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Ethanolyses of 3,4,6-Tri-O-Methyl-1,2-O-(Alkyl Orthoacetyl)-α-D-Glucopyranoses

David P. Hultman

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ETHANOLYSES OF 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOPYRANOSES

A thesis submitted by

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SUMMARY

Ethanolyses of \textit{exo}-OR 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}- (alkyl orthoacetyl)-\textit{\alpha}-D-glucoses (alkyl = ethyl and isopropyl) were studied at 25.0°C. in 0.005N 2,6-dichlorobenzoic acid.

Initially, the ethanolysis of either orthoester resulted in rapid formation of a 20% \textit{endo}-OR-80% \textit{exo}-OR equilibrium mixture of 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}- (ethyl orthoacetyl)-\textit{\alpha}-D-glucose. The isomerization was verified by NMR by observing the \textit{endo}-OR and \textit{exo}-OR orthoacetyl methyl group singlets with time. Reactions in ethanol-water mixtures indicated that a minimum of 300 alkoxy exchange (isomerization) reactions occurred for every reaction causing loss of 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha}-D-glucose by ethanolysis.

The disappearance of 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha}-D-glucose and simultaneous appearance of equivalent amounts of products were followed quantitatively by a GLC method using an internal standard. The GLC analysis involved removal of ethanol, hydrolysis of remaining orthoester, and propanoylation to result in a system of components which could be separated and quantitatively measured. The identities and quantities of products measured by GLC agreed with polarimetric data. The parallel first-order appearance of glucose products gave proportions of: ethyl 3,4,6-tri-\textit{O}-methyl-\textit{\beta}-D-glucoside (0.571), ethyl 3,4,6-tri-\textit{O}-methyl-\textit{\alpha}-D-glucoside (0.028), ethyl 2-\textit{O}-acetyl-3,4,6-tri-\textit{O}-methyl-\textit{\beta}-D-glucoside (0.196), and 3,4,6-tri-\textit{O}-methyl-\textit{\alpha}-D-glucose (0.209). Ethyl 2-\textit{O}-acetyl-3,4,6-tri-\textit{O}-methyl-\textit{\alpha}-D-glucoside was detected and measured only in ethanolyses with added salt. The 3,4,6-tri-\textit{O}-methyl-D-glucose formed was shown to be of \textit{\alpha}-configuration by the direction and magnitude observed for mutarotation.

Esters produced during ethanolysis, measured by saponification equivalent, were formed in equivalent amounts to the glucosides and were ethyl 2-\textit{O}-acetyl-3,4,6-tri-\textit{O}-methyl-\textit{\beta}-D-glucoside and ethyl acetate. Ethyl acetate was identified by NMR and
GLC. Triethyl orthoacetate was formed in nearly equivalent amounts to 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose as determined by comparison of the glucose product data with ester data. Triethyl orthoacetate formation was further confirmed by NMR.

GLC, ester, and polarimetry data gave similar and reproducible rate constants by parallel-first-order kinetic treatment. Deviations from parallel first-order kinetics were noticed after 70% 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose disappearance and were found to be caused by slow reaction of 3,4,6-tri-O-methyl-D-glucose and triethyl orthoacetate.

The ethanolysis of 3,4,6-tri-O-methyl-D-glucose (\(\alpha\) anomer initially) in the presence of triethyl orthoacetate was studied kinetically by a method similar to that for studying the disappearance of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses. The analyses yielded a mole balance of glucose moiety. Minimum values for the amount of intermediate glucose orthoesters present, due to trans-orthoesterification, were measured and attributed to 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucoses and four other glucose orthoesters, both \(\alpha\) and \(\beta\), having only one orthoester linkage to the sugar. The glucosides formed were ethyl 3,4,6-tri-O-methyl-\(\beta\)-D-glucoside, ethyl 3,4,6-tri-O-methyl-\(\alpha\)-D-glucoside, and ethyl 2-O-acetyl-3,4,6-tri-O-methyl-\(\beta\)-D-glucoside. The relative proportions of the above glucosides decreased, increased, and increased, respectively, with time. The amounts of unacetylated glucosides were formed in larger proportions than would be predicted from ethanolysis of intermediate 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucoses alone. This indicated that 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucoses were also intermediates and could form glucosides by ethanolysis. Using logical assumptions and the data obtained, it was predicted that 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-\(\alpha\)-D-glucose would stereoselectively form the \(\beta\) anomer of ethyl 3,4,6-tri-O-methyl-D-glucoside by a factor of 16:1.
2,3,4,6-Tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose, a compound similar to 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose, was studied kinetically using the same ethanolysis conditions and similar analysis procedures as those used for 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses. The analyses gave a mole balance with time. The parallel-first-order rate constant was considerably greater than that observed for 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses. Product proportions were: ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside (0.354), ethyl 2,3,4,6-tetra-O-methyl-α-D-glucoside (0.012) and 2,3,4,6-tetra-O-methyl-D-glucose (0.633). The primary salt effects using lithium p-toluenesulfonate were a large increase in the α-glucoside formed and a decrease in the amount of reducing sugar formed. These are the same types of primary salt effects observed in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose.

Acid-catalyzed transacetylations, Fisher glycosidation, and glucoside anomerization were undetected at any experimental conditions and reaction times used.
INTRODUCTION

Perhaps the most abundant class of natural organic compounds is the glycosides. Even today man is still largely dependent upon nature for his supply of even the simplest of glycosides. This dependence on nature means that a valuable glycoside or potentially valuable glycoside cannot always be found or, for that matter, the particular glycoside may not even exist in sufficient quantity in nature. Thus, synthesis of glycosides constitutes a pressing problem in organic chemistry. Methods of producing glycosides are known; however, control of these reactions has rarely been completely satisfactory, and the methods lack inherent generality of use. Thus, considerable effort has concentrated on either new methods of producing glycosides or on a better understanding of existing methods in the hope of increasing man's ability to produce specific glycosides. One of the newer and least understood methods of producing glycosides is the acid-catalyzed reaction of carbohydrate 1,2-orthoesters, such as 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose, with a potential aglycone. This thesis was undertaken in the hope that the results and knowledge gained would aid in the utility of this reaction.
LITERATURE REVIEW

Because of the asymmetric carbon (asterisk) in the orthoester group, two diastereomers are possible (1). Configurational assignments when made, have been on the basis of nuclear magnetic resonance spectrometry (2, 3). Although both isomers may be discerned by NMR, the assignment of configuration on this basis is not necessarily absolute (2). For D-glucopyranose and D-mannopyranose, the isomer which exhibits the orthoacetyl methyl singlet at lowest field has been tentatively designated as the exo-OR isomer, i.e., the OR group is trans to the sugar ring (2, 3). Two examples of both isomers being crystalline have been reported (2, 4) while in the majority of cases only the exo-OR isomer is known to be crystalline or has been obtained as a pure sirup or oil.

The stereomeric factors which control the formation of sugar 1,2-orthoesters from O-acyl glycosyl halides requires a 1,2-trans configuration in the halide to result in the 1,2-cis configuration of the sugar 1,2-orthoesters (5). Of the known sugar 1,2-orthoesters, the -OR group may be alkoxy, aryloxy, or glycosyloxy and the R' group may be alkyl or aryl.

The 1,2-orthoester group on sugars is stable in mild alkaline media but is extremely reactive in acid-catalyzed hydrolyses to form glycosyl esters (1). The hydrolysis rate, under comparable acidic conditions, of sugar 1,2-orthoesters is of the order of $10^{11}$ times that for methyl α-D-glucoside* (1).

Dale (6) was the first worker to report the formation of a glycoside from a reaction of a sugar 1,2-orthoester with an alcohol. Methyl 2,3,4,6-tetra-Ω-acetyl-β-D-mannoside was isolated in 7% crystalline yield as the only identified product.

*The pyranose form should be understood for any sugar not specifically specified.
of the hydrogen chloride-catalyzed methanolysis of 3,4,6-tri-O-acetyl-1,2-O-(methyl orthoacetyl)-β-D-mannose.

