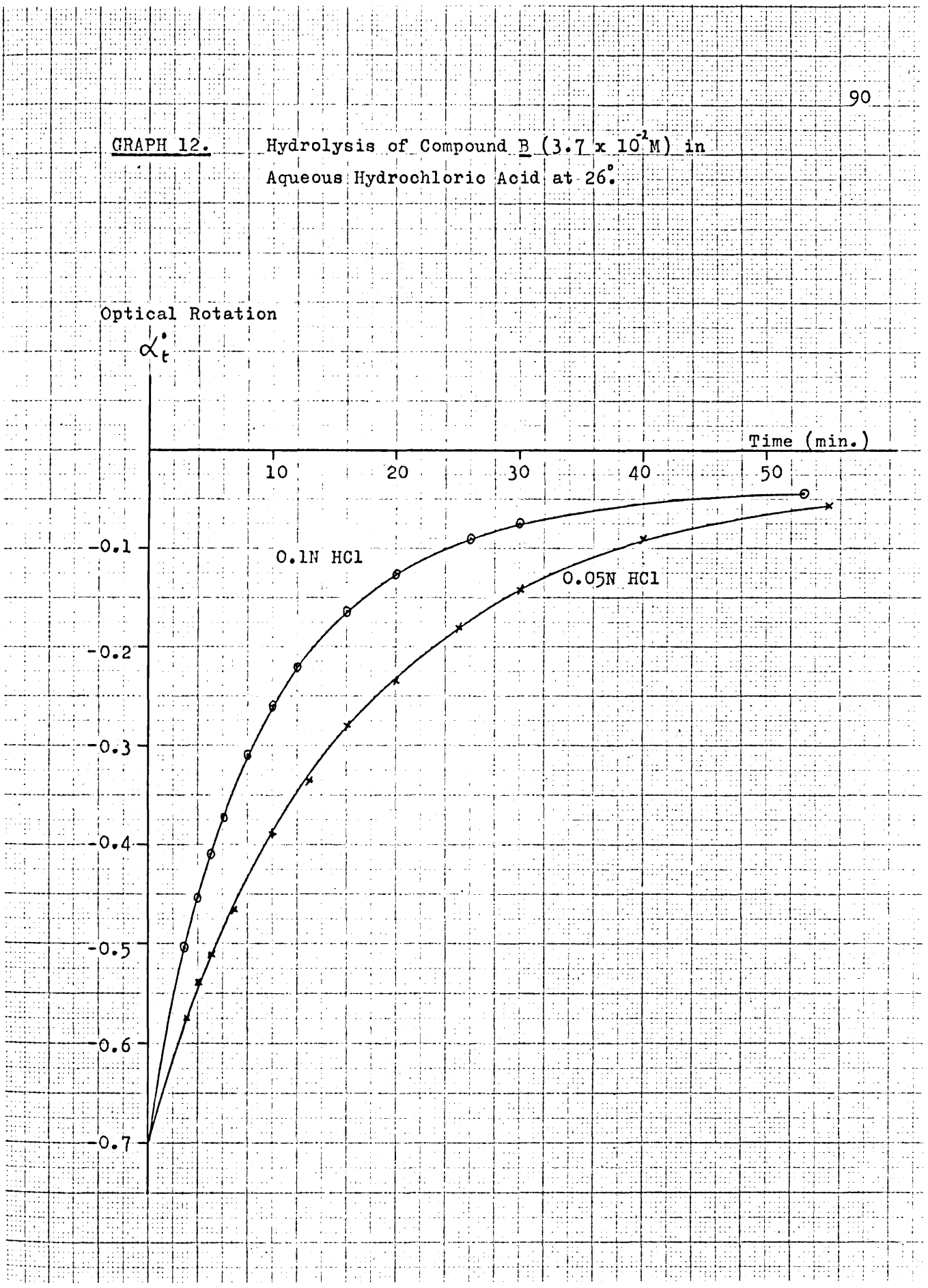
The following work was carried out on a sample of Compound B with m.p. 127-130° although, in fact, it was not a pure diastereoisomer. It was felt that the nature of this work was such that it did not warrant the special preparation of a single diastereoisomer, with the considerable losses that were incurred with repeated recrystallizations.

Hydrolysis

To follow, polarimetrically, the hydrolysis of Compound B, in aqueous hydrochloric acid of concentration exceeding 0.5N, proved to be impracticable, owing to the very rapid change in optical rotation. The hydrolysis was therefore conducted in 0.1N and 0.05N acid solutions (Expt. 35, p.178), and the variation of optical rotation with time has been represented in Graph 12 (p.90). An idea of the changing composition of the mixture was obtained by GLC analysis (Fig. xxvii, p.91), and borate ionophoresis, of samples taken from the reaction at various stages.

The major process, the disintegration of Compound B into the aldehyde and polyhydric alcohol was clearly shown by the decrease in peak area of the acetal, paralleled by an increasing D-glucitol peak. However, right from the early stages, detectable amounts of other monoacetals formed in the system.

GRAPH 12. Hydrolysis of Compound B (3.7×10^{-2}M) in Aqueous Hydrochloric Acid at 26°.



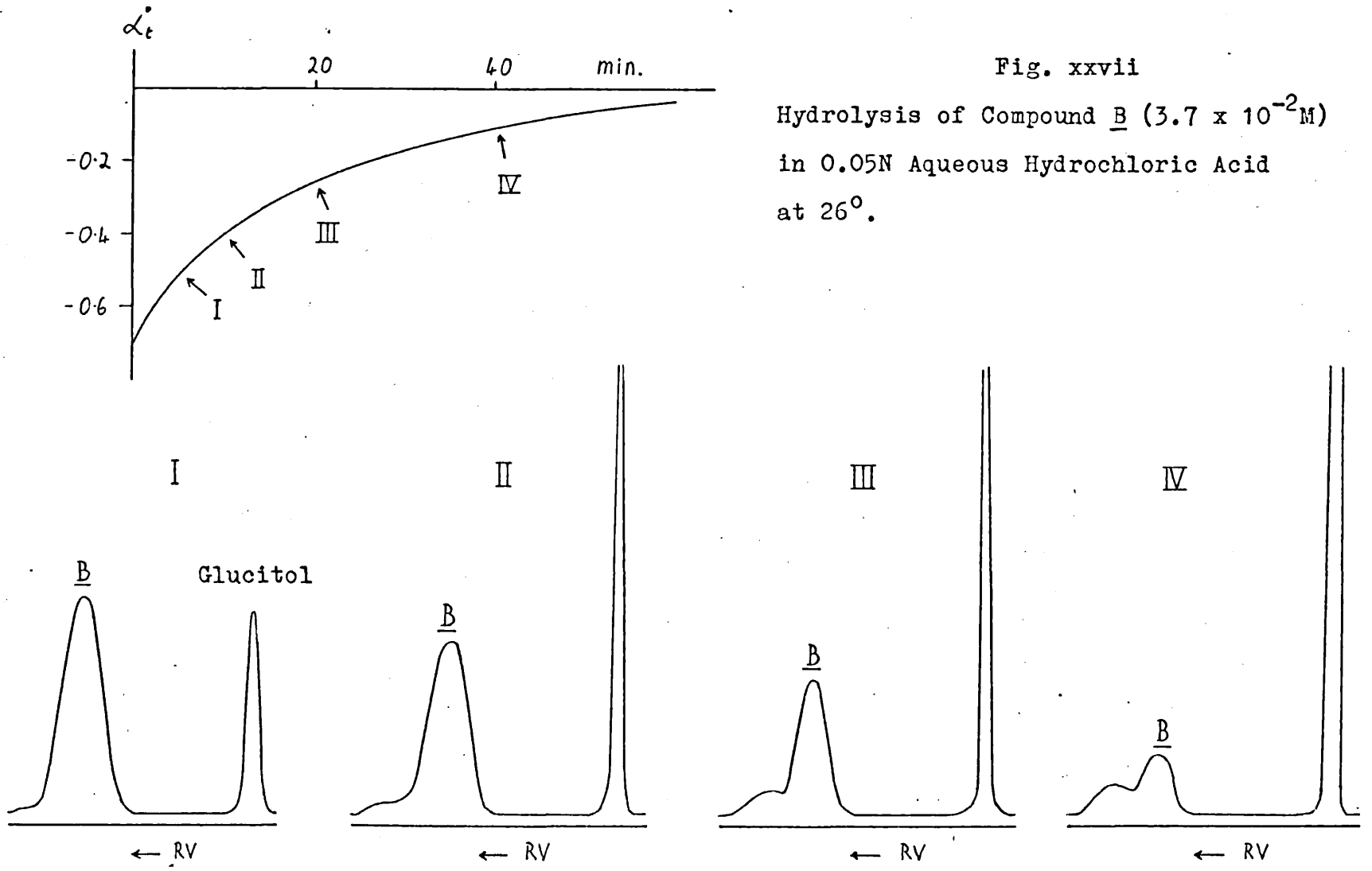


Fig. xxvii

Hydrolysis of Compound B (3.7×10^{-2}M) in 0.05N Aqueous Hydrochloric Acid at 26°.

It was interesting to compare this hydrolysis with that of Compound A in N aqueous hydrochloric acid (Fig. xxi, p.66), where other reactions appeared to be negligible during, at least the first 30% of the reaction.

Evidence from GLC and paper ionophoresis suggested that 2,4-O-benzylidene-L-glucitol was chief among the newly formed monoacetals. It might well have arisen as a result of a ring migration.

The chromatograms indicated that this hydrolysis was probably too complex to obtain any reliable kinetic information from polarimetric data. But, an idea of the relative rapidity of this reaction, to that of the hydrolysis of Compound A, could to obtained by comparing the times taken for half of the overall change in optical rotation ($t_{\frac{1}{2}}$).

Compound B in 0.1N hydrochloric acid $t_{\frac{1}{2}}$ = 6 min.

Compound A in 1.0N hydrochloric acid $t_{\frac{1}{2}}$ = 13 min.

A similar comparison has been made of the hydrolyses in sulphuric acid of 1,3-O-benzylideneglycerol and 1,3-O-methyleneglycerol.[59]

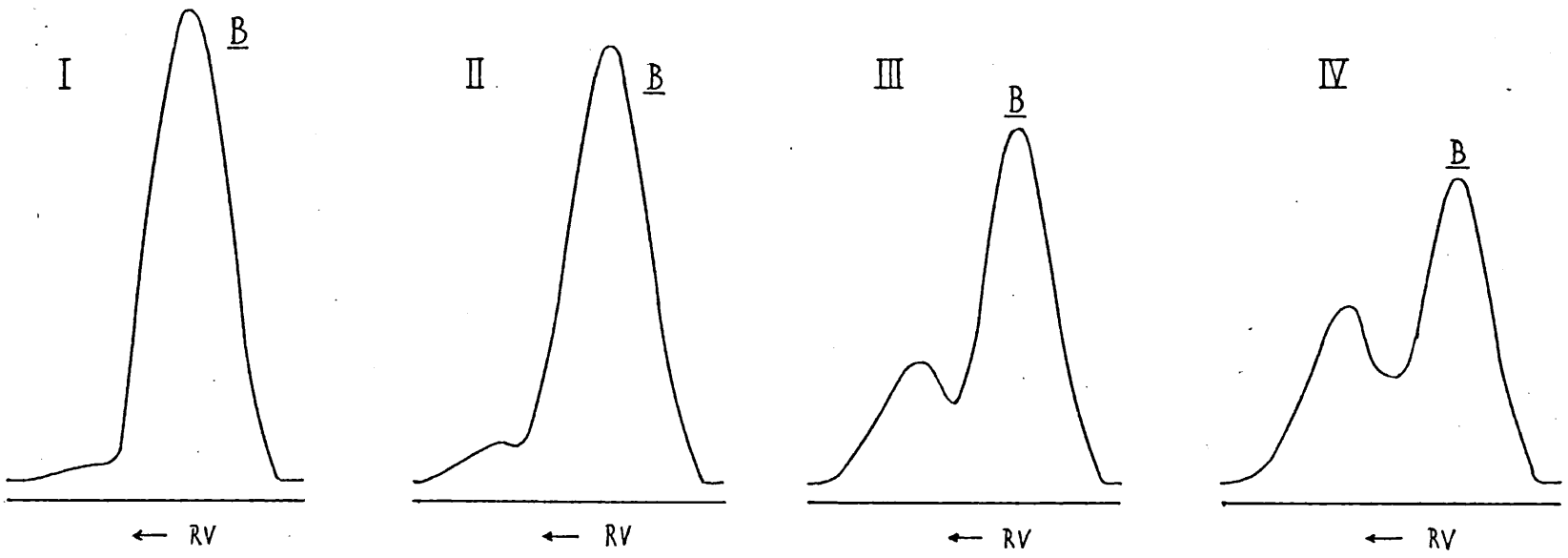
The reason for the greater rate of hydrolysis of the benzylidene acetals is probably the fact that the intermediate oxocarbonium ion, formed in the rate-determining step, can be further stabilized by resonance interaction with the benzene ring. (see Fig. viii, p. 14).

Ring Migration

In non-aqueous acid media also, Compound B was more labile than Compound A.

Compound B underwent ring migrations in DMF in the presence of hydrogen chloride (Expt. 36, p.179), and the change was detected by a comparatively rapid increase in optical rotation of the solution (see Table 18, p.221). The gas chromatograms (Fig. xxviii, p.94) showed that Compound B was gradually replaced by acetals with larger RV values. The same samples were analysed by paper ionophoresis in borate buffer, and it was seen that at least two new acetals had formed, the most abundant migrating to the same extent as 2,4-O-benzylidene-D-glucitol.

Theoretically, a wide variety of isomers was possible from ring migrations, depending upon which C-O bond in the ring was cleaved, the position of recyclisation, the number of migrations and diastereoisomerism. Nevertheless, the relative abundances of the final products must inevitably have reflected their thermodynamic stabilities. In this case, evidence from GLC and paper ionophoresis was in support of the prediction that 2,4-O-benzylidene-D-glucitol should be the major product.[4]



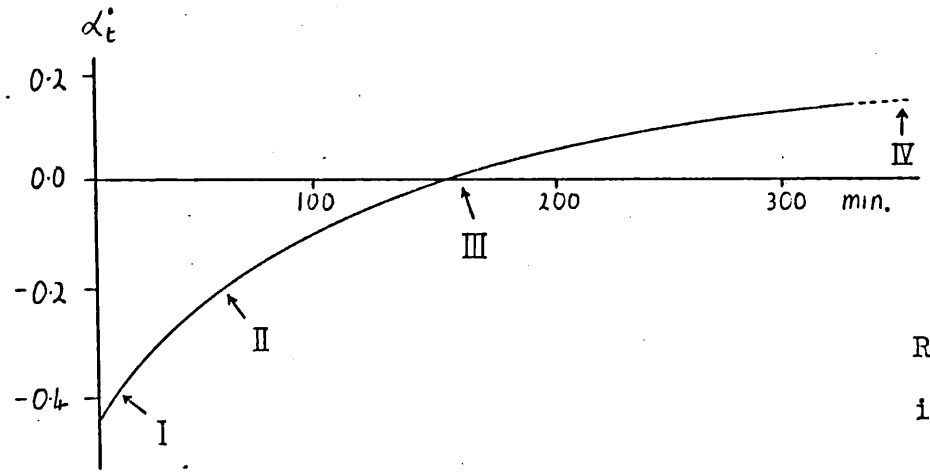


Fig. xxviii

Reaction of Compound B (3.5×10^{-2} M) in DMF containing HCl (0.25M) at 25°.

IV. METHYLENE-D-GLUCITOLS

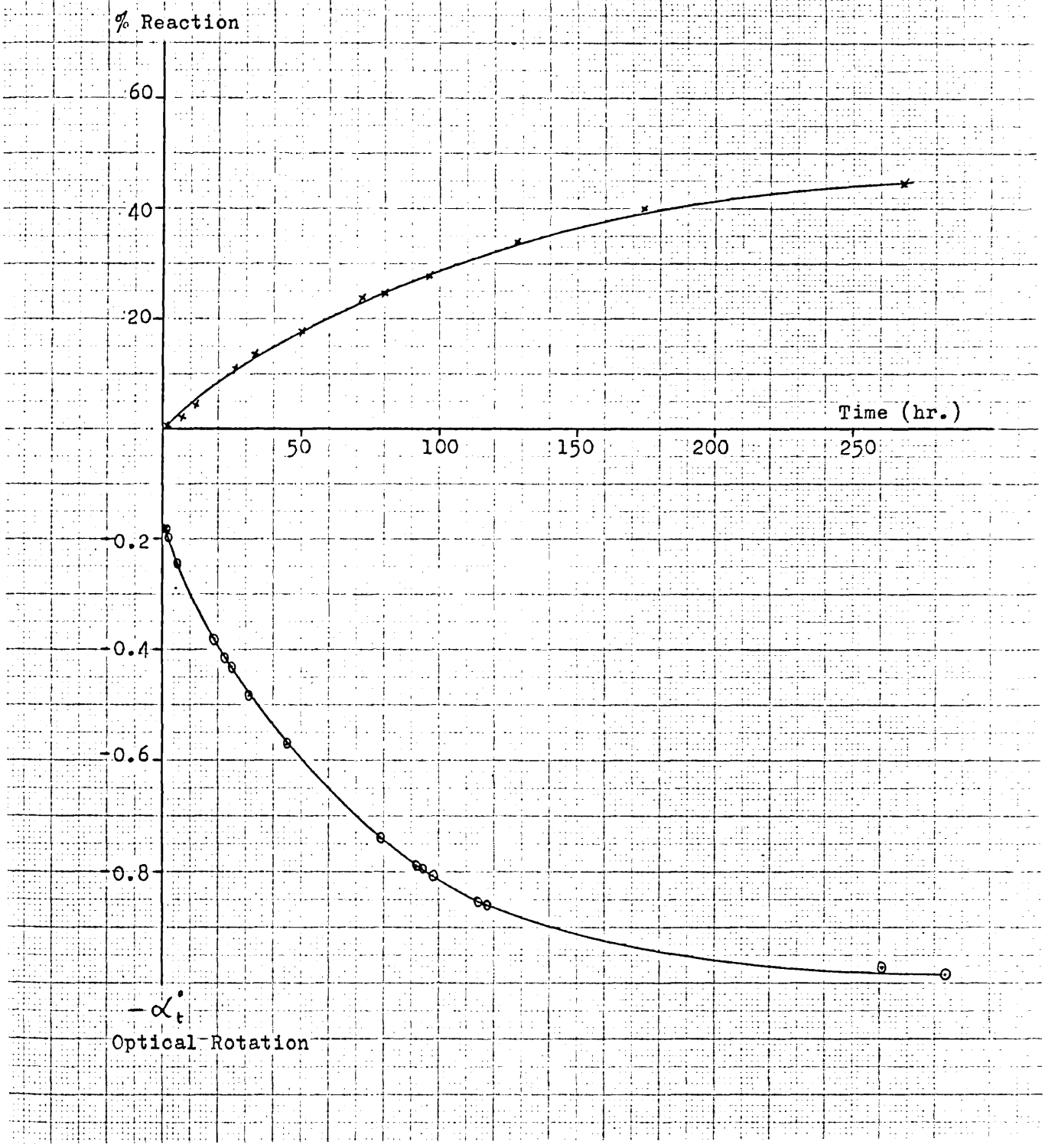
In 1894 Schulz and Tollens[60] prepared a trimethylene-D-glucitol by warming D-glucitol with 40% formaldehyde solution in the presence of hydrochloric acid. Fifty years later this compound was assigned the 1,3: 2,4: 5,6 ring structure as a result of the independent investigations of two groups of workers.[23,61]

Hess, Hann and Hudson[23] succeeded in also isolating 1,3: 2,4 di-O-methylene-D-glucitol during the preparation of the triacetal and, by acetolysis of the triacetal followed by treatment with sodium methoxide, they obtained 2,4-O-methylene-D-glucitol. The 2,4-monoacetal and 1,3: 2,4-diacetal were also obtained by Bourne and Wiggins[61] by partial acidic hydrolysis of the triacetal.

There appeared to be no reports of studies carried out on the actual course of the acid catalysed methylenation of D-glucitol. The reactions of n-butyraldehyde, and benzaldehyde, with D-glucitol in dilute aqueous hydrochloric acid had been shown to give rise, in the first instance, mainly to the 2,3-monoacetal, which was subsequently converted into other isomers, principally the 2,4-monoacetal. Simultaneously, Dr. D. Lewis[32] showed that acetaldehyde reacted likewise with D-glucitol, and, judging from the shapes of the polarimetric

curves (Graphs 1 and 2, pp.25-6), similar reactions would be expected from propionaldehyde and iso-butyraldehyde. It was therefore somewhat surprising to find in the Preliminary Investigations (I), that the polarimetric curve for the reaction involving formaldehyde (Graph 5, p. 29) was anomalous.

GRAPH 13. Reaction of Formaldehyde (0.25M) with D-Glucitol (0.25M) in 2N Aqueous Hydrochloric Acid at 25°.



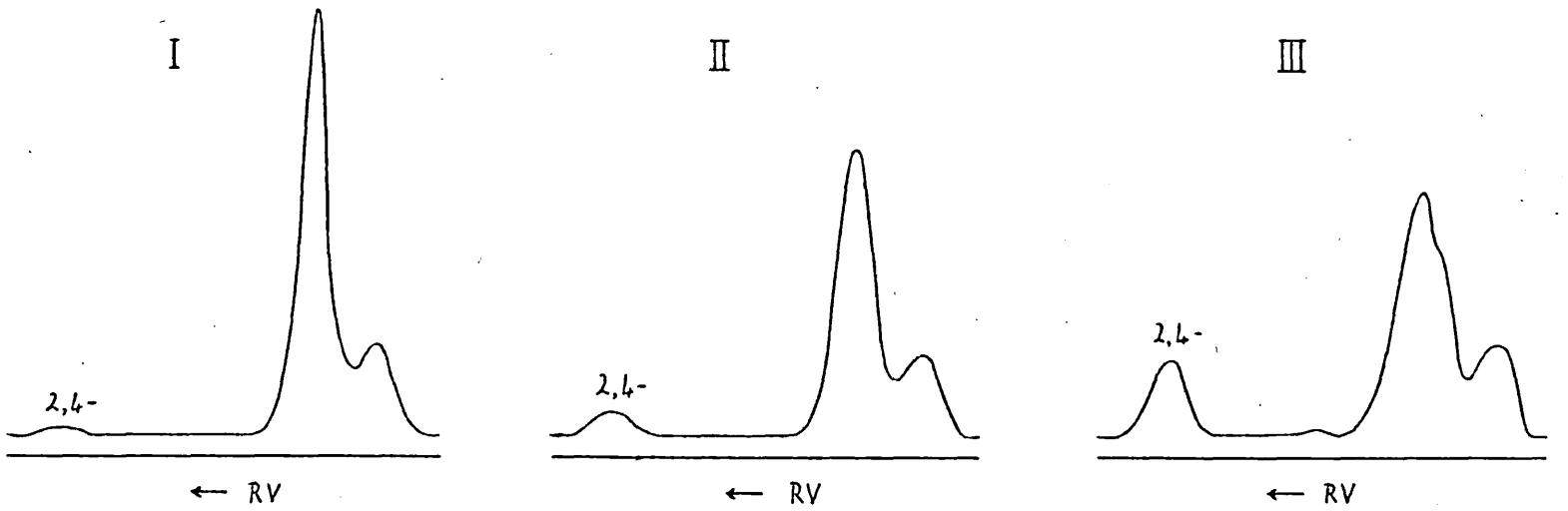
Formation of O-Methylene-D-glucitols

The change in optical rotation (Graph 13, p. 97) during the reaction of formaldehyde with D-glucitol (0.25M) in 2N aqueous hydrochloric acid took place, at 25°, over a period of many hours.

A better impression of the reaction speed was obtained by following the decreasing concentration of formaldehyde. This was done (Expt. 37, p. 180) by withdrawing aliquots from the system at particular times, oxidizing the formaldehyde with a known excess of iodine as sodium hypoiodite, and then acidifying to liberate the unused iodine which was titrated against a standard solution of sodium thiosulphate. Graph 13, (p. 97) has depicted the rate of reaction of formaldehyde with D-glucitol and from this it was obvious that, compared with that of n-butyraldehyde, this reaction was indeed very slow. A state of equilibrium was not attained even after 500 hours.

Following the procedure that had been successfully adopted for reactions involving butylidene-D-glucitols, samples were taken from the reaction mixture, at particular times, and analysed by GLC as their TMS derivatives. (Expt. 38, p. 181).

The peaks, in the gas chromatograms, due to the reaction products have been represented in Fig. xxix (p. 99), and here



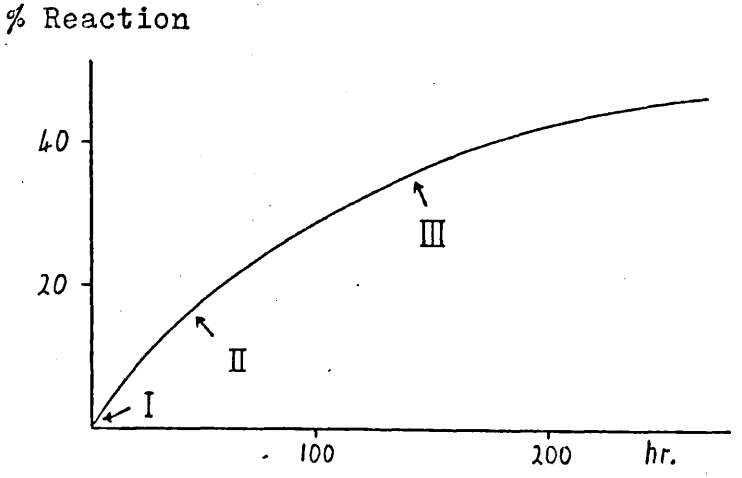


Fig. xxix

Gas Chromatograms showing Products during the Reaction of Formaldehyde (0.25M) with D-Glucitol (0.25M) in 2N Aqueous Hydrochloric Acid at 25°.

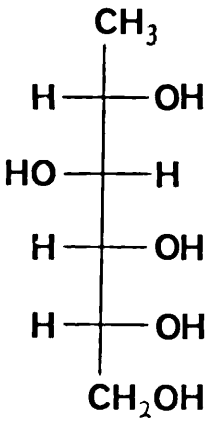
it could be plainly seen that the main initial product was not 2,4-O-methylene-D-glucitol, but a compound with smaller retention volume. As the reaction proceeded, so the proportion of the 2,4-monoacetal in the mixture increased. In this respect the reaction bore resemblance to those of other aldehydes with D-glucitol which have already been discussed.

A mixture taken after 10% reaction was passed through a cellulose column, using n-butanol saturated with water as the eluent, in order to remove the unreacted D-glucitol, and it was then examined by paper ionophoresis in borate and molybdate buffers. At least five products were indicated. It could be that not only monoacetals but also heniacetals and possibly oxydimethylene compounds were present here.

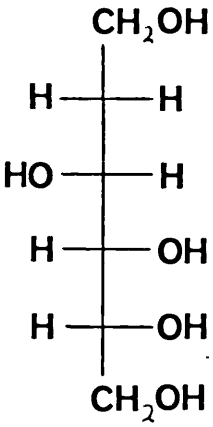
V. BUTYLIDENE DERIVATIVES OF COMPOUNDS RELATED TO D-GLUCITOL

Up to this point it had been noticed that during the reactions of several simple aldehydes with D-glucitol, in dilute aqueous acid, the most thermodynamically stable product, the 2,4-monoacetal, was not immediately the major product. The first phase of these reactions was, in fact, kinetically controlled, and certainly in the cases of acetaldehyde, n-butyraldehyde and benzaldehyde the result was the formation of 2,3-monoacetal. Since this phenomenon was common to a number of aldehydes, and appeared to be independent of the acid catalyst, it seemed likely that it was, in some way, associated with D-glucitol.

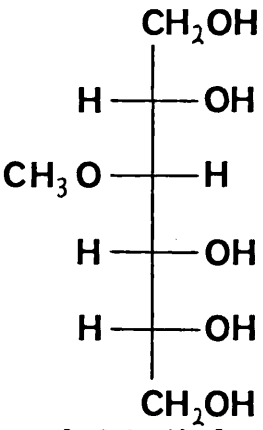
With this thought in mind, it was decided to investigate the effects on the course of the reaction of obstructing one of the reactive sites in the D-glucitol molecule. For this purpose, compounds were selected whose structures were not essentially different from that of D-glucitol itself, but in which one of the six possible positions was rendered inaccessible to the attacking aldehyde. The compounds used were the 1-deoxy,2-deoxy-, and 3-O-methyl-D-glucitols (Fig. xxx), and their reactions with n-butyraldehyde have been studied in the same way as that of D-glucitol (Section II).



1-Deoxy-
D-Glucitol



2-Deoxy-
D-Glucitol



3-O-Methyl-
D-Glucitol

Fig. xxx

V. (i) Butylidene-1-Deoxy-D-Glucitols

Baggett et al.[12] have suggested that primary hydroxyl groups are preferentially involved in the initial, hemiacetal stage, of cyclic acetal formation, and have argued that the inductive effects in simple polyhydric alcohols are such that primary hydroxyl groups tend, in general, to be more susceptible to electrophilic attack by the protonated aldehyde.

In the case of a polyhydric alcohol as complex as D-glucitol it is not easy to evaluate the relative susceptibilities of the various hydroxyl groups to electrophilic attack, on the basis of electronic effects. However, from a stereochemical standpoint, it might be expected that the primary hydroxyl groups were the more accessible to an attacking species.

It was therefore a little surprising to find that, in the acid catalysed acetal condensation of D-glucitol, the kinetically controlled product that was isolated was the 2,3-monoacetal, which involved hydroxyl groups both at secondary positions. Nevertheless, the possibility of an attack at a primary hydroxyl group followed by a rapid ring migration, as an essential first step, could not be entirely disregarded, and so the reaction of 1-deoxy-D-glucitol with n-butyraldehyde was studied.

Preparation of 1-Deoxy-D-Glucitol

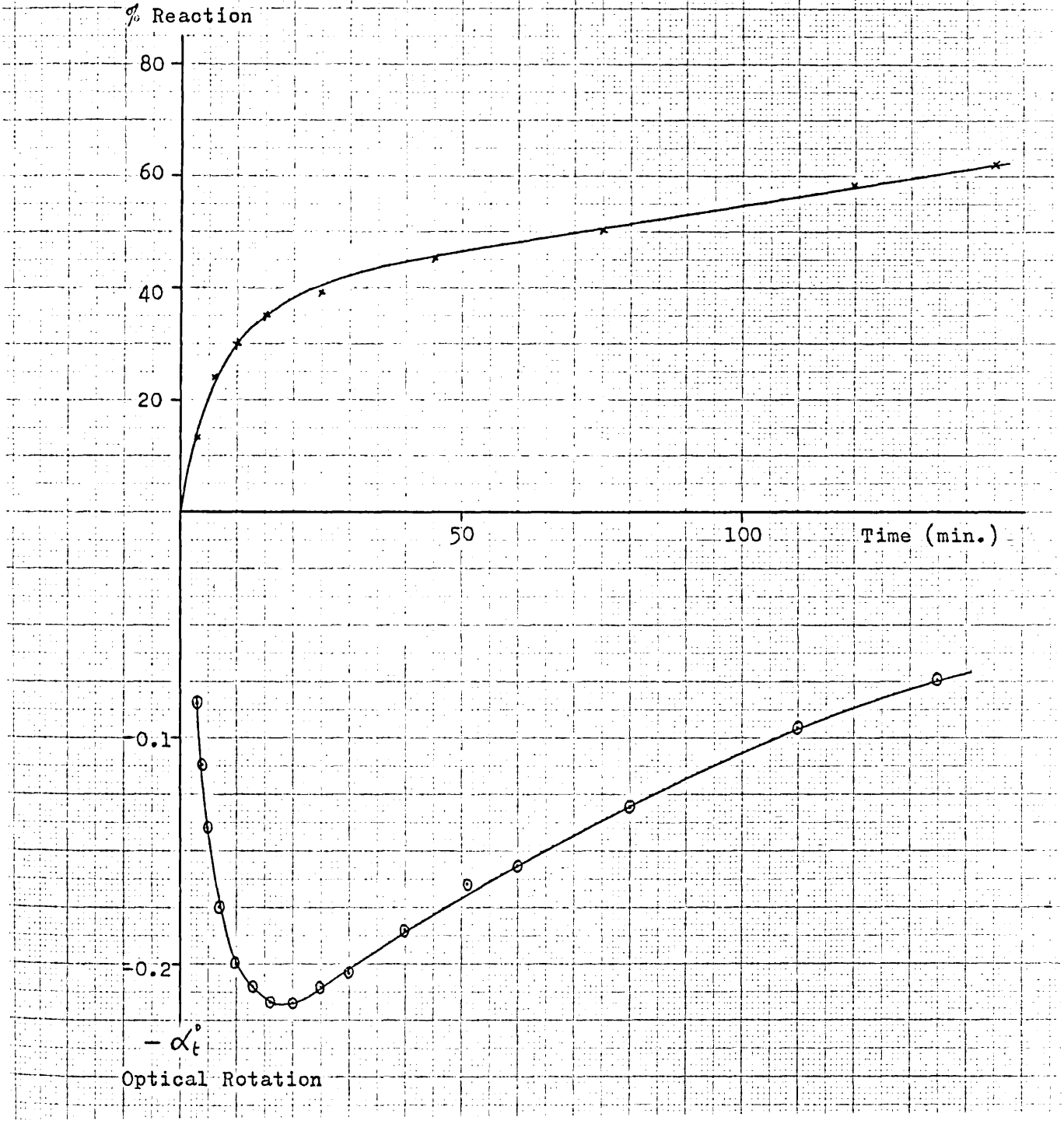
1-Deoxy-D-glucitol was prepared (Expt. 39, p.183), according to the method of De Belder and Weigel,[62] by borohydride reduction of D-glucose-toluene-p-sulphonylhydrazone. It was obtained in a beautiful crystalline form, and was also characterized as its penta-acetate.

Reaction of 1-Deoxy-D-Glucitol with n-Butyraldehyde

When the reaction of 1-deoxy-D-glucitol with n-butyraldehyde (0.1M) in aqueous acid at 25° was followed (Expts. 42 and 43, p.187), a polarimetric curve was obtained (Graph 14, p. 105) having the same form as that for the reaction of D-glucitol. Minimum optical rotation was attained after 36% of the aldehyde had reacted, and thereafter the rotation slowly increased to approach an equilibrium value at 74%.

Samples from the reaction mixture were removed at various times, and analysed by GLC. As was expected, the by now familiar process, whereby one product rapidly formed and subsequently gave way to a compound with a larger RV value was seen to operate here also. The main final product was temporarily named Compound C, and that formed under kinetic control was called Compound D.

GRAPH 14. Reaction of n-Butyraldehyde (0.1M) with 1-Deoxy-D-Glucitol (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.



Isolation of Compound C

An equimolar mixture of n-butyraldehyde and 1-deoxy-D-glucitol in aqueous hydrochloric acid was allowed to equilibrate at room temperature (Expt. 44, p.188) so that Compound C was the major reaction product, and it was found that this substance could be isolated by leaching the concentrated mixture with hot benzene, whereupon it passed into solution. Compound C was purified by recrystallization from benzene, and elemental analysis indicated it to be a mono-O-butylidene-deoxy-D-glucitol.

Structural Analysis of Compound C

By warming an aqueous solution with cation exchange resin Compound C was hydrolysed (Expt. 46, p.190), and the fragments were identified as n-butyraldehyde and 1-deoxy-D-glucitol. Thus the compound must have been a butylidene acetal of 1-deoxy-D-glucitol.

On oxidation with aqueous sodium metaperiodate, one mol. of Compound C consumed one mol. of the oxidant, and liberated one mol. of formaldehyde and no formic acid (Expts. 47-49, p.191). This meant that the hydroxyl groups, at positions 5 and 6, could not have been involved in the acetal ring. But, the oxygen atom at position 4 must have been a part of the ring system, and so two possible structures, the 3,4- and 2,4-monoacetals, were permitted. (Fig. xxxi).

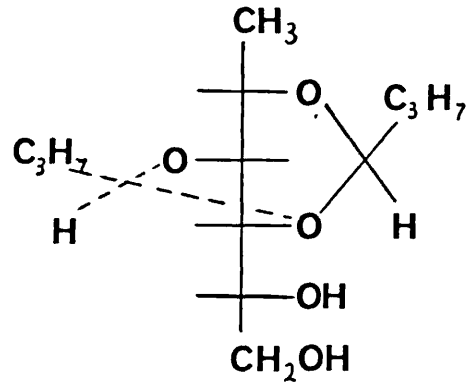


Fig. xxxi

In the case of the 3,4-monoacetal, the butylidene group would span vicinal positions on the carbon chain, and therefore, if the acetal were fully methylated and then the ring were to be removed by hydrolysis, the resulting diol would be expected to be oxidizable with aqueous sodium metaperiodate. On the other hand, the corresponding product from the 2,4-monoacetal should resist periodate oxidation.

Compound C was methylated with methyl iodide in DMF in the presence of silver oxide, and the product was obtained as a white crystalline, low melting point, solid (Expt. 50, p.192). This material was readily soluble in all of the common solvents, and consequently attempts to recrystallize it were to no avail. However, gas chromatographically, it appeared to be pure, and the results of its elemental analysis were as for the fully methylated derivative of Compound C.

The acetal ring was removed from this derivative by hydrolysis, catalysed with cation exchange resin (Expt. 51, p.194), and the result was a clear colourless syrup. The presence of free hydroxyl groups in this syrup was indicated by the fact that it formed a TMS derivative, giving a single peak when analysed by GLC and its elemental analysis figures were as calculated for a tri-O-methyl-deoxy-D-glucitol. But, the fact that the free hydroxyl groups were not situated on adjacent carbon atoms was demonstrated when the compound was found to be resistant to periodate oxidation (Expt. 52, p.194).

Thus it was shown that Compound C could not have contained a butylidene group spanning two adjacent carbon atoms, and must therefore have been 2,4-O-butylidene-1-deoxy-D-glucitol.

Isolation of Compound D

Compound D was isolated from a mixture of n-butyraldehyde and 1-deoxy-D-glucitol in the early stages of reaction, by chromatography on an alumina column. The method (Expt. 45, p.189) was analogous to that for the production of Compound A and, like the latter, Compound D was eluted first from the column to be obtained, on evaporation, as a crystalline solid.

Recrystallization presented some difficulty, since it was noticed that in several solvents, particularly those containing

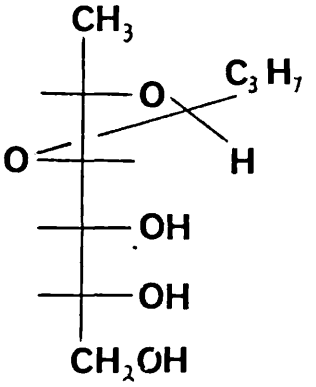
benzene, the sample had a tendency to form strong gels. The solvent eventually used consisted of a mixture of diethyl ether and light petroleum (b.p. 40-60°), which yielded Compound D in the form of light silky crystals.

Structural Analysis of Compound D

Owing to the low yield from its preparation, coupled with the comparative scarcity of 1-deoxy-D-glucitol, Compound D was only available in limited quantities. The results of its elemental analysis indicated a mono-O-butylidene-1-deoxy-D-glucitol, and, in view of the identity of Compound C, it seemed reasonable to assume that Compound D was another such monoacetal.

When subjected to periodate oxidation one mol. of Compound D was found to consume two mol. of oxidant and to release one mol. each of formaldehyde and formic acid (Expts. 47-49, p.191). These observations could only be fully taken into account if the free hydroxyl groups were situated at positions 4,5 and 6, which required the 2 and 3 positions to be involved in the acetal ring. Hence Compound D was 2,3-O-butylidene-1-deoxy-D-glucitol. (Fig. xxxii). The question of the stereochemistry at the acetal carbon atom remained unanswered.

Fig. xxxii

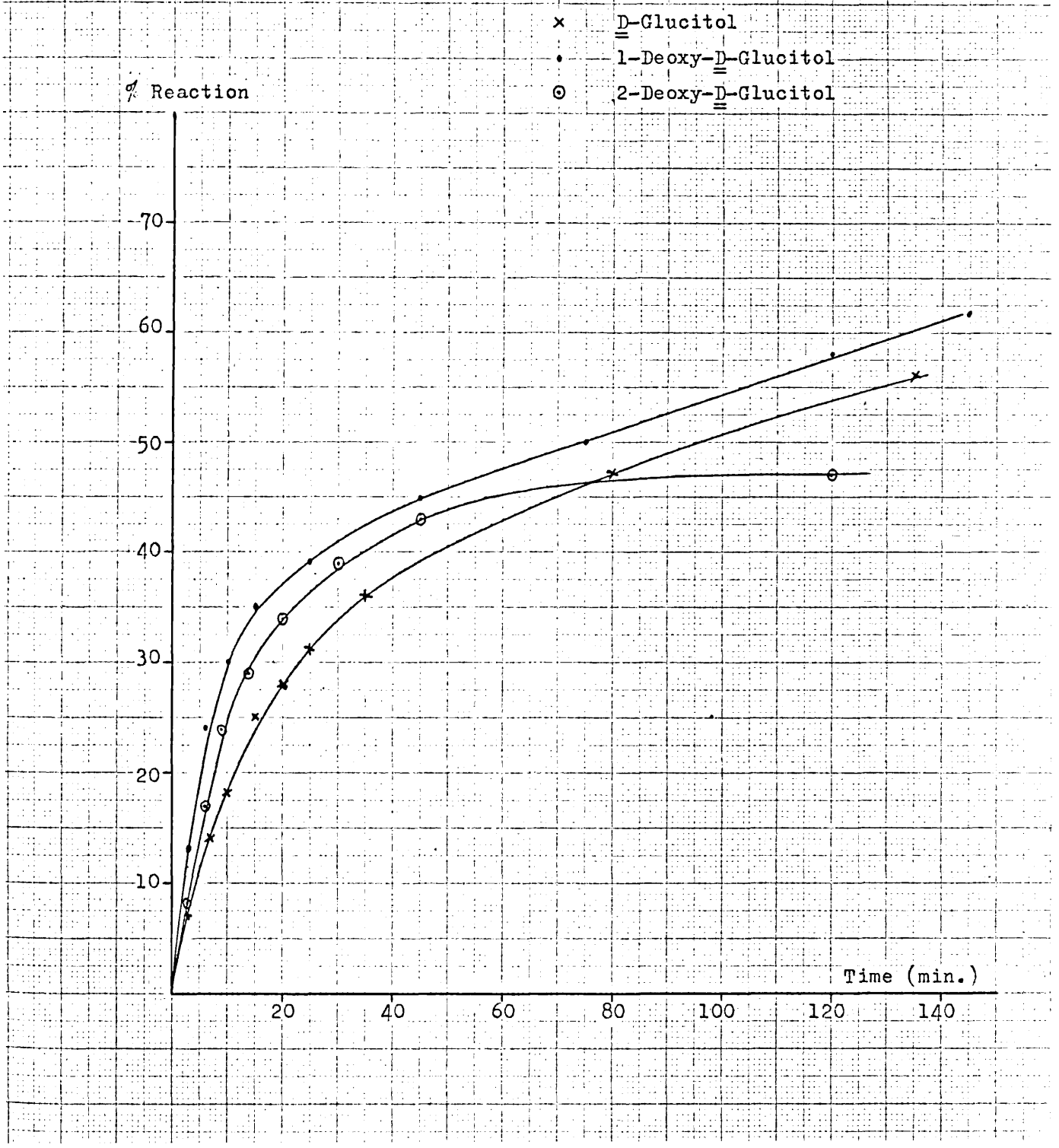


General Considerations

The preceding account has emphasized that the reaction of n-butyraldehyde with 1-deoxy-D-glucitol in dilute aqueous hydrochloric acid at room temperature was, in the first instance, kinetically controlled and led to the formation of the 2,3-monoacetal (Compound D), which latterly gave way in favour of the 2,4-monoacetal (Compound C). In fact, it was directly analogous to that with D-glucitol itself (Section II).

In Graph 15 (p.111) the uptake of n-butyraldehyde by D-glucitol, and by its 1-deoxy derivative under the same conditions, have been compared. It could be seen that the initial rates of consumption of aldehyde were, in both cases, of the same order, and that the reaction with the 1-deoxy compound was indeed slightly faster. The replacement of the terminal hydroxymethyl group in D-glucitol by an electron-donating methyl group probably has the effect of making the oxygen atom at position 2 more nucleophilic than in D-glucitol, and this may provide the explanation for the greater rate of

GRAPH 15. Reactions of n-Butyraldehyde (0.1M) with D-Glucitol and its 1- and 2-Deoxy- Derivatives (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.



initial reaction that was observed with 1-deoxy-D-glucitol.

Nevertheless, the considerable similarity of these two reactions must suggest that the presence of a hydroxyl group at position 1 in D-glucitol is not essential for the operation of the observed sequence of events.