After the work of Dale (6), approximately thirty years elapsed before the glycoside-forming ability of sugar 1,2-orthoesters began to be studied extensively. Mechanistic studies of glycoside formation from sugar 1,2-orthoesters have so far been neglected. However, a considerable number of studies have focused on the products of the acid-catalyzed reactions of sugar 1,2-orthoesters in a variety of systems. All products isolated or otherwise measured can be viewed as either transorthoesterification* products or glycosides when the reaction is carried out in the absence of water. The reactions used for glycoside formations may be classed as (1) alcoholyses, (2) rearrangements, or (3) polymerizations.

ALCOHOLYSES

The alcoholyses classification for reactions of sugar 1,2-orthoesters is broad and encompasses the classical alcoholyses to reactions in which the mole ratio of alcohol to sugar 1,2-orthoester is actually less than one. This classification may seem strange to the reader; however, there is a good reason for it. It is apparent from the products reported in the literature that there is no actual change in the number of alcoholic hydroxyl groups during reactions of this type. However, new alcoholic species are generated.

Perlin (7) studied the methanolysis of exo-OR 3,4,6-tri-O-acetyl-1,2-O-(methyl orthoacetyl)-β-D-mannose catalyzed by 0.0012N hydrogen chloride at 25°C. The

*A transorthoesterification reaction is defined as a reaction of an orthoester to form another orthoester. Other terms used in the literature are: transesterification, transetherification, reesterification, and deorthoesterification. In this thesis, the term transesterification will be used for the reaction of an ester to form another ester.
polarimetric rate constant was 0.06 min.$^{-1}$ and 3,4,6-tri-O-acetyl-D-mannose was isolated as the major product while α- and β-mannosides were also detected. The methanolysis of exo-OR 3,4,6-tri-O-acetyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose under the above conditions gave equal amounts of 3,4,6-tri-O-acetyl-D-glucose and methyl 3,4,6-tri-O-acetyl-β-D-glucoside at a rate constant of 0.10 min.$^{-1}$. Perlin concluded that several concurrent reactions appear to take place in methanol, initiated by protonation of different oxygen atoms of the orthoester. Comparable products have been reported with other sugar 1,2-orthoesters under similar conditions (8, 9).

Lemieux (10) reacted 3,4,6-tri-O-acetyl-1,2-O-(ethyl and isopropyl orthoacetyl)-α-D-glucoses with ethyl and isopropyl alcohols, respectively, in dichloromethane with p-toluenesulfonic acid as a catalyst. The products claimed were alkyl 3,4,6-tri-O-acetyl-α-D-glucoside (60-70%), alkyl 3,4,6-tri-O-acetyl-β-D-glucoside (20-30%) and 3,4,6-tri-O-acetyl-D-glucose (6-15%). This appears to be the only instance in which the major product is claimed to be a 1,2-cis glycoside. The reaction mechanism postulated involves 1,2-anhydro-3,4,6-tri-O-acetyl-α-D-glucose as an intermediate. Hickenbottom (11) has shown that the ethanolysis of 1,2-anhydro-3,4,6-tri-O-acetyl-α-D-glucose results in 1,2-trans glucosides predominantly. Hence, Lemieux's postulated mechanism does not appear to be consistent with the results he has claimed.

Franks and Montgomery (12, 13) have studied the reaction of exo-OR 3,4,6-tri-O-benzyl-1,2-O-(methyl orthoacetyl)-β-D-mannose with equivalent amounts of methanol in dichloromethane and nitromethane catalyzed by p-toluenesulfonic acid or mercuric bromide. The products isolated by column chromatography were identified as: methyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannoside (65-74%), methyl 3,4,6-tri-O-benzyl-α-D-mannoside (20-22%), and methyl 3,4,6-tri-O-benzyl-β-D-mannoside (5-6%). An
increase in methanol concentration relative to orthoester was said to cause little change in the stereoselective formation of α-mannosides, but a slightly higher proportion of methyl 3,4,6-tri-O-methyl-α-D-mannoside relative to the 2-O-acetyl analog was formed. It was claimed, but not demonstrated, that this was due to acid-catalyzed transacetylation after methanolysis (13). The identification of acetic acid by NMR (13), which was assumed to be formed by hydrolysis, is probably in error since the first hydrolysis product of an orthoester is an ester (14). At the time (5 min.) and conditions used (45°C., 0.06N p-toluenesulfonic acid in 1% methanol — 99% dichloroethane) no significant hydrolysis of esters would be expected. Methyl acetate could easily be mistaken for acetic acid when the identification only involves the chemical shift of the acetyl methyl group protons by NMR.

Kochetkov and coworkers (15, 16) were the first to utilize sugar 1,2-orthoesters in disaccharide and trisaccharide syntheses. These workers reacted a variety of acetylated sugar 1,2-orthoesters, all of which had the 1,2-O-(methyl or ethyl orthoacyl) group, with a properly protected sugar having at least one free hydroxyl group. The reaction system was boiling nitromethane with mercuric bromide as the acid catalyst. Yields of products having the 1,2-trans glycoside linkage and a 2-O-acyl group varied from 7 to 90% depending upon the compound synthesized. In one reported case the 1,2-cis glycoside linkage also formed but in much smaller quantity compared to the 1,2-trans glycosidic linkage (17). In all cases an undesired 1,2-trans glycoside, isomeric with the initial sugar 1,2-orthoester, was produced by an initial transorthoesterification and subsequent glycoside formation as shown on the following page. This undesired reaction, shown by the dotted arrows, is detrimental to the yield of the desired saccharide.
One means of decreasing the undesirable reaction (above) was found by an investigation of the effect of the OR group on these syntheses (18, 19). The less reactive the alcohol (ROH) formed by transorthoesterification compared to the sugar hydroxyl group (R"OH), the less important the undesirable reaction is. In the series, 3,4,6-tri-O-methyl-1,2-O-(R = ethyl, isopropyl, t-butyl, phenyl orthoacetyl)-α-D-glucose, the yield of the same reaction for a desired disaccharide was: ethyl < isopropyl < t-butyl < phenyl (18). More specifically, 3,4,6-tri-O-acetyl-1,2-O-(t-butyl orthoacetyl)-α-D-glucose reportedly (19) gives better yields than those obtained with 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in the synthesis of three disaccharides, but there were variations of reaction conditions for the two orthoesters.

The problem of the undesired reaction discussed above is completely eliminated if the sugar 1,2-orthoester is isomeric with the saccharide to be synthesized. The transorthoesterification reaction, which originally caused the undesired reaction
products in syntheses, can also be used for synthesizing sugar 1,2-orthoesters isomeric with the desired saccharide (15, 16, 20). The process involves the transorthoesterification of a simpler orthoester with the desired aglycone. The alcohol liberated from the simpler orthoester is removed by azeotropic distillation with the reaction solvent. Since transorthoesterifications are reversible, the orthoester isomeric with the required glycoside is produced (20).

The above process works because, either (1) transorthoesterification is much faster than glycoside formation, or (2) under the transorthoesterification conditions used no glycoside formation takes place. Kochetkov and coworkers (16, 20) have studied conditions for these transorthoesterifications and believe that the second reason is correct, but these workers have apparently not considered the first possible reason nor do their data eliminate this possibility. In one instance reported (21) glycoside formation did occur under the conditions usually used for the transorthoesterification reaction.

Once the sugar 1,2-orthoester is produced by the transorthoesterification reaction, an addition of more catalyst and a further reaction period will produce the isomeric glycoside (20). In some cases, the new sugar 1,2-orthoesters have been isolated by crystallization (20) and subsequently used in rearrangement reactions to be described next.

REARRANGEMENTS

Sugar 1,2-orthoesters reportedly can be readily rearranged to the isomeric glycosides in the presence of an acid catalyst. In these reactions the alkoxy group of the 1,2-orthoester group becomes the aglycone of the glycoside(s) formed.