V. (ii) Butylidene-2-Deoxy-D-Glucitols

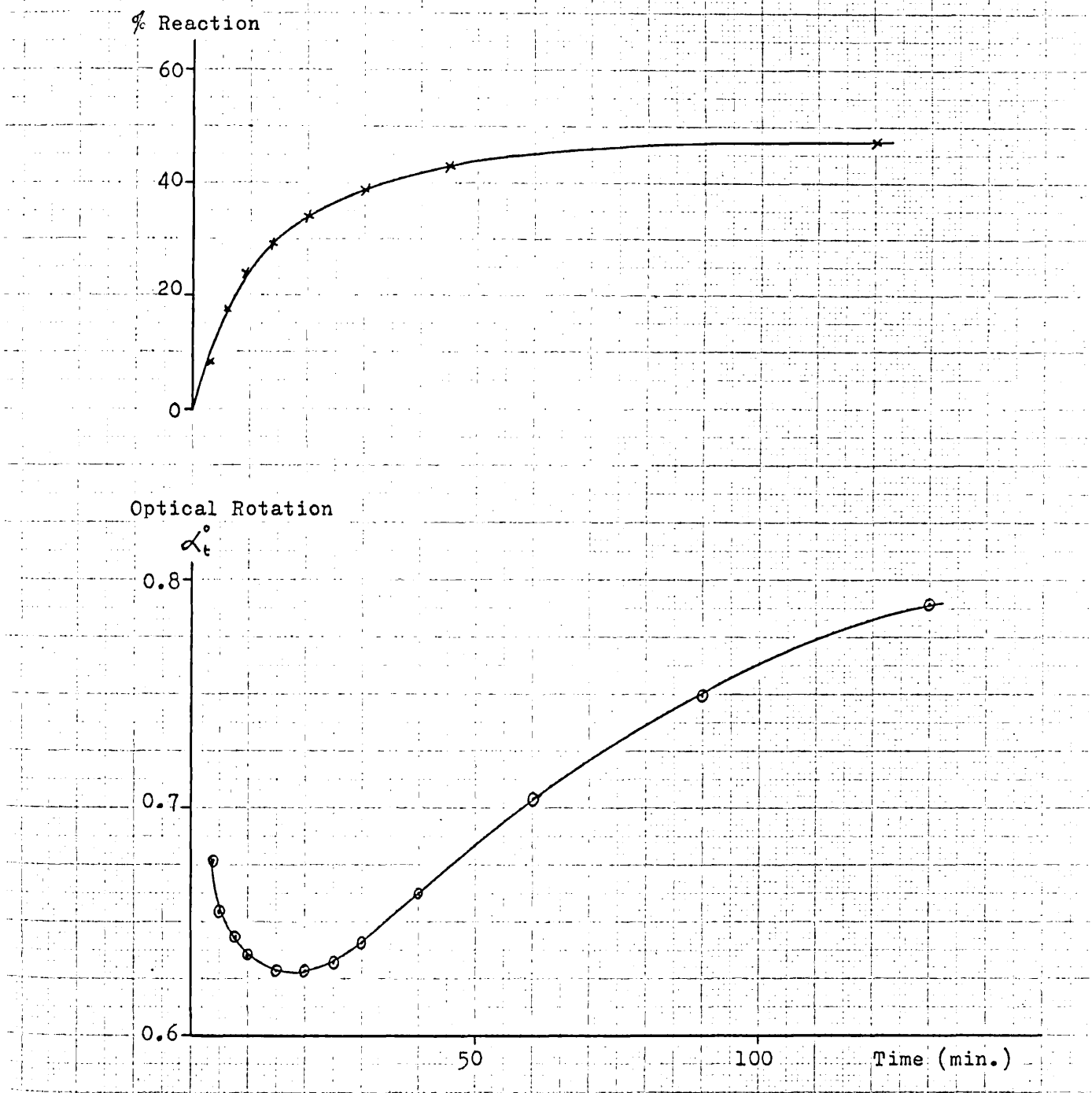
2-Deoxy-D-Glucitol was prepared as a white crystalline solid, after borohydride reduction of 2-deoxy-D-glucose, and it was further characterized as its penta-acetate (Expt. 40, p.186).

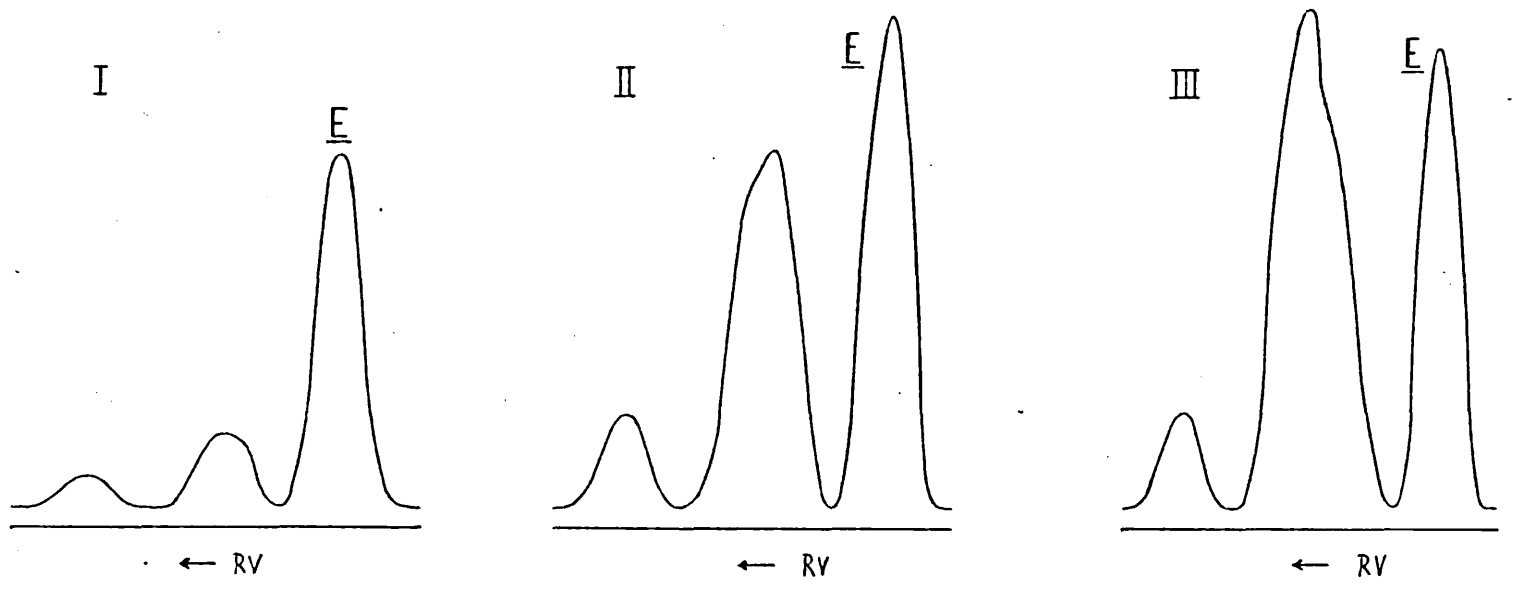
Reaction of 2-Deoxy-D-Glucitol with n-Butyraldehyde

The replacement of D-glucitol by its 2-deoxy derivative must necessarily have altered the pattern of the reaction with n-butyraldehyde in dilute aqueous hydrochloric acid at 25°, since the formation of both the 2,3- and 2,4-monoacetals was prevented. It was of particular interest therefore, to notice that the polarimetric curve for this reaction (Graph 16, p. 114) had the same characteristic shape as those for the reactions of D-glucitol and 1-deoxy-D-glucitol. The only apparent difference was that, in the latter stage, the optical rotation attained a maximum and then declined again slightly (see Table 4, p.209).

Samples were taken from the reaction mixture, for analysis, as it approached minimum rotation (after 10 min.), at about maximum rotation (after 300 min.) and after 24 hr. and the gas chromatograms of the products have been represented in Fig. xxxiii (p.115). It could be seen that the initial stage consisted primarily in the formation of a compound whose TMS

GRAPH 16. Reaction of n-Butyraldehyde (0.1M) with 2-Deoxy-D-Glucitol (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.





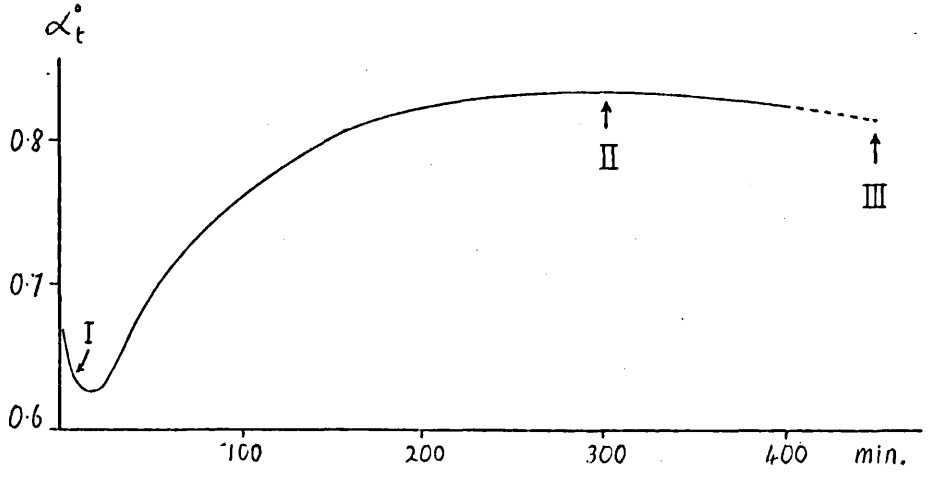


Fig. xxxiii

Gas Chromatograms showing Products during the Reaction of n-Butyraldehyde (0.1M) with 2-Deoxy-D-Glucitol (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.

derivative had a low retention volume, which will be known as Compound E. Subsequently the composition of the mixture was adjusted such that the proportion of this substance in the products was markedly reduced.

Isolation of Compound E

A reaction mixture, containing a high proportion of Compound E, was prepared by stopping the reaction at the point of minimum optical rotation, and this was fractionated on an alumina column. (Expt. 53, p.195). It was found that although 2-deoxy-D-glucitol could be removed from the mixture in this way, no satisfactory separation of the products could be achieved. However, when the semicrystalline residues from the fractions were combined and extracted several times with boiling light petroleum (b.p. 40-60°), some material passed into solution and was deposited as crystals on cooling. This material was recrystallized from light petroleum and had a low melting point (61.5-63.5°). Gas chromatographically it behaved as a single substance with retention volume as recorded for Compound E.

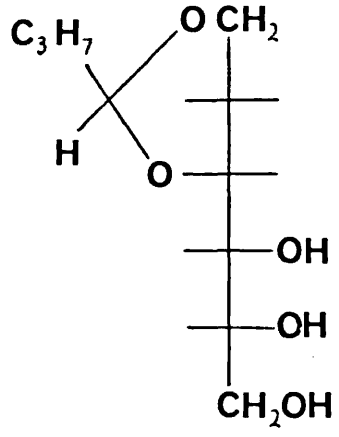
Thus it was possible to isolate Compound E, but the yield from this process was exceedingly small. In consequence, the substance was available only in milligram quantities, and therefore the work of characterisation and structural analysis

had, of necessity, to be confined to the barest minimum.

Structural Analysis of Compound E

An indication that Compound E was a monobutylidene acetal of 2-deoxy-D-glucitol was given by the determination of its carbon and hydrogen contents, and on this basis, it was assigned the appropriate molecular weight of 220.

One mol. of the Compound required two mol. of sodium metaperiodate for oxidation, and liberated one mol. each of formaldehyde and formic acid (Expts. 54-65 p.196). The only structure for a monoacetal of 2-deoxy-D-glucitol, that was consistent with these results, was one in which the butylidene group spanned positions 1 and 3. Thus Compound E was probably 1,3-O-butylidene-2-deoxy-D-glucitol. (Fig. xxxiv).



General Considerations

As with D-glucitol, and its 1-deoxy derivative, the reaction of 2-deoxy-D-glucitol appeared to be initially kinetically controlled. In this case, formation of the 2,3-monoacetal was precluded, and so it was interesting to observe the rapid formation of the 1,3-monoacetal.

In Graph 15 (p.111), where the uptake of n-butyraldehyde by D-glucitol and its 1- and 2-deoxy derivatives has been compared, it could be seen that the initial rate of reaction was slightly greater with 2-deoxy-D-glucitol than with D-glucitol itself. The CHOH group may well exert a small electron-withdrawing influence, and so it can be argued that the replacement of this group, at position 2, by a deoxy group may have the effect of increasing, to some extent, the nucleophilicity of the oxygen atoms at positions 1 and 3. Such an effect would tend to enhance the reaction of the protonated aldehyde at these positions.

V. (iii) Butylidene-3-O-Methyl-D-Glucitols

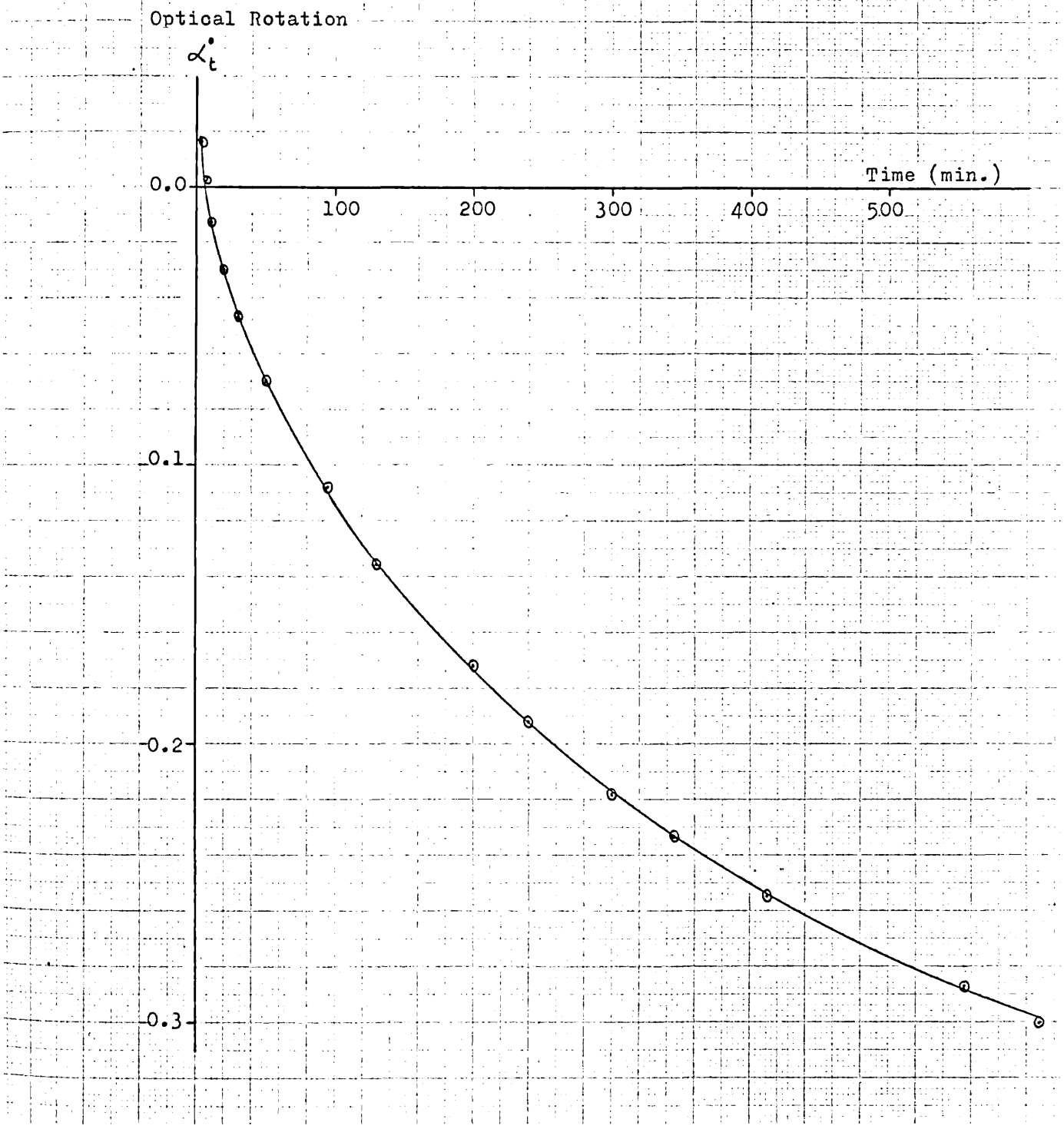
The prevention of acetal condensation of n-butyraldehyde at position 3 in D-glucitol presented more of a problem, since 3-deoxy-D-glucitol was not readily available, and its preparation would have involved a long and detailed synthesis. Instead, 3-O-methyl-D-glucitol was used, and it was prepared by borohydride reduction of 3-O-methyl-D-glucose (Expt. 41, p. 187). Unfortunately, the compound, as prepared, was an intractable syrup and consequently it was very difficult to purify. Indeed, it would appear that a crystalline form of 3-O-methyl-D-glucitol has never been reported. Gas chromatographically, as its TMS derivative, the sample obtained behaved as a single substance, and was therefore considered to be sufficiently pure for most purposes.

Reaction of 3-O-Methyl-D-Glucitol with n-Butyraldehyde

The reaction of 3-O-methyl-D-glucitol with n-butyraldehyde in dilute aqueous hydrochloric acid was conducted at 25° in Expt. 42 (p. 187). As can be seen in Graph 17 (p.120), the optical rotation of the mixture gradually diminished, and the curve showed no sign of turning after 96 hours.

Following the usual procedure, samples taken from the reaction at various times, were analysed gas chromatographically as TMS derivatives. At all stages, the mixture contained,

GRAPH 17. Reaction of n-Butyraldehyde (0.1M) with 3-O-Methyl-D-Glucitol (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.



besides 3-O-methyl-D-glucitol, a variety of products; the most prominent having RV 4.6 and 6.0, but it was not possible to detect the preferential formation of any one compound under kinetic control. The main product, which had RV 6.0, was provisionally named Compound F and attention was next concentrated on its isolation, characterisation and identification.

Isolation of Compound F

A mixture of n-butyraldehyde with 3-O-methyl-D-glucitol was allowed to react in dilute aqueous hydrochloric acid, at room temperature, for 96 hours. (Expt. 57, p.197). Examination of the mixture by paper chromatography then revealed that the major product, Compound F, could be separated from some lesser products which moved slightly faster.

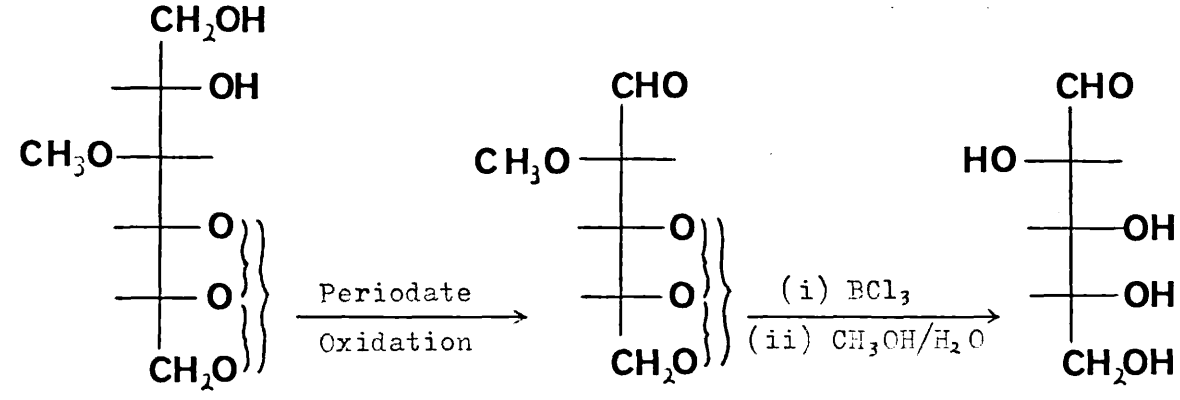
The mixture was therefore passed through a cellulose column using methyl ethyl ketone saturated with water as the eluent. Several fractions, on evaporation, afforded an attractive crystalline material in 50% yield, and this corresponded chromatographically to Compound F.

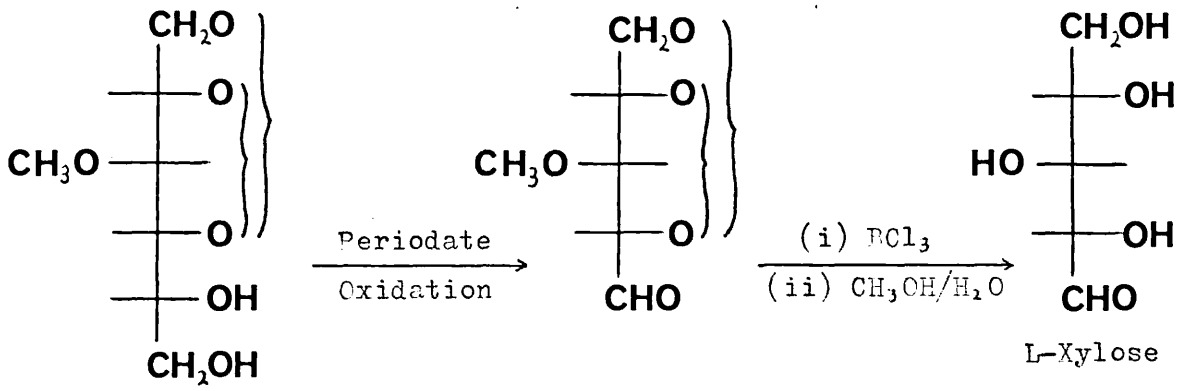
Structural Analysis of Compound F

When Compound F was hydrolysed (Expt. 58, p.198) it disintegrated into two fragments:- a carbonyl compound, which was isolated as its 2,4-dinitrophenyl-hydrazone derivative, and identified as n-butyraldehyde, and a polyhydric alcohol

whose chromatographic behaviour was the same as that of 3-O-methyl-D-glucitol. Thus Compound F was indicated to be a butylidene acetal of 3-O-methyl-D-glucitol.

Elemental and methoxyl analyses suggested a mono-, rather than a diacetal, and this was confirmed by the fact that the compound was subject to periodate oxidation. Moreover, one mol. consumed one mol. of oxidant and liberated one mol. of formaldehyde (Expts. 59-60, p. 199). To give these results, free hydroxyl groups must have existed at either positions1and 2 or 5 and 6 . (Fig. xxxv).





Depending on the position of oxidative scission, the larger fragment must have been a butylidene acetal of 2-O-methyl-D-arabinose or 3-O-methyl-L-xylose, and, on treatment with boron trichloride followed by aqueous methanol,[17] these compounds would be expected to undergo degradation to the parent sugars. (Fig. xxxv). This process was carried out in Expt. 61, (p.199) and the product, chromatographically, had no resemblance to D-arabinose, although it compared favourably with a sample of D-xylose. It was therefore concluded that L-xylose was formed, and this could only have originated from 1,4- or 2,4-O-butylidene-3-O-methyl-D-glucitol.

The problem was now reduced to one of demonstrating whether a molecule of compound F contained one or two primary hydroxyl groups. To this end attempts were made to prepare derivatives with reagents which were known to react preferentially with primary hydroxyl groups. A crystalline trityl derivative could not be formed. However, the compound readily formed a crystalline derivative when treated with two equivalents of benzoyl chloride in pyridine at room temperature (Expt. 62, p.201), and elemental analysis indicated this to be a dibenzoate.

By treating 2,4-O-benzylidene-D-glucitol with a limited amount of benzoyl chloride in pyridine, von Vargha[53] succeeded

in esterifying, exclusively, the hydroxyl groups at positions 1 and 6. Furthermore, when D-glucitol itself was benzoylated under similar conditions,[63] it was the terminal positions that were reactive. Unlike tritylation, however, benzoylation has not been firmly established as a reaction which preferentially engages primary hydroxyl groups, and so the results of benzoylating Compound F must be interpreted with caution. Nevertheless, the general inference was that Compound F contained two primary hydroxyl groups; leaving positions 2 and 4 to be involved in the acetal ring.

The alternative structure, with the butylidene group spanning the 1 and 4 positions, entailed a seven-membered (γ-) ring which has a very low rating in the order of preference.[16] Seven-membered rings appear to form only when smaller rings are not possible, and as yet no examples have been encountered among the cyclic acetals of D-glucitol. Conformationally, the 2,4-monoacetal would be, by far, the most favourable structure for Compound F.

The work presented here has merely scratched the surface of a very extensive field of study. It could be continued to include a large number of polyhydric alcohols and their derivatives, and on the other hand a wide variety of carbonyl compounds.

The final results of many acid catalysed acetal condensations have already been well documented and theory now permits adequate explanations and predictions. In contrast, the paths of these reactions have received comparatively little attention.

This work has revealed several instances, among the reactions of D-glucitol and its derivatives, with aldehydes, where kinetic control is initially operative and, at the moment, there is little basis for logical explanations. However, a deeper insight into the courses of many more such reactions may be informative, and perhaps beneficial in that one may sometimes be enabled to synthesize hitherto unknown, and possibly useful products.

EXPERIMENTAL SECTION

GENERAL TECHNIQUES

Polarimetry

Most of the optical rotation measurements were made with the mercury 5461 line, using a Hilger Watts M.511 photoelectric polarimeter in conjunction with a jacketed, thermostated sample tube. For characterizing some compounds, the sodium D line was also employed, using a Bellingham and Stanley polarimeter.

Spectrophotometry

In order to record ultraviolet spectra of compounds in solution a Perkin-Elmer Model 137 UV spectrophotometer was used. Optical density measurements were made with either a Hilger 'Uvispek', or a Unicam SP.500 spectrophotometer.

Kinetic work, involving the spectrophotometric estimation of n-butyraldehyde by its absorption at 281 mμ., was carried out with the 'Uvispek'. Silica cells (2 cm.) were used, surrounded by a constant-temperature water jacket.

It was noticed that the optical density, at 281 mμ., of an aqueous solution of n-butyraldehyde slowly diminished after an initial exposure to light of this wavelength. Many carbonyl compounds are known to undergo photodecomposition when irradiated with ultraviolet light, and a reaction of this sort was presumably occurring here.

To minimise this effect, reactions were therefore conducted outside the instrument, in flasks immersed in the constant temperature bath. Samples were transferred from the reaction mixture to the cell and placed in the instrument, and after measurement of the optical density the solutions were discarded.

Paper Chromatography

Whatman No.1 chromatography paper was used, with the following solvent systems, for descending chromatography.

MEK/H_2O - The stationary phase was water and the mobile phase was methyl ethyl ketone saturated with water.

This solvent was particularly suitable for the separation of configurational isomers of monoacetals of D-glucitol and its 1- and 2-deoxy- and 3-O-methyl-derivatives.

B/E/W[36] - A stationary phase of water with a mobile phase containing n-butanol, ethanol and water in the proportions by volume 40/11/19 respectively.

This solvent was employed principally for analyses of mixtures containing 1-deoxy-, 2-deoxy- or 3-O-methyl-D-glucitols, during the preparations of these compounds.

B/P/W - A stationary phase of water with a mobile phase containing n-butanol, pyridine and water in the proportions by volume 6/4/3 respectively.

This solvent was only used in Expt. 61 (p.199) where it was required to distinguish between xylose and arabinose.

Having dried the chromatograms, the compounds were located by one of the following methods.

(a) The chromatogram was dipped in a silver nitrate solution [a saturated aqueous solution of silver nitrate (2.5 ml.) in acetone (490 ml.) with water (10 ml.)] and allowed to dry at room temperature. It was then dipped in ethanolic sodium hydroxide [sodium hydroxide (2 g.) in ethanol (98 ml.) with water (2 ml.)] and the compounds appeared as brown spots. For preservation, these chromatograms were 'fixed' by dipping in aqueous sodium thiosulphate (2.5% w/v).

These reagents were found suitable for sugars and polyhydric alcohols. For compounds with fewer hydroxyl groups, such as mono- and diacetals, development was often assisted by lightly spraying the paper with a saturated aqueous solution of potassium metaperiodate and drying in the oven at 100° prior to application of the reagents.[32]

(b) The chromatogram was sprayed with a solution of 2,4-dinitrophenylhydrazine (0.4% w/v) in 2N aqueous hydrochloric acid and then dried in the oven at about 100°. This reagent was used for cyclic acetals, and in particular the benzylidene compounds. The acid solution hydrolysed the acetal and the

carbonyl fragment then formed a 2,4-dinitrophenylhydrazone which appeared as a yellow spot on the paper. Fixation of these chromatograms was achieved by dipping in dilute aqueous sodium hydroxide.

Chromatographic mobilities of compounds have been calculated relative to the solvent front (R_F), D-glucose (R_G) or D-glucitol (R_S)

Paper Ionophoresis

Ionophoresis was carried out on Whatman No.3 paper using a Shandon High Voltage Electrophoresis Apparatus. The following electrolytes were used.

Sodium borate [Boric acid (14.9 g.) and sodium hydroxide (8 g.) in water (2 l.)] pH 9.8-10. 2,3,4,6-Tetra-O-methyl-D-glucose was used as nonmigrating marker.

Sodium molybdate[48] [Sodium molybdate dihydrate (25 g.) in water (1200 ml.) adjusted to pH 5 with concentrated sulphuric acid]. Glycerol was used as nonmigrating marker.

Sodium metavanadate[56,57] an aqueous solution of sodium metavanadate (1.5% w/v).

For ionophoretograms prepared in borate or molybdate buffers, compounds were located with the same reagents as were used for paper chromatography. The sodium metavanadate solution was used to distinguish hexitols, and here it was

sufficient to heat the ionophoretogram at c. 100° for 10 min. in order to locate the compounds as bluish spots on a yellow background.

Where ionophoretic mobilities of compounds have been recorded they have been measured with respect to D-glucitol (M_s = 1.0).

Gas-Liquid Chromatography (GLC)

A Pye Argon Chromatograph, with β-ionization detector and glass columns (4 ft. x 4 mm), was used, with argon as the carrier gas at a rate of 70-80 ml/min. The following stationary phases were employed:-

PPE - 10% (w/w) m-bis(m-phenoxyphenoxy)benzene on silane-treated celite.[64]

BDS - 15% (w/w) butane-1,4-diol succinate polyester on silane-treated celite.[64]

SE-30 (a methyl silicone) 3% (w/w) on Gas Chrom P.

With the exception of some fully methylated derivatives all samples were gas chromatographed as their trimethylsilyl ethers (TMS derivatives) which were prepared in accordance with the method of Sweeley et al.[44] The substance (c. 10 mg.) was dissolved in dry pyridine (1 ml.) in a 1 dram screw-topped vial, and hexamethyldisilazane (0.2 ml.) and trimethylchloro-

silane (0.1 ml.) were added (where only minute quantities of substance were available the scale was appropriately reduced). After shaking for about 0.5 min. the mixture was allowed to stand at room temperature for 20 min. before centrifuging. The clear liquid was then decanted from the white precipitate, rotary evaporated to low bulk, and taken up in diethyl ether (1 ml.). This solution (c. 0.5 μl) was injected into the column with a Hamilton syring (1 μl., 7 cm. needle length).

Retention volumes (RV) were always recorded relative to the TMS derivative of D-glucitol (RV = 1).

Infrared Spectroscopy (IR)

Infrared spectra were recorded with the aid of a Perkin-Elmer 337 Grating Infrared Spectrophotometer. Samples were examined between plates of sodium chloride, either as syrups, or in the form of mulls with 'Nujol'.

Proton Magnetic Resonance Spectroscopy (PMR)

The 60 Mc. nuclear magnetic resonance spectrometer (Perkin-Elmer R.10) of the University of London Intercollegiate Research Service was used. Samples were examined, at normal working temperature, as c. 10% (w/v) solutions in deuterated dimethylsulphoxide, with tetramethylsilane as the internal reference.

Elemental Analyses

Analyses for carbon and hydrogen, and methoxyl estimations were carried out by Alfred Bernhardt. (Mülheim (Ruhr), Germany).

Materials

Pyridine was distilled at atmospheric pressure, at 115-117° and stored over sodium hydroxide pellets.

N,N-Dimethylformamide (DMF) was distilled at atmospheric pressure at c. 153° from anhydrous calcium chloride. For use as an anhydrous medium for reactions, this distillate was also allowed to stand over molecular sieves (Type 4A) for several days. The water content was then estimated by a modified Fischer method[65] and samples were found to contain <0.004% water.

To prepare a solution of hydrogen chloride in DMF, the gas, from a cylinder, was first dried by slow passage through concentrated sulphuric acid and then passed into DMF through a sintered glass bulb. The concentration of hydrogen chloride in the DMF was periodically estimated by titration of aqueous samples with standard sodium hydroxide solution.

2,4-O-Butylidene-D-Glucitol was prepared by condensation of D-Glucitol and n-Butyraldehyde in the presence of aqueous sulphuric acid, as described by Bonner et al.[35]

The following compounds were kindly supplied by Dr. D. Lewis (Royal Holloway College).

3,4- and 4,6-O-butylidene-D-glucitols

1,3:2,4-di-O-butylidene-D-glucitol

2,4-O-benzylidene-D-glucitol

2,4-O-methylene-D-glucitol

2,5-O-methylene-D-mannitol

Triphenylcarbinol

I. PRELIMINARY INVESTIGATIONS

Expt. 1. Variation of Optical Rotation with Time During the Reactions of some Aldehydes with D-glucitol in Aqueous Hydrochloric Acid at 25°.

In each reaction, the reactants were initially in equimolar proportions (0.25N). The following procedure was adopted.

The calculated weight of aldehyde was transferred to a 25 ml. standard flask, from a weighing pipette (except with chloral hydrate), and dissolved in a small amount of water. D-glucitol (1.14 g.) was added and dissolved, and the flask was immersed in the constant temperature bath at 25° for about 10 min. The required volume of 5N aqueous hydrochloric acid, also stored in the bath, was then introduced from a pipette, and a clock was started. The solution was immediately made up to 25 ml. with water. After shaking gently for about 0.5 min., to ensure complete mixing, the reaction mixture was poured into the water-jacketed polarimeter tube, and placed in the polarimeter. Readings of optical rotation (a_t) were recorded with time.

(a) n-Butyraldehyde (0.450 g.)

Purified by distillation b.p. 74-77°.

Tables 1(a) and 1(c) Graphs 1,2,3 and 9 (pp. 25-27 and 42)

(b) Acetaldehyde (0.275 g.)

Purified by distillation b.p. 21°.

Table 7 Graph 1 (p.25)

(c) Propionaldehyde (0.363 g.)

Purified by distillation b.p. 49°.

Table 8 Graph 1 (p.25)

(d) iso-Butyraldehyde (0.450 g.)

Purified by distillation b.p. 64-67°

Table 9 Graph 2 (p.26)

(e) Benzaldehyde (0.663 g.)

Purified by distillation b.p. 178-182°. Owing to the very low solubility of this aldehyde in water, the reactions were carried out in DMF containing water (20% v/v).

Table 10 Graphs 4 & 7 (pp.28,34)

(f) Formaldehyde

Formaldehyde was available in the form of formalin solution (Analar). This was estimated[66] to be a 34.2% (w/w) solution, by oxidation in alkaline conditions with a known volume of standard iodine solution, liberation of excess iodine with hydrochloric acid, and titration with standard sodium thiosulphate solution. Since 2.92 g. of formalin were equivalent to 1 g. of formaldehyde,

0.547 g. were weighed out and dissolved in the reaction mixture (25 ml.).

Table 12(a) & 12(b) Graphs 5 & 13 (pp.29.97)

(g) Trichloroacetaldehyde

Trichloroacetaldehyde was available in the form of crystalline chloral hydrate (1.034 g.)

Table 13

Expt. 2. Variation of Optical Rotation with Time during the Reactions of some Aldehydes with D-glucitol in DMF in the presence of HCl at 25°

The reactants were initially in equimolar proportions (0.25M), The calculated weights of aldehyde and D-glucitol were dissolved in dry DMF, in a standard flask, and the required volume of a concentrated solution of hydrogen chloride in DMF was added to give a 0.5N solution when the liquid was made up to the mark. Reaction was assumed to begin on addition of the acid, and was followed polarimetrically at 25°.

(a) n-Butyraldehyde

Table 2 Graph 6 (p. 33)

(b) Benzaldehyde

Table 11 Graph 7 (p. 34)

II. BUTYLIDENE-D-GLUCITOLS

Expt. 3. To Follow the Formation of 2-ethyl-2-hexenal in a Solution of n-Butyraldehyde in Aqueous Hydrochloric Acid

Solutions (0.25M) of n-butyraldehyde (1.8 g.) in N&2N aqueous hydrochloric acid (100 ml.) were made up, and maintained at 25°. After suitable time intervals, aliquots were removed from the solutions, and optical density readings taken at 233 mμ. The variation, of optical density of the solutions with time is shown in Table 6 (p. 211) and Graph 8 (p. 40).

After a few days, both reaction mixtures contained a fine suspension of oily droplets. When 8 days had elapsed, the mixture in 2N hydrochloric acid was extracted with diethyl ether (2 x 25 ml.). The ether extract was washed with (i) 5% aqueous sodium carbonate solution (2 x 25 ml.), (ii) water (4 x 25 ml.) and then dried over anhydrous sodium sulphate. Having filtered out the drying agent, the extract was evaporated to a colourless oil (0.22 g.).

A 2,4-dinitrophenylhydrazone derivative of this oil was easily formed by addition of excess of a solution of 2,4-dinitrophenylhydrazine in methanol and sulphuric acid. The derivative was recrystallized from methanol, as lustrous

orange scales, m.p. 122-123°. A mixture of this sample, with 2-ethyl-2-hexenal-2,4-dinitrophenylhydrazone suffered no depression of melting point.

Expt. 4. Preparation of 2-Ethyl-2-Hexenal

n-Butyraldehyde (7 ml.) was dissolved in water (200 ml.) and the solution was cooled in an ice-bath. Sodium hydroxide (8 g.) was added and dissolved, and, almost immediately, oily drops of condensation products separated out. The mixture was allowed to stand for 1.5 hr., after which it was neutralized with hydrochloric acid. The suspended oil was extracted three times with diethyl ether (25 ml.), and the extracts were combined and dried over anhydrous sodium sulphate. After filtering off the drying agent, and rotary evaporating, to remove the ether, there remained an oil (3.4 g.).

On distillation, the first fraction boiled in the range 73-83°, and was probably mainly unreacted n-butyraldehyde. 2-ethyl-2-hexenal was collected as a colourless oil (1.3 g.) with a strong, characteristic odour, b.p. 170-173°, n_D^{20} 1.4470 Molar extinction coefficient ε_{238} 1.36 x 10^4 (water), 1.42 x 10^4 (2N aqueous HCl).

The sample readily formed a 2,4-dinitrophenylhydrazone, which was recrystallized from methanol as lustrous orange scales, m.p. 121-123° (lit.[42] 121.5-122).

Expt. 5. To Follow the Reaction of n-Butyraldehyde with D-Glucitol by Spectrophotometric Estimation of n-Butyraldehyde.

The reactants were initially in equimilar proportions (0.25M), and the mixture was prepared as in Expt. 1 and maintained at 25°.

Periodically, aliquots (2 ml.) were removed from the flask, and diluted rapidly with water to 10 ml. in a standard flask. The optical density of this diluted solution (at 281 mμ.) was immediately measured. It was assumed that, on dilution fivefold, the reaction rate would be very much reduced, so that no significant errors would be incurred before the optical density reading was taken. Optical density data was converted to values of n-butyraldehyde concentration by means of a calibration graph, and multiplied by five, to allow for the dilution. Hence the amount of n-butyraldehyde reacted after a given time was calculated. (Tables 1(b) & 1(d) pp.203-, Graph 9, p.42).

Expt. 6. To Stop the Reaction of n-Butyraldehyde with D-Glucitol in Aqueous Acid, by Neutralization

Equimolar quantities (0.22M) of n-butyraldehyde and D-glucitol were allowed to react in N aqueous hydrochloric acid,

and the reaction was followed polarimetrically. After 30 min. an aqueous solution of sodium hydroxide (7.3 ml.) was added to the reaction mixture (25 ml.), thereby increasing the pH to 5.2. The optical rotation of this solution was measured at various times, and compared with a figure calculated from the dilution.

Time	α_t
5 min.	-0.592
8	-0.775
12	-0.940
16	-1.055
20	-1.140
25	-1.220
28	-1.256
30	-1.280

After addition of sodium hydroxide solution

Time	α_t
46 min.	-0.980
60	-0.987
120	-0.987
270	-0.975
2 days	-1.010

The optical rotation of the solution, after neutralization remained virtually constant: $\underline{\underline{-0.988^{\circ}}}$ (average)

On addition of sodium hydroxide solution, the reaction mixture was diluted from 25 ml. to 32.3 ml.

$\therefore$ Calculated optical rotation $-1.280 \times \frac{25}{32.3} = \underline{\underline{-0.991}}$

Expt. 7. Analysis of the Reaction Mixture, at Particular Times during the Reaction of n-Butyraldehyde with D-Glucitol in Aqueous Acid.

The Reaction was conducted in N aqueous hydrochloric acid, exactly as described in Expt. 1(a). After 10 min.. (60%), 30 min. (71%), and 2 days (89%), aliquots (2 ml.) were removed from the reaction mixture and neutralized with aqueous sodium hydroxide. Each solution was freeze-dried, the residues triturated with warm pyridine (5 ml.), and the insoluble sodium chloride filtered off.

These pyridine solutions were examined by paper chromatography (EtOAc/H_2O) along with some known standard acetals; 2,4-, 3,4- and 4,6-O-butylidene-D-glucitols. In each sample, the presence of D-glucitol, 2,4- and 3,4- and/or 4,6-O-butylidene-D-glucitol was indicated. When 0.2% (w/v) of phenylboronic anhydride was included in the chromatographic solvent, the presence of the 3,4-acetal was inferred, since in this system it has been shown that 3,4-monoacetals run slower than 2,4- and 4,6-.[32] The equilibrium mixture contained a trace of a component which ran almost with the solvent front (probably a diacetal).

Each pyridine extract (1 ml.) was converted into trimethylsilyl (TMS) derivatives (see p.131), and analysed by

GLC using m-bis(m-phenoxyphenoxy)benzene (PPE) as stationary phase at 175°. The gas chromatograms showed the presence, in each sample, of D-glucitol, 2,4-O-butylidene-D-glucitol (RV 4.1-4.3), and several other unidentified monoacetals, the most prominent having RV c. 2.7. Traces of a diacetal (RV c. 13.0) also appeared in the equilibrium mixture. The peaks due to monoacetals, on these chromatograms are shown in Fig. xv (p. 46).

Expt. 8. Isolation of the Diacetal, Present in the Equilibrium Mixture of O-Butylidene-D-Glucitols, by Column Chromatography

An equimolar mixture (0.25M) of n-butyraldehyde and D-glucitol was made up in N aqueous hydrochloric acid, and left for three days to attain equilibrium. After neutralizing with aqueous sodium hydroxide, the solution was freeze-dried, and then triturated with boiling ethanol. The insoluble sodium chloride was filtered off, and the ethanolic extract rotary evaporated to a syrup, which partially solidified when stored for some hours in a refrigerator.

A glass column (2.5 cm. diameter) was packed with aluminium oxide (30 g.) in ethanol. The mixture (1 g.), prepared above was dissolved in warm ethanol (15 ml.) and poured on to the column. The column was eluted with ethanol

and fractions were collected. When evaporated to dryness, the fractions yielded a fine crystalline solid (c. 0.2 g.) (RV c. 12.8, TMS derivative, PPE at 175°). After recrystallizing from benzene the substance had m.p. 130-131.5°. A sample of 1,3:2,4-di-O-butylidene-D-glucitol had m.p. 130-132°, and the mixed m.p. was not depressed.

The column was next eluted with 90% (v/v) ethanol/water. Fractions, on evaporation, gave solid residues which, when examined by GLC (TMS derivatives, PPE at 175°), were found to contain a mixture of several monoacetals, but no D-glucitol.

Expt. 9. Isolation of Compound A from a Mixture Taken from the Early Stages of Reaction of n-Butyraldehyde and D-Glucitol.

n-Butyraldehyde (6.5 ml.) and D-glucitol (13.4 g.) were dissolved in water (200 ml.). 5N aqueous hydrochloric acid (50 ml.) was added, and a clock was started. After 10 min., the reaction was stopped by introducing aqueous sodium hydroxide until the pH of the solution was about 7. The solution was freeze-dried, and then triturated with hot ethanol (150 ml.). Insoluble material was filtered from the hot solution, and the filtrate was rotary evaporated to a syrup (18 g.) which, on storage, set to a glassy solid mass. A gas chromatogram of this mixture (TMS derivatives, PPE at 175°) showed the presence of D-glucitol, 2,4-O-butylidene-D-

glucitol (RV 4.13), Compound A (RV 2.74), and traces of other monoacetals.

A glass column (5 cm. diameter) was packed with aluminium oxide (100 g.) in ethanol. The mixture (5 g.) prepared above, was dissolved in warm ethanol (25 ml.) and poured on to the column. The column was eluted first with ethanol (25 ml.) and then with ethanol/water mixtures of 96% (v/v) (25 ml.), 94% (v/v) (25 ml.) and 93% (v/v) (125 ml.), whilst fractions (25 ml.) were collected, and rotary evaporated to dryness.

Early fractions contained minute traces of oil (probably mainly polymerization or decomposition products of n-butyraldehyde, and possibly some traces of polyacetals). The first 0.4 g. of solid material was pure Compound A (RV 2.76). Further material, taken from the column, contained other monoacetals in increasing amounts. This was collected, and purified by a second fractionation process.

Compound A was recrystallized from chloroform (1 g. in 500 ml.) to give light, fluffy crystals. Although GLC indicated a pure compound, the m.p's of samples obtained varied between 111° and 119°. By repeated recrystallization, the highest m.p. attained was 117-119°. $[\alpha]_D^{26}$ -39°, $[\alpha]_{Hg\ 5461}^{26}$ -46° (c. 1 in H_2O). Analysis indicated a mono-O-butylidene-glucitol (Found: C,50.5; H,8.4; $C_{10}H_{20}O_6$ requires C,50.8; H,8.5%) M_s (Borate) 0.50.

Expt. 10. Hydrolysis of Compound A, and Identification of the Products

(a) Carbonyl portion.