Franks and Montgomery (12, 13) have rearranged exo-OR 3,4,6-tri-O-benzyl-1,2-O-(methyl, isopropyl, and cyclohexyl orthoacetyl)-β-D-mannose in dichloromethane
and in nitromethane using p-toluenesulfonic acid or mercuric bromide at 45°C. The major products, isomeric with the initial orthoesters, were alkyl 2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannosides (72-83%) while smaller amounts of alkyl 3,4,6-tri-O-benzyl-α-D-mannosides (7-16%) and alkyl 3,4,6-tri-O-benzyl-β-D-mannoside (0-1%) were found. Isomerization (transorthoesterification) to yield the endo-OR 3,4,6-tri-O-benzyl-1,2-O-(methyl orthoacetyl)-α-D-mannose was observed to be slower than mannose formation.

Helferich and Weis (22) rearranged 3,4,6-tri-O-benzoyl-1,2-O-(methyl ortho-benzoyl)-α-D-glucose in nitromethane with mercuric bromide and hydrogen chloride to yield 57% crystalline methyl 2,3,4,6-tri-O-benzoyl-β-D-glucoside.

Kochetkov and coworkers (20) have rearranged 3,4,6-tri-O-acetyl-1,2-O-(1,2,3,4-tetra-O-acetyl-β-D-glucosyl-6-orthoacetyl)-α-D-glucose to the isomeric disaccharide with a 1,2-trans glycosidic linkage. The synthesis proceeds at a much faster rate at constant catalyst concentration if a small quantity of 1,2,3,4-tetra-O-acetyl-β-D-glucose is added (20). This led these workers to speculate that small quantities of hydroxylic impurities such as water serve as the initiator in "rearrangement" reactions of orthoesters.

POLYMERIZATIONS

Polymerization of sugars by orthoester methods have been shown to give good yields of polysaccharides (22-27). The polysaccharides produced contain predominantly 1,2-trans glycosidic linkages.

One method of polymerization involves use of bifunctional molecules having a free hydroxyl group and an 1,2-O-(alkyl orthoacetyl) group (23-25). The polysaccharide syntheses proceed in the same manner as the disaccharide syntheses already reviewed.
Another polymerization method uses orthoesters such as cyclo-tri-(4,6-\(\alpha\)-benzylidene 1,2,3'-\(\alpha\)-orthoacetyl)-\(\alpha\)-D-glucose (28) which are synthesized by transorthoesterification of sugar 1,2-orthoesters. The mercuric bromide-catalyzed rearrangement of such orthoesters in nitromethane produces polymers (26, 27). For every glycosidic linkage formed a new hydroxyl group is also formed. Thus, the disappearance of an orthoester group produces the hydroxyl group necessary for formation of the next glycoside linkage. In one case, where a sugar having a free hydroxyl group was used as a polymerization initiator, the reducing end unit of the polysaccharide was found to be the initiator sugar (26).

ANALYSIS AND STATEMENT OF THE PROBLEM

There is not a single instance in the literature where it can be said that the reaction of a sugar 1,2-orthoester with a hydroxylic compound has been described completely. A complete description would encompass the identification of all products, the rate of disappearance of reactant, the rate(s) of appearance of all products, and the identification of intermediates and finally a description of the reaction mechanisms involved. This thesis work was undertaken as an attempt to provide a complete description for a narrowly defined system involving a sugar 1,2-orthoester. The description of the reaction would provide a basis for an interpretation of the effects of variables on the mechanisms involved and thus, result in increased usefulness of 1,2-orthoesters in syntheses. Briefly, the proposed and subsequently (of necessity) revised study involved determination of: (1) kinetics and product formation studies, (2) the behavior of potential intermediates or related compounds in the reaction, (3) the effect of orthoester structure, and (4) the effect of added salts and water on product ratios and rates of reaction.

The need for such a study was indicated by confusion or disagreement in the literature. In this respect the following should be noted: (1) disagreement on
the stereoselectivity of the reactions with respect to glycoside formation, (2) the variation of quantities of analogous products, and (3) the usually incomplete analysis for products. The reaction, though usually poorly defined, is of considerable usefulness.

What possible reactions can occur is the central question to be asked about acid-catalyzed reactions of sugar 1,2-orthoesters. Initiation of a reaction(s) undoubtedly occurs by protonation of one of the orthoester oxygen atoms and subsequent or simultaneous carbon-oxygen bond cleavage at either a, b, c, or d depending upon the oxygen atom protonated. All of these sites for carbon-oxygen bond cleavage are in agreement with either acetal carbon-oxygen bond or orthoester carbon-oxygen bond cleavage in acetals and orthoesters which take place in acid-catalyzed hydrolyses (14). This analysis, if completed, can explain any product, or combination of products ever reported. Further, more mechanisms are predicted by this analysis than are postulated in the literature. Only one mechanism predicts a 1,2-cis glycoside having a 2-O-acyl group while any other product can be predicted by two mechanisms.

Bond cleavage between the pyranose ring oxygen and C-1 is not considered to be important under reaction conditions which yield glycosides from carbohydrate 1,2-orthoesters. The bond between the dioxolane oxygen and C-1 (bond a) would be expected to be much more reactive than the pyranose ring oxygen-(C-1) bond. This follows because sugar 1,2-orthoesters form glycosides at a rate which is extremely
large relative to the rate of acid-catalyzed reactions of glycosides such as anomerationization or transglycosidation which theoretically could occur by cleavage of the pyranose ring oxygen-(C-1) bond.

Other positions for carbon-oxygen bond cleavage, the C-2 carbon-oxygen bond and alkyl-oxygen fission in the alkoxy group, are not likely possibilities because of expected predominant orthoester carbon-oxygen bond cleavage \(^{(14)}\). Also cleavage at these two positions would not be expected either on the basis of previously reported reaction products or on carbonium ion stability.

**SELECTION OF SYSTEM**

There were three important variables considered in selecting a suitable system to study. These were: (1) the identities of orthoesters to be used, (2) the reaction medium, and (3) the catalyst.

The orthoesters, \(\text{exo-OR} \, 3,4,6\text{-tri-O-methyl-1,2-O-(ethyl orthoacetyl)} - \alpha\-D-glucose\) and \(\text{exo-OR} \, 3,4,6\text{-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)} - \alpha\-D-glucose\), were selected because the 3,4,6-tri-O-acetyl precursors are crystalline and easily purified. The 3,4,6-tri-O-methyl substitution was considered essential to isolate the reaction to the C-1 and C-2 positions of the sugar and to ease analyses problems. A study of structural effects on reactivity was made possible by incorporation of the ethyl and isopropyl groups on the 1,2-O-(alkyl orthoacetyl) group. Another orthoester, \(2,3,4,6\text{-tetra-O-methyl-1-O-(diethyl orthoacetyl)} - \alpha\-D-glucose\), was included in the study later to isolate the reaction to C-1.

Ethanol was chosen as the reaction medium. This selection guaranteed all aglycones on the glucosides formed would be of one type. Also, in comparison to other alcohols, ethanol is pleasant to work with and provided a convenient rate of reaction with the catalyst selected.
The catalyst selection was made on the basis that a reasonable rate of reaction using a reasonable amount of catalyst was needed for convenient kinetic measurements. By necessity the selection was based on experiments with catalysts over a wide range of acid strengths. For example, at 25.0°C. ethanolic 0.00061N p-toluenesulfonic acid gave a polarimetric half-life of less than four minutes while ethanolic 0.0059N monochloroacetic acid gave a polarimetric half-life of several days. The catalyst finally selected, 2,6-dichlorobenzoic acid, was of intermediate acid strength between p-toluenesulfonic acid and monochloroacetic acid. 2,6-Dichlorobenzoic acid has the advantages that it is colorless, easily purified, not hygroscopic and is free from esterification reactions except under extremely drastic conditions (29).
The reaction scheme shown in Fig. 1 represents the overall reaction involved in the ethanolysis of exo-OR 3,4,6-tri-O-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucose (alkyl = ethyl and isopropyl) at 25.0°C at an orthoester concentration of 2% (w/v) and 0.005N 2,6-dichlorobenzoic acid. This description of the overall reaction results from a study of the reaction, as a function of time, by gas-liquid partition chromatography (GLC), polarimetry, NMR, and volumetric analysis.