A solution (40 ml.) of 2,4-dinitrophenylhydrazine (0.25% w/v) in 2N aqueous hydrochloric acid was warmed in a 250 ml. beaker over a water bath. Compound A (0.0973 g.) was dissolved in a little water, and washed into the beaker. The solution was stirred, whilst precipitation of the yellow 2,4-dinitrophenylhydrazone derivative occurred. For 30 min. the precipitate was digested over the gently simmering water-bath, and then the beaker was allowed to cool. The precipitate was collected on a preweighed sintered-glass crucible, washed with water, and dried in the oven, at 95°, to constant weight.

Weight of precipitate 0.1001 g.

Weight of derivative calculated for a mono-O-butylidene hexitol 0.1044 g.

Weight of derivative calculated for a di-O-butylidene hexitol 0.1700 g.

The derivative was recrystallized twice from industrial methylated spirits (10 ml.) and had m.p. 119-121°. An authentic sample of n-butyraldehyde-2,4-dinitrophenylhydrazone had m.p.120-121° and the mixed m.p. was not depressed.

(b) Polyhydric Alcohol portion.

Compound A (0.1 g.) was dissolved in N aqueous hydrochloric acid (20 ml.), and warmed over a boiling water-bath for 20 min. The solution was neutralized, by addition of barium carbonate (2.5 g.), filtered, and the filtrate rotary evaporated to dryness. The solid residue was triturated with pyridine (10 ml.), the insoluble barium chloride being then filtered off. After concentrating, by rotary evaporation, the pyridine extract was taken up in a solution (2 ml.) containing acetic anhydride (1 vol.) and pyridine (2 vol.), and was left to stand for 1 hr. at room temperature. The solution was then poured into iced-water (20 ml.) and stirred, whilst oily droplets separated out, and gradually solidified. This precipitate was filtered off, washed with water, and dried (yield 0.04 g, 22%). It was recrystallized from 25% (v/v) ethanol/water (3 ml.) m.p. 97.5-99°. An authentic sample of D-glucitol hexa-acetate had m.p. 98-99°, and the mixed m.p. with the specimen was not depressed.

Expt. 11. Determination of the Number of Free Hydroxyl Groups per Molecule of Compound A, by Acetylation

The acetylating reagent was prepared by mixing acetic anhydride (2 ml.) with pyridine (40 ml.). This solution (4 ml.) was transferred to a 50 ml. flask, and boiled under

reflux for 5 min. It was then carefully washed, into a 250 ml. conical flask, with water (c. 40 ml.), and titrated against standard 0.1N sodium hydroxide solution, using phenolphthalein as indicator. This procedure was repeated several times to obtain an average 'control' titre.

Compound A (about 0.05 g.) was weighed out accurately, and dissolved in the acetylating reagent (4 ml.). The solution was boiled under reflux for 1 hr., and then washed into the titrating flask with water (c. 40 ml.), and titrated against the 0.1N sodium hydroxide solution, as before. The difference between this titre and the control titre was a measure of the acetic anhydride required to acetylate the compound.

As a standard for the method, a sample of 2,4-O-butylidene-D-glucitol was acetylated, and the acetic anhydride consumption determined in the same way. The results have been tabulated below.

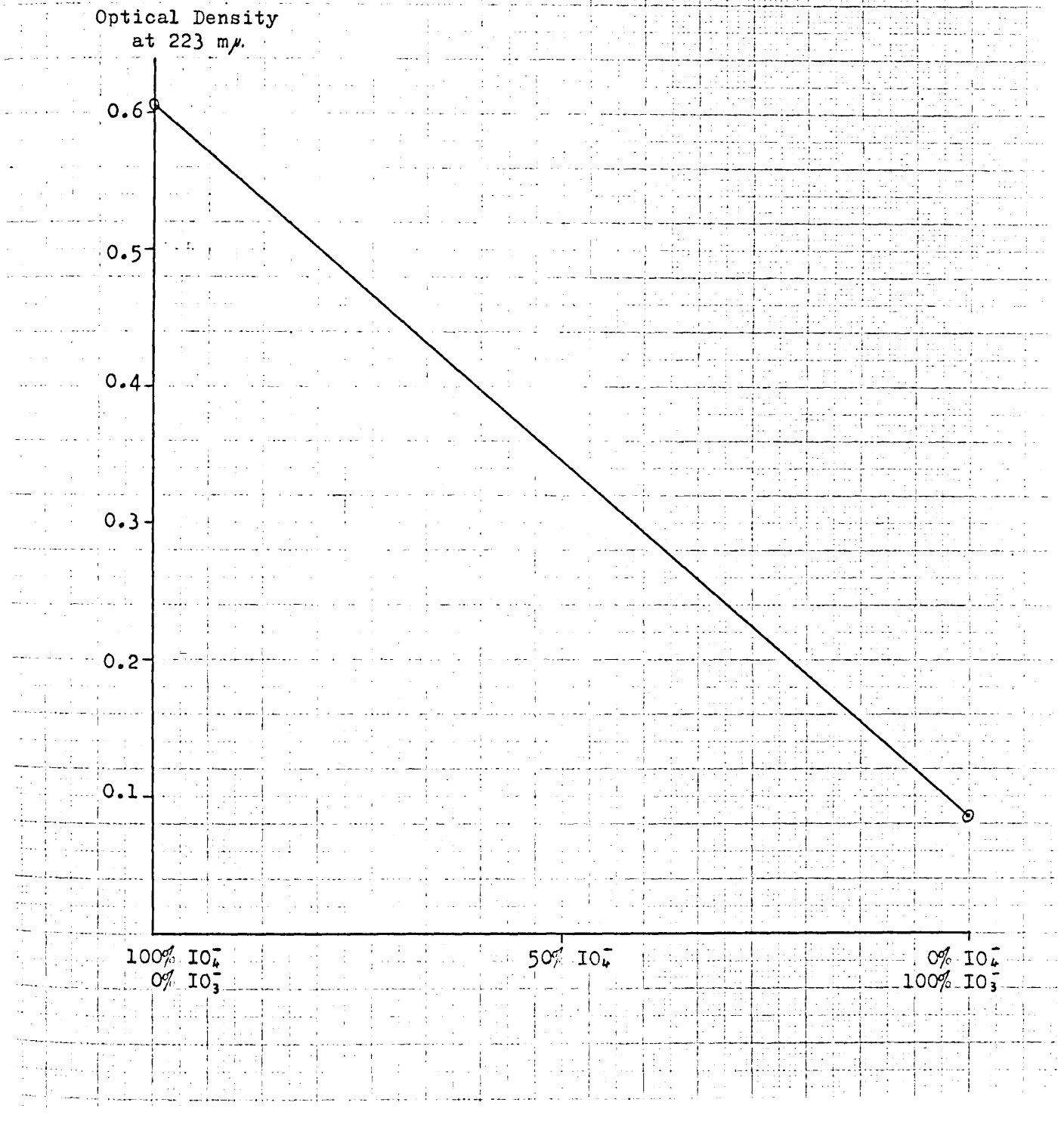
Compound	Weight	'Control' Titre	'Sample' Titre	Ac.OH consumed per mol. of compound
2,4-O-butylidene-D-glucitol	0.0504 g.	42.30 ml.	33.60 ml.	4.07
=	0.0563	"	32.90	3.94
A	0.0445	"	34.95	3.90
"	0.0445	"	35.50	3.61
"	0.0534	33.80	30.60	3.62

An average of 3.71 mol. of acetic acid was consumed per mol. of Compound A. (i.e. approximately 4 mol.). Therefore Compound A had 4 free hydroxyl groups per molecule.

Expt. 12. To Determine the Number of Pairs of Vicinal Hydroxyl Groups per Molecule of Compound A, by Periodate Oxidation.[45]

Solutions (0.015M) of sodium metaperiodate and potassium iodate, were made up by dissolving in both cases, 0.321 g. in water (100 ml.). Aliquots (1 ml.) of the solutions were diluted 250 times, and the optical densities, of the resulting solutions, were measured at 223 mμ. with water as the reference. Considering the periodate solution to contain 0% IO_3^- and 100% IO_4^-, and the iodate solution 100% IO_3^- and 0% IO_4^-, a linear calibration graph, relating optical density to the percentage composition of any solution containing a mixture of the two ions at this dilution, was drawn, (Graph 18, p.151).

GRAPH 18. Calibration Graph relating Optical Density Measurements to Percentage Consumption of Periodate. (Expt. 12.)



$\%IO_3^-$	$\%IO_4^-$	Optical Density at 223 mμ.
0	100	0.606
100	0	0.085

Compound A (c. 0.01 g.) was weighed out accurately and dissolved in the 0.015M sodium metaperiodate solution (10 ml.). At convenient time intervals, aliquots (1 ml.) were removed from the solution, diluted 250 times, and the optical densities measured. From the calibration graph, the $\%IO_3^-$ in the solution could be deduced, and this represented the percentage of IO_4^- reduced by the compound. Hence, the number of mol. of periodate reduced by one mol. of Compound A was calculated. The method was checked by using 2,5-O-methylenemannitol as a standard compound.

Compound	Weight	Time	$\%IO_4^-$ Consumed	Mol. IO_4^- per mol. of Compound
2,5-O-methylene-mannitol	0.0093g.	1.5 hr	31.8	0.99
	"	2.0	31.8	0.99
A	0.0098	2.5	53.7	1.94
"	"	3.5	53.7	1.94

Since one mol. of Compound A required approximately 2 mol. of periodate, for oxidation, it must have contained two pairs of vicinal hydroxyl groups per molecule.

Expt. 13. Estimation of the Formaldehyde Liberated by Periodate Oxidation of Compound A.

The formaldehyde was estimated spectrophotometrically, by its colour reaction in the presence of chromotropic acid reagent.[46] The reagent was prepared by dissolving chromotropic acid sodium salt (0.2 g.) in water (20 ml.) and adding 12.5M sulphuric acid (80 ml.) (i.e. H_2O (1 vol.) + conc. H_2SO_4 (2 vol.)).

The same solutions of 2,5-O-methylene-mannitol, and Compound A, in sodium metaperiodate solution, were used, as for the preceding experiment. After 20 hr., aliquots (1 ml.) from the 2,5-O-methylene-mannitol solution (0.0093 g./10 ml.) were diluted accurately with water to 10 ml., 20 ml., and 50 ml. The solution of Compound A (0.0098 g./10 ml.) (1 ml.) was diluted to 16 ml. in water. From the diluted solutions, 1 ml. was transferred to 20 ml. stoppered test tubes, and a fifth tube contained water (1 ml.) as a "blank". Into each tube was delivered 20% aqueous sodium sulphite solution (0.1 ml.) from a microburette, and chromotropic acid reagent (8.4 ml.) from a burette.

The five tubes were heated for 1 hr. in a boiling water bath, during which time, violet colourations of varying intensities developed. After cooling, 0.4% aqueous thiourea solution (0.5 ml.) was added to the solutions from a pipette,

thus bringing the total volume of liquid in each tube to 10 ml. The optical densities at 570 mμ. of the four sample solutions were measured, with the "blank" solution in the reference cell.

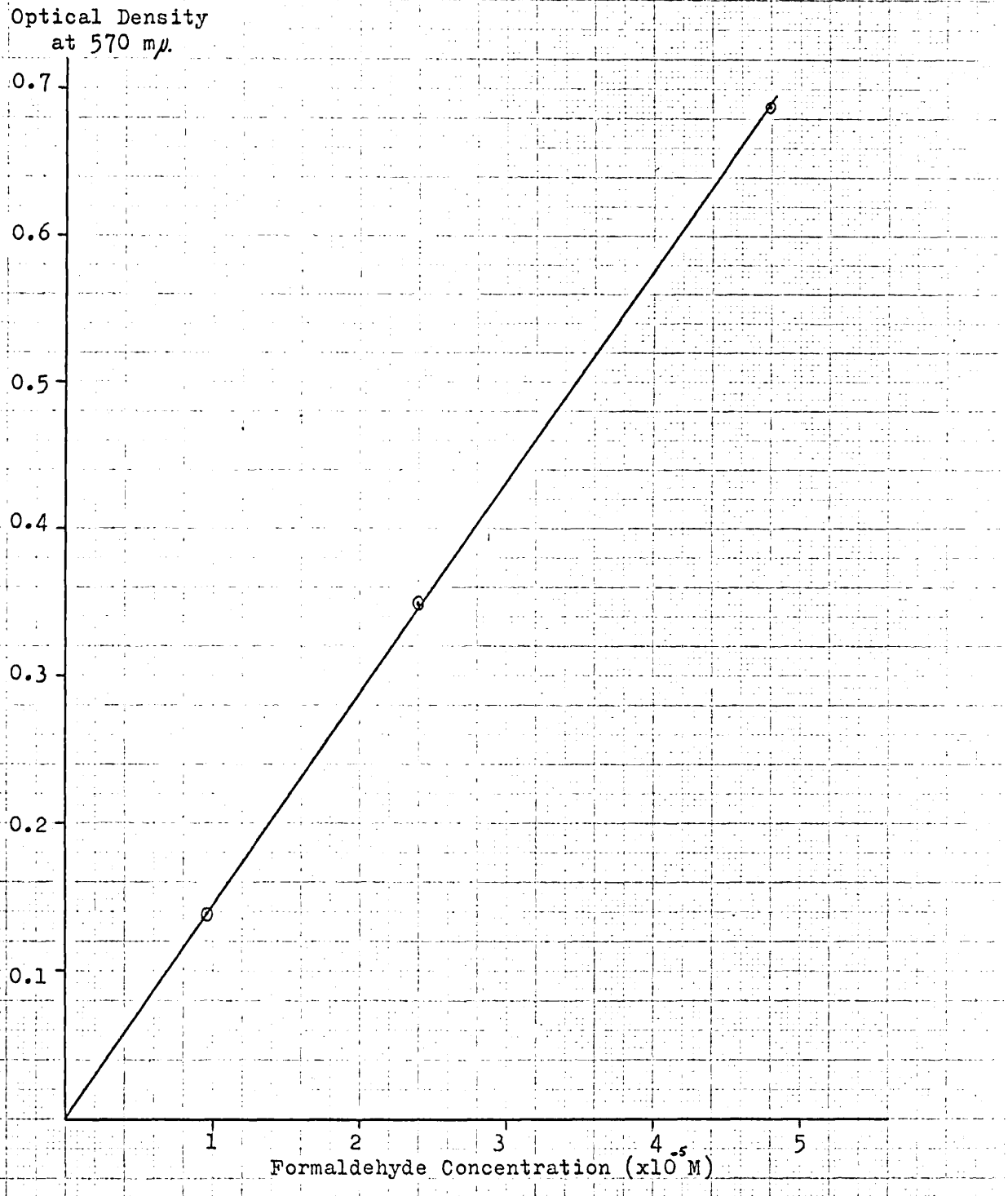
Under the conditions of the test, 2,5-O-methylene-mannitol gave rise to an equimolar quantity of formaldehyde, and by plotting the optical density against this calculated formaldehyde concentration, a linear calibration graph (Graph 19, p.155) was obtained.

Formaldehyde Concentration	Optical Density at 570 mμ.
4.79×10^{-5} M	0.688
2.40×10^{-5}	0.349
0.96×10^{-5}	0.138

The sample solution prepared from Compound A had optical density 0.414, and from the calibration graph this corresponded to a formaldehyde concentration of 2.86×10^{-5}M. The concentration of Compound A in the solution was 2.59×10^{-5}M

$\therefore$ 1 mol. Compound A gave $\frac{2.86}{2.59} = \underline{\underline{1.10}}$ mol. formaldehyde on periodate oxidation.

GRAPH 19. Calibration Graph relating Optical Density Measurements to Formaldehyde Concentration. (Expt. 13.)



Expt. 14. Estimation of the Formic Acid Produced by Periodate Oxidation of Compound A.[47]

A solution of a known weight of Compound A (c. 0.01 g.) was made up in (0.015M) sodium metaperiodate solution (10 ml.). After several hours, 5 ml. were withdrawn with a pipette, and transferred to a small flask. Two drops of ethylene glycol were added to reduce the excess periodate, and the solution was titrated against standard (1.89×10^{-2}N) sodium hydroxide solution, using methyl red as indicator. A titration was also carried out on a similar solution, from which Compound A had been omitted. The difference in the titres was due to the acid produced by periodate oxidation of Compound A.

Time	Weight of A in 10 ml. solution	Titre	Mol. of Acid per mol. of A
2 hr.	0.0088 g.	0.92 ml.	0.93
48 "	0.0088 g.	1.05	0.96

Thus 1 mol. of Compound A gave 1 mol. of Formic Acid on Periodate Oxidation.

Expt. 15. Identification of the Sugar Formed by Periodate Oxidation followed by Acid Hydrolysis of Compound A.

Sodium metaperiodate (0.96 g.) and Compound A (0.3 g.) were dissolved in water (300 ml.), and allowed to stand for 3 hr.

The solution was then freeze-dried, and the residue triturated with boiling chloroform (50 ml.). Insoluble inorganic material was filtered out, and the chloroform extract was rotary evaporated to a syrup (0.23 g.).

The syrup (0.15 g.) was boiled under reflux with a 10% (v/v) solution of acetic acid in water (5 ml.) for 1 hr. The solution was concentrated, by rotary evaporation, and the residual syrup taken up in water (3 ml.). This solution was extracted three times with diethyl ether (2 ml.), and the aqueous phase evaporated to a syrup (0.09 g.). M_s(Molybdate) 0.56. (lit.[48] L-Threose M_s 0.60, D-Erythrose M_s 0.90).

A phenylosazone derivative was prepared by dissolving the syrup (0.05 g.) in water (1 ml.), and adding the reagent (2 ml.), containing water (5 ml.), glacial acetic acid (2 ml.) and phenylhydrazine (2 ml.). This mixture was heated in a boiling water bath for 45 min., and then cooled rapidly under the tap, whereupon crystals of the yellow phenylosazone separated out. The derivative was filtered off, dried, and recrystallized from a 25% methylated spirits/water mixture. m.p. 163-166 (lit.[67] tetrose phenylosazone m.p.164°).

The syrup was examined by GLC (TMS derivative, PPE at 150°). Two peaks were observed, RV 0.25 and 0.28. A standard sample of D-erythrose had RV 0.28 and 0.33, and D-threose

had RV 0.25 and 0.23. A mixture of the sample with D-threose showed only two peaks, whereas, a mixture with D-erythrose gave three peaks.

Expt. 16. Methylation[49] of 2,4-O-Butylidene-D-Glucitol.

2,4-O-Butylidene-D-glucitol (4 g. 1 mol.) was dissolved in DMF (80 ml.) in a 250 ml. conical flask. Silver oxide (16 g. 4 mol.) and freshly distilled methyl iodide (12.8 ml. 12 mol.) were added. The flask was warmed slightly, firmly stoppered (on cooling the slight contraction of the enclosed vapours would hold the stopper in place), and shaken vigourously for 24 hr.

The mixture was filtered, the residue washed with DMF, and the combined filtrate and washings were rotary evaporated to a yellow syrup. On addition of chloroform (100 ml.) silver iodide was precipitated and filtered off. The filtrate was washed three times with water (50 ml.),and then dried over anhydrous sodium sulphate. After filtering off the drying agent and rotary evaporating, a pale yellow syrup (4.2 g.) was obtained.

The syrup was examined by GLC (BDS at 175°), which revealed a mixture of products, the most predominant having RV 11-14. The IR spectrum (NaCl plates) showed a small -OH

band at about 3400 cm.$^{-1}$, indicating that the bulk of the product was fully methylated. There were several peaks in the region 1650 - 1850 cm.$^{-1}$, which were probably due to impurities.

The crude product was distilled under 0.5 mm. Hg pressure, and the following fractions were collected as clear colourless syrups:-

117-127° (1.5 g.)

127-132°

> 132°

GLC showed that the fraction with the lowest b.p. was the most pure. This fraction was redistilled, b.p. 118-122° and, on storage of the syrup, in the deep-freeze, it crystallized m.p. 13-17°. Analysis indicated the tetra-O-methyl derivative of 2,4-O-butylidene-D-glucitol (Found: C,57.3; H,9.9; OMe, 40.1. $C_{14}H_{28}O_6$ requires C,57.5; H,9.6; OMe, 42.4%).

Expt. 17. Methylation[49] of Compound A

Compound A (3.5 g., 1 mol.) was dissolved in DMF (70 ml.) in a 250 ml. conical flask. Silver oxide (14 g., 4 mol.) and freshly distilled methyl iodide (11.2 ml., 12 mol.) were added. The flask was warmed slightly and firmly stoppered, and the contents were shaken vigorously for 24 hr.

The mixture was filtered, the residue washed with DMF and the combined filtrate and washings were rotary evaporated to a yellow syrup. On addition of chloroform (100 ml.), silver iodide was precipitated and filtered off. The filtrate was washed three times with water (50 ml.), and then dried over anhydrous sodium sulphate. After filtering off the drying agent and rotary evaporating, a pale yellow syrup (3.4 g.) was obtained.

The syrup was examined by GLC (BDS at 175°), which revealed a mixture of products, the most predominant with RV 9-10.

The crude product was distilled under 0.2 mm. Hg pressure, and the following fractions were collected as clear colourless syrups:-

94-104° (1.4 g.).

104-111° (1.3 g.).

GLC showed that the fraction with the lower b.p. range was virtually a pure compound with RV 9-10, and the IR spectrum (Na Cl plates) of this fraction was similar to that of tetra-O-methyl-2,4-O-butylidene-D-glucitol. Analysis indicated a tetra-O-methyl-mono-O-butylidene-D-glucitol. (Found: C,58.0; H,9.3; OMe, 40.9; $C_{14}H_{28}O_6$ requires C,57.5; H,9.6; OMe, 42.4%).

Expt. 18. Removal of the Acetal Rings from the Methylated Derivatives of 2,4-O-Butylidene-D-Glucitol and Compound A, by Acid Hydrolysis.

Tetra-O-methyl-2,4-O-butylidene-D-glucitol (0.7 g.) was dissolved in ethanol (4 ml.) and 0.1N aqueous sulphuric acid (60 ml.), and was heated, under reflux, on a boiling water bath for 4 hr. After cooling, the solution was extracted three times with light petroleum (b.p. 40-60°) (20 ml.). The aqueous portion was neutralized by stirring with barium carbonate, and then filtered through celite. The clear filtrate was shaken four times with chloroform (20 ml.), and the combined chloroform extracts were dried over anhydrous sodium sulphate. Having removed the drying agent, the solution was evaporated to a syrup (0.15 g.).

The tetra-O-methyl derivative of Compound A was hydrolysed in the same manner, and a syrup (0.2 g.) was obtained.

IR spectra (NaCl plates) of the two hydrolysates were similar, and showed strong bands due to hydroxyl groups, at c.3400 $cm.^{-1}$. The products were analysed by GLC (TMS derivatives, PPE at 175°), and both were seen to consist of single compounds. That obtained from the 2,4-acetal had RV 1.16, and was barely separable from the product from Compound A RV 1.14. Since neither of the syrups could be crystallized, no further purification was attempted.

Expt. 19. To Establish, by means of Periodate Oxidation, whether the Hydrolysed Tetra-O-Methyl Derivative of Compound A has a Pair of Vicinal Hydroxyl Groups.

The method used has already been described in Expt. 12 (p.150). Found: Mol. periodate consumed per mol. of hydrolysed tetra-O-methyl Compound A. 0.93 (after 3 hr.,) 0.89 (after 4 hr.).

As a check, the oxidation was also carried out on the sample of hydrolysed tetra-O-methyl-2,4-O-butylidene-D-glucitol. Found: Mol. periodate consumed per mol. of sample 0.03 (after 2.5 hr.), 0.04 (after 5 hr.).

Thus the hydrolysed tetra-O-methyl derivative of Compound A contained a pair of vicinal hydroxyl groups.

Expt. 20. Attempted Preparation of the Bis-triphenylmethyl Derivative of Compound A.

(a) Compound A (0.3 g. 1 mol.) and triphenylchloromethane (0.68 g. 2 mol.) were dissolved in dry pyridine (3 ml.) and the solution was maintained at room temperature for 24 hr. Crystals, presumably of pyridine hydrochloride, separated out. The mixture was then poured into iced water (60 ml.) whereupon an oil precipitated which could not be induced to solidify after standing for several days with frequent stirring and scratching. The aqueous layer was decanted off, and the oil washed with a little cold aqueous ethanol (50% v/v). All

attempts to crystallize the oil from aqueous ethanol, were unsuccessful.

(b) Compound A (0.1 g. 1 mol.) and triphenylchloromethane (0.26 g., 2.2 mol.) were dissolved in dry pyridine (3 ml.), and heated, under reflux, over a boiling water bath for 3 hr. The solution was poured into iced water (20 ml.) and stirred, whilst an oil precipitated out and partially solidified. When the aqueous layer was decanted away a sticky semi-solid mass remained in the beaker. This was washed with water and dissolved in chloroform (10 ml.). The chloroform solution was dried over anhydrous sodium sulphate, and evaporated to a syrup (0.3 g.) which crystallized, to some extent, on cooling.

Attempts to recrystallize the syrup from petroleum ether (b.p. 60-80°), and from mixtures of diethyl ether with petroleum ether (b.p. 40-60°), failed. Crystals were however, obtained from a solution of the syrup in aqueous ethanol. They had m.p. 158-160°, and the IR spectrum ('Nujol' mull, Na Cl plates) was identical to that of triphenylcarbinol. The m.p. of a mixture of the substance with triphenylcarbinol was not depressed.

Expt. 21. Preparation of Bis-triphenylmethyl-Diacetate Derivative of Compound A.

Compound A (1 g., 1 mol.) and triphenylchloromethane (2.4 g. 2 mol.) were dissolved in dry pyridine (20 ml.).

The solution was allowed to stand for 25 hr. at room temperature, during which time crystals of pyridine hydrochloride separated out, and then poured into iced water (100 ml.). An oil precipitated to form a white emulsion, which was stored in a refrigerator for several days with occasional stirring and scratching. A white sticky mass adhered to the sides of the beaker, but it did not set to a solid. The aqueous phase was decanted off, and the residue washed with cold water, and then dissolved in diethyl ether (25 ml.). After drying over anhydrous sodium sulphate, and removing the drying agent, the ether solution was evaporated to a syrup (3 g.).

The syrup was dissolved in a mixture (10 ml.) of acetic anhydride (1 vol.) and pyridine (2 vol.) and was left at room temperature. After 2.5 hr. the solution was poured into iced water (100 ml.), whereupon a white oil precipitated, which set to a semi-solid mass when left to stand in the refrigerator for some days. The product was filtered off and washed with water.

The sticky mass was dissolved in ethanol, and water was added, dropwise, until the solution was faintly opalescent. After leaving for some hours and occasionally scratching the interior sides of the vessel, a white solid separated out (0.2 g.). This was recrystallized, three times, from ethanol

to yield a fine crystalline substance with m.p. 144-145° (Found: C,77.2; H,6.3; $C_{52}H_{52}O_8$ requires C,77.6; H,6.5%). An IR spectrum of the sample ('nujol' mull) showed no bands due to hydroxyl groups, but a sharp peak at 1740-1760 cm.$^{-1}$ was probably due to the acetate groups. The acetyl content could not be estimated owing to the scarcity of the sample, and its poor solubility in aqueous alcoholic alkalis.

The liquors, from which the sample was first crystallized were evaporated to a white sticky mass (1.8 g.) which was redissolved in the ethanol/water solvent as before. Solid material which separated out was recrystallized from aqueous ethanol, and had m.p. 159-161°. The IR spectrum ('nujol' mull, Na Cl plates) of this substance was totally different to that of the previous fraction. It showed a strong OH band at 3400-3500 cm.$^{-1}$, and generally bore resemblance to the IR spectrum of triphenylcarbinol. A mixed m.p. determination of this sample with an authentic specimen of triphenylcarbinol suffered no depression.

Finally, the liquors were left standing for about two weeks. More solid material (c. 1.4 g.) separated out, with m.p. (crude) from 80°. The IR spectrum ('nujol' mull, Na Cl plates) was very complex; having bands characteristic of both of the previous fractions.

Expt. 22. Hydrolysis of Butylidene-D-Glucitols (3.18×10^{-2}M) in N Aqueous Hydrochloric Acid at 26°, Followed Polarimetrically and with GLC.

(a) Compound A

Compound A (0.375 g.) was dissolved in a little water in a 50 ml. standard flask. 5N aqueous hydrochloric acid (10 ml.) was added, the clock was started, and the solution was immediately made up to the mark with water. The solution was maintained at 26°, and the reaction followed polarimetrically, (Table 14(a), p.218, Graph 10, p. 64).

After 5, 10, 20, 40 and 200 min., aliquots (5 ml.) were removed from the reaction mixture, and neutralized with aqueous sodium hydroxide. The samples were each freeze-dried, and then triturated with warm pyridine (4 ml.). Insoluble material was filtered off, and from the filtrates TMS derivatives were prepared for examination by GLC (PDE at 175°) (see Fig. xxi, p. 66).

The reaction mixture was stored, and a final sample was taken after several days. The gas chromatogram of this mixture, was similar to that obtained in the final stages of the reaction of equimolar quantities of n-butyraldehyde and D-glucitol in N aqueous hydrochloric acid. (Fig. xiv, p.45).

(b) 2,4-O-Butylidene-D-Glucitol

A solution of 2,4-O-butylidene-D-glucitol (0.188 g.) was made up in N aqueous hydrochloric acid (25 ml.), and the change in optical rotation at 26° was followed as before. (Table 15 (a) p.219, Graph 10 p.64).

After 1 hr., 3 hr., and 54 hr., aliquots (4 ml.) were removed from the reaction mixture, neutralized and evaporated to dryness. TMS derivatives were prepared from the pyridine extracts of these residues, and examined by GLC (PPE at 175°). The chromatograms showed a gradual decrease in concentration of the 2,4-acetal paralleled by an increase in concentration of D-glucitol, and also the formation of other monoacetals. The final chromatogram was of the same form as that obtained after the hydrolysis of Compound A.

Expt. 23. Hydrolysis of Butylidene-D-Glucitols (3.18×10^{-2}M) in N Aqueous Hydrochloric Acid at 26° Followed Spectrophotometrically.

(a) Compound A

Compound A (0.375 g.) was hydrolysed in N aqueous hydrochloric acid (50 ml.) at 26°, as in Expt. 22 (a). After convenient time intervals, aliquots were removed from the reaction vessel, and their optical densities measured at 281 mμ. By means of a calibration graph, optical density

data was converted into values of n-butyraldehyde concentration, and hence the percentage of hydrolysis at given times could be estimated. (Table 14 (b), p.218, Graph 10, p.64).

(b) 2,4-O-Butylidene-D-Glucitol

2,4-O-Butylidene-D-Glucitol (0.375 g.) was hydrolysed in N aqueous hydrochloric acid (50 ml.) at 26°, and the reaction was followed spectrophotometrically, in the same way as with Compound A. (Table 15(b), p.219, Graph 10, p.64).

Expt. 24. To Investigate the Reactivity of Compound A (3.4×10^{-2}M) in Dry DMF Solution, in the Presence of HCl (0.25N) at 25°.

Compound A (0.16 g.) was dissolved in some dry DMF in a 20 ml. standard flask. A concentrated (5.6N) solution of hydrogen chloride in DMF (0.9 ml.) was added from a burette, and the clock was started. The solution was immediately made up to the mark with DMF, and the change in optical rotation with time was followed at 25° (Table 16, p.220).

Periodically, aliquots (1 ml.), were removed from the solution, and neutralized with dry pyridine (1 ml.). TMS derivatives for GLC were prepared directly from these samples. The gas chromatograms showed that Compound A was slowly converted into other monoacetals, principally 2,4-O-butylidene-D-glucitol (RV 4.3) (Fig. xxii p.72).

III. BENZYLIDENE-D-GLUCITOLS

Expt. 25. Analysis of the Mixture at Particular Times during the Acid Catalysed Reaction of Benzaldehyde with D-Glucitol in Aqueous DMF

The reaction was conducted in DMF containing water (20%) and hydrochloric acid (0.5N), as described in Expt. 1(e) (p.137). After 15 min., 60 min., and 24 hr. (Graph 4 p.28), aliquots (2 ml.) were removed from the reaction mixture and neutralized with aqueous sodium hydroxide. The solutions were each rotary evaporated to dryness, and the organic constituents of the residues extracted into pyridine (10 ml.).

TMS derivatives were prepared from the pyridine solutions, and analysed by GLC using an SE-30 stationary phase at 175°. The chromatograms showed that each sample contained D-glucitol, and several monoacetals which were incompletely resolved, within the range RV 3.5-5.0. In the first two samples, the most prominent monoacetal peak had RV c.3.8. A shoulder on this peak, with larger RV was very much increased in size in the sample taken after 24 hr.

A sample of 2,4-O-benzylidene-D-glucitol TMS gave a peak of RV 4.51.

Expt. 26. Isolation of Compound B from a Mixture Taken from the Early Stages of Reaction of Benzaldehyde and D-Glucitol.

Benzaldehyde (2 ml.) and D-Glucitol (3.6 g.) were dissolved in DMF (10 ml.) and water (6 ml.). 5N aqueous hydrochloric acid (2 ml.) was added and a clock was started. After 15 min., the reaction was stopped by neutralizing the solution with aqueous sodium hydroxide. The solution was rotary evaporated to a syrup which was washed several times, by shaking with diethyl ether, to remove residual benzaldehyde and DMF. This syrup was warmed with ethanol (50 ml.), and the precipitated sodium chloride was filtered off. The filtrate was then rotary evaporated to a syrup (5.5 g.), which was analysed by GLC (TMS derivatives, SE-30 at 175°). The principal monoacetal component of the mixture had RV 3.72.

A glass column (5 cm. diameter) was packed with aluminium oxide (125 g.) in ethanol. The syrupy mixture, prepared above, (5 g.) was dissolved in warm ethanol (25 ml.) and poured on to the column. The column was eluted first with ethanol (25 ml.), and then with ethanol/water mixtures of 96% (v/v) (50 ml.), 94% (v/v) (50 ml.) and 92% (v/v) (200 ml.), whilst fractions (25 ml.) were collected and evaporated to dryness.

Early fractions contained small amounts of oily, ether-soluble material (probably traces of benzaldehyde, DMF etc.).

The first 0.5 g. of solid material was pure Compound B (RV 3.73). Further material from the column, was increasingly contaminated with other monoacetals and was purified by a second fractionation process.

Compound B was recrystallized from ethyl acetate (0.5 g. in 20 ml.) as very small, colourless crystals m.p. 123-127°. (Found: C,58.4; H,6.9; $C_{13}H_{18}O_6$ requires C,57.8; H,6.7%). By repeatedly recrystallizing the sample, the m.p. was raised to 131-133°. The combined liquors, from the recrystallizations, were evaporated to dryness, and the residue, when crystallized from ethyl acetate had m.p.113-119°. Chromatographically, this sample appeared to be a single substance (RV 3.73), as did all samples of Compound B having m.p. within the range 123-133°. Paper ionophoresis (Borate) did not reveal any variation in samples of Compound B with differing melting points. M_s = 0.49.

Expt. 27. Hydrolysis of Compound B, and Identification of the Products.

A solution of Compound B (0.2 g.) in water (3 ml.) was warmed with Amberlite IR-120 (H^+) resin (1 ml.), over a boiling water-bath, for 0.5 hr., during which time a strong odour of benzaldehyde developed. The resin was then filtered off, washed with a little ethanol and the washings were added to the filtrate.

The filtrate was examined by paper ionophoresis (metavanadate),[56,57] along with standard samples of glucitol, mannitol and dulcitol, at 2500 v for 1.5 hr., and the ionophoretogram was developed by heating the paper in the oven at 120° for 10 min. The hexitols appeared as blue spots and were well separated. The sample from the hydrolysis of Compound B migrated to the same extent as glucitol.

To the filtrate was added a solution (3 ml.) containing phenylhydrazine hydrochloride (0.5 g.) and sodium acetate trihydrate (1 g.) in water (5 ml.). A cream precipitate separated. The mixture was warmed for 15 min. over a water bath, cooled and filtered, and the crude derivative was then recrystallized from light petroleum (b.p. 60-80°) (10 ml.). The m.p. of the substance was 154-156°, and that of a mixture with benzaldehyde phenylhydrazone was the same.

Expt. 28. To Determine the Number of Pairs of Vicinal Hydroxyl Groups per Molecule of Compound B, by Periodate Oxidation.

The method was identical to that used in Expt. 12 (p. 150) for Compound A. Oxidation was followed over a period of 30 hr. and the results have been tabulated below.

Time	Mol. IO_4^- per mol. of Compound B
1.0 hr.	1.90
3.0	1.94
5.0	1.94
6.5	1.96
11.3	2.13
22.0	2.33
30.0	2.52

Thus Compound B contained two pairs of vicinal hydroxyl groups. Some overoxidation also took place.

Expt. 29. Estimation of the Formaldehyde Liberated by Periodate Oxidation of Compound B.

The method used has been described in detail in Expt.13 (p.153).

Found: Mol. formaldehyde liberated per mol. of Compound B, 0.95.

Expt. 30. Estimation of the Formic Acid Produced by Periodate Oxidation of Compound B.

The same method was employed here as for Compound A (Expt. 14, p.156), and the results are shown below.

Time	Mol. of Acid per mol. of B
1.5 hr.	0.94
3.5	0.97
8.0	1.05
24.0	1.46

Thus 1 mol. of Compound B produced initially 1 mol. of formic acid.

Expt. 31. Identification of the Sugar Formed by Periodate Oxidation, Followed by Acid Hydrolysis of Compound B

Sodium metaperiodate (0.8 g.) and Compound B (0.5 g.) were dissolved in water (250 ml.), and the solution was stored in the dark for 2 hr. 0.1N Aqueous sodium hydroxide (19 ml.) was added to neutralize the acid produced by the oxidation, and the solution was then freeze-dried. The white solid residue was extracted twice with hot chloroform (25 ml.), and, after filtering off the insoluble material, the extract, on evaporation, yielded a syrup (0.4 g.).

The syrup (0.2 g.) was dissolved in a 10% (v/v) solution of acetic acid in water (5 ml.), and boiled under reflux for 1 hr. The solution was then concentrated, by rotary evaporation, to a sticky semicrystalline mass. A solution of this

residue in water (5 ml.) was extracted three times with diethyl ether (2 ml.), to remove benzaldehyde and benzoic acid, and the aqueous layer was evaporated to a pale yellow syrup (0.09 g.) M_s (molybdate) 0.54 (lit.[48] L-Threose M_s 0.60, D-Erythrose M_s 0.90).

When examined by GLC (TMS derivative, PPE at 150°) the syrup gave two peaks with RV's identical to those of the tetrose obtained by a similar treatment of Compound A (Expt.15, p.156). A mixture of the sample with D-erythrose gave three peaks. Thus the sugar formed must have been L-Threose.

Expt. 32. Methylation[49] of Compound B.

Compound B (4 g., 1 mol.) was dissolved in DMF (120 ml.) in a 250 ml. stoppered conical flask. Silver oxide (32 g. 9.3 mol.) and freshly distilled methyl iodide (25 ml. 27.1 mol.) were added. The flask was warmed slightly and then firmly stoppered such that, on cooling, the small contraction of the enclosed vapour would hold the stopper in place. The mixture was then shaken vigorously for 24 hr.

Solid material was filtered off, and washed with DMF, and the combined filtrate and washings were rotary evaporated to a yellow semi-solid mass. On addition of chloroform (c. 75 ml.), silver iodide was precipitated and, after

filtering, the chloroform solution was washed four times with water (50 ml.) and then dried over anhydrous sodium sulphate. The drying agent was removed by filtration and the clear solution evaporated to a pale yellow syrup (3.8 g.).

GLC of the syrup (SE-30 at 175°) revealed the main component with RV 1.14, and several minor components having larger RV's.

Since the crude product could not be induced to crystallize from light petroleum (b.p. 60-80°), it was distilled 'in vacuo'. The following fractions were collected as clear colourless syrups under 0.03 mm. Hg pressure.

137-150°	(1.6 g.)
150-162°	(0.9 g.)

Owing to the high viscosity of the distillate, losses within the apparatus were considerable.

The fractions were analysed by GLC (SE-30 at 175°) and shown to consist purely of a compound with RV 1.16. Elemental analysis of the first fraction indicated it to be the fully methylated derivative of a mono-O-benzylidene-D-glucitol. (Found: C,61.6; H,7.8; OMe, 37.1. $C_{17}H_{26}O_6$ requires C,62.6; H,8.0; OMe, 38.0%).

Expt. 33. Removal of the Acetal Ring from the Methylated Derivative of Compound B, by Acid Hydrolysis.

Fully methylated Compound B (0.6 g.) was dissolved in ethanol (4 ml.) and 0.1N aqueous sulphuric acid (50 ml.) and heated on a boiling water-bath for 4 hr. After cooling, the solution was extracted, four times, with light petroleum (b.p. 60-80°) (20 ml.), to remove benzaldehyde, and then neutralized with excess of barium carbonate. The suspended solid material was separated by filtration through celite, and the filtrate was extracted, five times, with chloroform (20 ml.). Having dried the chloroform extract over anhydrous sodium sulphate, it was rotary evaporated to a syrup (0.15 g.).

Analysis of the product by GLC (TMS derivative, FIE at 175°) showed it to be a single substance RV 1.14. The infra-red spectrum (NaCl plates) was identical to that of hydrolysed tetra-O-methyl-Compound A, prepared in Expt. 18 (p.161).

Expt. 34. To Establish, by means of Periodate Oxidation, whether the Hydrolysed Tetra-O-Methyl Derivative of Compound B has a Pair of Vicinal Hydroxyl Groups.

The method used has been described in Expt. 12 (p.150) Found: Mol. periodate consumed per mol. of hydrolysed

tetra-O-methyl Compound B: 0.86 (after 1 hr.), 0.91 (after 3 hr.), 0.92 (after 7 hr.).

The fact that the sample was a syrup, and received no purification, probably accounted for the slightly low figures. Thus the hydrolysed tetra-O-methyl derivative of Compound B contained one pair of vicinal hydroxyl groups.

Expt. 35. To Follow the Hydrolysis of Compound B (3.7×10^{-2}M) in Aqueous Hydrochloric Acid at 26°.

Compound B (0.2 g.) was dissolved in a little water in a 20 ml. standard flask. The reaction was started by addition of N aqueous hydrochloric acid (2 ml.), and immediately the volume was made up to the mark with water to give a 0.1N acid solution. In the same way, hydrolysis of Compound B was also conducted in 0.05N acid solution. Both reactions were followed polarimetrically at 26°, and the data has been shown in Table 17 (p. 220) and Graph 12 (p. 90).

Aliquots (1 ml.) were withdrawn from the reaction in 0.05N acid after 5, 10, 20 and 40 min., neutralized with aqueous sodium hydroxide, and freeze dried. The residues were extracted with pyridine (1 ml.), and TMS derivatives were prepared from the pyridine solutions for analysis by GLC (SE-30 at 175°). The gas chromatograms have been shown in

Fig. xxvii (p.91). The pyridine extracts were also examined by paper ionophoresis (Borate). All samples showed, in addition to D-glucitol and Compound B (M_s 0.49), traces of another monoacetal which migrated to the same extent as 2,4-O-benzylidene-D-glucitol (M_s 0.57).

Expt. 36. To Investigate the Reactivity of Compound B (3.5×10^{-2}M) in Dry DMF Solution, in the Presence of HCl (0.25N) at 25°.

A solution of Compound B (0.19 g.) in DMF (20 ml.) containing dissolved hydrogen chloride (0.25N) was made up according to the procedure described in Expt. 24 (p.168) for Compound A. The reaction was followed polarimetrically at 25° (see Table 18, p.221).

After 10, 55, 155 min. and 10 hr., aliquots (1 ml.) were taken from the reaction mixture and neutralized with pyridine. These samples were analysed by GLC (TMS derivatives, SE-30 at 175°), and the chromatograms have been reproduced in Fig. xxviii (p.94).

Paper ionophoresis (Borate) of the samples showed that the decrease in concentration of Compound B (M_s 0.49), during the reaction, was accompanied by the formation of two more monoacetals with M_s 0.57 and >0.61.

IV. METHYLENE-D-GLUCITOLS

Expt. 37. To Follow the Reaction of Formaldehyde with D-Glucitol in Aqueous Hydrochloric Acid, by Titrametric Estimation of Formaldehyde.[66]

An equimolar mixture (0.25M) of the reactants, in 2N aqueous hydrochloric acid (100 ml.), was prepared as in Expt. 1 (f) (p. 137) and maintained at 25°. After periods of several hours, aliquots (5 ml.) were withdrawn from the mixture and run into N aqueous sodium hydroxide (20 ml.). Standard (0.1N) iodine solution (50 ml.) was added and the pale yellow solution was allowed to stand for about 4 min., whilst the formaldehyde was oxidized by hypoiodite. The solution was then acidified with dilute hydrochloric acid in order to liberate unused iodine, which was titrated against standard sodium thiosulphate solution using sodium starch glycollate as indicator.

Since, 0.1N Iodine solution (1 ml.) ≡ Formaldehyde (0.0015 g.) the concentration of formaldehyde in the mixture could be estimated, and, knowing the initial concentration (7.5 g/l), the percentage of formaldehyde reacted at a particular time could be deduced. (Table 12(c) p. 216, Graph 13 p. 97).

Expt. 38. Analysis of the Mixture at Particular Times during the Reaction of Formaldehyde with D-Glucitol in Aqueous Hydrochloric Acid.

The mixture was prepared in 2N aqueous hydrochloric acid (25 ml.) as described in Expt. 1(f) (p. 137) and the reaction was allowed to proceed at 25°. After 2 hr. (< 1%), 45 hr. (17%) and 139 hr. (35%) aliquots (1 ml.) were removed and neutralized with aqueous sodium hydroxide. The solutions were rotary evaporated to dryness, triturated with pyridine (4 ml.) and, having filtered off the insoluble material, TMS derivatives were prepared from the pyridine extracts.