Kinetically, the overall reaction is extremely complex but the ultimate result, in the absence of hydrolysis, is that the 3,4,6-tri-O-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucose is converted into equivalent amounts of both ester and glucoside. The reaction exhibits three distinct phases, each of which is characterized by one predominant "type" of reaction. Listed in order of decreasing rate, these phases are: (1) Isomerization (or alkoxy exchange) to form an equilibrium mixture of exo-OR and endo-OR 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose, (2) the disappearance of 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose, and (3) the disappearance of 3,4,6-tri-O-methyl-D-glucose and triethyl orthoacetate. To the author's knowledge none of these reactions have been completely described previously. The reaction(s) in the third time phase has not been reported previously.

Most of the remainder of the results and discussion is divided into sections which correspond to the distinct time phases exhibited by the ethanolysis. Because of certain relationships between the reactions occurring in each time phase, the separation cannot be made completely rigid.
Figure 1. The Overall Reaction of the Ethanolysis of Exo-OR 3,4,6-Tri-O-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucoses
INITIAL ETHANOLYSIS PRODUCTS OF EXO-OR 3,4,6-TRI-O-METHYL-
1,2-O-(ALKYL ORTHOACETYL)-\(\alpha\)-D-GLUCES

The ethanolysis of either exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose or 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose results in the formation of both isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose by transorthoesterification before there is significant loss of 1,2-O-(alkyl orthoacetyl) group. The rate of loss of the 1,2-O-(alkyl orthoacetyl) group is so slow in comparison to the rate(s) of transorthoesterification that the two isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose reach essentially an equilibrium with each other. These conclusions are based on the interpretation of NMR, GLC, polarimetry, and water scavenging data discussed below.

EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ISOPROPYL ORTHOACETYL)-\(\alpha\)-D-GLUCOSE

Initial Orthoester Products

The glucose products isolated in total from an ethanolysis of exo-OR 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose which was stopped after 15 minutes reaction gave an NMR spectrum (Fig. 2a, Spectrum A) characteristic of a mixture of both isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose. The loss of the isopropoxy group from the 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose is illustrated by the absence of the characteristic isopropoxy methyl group doublet: \(J = 6\) cps, \(\delta = 1.18\) p.p.m. (e.g., Spectrum B, Fig. 2a). The generation of isomeric 1,2-O-(ethyl orthoacetyl) groups is illustrated by two ethoxy methyl triplets: \(J = 7\) cps, \(\delta = 1.22\) p.p.m. and 1.18 p.p.m. The ratio of isomers (16% endo-OR and 84% exo-OR) can be estimated from the integrals of the orthoacetyl methyl group singlets (\(\delta = 1.67\) p.p.m., exo-OR; and \(\delta = 1.53\) p.p.m., endo-OR). The spectra of authentic samples of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucoses are shown in Fig. 2b for comparison. Spectrum C is of the pure...
Figure 2a. NMR Spectra: A, 15 Min. Ethanolysis Products of Exo-OR 3,4,6-Tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose; B, Exo-OR 3,4,6-Tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose.
Figure 2b. NMR Spectra: C, Exo-OR 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose; D, 19.6% Endo-OR 80.4% Exo-OR 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose
exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose and Spectrum D is
of a mixture of 80.4% exo-OR and 19.6% endo-OR isomers. As expected from the dis-
cussion above, Spectrum A and Spectrum D are nearly identical.

1,2-O-(Isopropyl Orthoacetyl) Group Fragments

The fast ethanolysis of exo-OR 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-
α-D-glucose to form 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose was
confirmed by the fast rate of isopropanol formation and the much slower rate of
alkyl acetate formation as determined by GLC. Two chromatograms illustrated in
Fig. 3 show this. Chromatograms A and B were at approximately 1 and 98% disappear-
ance of the 1,2-O-(alkyl orthoacetyl) group*, respectively. The samples contained
equivalent amounts of internal standard (n-butyl acetate). A comparison of the
isopropanol peak size in Chromatograms A and B shows that the isopropanol formation
was very fast relative to the loss of 1,2-O-(alkyl orthoacetyl) group (indicated
by alkyl acetate formation). In fact, it would appear that alkoxy exchange yield-
ing isopropanol was nearly complete in less than 8 minutes. The much slower forma-
tion of ethyl acetate and absence of isopropyl acetate indicates that the alkyl
acetate must have been formed from the 1,2-O-(ethyl orthoacetyl) group instead of
the 1,2-O-(isopropyl orthoacetyl) group. Acid-catalyzed transesterification of
isopropyl acetate to ethyl acetate would be too slow to account for the results
(30).

*As determined as any of the possible 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-
α-D-glucoses. The method used does not differentiate between the four possibilities.
Figure 3. GLC Chromatograms of the Ethanolysis Fragments of the 1,2-0-(Isopropyl orthoacetyl) Group: A, 8 Min.; B, 2779 Min.
EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL-d$_5$ ORTHOACETYL)-a-D-
GLUCOSE ISOMERIZATION

Because exo-OR 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-a-D-glucose quickly forms both isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-a-D-glucose upon ethanolysis, it is reasonable to expect that exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-a-D-glucose will also isomerize during ethanolysis. The rate of isomerization and the isomeric ratio are of interest. To determine this, ethanolyses of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-a-D-glucose were run in d$_5$-ethanol-OH and followed by NMR (approximately 60% CD$_3$CD$_2$-OH and 40% orthoester, v/v, containing several mg. picric acid per ml. at 45°C.). Three partial NMR spectra of the reaction (Run B, Appendix I) are shown in Fig. 4.

A 1,2-O-(ethyl-d$_5$ orthoacetyl) group must react during ethanolysis to form either an acetyl group or an orthoacetyl group* (transorthoesterification). Thus, the sum of the appropriate NMR signal intensities of the acetyl and orthoacetyl methyl group singlets constitutes a mole balance on the original orthoester. The intensities of the acetyl and orthoacetyl methyl group singlets can, therefore, be used to calculate extent of reaction and product ratios. The data, expressed as the signal height of the appropriate signals, are recorded in Appendix I. These signal heights were used to construct Fig. 5 by employing the TMS signal height as an internal standard.

Examination of Fig. 5 shows that equilibrium between endo-OR and exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-a-D-glucose was approached before there was significant loss of 3,4,6-tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-a-D-glucose. An isomeric equilibrium of approximately 20% endo-OR and 80% exo-OR is indicated in Fig. 5.

*It will be proven later that the sum of the amounts of acetyl and orthoacetyl group is a constant throughout the ethanolysis.
Figure 4. Partial NMR Spectra of the d$_5$-Ethanolysis of Exo-OR 3,4,6-Tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-α-D-glucose:
A, 2.3 Min.; B, 15.9 Min.; C, 60 Min., D$_2$O Added
Figure 5. Isomerization of Exo-OR 3,1,6-Tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-\(\alpha\)-D-glucose Versus Disappearance of Isomers
Since NMR signal heights were assumed to be proportional to the amount of each component present, the values plotted in Fig. 5 are somewhat in error. An estimate of the error involved in using signal heights in this manner can be obtained from other data. Using the peak heights of Spectrum D, Fig. 2b gives 23% endo-OR isomer while the integrated value is 19.6%.

POLARIMETRIC MAXIMUM IN ETHANOLYSIS

Ethanolysis of \textit{exo-OR} 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose} exhibits maximum in optical rotation-time curves. This maximum illustrated by Run 2 plotted in Fig. 6, occurs at short time corresponding to about 5% disappearance of 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose}. Data are in Appendix II.

Perlin (7) did not note a maximum in the optical rotation data for the methanolysis of \textit{exo-OR} 3,4,6-tri-\textit{O}-acetyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose} catalyzed by 0.0012N hydrogen chloride at 25.0°C. However, under the conditions used a very fast rate of reaction was observed which would make detection of the maximum difficult, if not impossible. Thus, the failure to note a polarimetric maximum under the above conditions is not in disagreement with this work.