GLC of the TMS derivatives was carried out using the PTE column at 175°, and the peaks due to the reaction products in the gas chromatograms have been shown in Fig. xxix (p. 99). For the samples taken from the early stages of reaction, the most prominent peak had RV 2.36 and a smaller peak was of RV 2.00. As the reaction progressed, a compound slowly developed having a peak of RV 4.16. A standard sample of 2,4-O-methylene-D-glucitol TMS was also chromatographed, and it gave a single peak with RV 4.10.

A mixture obtained from the reaction after 25 hr. (10%) contained, besides D-Glucitol, traces of material having

R_F c.0.4 (B/E/W). This mixture (0.5 g.) was placed on a column of Whatman CF. 11 cellulose (75 g.), packed in a solvent of n-butanol saturated with water, and was eluted with this solvent. Fractions were collected, and those containing material with R_F c.0.4 were combined and evaporated to a syrup (0.05 g.). Borate ionophoresis of the syrup revealed at least five compounds with M_s values ranging from 0.6-1.0. Two or more components also migrated on ionophoresis in molybdate buffer M_s 0.9 and 1.0.

V. BUTYLIDENE DERIVATIVES OF COMPOUNDS RELATED TO D-GLUCITOL

Expt. 39. Preparation of 1-Deoxy-D-Glucitol[62]

Toluene-p-sulphonylhydrazide (9.5 g.) was dissolved in warm ethanol (75 ml.), and the solution was added to a solution of D-glucose (9 g.) in 50% aqueous acetic acid (20 ml.). The mixture was allowed to stand, at room temperature, for 6 hr. whilst crystals of D-glucose-toluene-p-sulphonylhydrazone (tosylhydrazone) separated out. These crystals were filtered off, washed with water, ethanol and diethyl ether and dried (12 g. 69%) m.p. c.165° (lit.[68] m.p.170°).

A suspension was made of D-glucose-tosylhydrazone (5 g.) in methanol (50 ml.), and to this was added a suspension of potassium borohydride (3 g.) in methanol (50 ml.). On warming the mixture, there was vigorous effervescence as hydrogen was liberated, and the suspended material gradually dissolved. The solution was boiled under reflux overnight.

Methanol was removed by rotary evaporation, and the residual syrup was taken up in water (100 ml.). IR-120(H^+) resin (40 ml.) was then added, to destroy any excess borohydride and to deionize the solution, and after about 10 min. the solution was filtered. The filtrate was rotary evaporated to a crystalline sludge, dissolved in methanol (30 ml.) and

re-evaporated to a syrup. This process was repeated five times, after which a flame test on a sample of the syrup revealed that the borate ions had been removed as volatile methyl borate.

Paper chromatography of the syrup (B/E/W) showed that it contained three main constituents: D-glucose R_G 1.0 1-deoxy-D-glucitol R_G 1.75 and D-glucose-tosylhydrazone R_G 3.0 and these were separated on a cellulose column in the following way.

Cellulose powder, Whatman CF.11 (200 g.) was packed into a glass column (4 cm. diameter) in the form of a thin slurry with n-butanol saturated with water. A solution of the mixture, prepared above, in saturated aqueous n-butanol (40 ml.) was poured on to the column and allowed to pass into the cellulose. The column was then eluted with the same solvent, and fractions (25 ml.) were collected and examined by paper chromatography (B/E/W). The components of the mixture were found to be well separated, and fractions containing material with R_G c.1.75 were evaporated to dryness to yield a white powdery mass. After triturating with a minimum of ethanol, the crude 1-deoxy-D-glucitol was filtered off. (1.2 g. 50%).

The product was recrystallized from ethyl acetate (1 g. in 500 ml.), and obtained as crystals of extraordinary beauty

m.p. 127-129°. The melting point was unchanged when the sample was mixed with an authentic specimen of 1-deoxy-D-glucitol.

An acetate derivative was prepared by dissolving the product (0.05 g.) in a solution (2 ml.) consisting of acetic anhydride (1 vol.) and pyridine (2 vol.). After standing for 4 hr. at room temperature, the solution was evaporated to half-bulk and then poured into iced water (15 ml.). Oily droplets separated, and solidified after scratching for a few minutes. The crude derivative (0.08 g. 71%) was filtered off and recrystallized from a 25% (v/v) solution of ethanol in water m.p. 103-104° (lit.[62] 1-deoxy-D-glucitol-penta-acetate m.p. 103-104°).

Expt. 40. Preparation of 2-Deoxy-D-Glucitol.

2-Deoxy-D-glucose (α and β) (20 g.) and sodium borohydride (0.4 g.) were dissolved in water (20 ml.), and the solution was allowed to stand for 24 hr. at room temperature. Excess borohydride was then destroyed, and sodium ions removed, by addition of Amberlite IR-120(H^+) resin. After filtering out the resin, the solution was evaporated to a syrup which was dissolved in methanol (10 ml.) and re-evaporated six times in order to remove borate ions as methyl borate. The final syrup was of a deep red colour and crystallized on standing. This product was recrystallized from ethanol (25 ml.), having first decolourized the solution with activated charcoal. A white crystalline material (1.4 g. 69%) was obtained m.p. 105-106° (lit.[69] 2-deoxy-D-glucitol m.p. 104-106°) R_F 0.29 (B/E/W).

An acetate derivative was prepared by dissolving the product (0.05 g.) in a solution (2 ml.) consisting of acetic anhydride (1 vol.) and pyridine (2 vol.). After standing for 4 hr. at room temperature, the solution was evaporated to low bulk and poured into iced water (15 ml.). Oily droplets precipitated, and very slowly dissolved in the water. After 2 hr. some droplets began to solidify, and when the volume of water was reduced, by evaporation, a white solid

material separated out which was filtered off (0.08 g. 71%). The crude derivative was recrystallized from a 10% solution of ethanol in water m.p. 83.5-84.5° (lit.[69] 2-deoxy-D-glucitol-penta-acetate m.p. 86-87°).

Expt. 41. Preparation of 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 the solution was allowed to stand overnight at room temperature. Excess borohydride was then destroyed, and sodium ions removed from the solution, by addition of Amberlite IR-120(H^+) resin (20 ml.). After filtering out the resin, the solution was rotary evaporated to a crystalline sludge, which was dissolved in methanol (20 ml.) and re-evaporated, six times, in order to remove the borate ions as methyl borate. 3-O-Methyl-D-glucitol was finally obtained in the form of a colourless syrup (1.9 g.) R_F 0.26 (B/E/W), RV 1.12 (TMS derivative, PPE at 175°.

Expt. 42. To Follow the Reactions of n-Butyraldehyde with 1-Deoxy, 2-Deoxy and 3-O-Methyl-D-Glucitols in Aqueous Hydrochloric Acid at 25° by means of Polarimetry and GLC.

For each reaction the reactants were initially in equimolar proportions (0.1M). The reactions were carried out at 25° in 0.5N aqueous hydrochloric acid, following the procedure described in Expt. 1 (p.136). Polarimetric data has been assembled in Tables 3(a), 4(a) and 5 (pp. 207-)

Periodically, aliquots (0.5ml.) were withdrawn from the reaction mixtures, neutralized with aqueous sodium hydroxide, and rotary evaporated to dryness. The residues were triturated with pyridine (1 ml.), filtered, and the filtrates were used to prepare TMS derivatives for analysis by GLC (FFE at 175°). The results have been described in the discussion.

Expt. 43. To Follow the Reactions of n-Butyraldehyde with D-Glucitol, and its 1- and 2-Deoxy Derivatives in Aqueous Hydrochloric Acid at 25°, by Spectrophotometric Estimation of n-Butyraldehyde.

For each reaction, the reactants were initially in equimolar proportions (0.1M). The reactions were conducted at 25° in 0.5N aqueous hydrochloric acid, and followed spectrophotometrically as described in Expt. 5 (p.141). Variation of n-butyraldehyde concentration with time has been shown in Tables 1(e), 3(b) and 4(b) (pp.206-).

Expt. 44. Isolation of Compound C from a Reaction Mixture of n-Butyraldehyde and 1-Deoxy-D-Glucitol at Equilibrium.

n-Butyraldehyde (1.74 g.) and 1-deoxy-D-glucitol (4.0 g.) were dissolved in water (80 ml.), and 5N aqueous hydrochloric

acid (20 ml.) was added. After standing for 24 hr. at room temperature, the reaction mixture was neutralized with aqueous sodium hydroxide, and then evaporated to a solid mass which was triturated with warm ethanol (100 ml.). Insoluble material was filtered off, and the filtrate evaporated to a solid residue (5.0 g.).

This residue was leached with boiling benzene (50 ml.), and the hot solution was decanted into another vessel and allowed to cool, whereupon a crystalline deposit separated. The crude product (2.3 g. 43%) was filtered out and recrystallized twice from benzene (150 ml.) m.p. 128-130° RV 2.02 (TMS derivative, ECC at 175°), R_F 0.85 (MEK/H_2O) $[\alpha]_{Hg\ 5461}^{25}$ -1.2° (c. 0.8 g. in H_2O) (Found: C,54.6; H,9.0. $C_{10}H_{20}O_5$ requires C,54.5; H,9.1%).

Expt. 45. Isolation of Compound D from a Mixture taken from the Early Stages of Reaction of n-Butyraldehyde and 1-Deoxy-D-Glucitol.

n-Butyraldehyde (0.29 g.) and 1-deoxy-D-glucitol (0.66 g.) were dissolved in water (36 ml.). The reaction was started by addition of 5N aqueous hydrochloric acid (4 ml.), and stopped after 10 min., by neutralizing with aqueous sodium hydroxide. The solution was evaporated to a solid mass, and then triturated with warm ethanol (25 ml.) and filtered. On

evaporation of the filtrate, a syrup (0.85 g.) was obtained, and GLC of the syrup (TMS derivatives, PPE at 175°) showed that the main product was Compound D, RV 1.19.

A glass column (2.5 cm. diameter) was packed with aluminium oxide (50 g.) in ethanol. The syrup was dissolved in ethanol (10 ml.), and poured on to the column. The column was eluted first with ethanol (40 ml.), and then with ethanol/water mixtures of 99% (v/v) (100 ml) and 98% (v/v) (150 ml.), whilst fractions (25 ml.) were collected, rotary evaporated to dryness, and analysed by GLC. The first 0.05 g. of crystalline material was almost pure Compound D RV 1.22. It was recrystallized from a solvent pair (30 ml.) containing diethyl ether (3 vol.) and light petroleum (b.p. 40-60°) (7 vol.), and obtained in the form of light silky crystals (0.03 g.). m.p. 88-90° R_F 0.88 (MEK/H_2O) (Found: C,54.7; H,9.0. $C_{10}H_{20}O_5$ requires C,54.5; H,9.1%).

Expt. 46. Hydrolysis of Compound C and Identification of the Products.

To a solution of Compound C (0.05 g.) in water (50 ml.) was added Amberlite IR-120(H^+) resin (2 ml.), and the mixture was heated for 2.5 hr. over a boiling water-bath. After filtering off the resin the filtrate was evaporated to a crystalline residue (0.04 g.) which, on recrystallizing from

ethyl acetate (20 ml.) had m.p. 128-130°. This sample was shown to be 1-deoxy-D-glucitol by the fact that the m.p. of its mixture, with an authentic specimen was not depressed.

A further 0.05 g. of Compound C was added to a 0.25% solution (20 ml.) of 2,4-dinitrophenylhydrazine in 2N aqueous hydrochloric acid. The carbonyl fragment, released by hydrolysis, formed a derivative which appeared as a yellow precipitate, and this was coagulated by warming for 0.5 hr. over a water bath. After cooling, the crude derivative was filtered out and recrystallized twice from methylated spirits (3 ml.) m.p. 120-121°. The m.p. of a mixture of the sample with n-butyraldehyde-2,4-dinitro-phenylhydrazone was also 120-121°.

Expt. 47. To Determine the Number of Pairs of Vicinal Hydroxyl Groups per Molecule of Compounds C and D, by Periodate Oxidation.

The method was identical to that used in Expt. 12 (p. 150) for Compound A.

Found: Mol. periodate consumed per mol. of Compound C 1.07 (after 1 hr.), 1.05 (after 3 hr.) and 1.00 (after 24 hr.)

Found: Mol. periodate consumed per mol. of Compound D 2.12 (after 1 hr.), 2.11 (after 3 hr.) and 2.12 (after 24 hr.).

Thus Compounds C and D contained one and two pairs of vicinal hydroxyl groups respectively.

Expt. 48. Estimation of the Formaldehyde Liberated by Periodate Oxidation of Compounds C and D.

The method used has been described in Expt. 13 (p. 153)

Found: Mol. of formaldehyde liberated per mol. of Compound C; 0.94.

Found: Mol. of formaldehyde liberated per mol. of Compound D; 1.01.

Expt. 49. Estimation of the Formic Acid Produced by Periodate Oxidation of Compounds C and D.

The same method was used as for Compound A (Expt. 14, p. 156).

Found: Mol. of formic acid produced per mol. of Compound C; 0.03.

Found: Mol. of formic acid produced per mol. of Compound D; 1.02.

Expt. 50. Methylation of Compound C.

Compound C (1.0 g., 1 mol.) was dissolved in DMF (25 ml.) in a 100 ml. conical flask. Silver oxide (6.5 g. 6.2 mol.) and freshly distilled methyl iodide (5.1 ml. 18 mol.) were added. The flask was warmed slightly, and then firmly stoppered and shaken vigorously for 24 hr.

Solid material was filtered off, washed with DMF, and the combined filtrate and washings were rotary evaporated to a yellow, semi-solid mass. On addition of chloroform (75 ml.), silver iodide was precipitated, and after filtering, the filtrate was washed four times with water (50 ml.), and finally dried over anhydrous sodium sulphate. The drying agent was removed by filtration, and the clear solution evaporated to a pale yellow syrup (1 g.) which crystallized on standing in the refrigerator.

The crude product appeared to be readily soluble in all common solvents, and so it could not be easily refined by recrystallization. In order to effect some purification, it was quickly triturated with a small volume of ice-cold water, whereupon a thin yellow film (presumably of residual silver iodide) adhered to the interior surface of the flask. The product was then filtered off as a white crystalline solid, which was dried by storage, in a desiccator, over calcium chloride (0.6 g. 50%) m.p.40-43°. RV 2.42 (PPE at 175°) (Found: C,59.2; H,9.9; OMe, 33.6. $C_{13}H_{26}O_5$ requires C,59.5; H,9.9; OMe, 35.5%).

Expt. 51. Removal of the Acetal Ring from the Methylated Derivative of Compound C, by Acid Hydrolysis.

Fully methylated Compound C (0.3 g.) was dissolved in ethanol (5 ml.) and water (25 ml.). Amberlite IR-120(H^+) resin (5 ml.) was added, and the mixture was heated over a boiling water bath for 3 hr. After filtering out the resin, the solution was evaporated to a yellow syrup (0.24 g.).

The syrup could not be induced to crystallize, but was purified, to some extent, by boiling with light petroleum (b.p. 60-80°) (10 ml.) and then decanting the hot solution from the insoluble sticky yellow impurities (probably largely resinous material). On evaporation of this solution, a clear colourless syrup was obtained. (0.18 g. 76%) RV 0.62 (TMS derivative, PPE at 175°). (Found C,52.0; H,9.6, $C_9H_{20}O_5$ requires C,51.9; H,9.6%).

Expt. 52. To Establish, by means of Periodate Oxidation, whether the Hydrolysed Tri-O-Methyl Derivative of Compound C has a Pair of Vicinal Hydroxyl Groups.

The method used has been described in Expt. 12 (p.150) Found: Mol. periodate consumed per mol. of hydrolysed tri-O-methyl Compound C: 0.03 (after 1 hr.), 0.05 (after 6 hr.). Thus the sample contained no vicinal hydroxyl groups.

Expt. 53. Isolation of Compound E from a Mixture taken from the Early Stages of Reaction of n-Butyraldehyde and 2-Deoxy-D-Glucitol.

n-Butyraldehyde (0.29 g.) and 2-deoxy-D-glucitol (0.66 g.) were dissolved in water (36 ml.). The reaction was started by addition of 5N aqueous hydrochloric acid (4 ml.), and stopped 20 minutes later (after 34%) by neutralizing with aqueous sodium hydroxide. The solution was evaporated to dryness, and the residue triturated with warm ethanol (25 ml.). After filtering, the ethanolic solution was evaporated to a syrup (0.9 g.), which slowly crystallized, and GLC analysis (TMS derivative, PPE at 175°) showed that the chief product was Compound E RV 2.12.

A glass column (2.5 cm. diameter) was packed with Aluminium Oxide (50 g.) in ethanol. The mixture was dissolved in ethanol (5 ml.), poured on to the column, and eluted first with ethanol (95 ml.), and then with ethanol/water mixtures of 99% (v/v) (100 ml.) and 98.5% (v/v) (200 ml.), whilst fractions (20 ml.) were collected. On evaporation, the latter fractions yielded syrups, which, with some difficulty, could be induced to partially crystallize. But, GLC analysis of these indicated that, although no 2-deoxy-D-glucitol was present, very little separation of the reaction products had been achieved.

The semicrystalline residues from the fractions were combined and boiled with several portions of light petroleum (b.p. 40-60°) and the clear warm extracts were decanted off. On cooling, crystals were deposited, which were filtered out and recrystallized from light petroleum (b.p. 40-60°) (10 mg. in 30 ml.). The product had m.p. 61.5-63.5°, R_F 0.84 (MEK/H_2O), RV 2.18 (TMS derivative, PPE at 175°) (Found: C,54.8; H,9.0. $C_{10}H_{20}O_5$ requires C,54.5; H,9.1%).

Expt. 54. To Determine the Number of Pairs of Vicinal Hydroxyl Groups per Molecule of Compound E, by Periodate Oxidation.

The method used was identical to that in Expt. 12 (p. 150) for Compound A.

Found: Mol. periodate consumed per mol. of Compound E 2.01 (after 1 hr.), 2.00 (after 4 hr.) and 2.00 (after 24 hr.). Thus Compound E contained two pairs of vicinal hydroxyl groups.

Expt. 55. Estimation of the Formaldehyde Liberated by Periodate Oxidation of Compound E.

The method used has been described in Expt. 13 (p. 153) Found: Mol. of formaldehyde liberated per mol. of Compound E; 0.96.

Expt. 56. Estimation of the Formic Acid Produced by Periodate Oxidation of Compound E.

The same method was used as for Compound A (Expt. 14. p. 156).

Found: Mol. of formic acid produced per mol. of Compound E; 0.97.

Expt. 57. Isolation of Compound F from a Reaction Mixture of n-Butyraldehyde and 3-O-Methyl-D-Glucitol.

n-Butyraldehyde (0.29 g.) and 3-O-methyl-D-glucitol (0.78 g.) were dissolved in water (36 ml.), and 5N aqueous hydrochloric acid (4 ml.) was added to start the reaction. After 4 days the solution was neutralized with aqueous sodium hydroxide and evaporated to dryness. The residue was triturated with warm ethanol (25 ml.), filtered, and the filtrate evaporated to a crystalline mass (1 g.).

The mixture was examined by paper chromatography (MEK/H_2O) Besides 3-O-methyl-D-glucitol, it contained a major product with R_F 0.76, presumably Compound F, and some lesser products R_F 0.84.

A glass column (2.5 cm. diameter) was packed with Whatman CF.11. cellulose powder (75 g.) as a slurry in acetone, and the cellulose was washed, first with acetone and then with methyl ethyl ketone saturated with water (MEK/H_2O).

The reaction mixture (0.5 g.) in MEK/H_2O (5 ml.) was introduced on to the column, and was eluted with this solvent whilst fractions (25 ml.) were collected and rotary evaporated to dryness.

After about 200 ml. of eluent had passed through the column, fractions yielded, at first a syrup containing all the products, and then a crystalline deposit (0.25 g.) consisting exclusively of material with R_F 0.76 (MEK/H_2O). This substance was recrystallized from benzene (0.1 g. in 30 ml.) and had m.p. 154-156°, RV 5.99 (TMS derivative, PPE at 175°), $[\alpha]_D^{25}$ -9.6°, $[\alpha]_{Hg.5461}^{25}$ -10.6° (c., 0.7 in H_2O) (Found: C,52.4; H,8.6; OMe, 13.3. $C_{11}H_{22}O_6$ requires C,52.8; H,8.8; OMe, 12.4%).

As an alternative to fractionation on a cellulose column, the reaction mixture (1 g.) was leached with boiling benzene (60 ml.) and the clear hot solution was decanted into another vessel. On cooling, crystals (0.3 g.) separated, and these were recrystallized several times from benzene to obtain pure Compound F. The yield could be increased by further extraction of the mixture with benzene.

Expt. 58. Hydrolysis of Compound F and Identification of the Products.

The details of this experiment were essentially the same as recorded in Expt. 46 (p. 190). Compound F was hydrolysed

in warm water in the presence of cation exchange resin and yielded a syrup, the chromatographic mobility of which was identical to 3-O-methyl-D-glucitol, R_F 0.26 (B/E/7).

The carbonyl portion of the hydrolysate formed a 2,4-dinitrophenylhydrazone m.p. 119-121°. This melting point was unaltered when the derivative was mixed with an authentic sample of n-butyraldehyde-2,4-dinitrophenylhydrazone.

Expt. 59. To Determine the Number of Pairs of Vicinal Hydroxyl Groups per Molecule of Compound F, by Periodate Oxidation.

The method used was identical to that for Expt. 12 (p. 150). Found: Mol. periodate consumed per mol. of Compound F, 0.99 (after 1 hr.), 1.01 (after 2 hr.) and 1.00 (after 3 hr.).

Expt. 60. Estimation of the Formaldehyde Liberated by Periodate Oxidation of Compound F.

The method used has been described in Expt. 13 (p. 153) Found: Mol. formaldehyde liberated per mol. of Compound F; 1.00.

Expt. 61. Examination of the Larger Fragment Resulting from the Periodate Oxidation of Compound F.

Sodium metaperiodate (0.32 g.) and Compound F (0.2 g.) were dissolved in water (100 ml.) and allowed to stand for

2 hr. at room temperature. The solution was then freeze-dried, extracted twice with hot chloroform (20 ml.), and the insoluble material was filtered off. On evaporation of the combined chloroform extracts, there remained a syrup (0.19 g.) which set to a glassy solid. Paper chromatography (B/E/W) indicated it to be a single substance R_F 0.90.

The product (20 mg.) was suspended in dry dichloromethane (4 ml.) in a small flask, and cooled to about -70° in a bath of acetone and dry-ice. Boron trichloride (2 ml.) was added and the mixture was maintained at this low temperature for 1 hr.[17] The flask, stoppered with a calcium chloride tube, was then removed from the freezing mixture, allowed to attain room temperature, and left overnight whilst the contents slowly evaporated. During this time the mixture gradually darkened.

The following day, the remaining solvent was removed by rotary evaporation to leave a dark syrup. To this was added 20% aqueous methanol (5 ml.) and the solution was allowed to stand for 1 hr., before again evaporating. The residue was treated with a further 5 ml. of 20% aqueous methanol, and finally evaporated to a white crystalline solid.

Comparison of this material was made with standard samples of D-Xylose and D-arabinose, by means of paper

chromatography with solvents B/E/W and B/P/W

Found: Rs	B/E/W	B/P/W
Product	1.63	1.31
D-Xylose	1.63	1.32
D-Arabinose	1.31	1.13

Thus it was shown that the product was not D-arabinose, but that it compared favourably with xylose.

Expt. 62. Preparation of a Dibenzoate of Compound F.

A solution of Compound F (0.1 g., 1 mol.) in pyridine (2 ml.) was cooled to below 10° in a freezing bath, and benzoyl chloride (0.1 ml., 2.1 mol.) was added. After standing at room temperature for 20 min., the mixture was poured into iced water (20 ml.). An oil was immediately precipitated and, with the aid of some stirring and scratching, it slowly solidified and was filtered off (0.09 g. 49%).

The crude derivative was recrystallized twice from light petroleum (b.p. 60-80°) (25 ml.) m.p. 108.5-110°.
(Found: C,66.4; H,6.6; OMe, 7.8. $C_{25}H_{30}O_8$ requires C,65.4; H,6.5; OMe, 6.8%).

T A B L E S

Table 1

Reaction of n-Butyraldehyde with D-Glucitol in Aqueous Hydrochloric Acid at 25°.

(a) 0.25M Reactants in HCl followed polarimetrically.

Time	a_t^o	Time	a_t^o
3 min.	-0.730	32 min.	-1.383
4	-0.837	39	-1.339
5	-0.940	55	-1.196
7	-1.087	85	-0.968
10	-1.275	102	-0.860
15	-1.360	128	-0.735
21	-1.415	142	-0.680
25	-1.423	162	-0.617
28	-1.412	∞	-0.524

(Graphs 1,2,3 and 9 pp.25-27 and 42).

(b) 0.25M Reactants in HCl followed spectrophotometrically.

Time	n-Butyraldehyde Concentration	% Reaction
0 min.	0.250M	0
1.5	0.180	28
2	0.163	35
4.5	0.129	48
6	0.117	53
8	0.109	56
10	0.099	60
13	0.091	64

(b) (contd)

Time	n-Butyraldehyde Concentration	% Reaction
16	0.086	66
20	0.081	68
27	0.075	70
35	0.069	72
50	0.063	75
127	0.045	82
∞	0.028	89

(Graph 9, p.42).

(c) 0.25M Reactants in 0.5N HCl followed polarimetrically.

Time	α_t^o	Time	α_t^o
4 min.	-0.492	50 min.	-1.409
6	-0.640	60	-1.423
10	-0.832	70	-1.420
13	-0.947	87	-1.385
20	-1.140	105	-1.335
29	-1.275	140	-1.210
35	-1.337	160	-1.137
40	-1.375	195	-1.022
45	-1.396	∞	-0.488

(Graphs 3 and 9, pp. 27 and 42).

(d) 0.25M Reactants in 0.5N HCl followed spectrophotometrically.

Time	n-Butyraldehyde Concentration	% Reaction
0 min.	0.250M	0
3	0.203	19
6	0.167	33
10	0.150	40
16	0.127	49
21	0.113	55
27	0.103	59
35	0.095	62
45	0.094	63
80	0.077	69
110	0.066	74
155	0.059	76
240	0.053	79
345	0.043	83
∞	0.027	89

(Graph 9, p.42).

(e) 0.1M Reactants in 0.5N HCl followed spectrophotometrically.

Time	n-Butyraldehyde Concentration	% Reaction
0 min.	0.100M	0
3	0.093	7
7	0.087	14
10	0.082	18
15	0.076	25
20	0.072	28
25	0.069	31
35	0.064	36
80	0.053	47
135	0.045	56
210	0.042	58
300	0.033	67
∞	0.018	82

(Graph 15, p.111).

Table 2

Reaction of n-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in DMF containing Hydrogen Chloride (0.5N) at 25°.

Time	a_t^o	Time	a_t^o
5 min.	-0.205	1.5 hr.	-0.386
6	-0.225	2.5	-0.386
8	-0.248	3.7	-0.375
10	-0.267	5.6	-0.360
15	-0.300	6.5	-0.353
20	-0.323	22.0	-0.290
25	-0.340	24.0	-0.277
30	-0.350	30.0	-0.268
45	-0.370	76.0	-0.127
60	-0.377	30 days	+0.220

(Graph 6, p.33).

Table 3

Reaction of n-Butyraldehyde with 1-Deoxy-D-Glucitol in Aqueous Hydrochloric Acid at 25°.

(a) 0.1M Reactants in 0.5N HCl followed polarimetrically.

Time	a_t^o	Time	a_t^o
3 min.	-0.086.	40 min.	-0.185
4	-0.112	51	-0.164
5	-0.140	60	-0.157
7	-0.175	80	-0.130

Table 3 (contd)

Time	a_t^o	Time	a_t^o
10	-0.200	110	-0.096
13	-0.210	135	-0.074
16	-0.218	160	-0.060
20	-0.218	210	-0.043
25	-0.211	230	-0.039
30	-0.204	∞	+0.030

(Graph 14, p.105).

(b) 0.1M Reactants in 0.5N HCl followed spectrophotometrically.

Time	n-Butyraldehyde Concentration	% Reaction
0 min.	0.100M	0
3	0.087	13
6	0.076	24
10	0.070	30
15	0.065	35
25	0.061	39
45	0.055	45
75	0.050	50
120	0.042	58
145	0.038	62
190	0.036	64
∞	0.026	74

(Graphs 14 and 15, pp. 105 and 111).

Table 4

Reaction of n-Butyraldehyde with 2-Deoxy-D-Glucitol in Aqueous Hydrochloric Acid at 25°.

(a) 0.1M Reactants in 0.5N HCl followed polarimetrically.

Time	a_t^o	Time	a_t^o
4 min.	+0.677	90 min.	+0.750
5	0.655	130	0.790
8	0.643	180	0.820
10	0.635	210	0.825
15	0.628	270	0.835
20	0.628	300	0.832
25	0.632	350	0.830
30	0.642	390	0.825
40	0.662	12 hr.	0.783
60	0.705	24 hr.	0.750

(Graphs 16, p.114).

(b) 0.1M Reactants in 0.5N HCl followed spectrophotometrically.

Time	n-Butyraldehyde Concentration	% Reaction
0 min.	0.100M	0
3	0.092	8
6	0.083	17
9	0.076	24

(b) (contd)

Time	n-Butyraldehyde Concentration	% Reaction
14	0.071	29
20	0.066	34
30	0.061	39
45	0.057	43
120	0.053	47
24 hr.	0.045	55

(Graphs 15 and 16, pp. 111 and 114).

Table 5

Reaction of n-Butyraldehyde (0.1M) with 3-O-Methyl-D-Glucitol (0.1M) in 0.5N Aqueous Hydrochloric Acid at 25°.

Time	α_t^o	Time	α_t^o
4 min.	+0.017	200 min.	-0.172
7	+0.002	240	-0.192
10	-0.013	300	-0.218
20	-0.030	345	-0.233
30	-0.047	412	-0.255
50	-0.070	555	-0.287
95	-0.108	610	-0.300
130	-0.136	24 hr.	-0.360

(Graph 17, p.120).

Table 6

Self condensation of n-Butyraldehyde (0.25M) in Aqueous Hydrochloric Acid at 25°.

(a) Reaction followed spectrophotometrically in NHCl.

Time	Optical Density at 238 mμ	Time	Optical Density at 238 mμ
5 min.	0.328	128 min.	0.512
10	0.346	150	0.575
17	0.346	171	0.650
28	0.350	195	0.732
48	0.370	236	0.910
84	0.422	276	1.093
105	0.464	300	1.222

(b) Reaction followed spectrophotometrically in 2NHCl.

Time	Optical Density at 238 mμ
10 min.	0.360
15	0.382
30	0.456
45	0.562
60	0.696
80	0.940
90	1.090
130	1.770
168	2.560

(Graph 8, p.40).

Table 7

Reaction of Acetaldehyde (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°, followed polarimetrically.

Time	α_t^o	Time	α_t^o
3 min.	-0.690	50 min.	-1.533
5	-0.870	57	-1.523
7	-1.010	83	-1.428
12	-1.220	101	-1.355
16	-1.330	126	-1.255
20	-1.402	160	-1.130
30	-1.505	200	-1.020
36	-1.530	223	-0.957
40	-1.537	288	-0.850
46	-1.540	∞	-0.580

(Graph 1, p.25).

Table 8

Reaction of Propionaldehyde (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°, followed polarimetrically.

Time	α_t^o	Time	α_t^o
3 min.	-0.736	35 min.	-1.456
5	-0.910	45	-1.423
8	-1.038	72	-1.283

Table 8 (contd)

Time	a_t^o	Time	a_t^o
10	-1.186	93	-1.164
12	-1.253	113	-1.072
16	-1.354	137	-0.975
20	-1.404	164	-0.890
26	-1.448	205	-0.790
29	-1.456	283	-0.680
32	-1.459	∞	-0.570

(Graph 1, p.25).

Table 9

Reaction of iso-Butyraldehyde (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°, followed polarimetrically.

Time	a_t^o	Time	a_t^o
3 min.	-0.703	32 min.	-1.406
5	-0.857	36	-1.415
7	-0.978	40	-1.413
12	-1.170	44	-1.405
20	-1.324	50	-1.390
24	-1.364	60	-1.355
28	-1.390	70	-1.307

(Graph 2, p.26).

Table 10

Reaction of Benzaldehyde with D-Glucitol in DMF containing Water (20% v/v) and Hydrochloric Acid at 25°.

(a) 0.25M Reactants in NHCl followed polarimetrically.

Time	a_t^o	Time	a_t^o
3 min.	-0.030	80 min.	-0.028
7	-0.090	100	+0.060
15	-0.162	116	+0.134
20	-0.186	130	+0.190
23	-0.197	158	+0.285
25	-0.200	197	+0.390
30	-0.193	248	+0.485
60	-0.113	∞	+0.753

(Graph 4, p.28).

(b) 0.25M Reactants in 0.5N HCl followed polarimetrically

Time	a_t^o	Time	a_t^o
4 min.	+0.074	70 min.	-0.192
6	+0.041	96	-0.143
10	-0.015	133	-0.055
20	-0.105	155	-0.003
30	-0.166	170	+0.034
40	-0.200	205	+0.107
48	-0.205	240	+0.158
53	-0.208	293	+0.227
60	-0.208	∞	+0.465

(Graphs 4 and 7, pp. 28 and 34).

Table 11

Reaction of Benzaldehyde (0.25M) with D-Glucitol (0.25M) in DMF containing Hydrogen Chloride (0.5N) at 25°.

Time	a_t^o	Time	a_t^o
4 min.	-0.046	55 min.	+0.163
6	-0.062	65	+0.250
10	-0.076	78	+0.343
15	-0.074	105	+0.510
20	-0.070	125	+0.610
25	-0.040	160	+0.743
30	-0.015	200	+0.840
45	+0.084	30 days	+1.336

(Graph 7, p.34).

Table 12

Reaction of Formaldehyde with D-Glucitol in Aqueous Hydrochloric Acid at 25°.

(a) 0.25M Reactants in N HCl followed polarimetrically.

Time	a_t^o	Time	a_t^o
0.0 hr.	-0.173	240 hr.	-0.478
3.2	-0.173	288	-0.510
4.5	-0.182	336	-0.540
5.3	-0.195	1008	-0.825
72.0	-0.300	1176	-0.877

(b) 0.25M Reactants in 2N HCl followed polarimetrically.

Time	α_t^o	Time	α_t^o
1 hr.	-0.185	79 hr.	-0.740
2	-0.197	92	-0.790
5	-0.245	94	-0.794
6	-0.250	98	-0.807
19	-0.382	114	-0.855
23	-0.415	117	-0.860
25	-0.432	261	-0.970
31	-0.486	284	-0.985
45	-0.573	42 days	-1.160

(Graphs 5 and 13, pp. 29 and 97).

(c) 0.25M Reactants in 2N HCl followed titrimetrically.

Time	Formaldehyde Concentration	% Reaction
0 hr.	7.50 g./l.	0.0
2	7.47	0.4
7	7.35	2.0
12	7.20	4.0
26	6.69	10.8
33	6.48	13.6
50	6.18	17.6
72	5.73	23.6
80	5.68	24.3

(c) (contd)

Time	Formaldehyde Concentration	% Reaction
96	5.44	27.5
128	4.97	33.8
174	4.52	39.7
268	4.17	44.3
504	3.33	55.6
1008	2.57	65.8

(Graph 13, p.97.)

Table 13

Reaction of Trichloroacetaldehyde (0.25M) with D-Glucitol (0.25M) in N Aqueous Hydrochloric Acid at 25°, followed polarimetrically.

Time	a_t^o	Time	a_t^o
0.1 hr.	-0.124	7 hr.	-0.120
0.2	-0.124	26	-0.122
0.4	-0.124	29	-0.122
2.2	-0.120	31	-0.122
2.7	-0.120	49	-0.130
4.0	-0.120	52	-0.126
5.0	-0.120	54	-0.120
6.8	-0.120	216	-0.127

Table 14

Hydrolysis of Compound A (3.18×10^{-2}M) in N Aqueous Hydrochloric Acid at 26°.

(a) followed polarimetrically

Time	a_t°	Time	a_t°
3.5 min.	-0.603	30 min.	-0.250
5	-0.570	40	-0.204
7	-0.530	55	-0.170
10	-0.467	94	-0.120
15	-0.390	190	-0.084
20	-0.327	∞	-0.080
25	-0.287		

(b) followed spectrophotometrically

Time	n-Butyraldehyde Concentration x 10^2	% Hydrolysis
3 min.	0.47 M	15
5	0.68	21
7	0.88	28
10	1.13	36
14	1.39	44
20	1.69	53
36	2.06	65
60	2.04	64
90	2.00	63
180	1.67	53
240	1.52	48
∞	1.22	33

(Graph 10, p.64).

Table 15

Hydrolysis of 2,4-O-Butylidene-D-Glucitol (3.13×10^{-2}M) in N Aqueous Hydrochloric Acid at 26°.

Time	a_t°	Time	a_t°
5 min.	-0.180	180 min.	-0.130
10	-0.178	225	-0.120
30	-0.172	270	-0.114
60	-0.161	340	-0.100
90	-0.154	405	-0.091
120	-0.146	∞	-0.065

(b) followed spectrophotometrically.

Time	n-Butyraldehyde Concentration x 10^2	% Hydrolysis
5 min.	0.05 M	1.5
10	0.08	2.5
20	0.12	4.0
40	0.24	7.5
60	0.35	11.0
80	0.43	13.5
110	0.55	17.0
150	0.67	21.0
200	0.77	24.0
265	0.89	28.0
360	0.99	31.0
∞	1.26	40.0

(Graph 10, p.64).

Table 16

Reaction of Compound A (3.4×10^{-2}M) in DMF containing Hydrogen Chloride (0.25N) at 25°.

Time	a_t^o	Time	a_t^o
0.1 hr.	-0.645	6.5 hr.	-0.546
0.5	-0.640	12.5	-0.485
0.8	-0.632	23.0	-0.380
1.2	-0.630	24.0	-0.370
2.2	-0.607	26.0	-0.348
3.6	-0.586	28.0	-0.326
4.2	-0.576	30.0	-0.310
5.3	-0.564	48.0	-0.210
6.0	-0.553	144.0	+0.001

Table 17

Hydrolysis of Compound B (3.7×10^{-2}M) in Aqueous Hydrochloric Acid at 26°, followed polarimetrically.

(a) in 0.1NHCl		(b) in 0.05N HCl	
Time	a_t^o	Time	a_t^o
3 min.	-0.504	3 min.	-0.574
4	-0.455	4	-0.540
5	-0.410	5	-0.512
6	-0.372	7	-0.467
8	-0.310	10	-0.390
10	-0.260	13	-0.337

Table 17 (contd)

Time	a_t^o	Time	a_t^o
12	-0.220	16	-0.280
16	-0.163	20	-0.235
20	-0.125	25	-0.180
26	-0.090	30	-0.143
30	-0.075	40	-0.090
53	-0.044	55	-0.057
∞	-0.040	∞	-0.020

(Graph 12, p.90).

Table 18

Reaction of Compound B (3.5×10^{-2}M) in DMF containing Hydrogen Chloride (0.25M) at 25°.

Time	a_t^o	Time	a_t^o
4 min.	-0.416	100 min.	-0.030
6	-0.404	130	-0.030
10	-0.382	155	+0.014
15	-0.360	195	+0.057
20	-0.334	220	+0.080
30	-0.293	240	+0.090
40	-0.250	330	+0.133
55	-0.202	10 hr.	+0.170

Table 19

GLC Retention Volume Data for some Polyhydric Alcohols and Related Compounds, as their TMS Derivatives.

(PPE at 175°)

Compound	Average RV
D-Glucitol	1.00
1-Deoxy-D-Glucitol	0.62
2-Deoxy-D-Glucitol	0.89
3-O-Methyl-D-Glucitol	1.12
1,3,5,6-tetra-O-methyl-D-Glucitol	1.16
1,4,5,6-tetra-O-methyl-D-Glucitol	1.14
3,5,6-tri-O-methyl-1-deoxy-D-Glucitol	0.62
2,3-O-Butylidene-D-Glucitol (Compound A)	2.76
3,4-O-Butylidene-D-Glucitol	3.04
4,6-O-Butylidene-D-Glucitol	3.31
2,4-O-Butylidene-D-Glucitol	4.23
2,3-O-Butylidene-1-deoxy-D-Glucitol (Compound D)	1.22
2,4-O-Butylidene-1-deoxy-D-Glucitol (Compound C)	2.02
1,3-O-Butylidene-2-deoxy-D-Glucitol (Compound E)	2.18
1,3:2,4-Di-O-butylidene-D-Glucitol	c.12.80
2,4-O-Methylene-D-Glucitol	4.10
2-Deoxy-D-glucopyranose (α + β)	1.03, 1.56
3-O-Methyl-α-D-Glucopyranose	1.36
(SE-30 at 175°)	
2,3-O-Benzylidene-D-Glucitol (Compound B)	3.73
2,4-O-Benzylidene-D-Glucitol	4.51

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A New Mono-*O*-butylidene-D-glucitol

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When equimolecular quantities (0·25M) of D-glucitol and *n*-butyraldehyde react in aqueous N sulphuric acid, an equilibrium mixture,[1] containing monoacetals together with traces of di- and tri-acetals is obtained. Under these conditions, *n*-butyraldehyde gives mainly the 2,4-acetal,[2] but the 3,4-acetal has also been identified.[1] On following the reaction polarimetrically, in either N sulphuric acid or N hydrochloric acid, a large optical rotation is observed (see Fig.) in the early stages of reaction. In order to isolate the intermediate product responsible for this, the reaction was stopped after 10 minutes by rapid neutralisation with alkali. By means of column chromatographic separation of the organic material, a monoacetal was isolated, m.p. 116–118°C. It was soluble in water, and had $[\alpha]_D^{26}$ -39·7°, $[\alpha]_{Hg5461}^{26}$ -45·5° (*c.*, 1 in H_2O). Analysis indicated a monobutylidene acetal (Found: C,50·5; H, 8·4. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5%). Hydrolysis gave D-glucitol, identified as its hexa-acetate, and *n*-butyraldehyde, identified as its 2,4-dinitrophenylhydrazone.

The acetal was distinguished from the other known monobutylidene acetals (2,4-, 3,4-, and 4,6-) by comparing the retention volumes of the *O*-trimethylsilyl derivatives[3] using a Pye Argon Chromatograph with *m*-bis(*m*-phenoxyphenoxy) benzene as stationary phase at 175°. Oxidation with sodium metaperiodate(1·94 mol. required) produced formaldehyde (1·12 mol.) and formic acid (0·96, 0·93 mol.), consistent with the structures of 1,3-, 2,3-, 4,5-, or 4,6-*O*-butylidene-D-glucitol. The product from oxidation was hydrolysed to give a tetrose sugar, identified by conversion into its phenylosazone. G.L.C. examination of the *O*-trimethylsilyl derivative showed a retention volume identical with that of threose but different from that of erythrose, indicating that the original monoacetal was a 1,3- or 2,3-D-glucitol derivative.

The monoacetal was methylated with methyl iodide and silver oxide in D.M.F. and the tetra-*O*-methyl derivative (Found: C, 58·0; H, 9·3; OMe, 40·9. $C_{14}H_{28}O_6$ requires C, 57·5; H, 9·6; OMe, 42·4%) collected as a colourless syrup at 94–104° under 0·2 mm. Hg. pressure. The acetal ring was removed by hydrolysis and the resulting syrup was found to undergo oxidation with sodium metaperiodate (0·91, 0·89, 0·93, 0·89 mol. required). A similar product obtained from the 2,4-monoacetal after methylation and hydrolysis consumed virtually no periodate. The new monoacetal was therefore 2,3-*O*-butylidene-D-glucitol.

The appearance of the 2,3-acetal as an initial product of the reaction raises the problems of (i) what reactivity and structural factors of D-glucitol are responsible for the kinetic control leading initially to

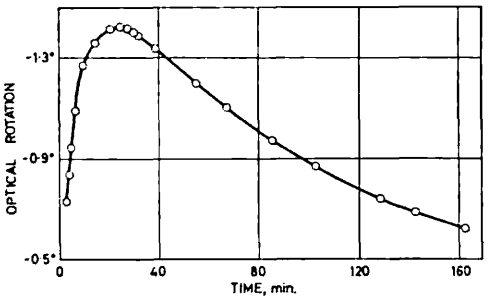

FIG.—*Variation in optical rotation during the reaction of* n-*butyraldehyde with* D-*glucitol (equimolar quantities,* 0·25 M*) in aqueous hydrochloric acid*

the formation of this particular acetal and (ii) whether or not the ultimate monoacetal products are formed intramolecularly from it. Information on (ii) has been obtained by following polarimetrically and spectrophotometrically (carbonyl absorption) the hydrolysis of the 2,3-acetal in N aqueous hydrochloric acid. The hydrolysis rate ($k = 7{\cdot}12 \times 10^{-4}$ sec.$^{-1}$) is considerably greater than for the 2,4-*O*-butylidene isomer ($k = 2{\cdot}25 \times 10^{-5}$ sec.$^{-1}$). Analysis by G.L.C. of the reaction mixture throughout hydrolysis by conversion of the products into their *O*-trimethylsilyl derivatives reveals that during the period in which the bulk of the 2,3-acetal disappears, there is little trace of any compounds other than D-glucitol and the 2,3-acetal. Ultimately the hydrolysate attains the same composition as that obtained at equilibrium from equimolecular concentrations of D-glucitol and *n*-butyraldehyde in the synthesis reaction carried out under the same experimental conditions. This indicates that after relatively rapid hydrolysis of the 2,3-acetal has produced the glucitol and aldehyde, these two compounds slowly react to give the monoacetals normally obtained in the synthetic reaction. The result suggests that the formation of the thermodynamically more stable monoacetals does not principally proceed by acid catalysed intramolecular ring migration from the 2,3-acetal, at least in the form in which the latter was isolated.

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