The observed maxima suggest the formation of a compound more dextrorotatory than \textit{exo-OR} 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose}. The three possibilities which might fit the requirement of high positive specific optical rotation are, (1) \textit{endo-OR} 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose}, (2) 3,4,6-tri-\textit{O}-methyl-1-\textit{O}-(diethyl orthoacetyl)-\textit{\alpha-D-glucose}, and (3) 3,4,6-tri-\textit{O}-methyl-2-\textit{O}-(diethyl orthoacetyl)-\textit{\alpha-D-glucose}. All three possibilities could result by transorthoesterification. \textit{Endo-OR} 3,4,6-tri-\textit{O}-methyl-1,2-\textit{O}-(ethyl orthoacetyl)-\textit{\alpha-D-glucose} is definitely more dextrorotatory than the \textit{exo-OR} isomer since a 19.6\% \textit{endo-OR} - 80.4\% \textit{exo-OR} mixture gave $[\alpha]_{546}^{25}$ nm. +71.5° while the pure \textit{exo-OR} isomer
Figure 6. Ethanoyses of 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose Followed Polarimetrically
gave $[\alpha]_{546}^{25}$ nm. $+67.0^\circ$ in toluene-triethylamine*. On the basis of optical rotations of compounds related structurally to the latter two possibilities, it would be expected that these possibilities would also be more dextrorotatory** than exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetate)-\(\alpha\)-D-glucose.

The ethanolysis of a near equilibrium mixture of 19.6% endo-OR - 80.4% exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetate)-\(\alpha\)-D-glucose (NMR Spectrum D, Fig. 2b) does not exhibit a maximum in the polarimetric curve (Fig. 6). Thus, the polarimetric maximum shown by the ethanolysis of the initially pure exo-OR isomer must be due to formation of the endo-OR isomer. If the maximum had been due to formation of polarimetrically significant quantities of either or both 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetate)-\(\alpha\)-D-glucose and 3,4,6-tri-O-methyl-2-O-(diethyl orthoacetate)-\(\alpha\)-D-glucose the maximum would have been apparent in both curves in Fig. 6.

The NMR data already discussed and polarimetric data are in agreement with respect to the observation that isomerization (or alkoxy exchange) is the only significant reaction occurring initially in the ethanolysis of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetate)-\(\alpha\)-D-glucose. However, this does not eliminate the possibility that 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetate)-\(\alpha\)-D-glucose and/or 3,4,6-tri-O-methyl-2-O-(diethyl orthoacetate)-\(\alpha\)-D-glucose may be important intermediates in transorthoesterifications such as isomerization or other reactions not yet discussed.

*This basic, nonpolar solvent was chosen to exclude any possibility of endo-OR isomer formation from the pure exo-OR sample.

**Specific optical rotations in chloroform: exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetate)-\(\alpha\)-D-glucose (+45°), 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetate)-\(\alpha\)-D-glucose (+115°), and 2-O-acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucose (+116°).
The obvious difference in the rate of ethanolysis of the pure exo-OR isomer and the exo-endo mixture (Fig. 6) demands some explanation. Runs 2 and 4 (exo-OR initially) were about 5 times faster than the run with the isomeric mixture based on the slopes of the curves at identical values of $[\alpha]_{546}^{25}$ nm. This is probably due to incomplete removal of pyridine from the isomeric mixture after column-chromatographic purification (see Experimental). Based on an estimated acid dissociation constant for 2,6-dichlorobenzoic acid in ethanol*, the concentration of 2,6-dichlorobenzoic acid and 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-$\alpha$-D-glucose, and an assumption of complete salt formation between 2,6-dichlorobenzoic acid and pyridine, the isomeric mixture of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-$\alpha$-D-glucose would require only 0.02% pyridine contaminant to slow the reaction 5 times. The distillation purification procedure used for the exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-$\alpha$-D-glucose used in kinetics precludes contamination by bases. Hence, samples of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-$\alpha$-D-glucose give reproducible reaction rates. Runs 2 and 4 shown in Fig. 6 are only one example of this reproducibility.

Determination of ethanolysis rate constants by polarimetry is discussed in Appendix III.

RATES OF ALKOXY EXCHANGE AND THE EFFECT OF WATER.

The rate of isomerization of exo-OR 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-$\alpha$-D-glucoses during ethanolysis is difficult to measure because of the fast rate involved without changing the catalyst concentration or conditions. However, a minimum estimate of the rate of isomerization relative to the rate of disappearance of

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*In water $K_a = 2.55 \times 10^{-2}$ (31). Assuming parallel behavior with benzoic acid (32) in water and ethanol, the value of $K_a$ would be $3.7 \times 10^{-8}$ for 2,6-dichlorobenzoic acid in ethanol.
1,2-orthoester can be obtained from the study of the effect of water contaminant on
the ethanolysis. The data obtained, which indicate extreme sensitivity to water,
are in Table I\(^1\).

Ethoxy exchange with the solvent, which in absolute ethanol is one of the
possible mechanisms of isomerization, results in hydrolysis products when the
exchange involves water. If it is assumed that (1) the reaction involving water
is irreversible\(^2\), (2) the reactivity of water and ethanol is the same\(^3\), and (3) the
relative rates do not differ between 98\% ethanol and absolute ethanol, then the
ratio of the number of alkoxy exchanges to the number of reactions producing ethan-
olysis products by disappearance of 3,4,6-tri-\(\text{O}\)-methyl-1,2-\(\text{O}\)-(ethyl orthoacetyl)-\(\alpha\)-
D-glucose can be estimated.

The ratio of hydrolysis products (0.974 mole fraction) to ethanolysis products
(0.063 mole fraction) found at complete reaction (Table I, Conditions A) indicates
that hydrolysis was 15 times faster than ethanolysis to cause disappearance of
3,4,6-tri-\(\text{O}\)-methyl-1,2-\(\text{O}\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucose. Due to the fact that with
Conditions A there were 19 molecules of ethanol for every molecule of water, the
rate of ethoxy exchange would be 20 times that indicated by hydrolysis. Hence, the
relative rate of alkoxy exchange to disappearance of 3,4,6-tri-\(\text{O}\)-methyl-1,2-\(\text{O}\)-(ethyl
orthoacetyl)-\(\alpha\)-D-glucose must have been approximately 3 \(\times\) 10\(^2\) or 20 \(\times\) 15.

\(^1\)The abbreviations used in Table I and in subsequent tables and figures are given
in the Nomenclature.

\(^2\)The orthoacid group, \(\overset{\text{RO}}{\text{C}}\overset{\text{OH}}{\text{R}'\text{O}}\overset{\text{Mc}}{\text{RO}}\), which forms by reaction with water, is
assumed to form ester completely in this case and in all subsequent cases en-
countered in this thesis.

\(^3\)A similar assumption has been made with water and methanol by Cordes (14) in
work of a similar nature.
### TABLE I

REACTION OF EXO-OR 3,4,6-TRI-O-METHYL-1,2-Q-(ETHYL ORTHOACETYL)-α-D-GLUCOSE AT 25.0°C. IN 0.0085M 2,6-DICHLOROBENZOIC ACID SOLUTIONS OF ETHANOL-WATER

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time, min.</th>
<th>Ethanolysis Products</th>
<th>Hydrolysis Products</th>
<th>Total Measured</th>
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<tr>
<td></td>
<td></td>
<td>β Et 2-Q-A</td>
<td>α Et</td>
<td>β Et</td>
</tr>
<tr>
<td>A</td>
<td>338</td>
<td>0.008 (2)</td>
<td>0.004 (1)</td>
<td>0.037 (3)</td>
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<tr>
<td>A</td>
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<td>0.009 (1)</td>
<td>0.004 (4)</td>
<td>0.038 (4)</td>
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<tr>
<td>B</td>
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<td>nd</td>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>B</td>
<td>1497</td>
<td>nd</td>
<td>d</td>
<td>d</td>
</tr>
</tbody>
</table>

d = detected but not measured because of insufficient quantities.
nd = not detected.

**(A)** Solvent: 5 mole % water, 95 mole % ethanol; 11.9 moles water/mole orthoester.
**(B)** Solvent: 30 mole % water, 70 mole % ethanol; 87.6 moles water/mole orthoester.

Figures in parentheses are the range of three GLC analyses on the same sample multiplied by 10³.

**b** The hydrolysis products are mono-Q-acetyl-3,4,6-tri-Q-methyl-α-D-glucoses only.
The reader may question why 3,4,6-tri-0-methyl-D-glucose is listed as an ethan-
olysis product only and not as a hydrolysis product in Table I while this compound 
might reasonably be considered to result from both reactions. Experimentally, there 
are two very good reasons for this. First, when an ethanolysis is carried out in 
anhydrous ethanol where hydrolysis does not take place, the product distribution 
includes 0.2 mole fraction 3,4,6-tri-0-methyl-D-glucose which is the same proportion 
listed in Table I for Conditions A. Second, when 3,4,6-tri-0-methyl-1,2-0-(alkyl 
orthoacetyl)-α-D-glucoses are hydrolyzed in pure water, 3,4,6-tri-0-methyl-D-glucose 
is not detected by either TLC or GLC. Hydrolyses of 3,4,6-tri-0-methyl-1,2-0-(alkyl 
orthoacetyl)-α-D-glucoses give quantitative yields of 1-0-acetyl- and/or 2-0-acetyl-
3,4,6-tri-0-methyl-α-D-glucose. In fact, both of these compounds were readily 
isolated in crystalline form from hydrolyses (see synthesis in Experimental). Perlin 
(7) detected analogous products in hydrolyses of mannose orthoesters but apparently 
acetyl retention, as indicated by lead tetraacetate oxidation, on the products was 
not complete.

Consequences of Alkoxy Exchange Studies

Kochetkov (cf. 16) claims that catalyst concentrations or combinations of 
catalysts and catalyst concentrations have been found which give only alkoxy exchange 
and no glycoside formation. In the systems just described for 3,4,6-tri-0-methyl-
1,2-0-(alkyl orthoacetyl)-α-D-glucoses, alkoxy exchange and also glycoside and reduc-
ing sugar formation were found to occur simultaneously. However, alkoxy exchange is 
so much faster than glycoside formation that one orthoester may be converted to 
another by alkoxy exchange prior to appreciable glycoside formation. This large 
difference in rate between the two reactions could also explain Kochetkov's results 
quite readily.
Water scavenging by sugar 1,2-orthoesters is probably one of the most important experimental difficulties to contend with in the utilization of sugar 1,2-orthoesters in glycoside syntheses. This fact has already been experimentally appreciated by Russian workers (18). The yields from Koenigs-Knorr reactions may also suffer from the orthoester water scavenging phenomenon. In support of this statement it should be noted that orthoesters have been proposed as intermediates in alcoholyses of 2,3,4,6-tetra-O-acetyl-α-D-glucosyl bromide (33) and have been reported as products in Koenigs-Knorr reactions (4, 34). Water in these reactions can be present as either a contaminant or as a result of neutralization of the liberated hydrogen halide by an acid acceptor (34).

DISAPPEARANCE OF 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE

Because of the fast rate of alkoxy exchange, the disappearance of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose during ethanolysis is nearly the same with respect to the product distribution and rate of reaction no matter whether \textit{exo}-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose or \textit{exo}-OR 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose is used as the reactant. In fact, the reactant in both cases should be essentially an equilibrium mixture of \textit{endo}-OR and \textit{exo}-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose before there is significant loss of 1,2-O-(alkyl orthoacetyl) groups by ethanolysis. The questions of which isomer is more reactive to ethanolysis product formation, or whether the same product distribution is obtained with both isomers, cannot be determined from the data obtained because of the rapid approach to \textit{endo}-OR - \textit{exo}-OR equilibrium compared to the rate of ethanolysis product formation. However, this may not be generally true for carbohydrate 1,2-orthoesters since 3,4,6-tri-O-benzyl-1,2-O-(alkyl orthoacetyl)-β-D-mannoses appear to behave differently in this respect (13).
The measurable ethanolysis products resulting from disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose are: ethyl 3,4,6-tri-O-methyl-β-D-glucoside, ethyl 3,4,6-tri-O-methyl-α-D-glucoside, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside, and 3,4,6-tri-O-methyl-α-D-glucose. Measurable amounts of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside are formed only in ethanolyses with added salts present. The ethanolysis products are formed in constant proportions until late in the ethanolysis; the rate of product formation is equal to the rate of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose disappearance; and the measured glucose moieties constitute a mole balance of original reactant. Data in Table II illustrate products and reactant analyses as a function of time for the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in the absence of salts. The methods of product identification and analysis are given in detail in the Experimental and additional data similar to that given in Table II are tabulated in Appendix IV.

As seen from Table II, the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose results in stereoselective formation of β-glucosides (27:1:0:α). In fact, the synthesis of crystalline ethyl 3,4,6-tri-O-methyl-β-D-glucoside on a preparative basis by the orthoester method was found to give yields (ca. 70%) comparable to those obtained using the Koenigs-Knorr synthesis. Methyl 3,4,6-tri-O-methyl-β-D-glucoside, which is a known crystalline compound (35) was prepared also by an orthoester methanolysis in 72% yield. These results leave little doubt as to the stereoselective formation of β-glucosides in methanolyses and ethanolyses.
TABLE II

ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE\textsuperscript{a}
AT 25°C. IN 0.00526\textsubscript{N} 2,6-DICHLOROBENZOIC ACID (RUN 3)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Product\textsuperscript{b} (X_{α Et})</th>
<th>Reactant\textsuperscript{b} (X_{β Et})</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0</td>
<td>-</td>
<td>-</td>
<td>1.015 (15)</td>
</tr>
<tr>
<td>80.3</td>
<td>0.031 (1)</td>
<td>0.004 (4)</td>
<td>0.851 (7)</td>
</tr>
<tr>
<td>169.6</td>
<td>0.061 (1)</td>
<td>0.009 (4)</td>
<td>0.699 (8)</td>
</tr>
<tr>
<td>269.9</td>
<td>0.085 (2)</td>
<td>0.013 (2)</td>
<td>0.556 (5)</td>
</tr>
<tr>
<td>417.0</td>
<td>0.116 (1)</td>
<td>0.016 (1)</td>
<td>0.409 (3)</td>
</tr>
<tr>
<td>589.0</td>
<td>0.138 (0)</td>
<td>0.020 (1)</td>
<td>0.409 (3)</td>
</tr>
<tr>
<td>787.0</td>
<td>0.156 (2)</td>
<td>0.022 (1)</td>
<td>0.398 (3)</td>
</tr>
<tr>
<td>1027.0</td>
<td>0.171 (2)</td>
<td>0.024 (3)</td>
<td>0.398 (3)</td>
</tr>
<tr>
<td>1332.0</td>
<td>0.180 (3)</td>
<td>0.023 (1)</td>
<td>0.398 (3)</td>
</tr>
<tr>
<td>1809.0</td>
<td>0.189 (4)</td>
<td>0.026 (3)</td>
<td>0.398 (3)</td>
</tr>
<tr>
<td>2808.0</td>
<td>0.192 (5)</td>
<td>0.028 (3)</td>
<td>0.398 (3)</td>
</tr>
<tr>
<td>4920.0</td>
<td>0.193 (5)</td>
<td>0.030 (3)</td>
<td>0.398 (3)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 1.8 g./200 ml.

\textsuperscript{b} Figures in parentheses are the range of three GLC Analyses on the same sample multiplied by 10\textsuperscript{3}; the analyses are illustrated by the chromatograms in Fig. 16a and 16b.
About 20% of the original 1,2-\(\text{O-}(\text{ethyl orthoacetyl})\) group is retained as acetyl on ethyl 2-\(\text{O-}\text{acetyl-3,4,6-tri-\(\text{O-}\text{methyl-\(\beta\)-D-glucoside. There was no loss of acetyl groups by transacetylation from this product in any ethanolysis run even in the case where the ethanolysis was followed up to 80 half-lives of 3,4,6-tri-\(\text{O-}\text{methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\alpha\)-D-glucose (Table XIV, Appendix IV). This indicates that transacetylation is unimportant in ethanolyses studied. The literature leaves some doubt as to acetyl retention on the glycosidic products and to the possibility of loss by transacylation. Franks and Montgomery (13) claim that transacetylation occurred after methanolysis of 3,4,6-tri-\(\text{O-}\text{benzyl-1,2-\(\text{O-}(\text{methyl orthoacetyl})\)-\(\beta\)-D-mannose causing lower yields of isolated methyl 2-\(\text{O-}\text{acetyl-3,4,6-tri-\(\text{O-}\text{benzyl-\(\alpha\)-D-mannoside with increasing concentration of methanol in inert solvent. Lemieux (10) reports no retention of acetyl groups on the C-2 oxygen of any glucose product in similar experiments with 3,4,6-tri-\(\text{O-}\text{acetyl-1,2-\(\text{O-}(\text{alkyl orthoacetyl})\)-\(\alpha\)-D-glucoses. However, Kochetkov and coworkers (16) report a 2-\(\text{O-}\text{acyl group on all isolated glycosides in their experiments on 1,2-orthoester of sugars.}

3,4,6-Tri-\(\text{O-}\text{methyl-D-glucose which was found would be expected as an ethanolysis product because of reported 3,4,6-tri-\(\text{O-}\text{acetyl-D-glucose and -D-mannose isolated from alcohólyses of 3,4,6-tri-\(\text{O-}\text{acetyl-1,2-\(\text{O-}(\text{alkyl orthoacetyl})\)-\(\alpha\)-D-glucoses and 3,4,6-tri-\(\text{O-}\text{acetyl-1,2-\(\text{O-}(\text{methyl orthoacetyl})\)-\(\beta\)-D-mannose (7, 10). Analogous products have been reported for other 1,2-orthoesters of sugars (8, 9).}

3,4,6-Tri-\(\text{O-}\text{methyl-D-glucose Anomeric Configuration}

The configuration of the 3,4,6-tri-\(\text{O-}\text{methyl-D-glucose formed in the ethanolysis of 3,4,6-tri-\(\text{O-}\text{methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\alpha\)-D-glucose is of considerable mechanistic importance and had to be determined. Either of the two transorthoesterification mechanisms proposed (1, 7) for the formation of this type of product predict the \(\alpha\)-anomer. Experimentally, the \(\alpha\)-anomer was shown to be formed (data in Appendix V).
Samples of the ethanolysis solution (Run 4) followed by polarimetry were stopped by addition of triethylamine at 408 min. and 3014 min. to observe the base-catalyzed mutarotation of the \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose which had formed during the acid-catalyzed ethanolysis. Both samples showed mutarotation downward (-0.14° and -0.07°, respectively) to constant rotation values proving that the \(\alpha\)-anomer must have been formed at least in quantities above that of the mutarotated \(\alpha,\beta\)-anomer equilibrium.

To show that only the \(\alpha\)-anomer is formed initially in the above ethanolysis, other data must be considered, i.e., the amount of \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose present, the rate of mutarotation of \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucoses in 0.0052N ethanolic 2,6-dichlorobenzoic acid at 25.0°C., and the value \([\alpha]_{\text{2546 nm}} = +155° + 116°\) (ethanol) for \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose. If only the \(\alpha\)-anomer is formed during ethanolysis (Run 4, sample at 408 min.), the \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose should exhibit mutarotation downward by -0.16°. Experimentally, addition of triethylamine caused base-catalyzed mutarotation of -0.14°. However, prior to triethylamine addition the \(3,4,6\)-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose would have already mutarotated approximately -0.02° in the acidic system. Thus, the experimental result is in excellent agreement with the calculated value which assumed that only the \(\alpha\)-anomer is formed during ethanolysis.

ESTER AND TRIETHYL ORTHOACETATE FORMATION

The formation of the glucose products (Table II) must be accompanied by products resulting from the 1,2-\(\alpha\)-(ethyl orthoacetyl) group. These products are experimentally found to consist of ester and triethyl orthoacetate in near equal proportions to glucosides and reducing sugar, respectively.
Because orthoesters are stable in alkaline media while esters consume an equivalent amount of alkali, it is possible to utilize these properties to measure the amounts of ester produced as a function of time during the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. The method makes no distinction as to the identity of the ester measured, hence this information must be supplied by other methods. From previous discussion of the glucose moieties measured it should be apparent that 20% of the 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose forms ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside (an ester). The remaining ester produced must be ethyl acetate since this is the only possibility other than glucose esters. The ethyl acetate formed was identified by NMR (Fig. 4) and GLC (Fig. 3). The measured ester is plotted in Fig. 7 as a function of time. The values of ester are slightly higher than the total measured mole fraction of glucosides (Table II). The probable reason for the ester values being different at long ethanolysis times for the two ethanolyses (Fig. 7) and slightly higher than the glucoside values will be discussed later in light of the probable behavior of the orthoester product of the ethanolysis.

The difference between the measured ester and original 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose is the amount of orthoester remaining, but the identity of the orthoester is not specified by the method. Residual 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose is given by the glucose moiety measurements (Table II). The underlying assumption that the total amount of orthoester and ester remains constant during ethanolysis was readily proved. The experimental proof of this is in the footnotes of Table XX of Appendix VI where the kinetic ester data for Runs 2 and 3 are given.

The measured values of ester do not approach the original quantity of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose even at long reaction times
Figure 7. Ester Appearance as Mole Fraction of Original 3',6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-D-glucose During Ethanolysis.
(Fig. 7). In fact, the values of ester mole fraction tend to level off between 0.8-0.9 at 2000 minutes ethanolysis with a much slower increase in ester thereafter. The value of orthoester (1.00-ester) after 2000 minutes is not due to significant amounts of unreacted 3,4,6-tri-O-methyl-1,2-Q-(ethyl orthoacetyl)-α-D-glucose (see Table II for Run 3 and compare to Fig. 7). Thus, after 2000 minutes ethanolysis there is approximately 0.14 mole fraction of original orthoester which probably is triethyl orthoacetate since this compound is the only reasonable possibility.

The formation of triethyl orthoacetate was expected because of the trans-orthoesterification mechanisms proposed by Pacsu (1) and Perlin (7) to explain the formation of products such as 3,4,6-tri-O-methyl-α-D-glucose. However, the trialkyl orthoacetate formation had never been demonstrated.

Confirming evidence for the formation of triethyl orthoacetate was obtained by the ethanolysis (d5-ethanol-OH) of exo-OR 3,4,6-tri-O-methyl-1,2-Q-(ethyl-d5 orthoacetyl)-α-D-glucose followed by NMR already described (Fig. 4). The singlet at δ = 1.41 p.p.m. corresponds to the orthoacetyl methyl group which is observed for triethyl orthoacetate. This signal increases in intensity during ethanolysis in accord with what would be expected for triethyl orthoacetate formation. Upon the addition of deuterium oxide the signal disappears with the exception of a signal from a small quantity of impurity originally present giving a signal at δ = 1.41 p.p.m. The ethyl acetate acetyl group singlet at δ = 1.98 p.p.m. increases in accord with the expected deuterolysis of triethyl orthoacetate to ethyl acetate*.

The quantity of triethyl orthoacetate formed in the NMR run should not be used as a quantitative estimate of the expected quantity formed in the ethanolysis under conditions usually used in this thesis work because of the different reaction conditions.

*This last point is more readily seen by inspecting the data in Appendix I for Run B. The signal heights should be compared relative to the internal standard.
The quantity of triethyl orthoacetate formed would be expected to be equivalent to the quantity of 3,4,6-tri-0-methyl-α-D-glucose formed. The value of 0.14 mole fraction triethyl orthoacetate after 3000 minutes (Fig. 7, Run 3) is somewhat lower (0.04) than the value of 3,4,6-tri-0-methyl-D-glucose measured at the same time (Run 3, Table II). This may be the result of water scavenging by the triethyl orthoacetate after its formation. This would explain why the results of Run 2 and 3 are somewhat different at long ethanolysis times (Fig. 7) because of the different ethanol samples used in these runs. Acyclic orthoesters are known to hydrolyze faster than sugar orthoesters (37). Hence, triethyl orthoacetate would be expected to be a more effective water scavenger than 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose and may scavenge water significantly while no sugar orthoester hydrolysis may be noted.

PARALLEL-FIRST-ORDER KINETICS

The kinetic form of 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose ethanolyses is of parallel-first-order to a good approximation.

The constants in the simplified equations* describing this kinetic form are readily understood and are valuable for the condensation of data. Either the glucose moiety or the 1,2-0-(ethyl orthoacetyl) group may be considered to be the reactant (R) in the equations below giving products (P₁, P₂, ..., Pₙ), since two mole balances are possible.

*Frost and Pearson (36) have described the mathematics of parallel-first-order kinetics. The equations given here are simplifications obtained by using the fact that the terms k₁/k₂ are identical to product mole fractions of original reactant.
The integrated rate equation for the disappearance of reactant is given by Equation (1):

\[ \ln X_t = -(\Sigma k_i) t \] (1)

where \( X_t \) is the mole fraction of original reactant remaining at time \( t \) in the ethanolysis exhibiting the pseudo-first-order rate constant \( \Sigma k_i \).

Product appearance is governed by Equation (2) for each product.

\[ \ln (X_{i,\infty} - X_{i,t}) = -(\Sigma k_i) t + \ln X_{i,\infty} \] (2)

where \( X_{i,t} \) is the mole fraction of product \( i \) (based on original reactant) which has appeared at time \( t \). The term \( X_{i,\infty} \) is a constant for each product and equal to the mole fraction of product at infinite time (or relative proportion of that product forming) and can be calculated from Equation (3).

\[ X_{i,\infty} = X_{i,t} / \Sigma X_{i,t} \] (3)

The value of each individual rate constant can be calculated from Equation (4).

\[ k_i = X_{i,\infty} (\Sigma k_i) \] (4)

A complete description of parallel first-order reactions can be given by the values of \( X_{i,\infty} \) and \( \Sigma k_i \) since any other quantities can be calculated from these constants by Equations (1)-(4). The determination of these constants and demonstrations of parallel-first-order kinetics is given below.

**Kinetics of Glucose Moiety Data**

The proportion of each glucose product forming \( (X_{i,\infty}) \) in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose was calculated by using the product data \( (X_{i,t}) \) from Table II and Equation (3). The values of \( X_{i,\infty} \).
calculated in this manner are inaccurate at either low or high percentage disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. At low percentage the values of $X_{\alpha,\infty}$ are inaccurate because of inaccurately measured $X_{\alpha,t}$ values. At high percentage disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose inaccuracy results because the 3,4,6-tri-O-methyl-D-glucose is somewhat reactive in the system and loss of this compound becomes important at longer ethanolysis times (Table II).

The values of $X_{\alpha,\infty}$ determined for Run 3 (Table II) for sample times of 269.9-1809 minutes were used in the parallel-first-order kinetic plot given in Fig. 8 for Table II data. The overall fit of Equations (1) and (2), which predict parallel and linear plots, are excellent out to about 73% disappearance (589 min.) of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. The deviation of the 3,4,6-tri-O-methyl-D-glucose data from first-order kinetics in Fig. 8 was the worst noted in this thesis work.

The slopes of the individual plots in Fig. 8 each give the rate constant $\sum k_\alpha$. These $\sum k_\alpha$ values were averaged (weighted according to mole fraction) to gain accuracy in the reported values.

**Kinetics of Ester Appearance**

The ester produced in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose is nearly equivalent to the proportion of glucosides produced. Hence, the kinetics of ester formation would be expected to be first-order [Equation (2)] with a theoretical mole fraction of ester ($X_{E,\infty}$) equal to 0.795. This value of $X_{E,\infty}$ is the sum of $X_{\alpha,\infty}$ values for the glucosides formed in Run 3 (see Fig. 8). The first-order kinetic plots for ester appearance are given in Fig. 9.
Figure 8. Parallel-First-Order Kinetic Plot of 3,4,6-Tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose Ethanolysis Data (Run 3)
Figure 9. First-Order Plot of Ester Appearance During Ethanolyses of 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose
The measured ester mole fractions for Run 3 fits first-order kinetics up to about 800 minutes ethanolysis corresponding to 82% disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. The downward trend of the data points after 800 minutes (Run 3) and 600 minutes (Run 2) probably is the result of ethyl acetate formation by triethyl orthoacetate water scavenging. The initial slopes of both curves agree and hence show reproducibility of the rate constant (3.8 x 10^{-5} sec.\(^{-1}\)), but the values are somewhat higher than given by the glucose moiety data (3.43 x 10^{-5} sec.\(^{-1}\)) for Run 3. This difference is the expected result for triethyl orthoacetate water scavenging. Another reason for the difference in rate constants noted would be postulated as the reversibility of triethyl orthoacetate and 3,4,6-tri-O-methyl-D-glucose formation to reform glucose orthoesters which may subsequently undergo ethanolysis to glucosides and ester. This postulate is consistent with the noted 3,4,6-tri-O-methyl-D-glucose disappearance at long times (Table II).

**IMPLICATIONS OF PARALLEL-FIRST-ORDER KINETICS AND PRODUCT ANALYSES**

The quantities and rates at which the glucose products, ester products, and triethyl orthoacetate are formed are consistent with the reaction scheme given in Fig. 1 for the disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. This reaction scheme shows the products which must be accounted for by any ethanolysis mechanisms postulated.

The parallel-first-order kinetics found implies one important property of the intermediates involved in the ethanolyses. Every product of the ethanolysis other than those which result in isomerization of the 1,2-orthoester must involve at least two, or more in the case of reversible steps, carbon-oxygen bond cleavages. This indicates that the overall reaction must be the result of a number of consecutive first-order reactions. The fact that parallel first-order kinetics are observed implies that each set of consecutive first-order reactions approximates a first-order
reaction. Hence, the concentration of any intermediate in the reaction must be approximately zero. This is the same as the steady state approximation for each set of consecutive first-order reactions such that:

\[
R \xrightleftharpoons[k'_{-1}]{k'_{1}} \text{Intermediate} \xrightarrow[k'_{2}]{k'_{-2}} P_i
\]

and \((k'_{-1} + k'_{2}) \gg k'_{1}\). The important consequence of these arguments is that any intermediate in the ethanolysis of the 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose must be much more reactive than the 1,2-orthoester itself.

**ETHANOLYSIS RESULTS SUMMARIZED**

The glucose product mole fractions \((X_{i,\infty})\) and rate constants \((\Sigma k_i)\) are presented in Table III for all ethanolyses of 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses. The agreement between the values of \(\Sigma k_i\) calculated from the different types of kinetic data increases the confidence which can be placed on any one value of \(\Sigma k_i\) and the description of the reaction. Also, the values of \(X_{i,\infty}\) are very reproducible as shown by the first three ethanolysis runs given in Table III.

The ethanolysis rate constant \((\Sigma k_i)\) for the ethanolysis using \text{exo}-OR 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose is about 23\% lower than the average value measured for ethanolyses using \text{exo}-OR 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose initially. The seemingly significant rate decrease may be due to 0.5\% (wt.) isopropanol present due to initial transorthoesterification to

*The step \(\text{Intermediate} \rightarrow P_i\) could have been considered reversible but in the parallel first-order kinetic treatment of data it was not. This results in an approximation for 3,4,6-tri-O-methyl-D-glucose formation where reversibility will be shown. However, this is a slow reaction and does not affect what is discussed above.*
TABLE III
RATE CONSTANTS, MOLE FRACTION SUMMARY, AND SALT EFFECTS FOR THE DISAPPEARANCE OF 3,4,6-TRI-O-
METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSES DURING ETHANOLYSIS

<table>
<thead>
<tr>
<th>Alkyl Orthoester</th>
<th>Salt</th>
<th>Glucose Product Mole Fractions (X&lt;sub&gt;α&lt;/sub&gt;)</th>
<th>Rate Constants (10&lt;sup&gt;5&lt;/sup&gt; Σ k&lt;sub&gt;i&lt;/sub&gt; sec&lt;sup&gt;-1&lt;/sup&gt;) from:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>α Et 2-O-A</td>
<td>β Et 2-O-A</td>
</tr>
<tr>
<td>Isopropyl</td>
<td>--</td>
<td>0.000</td>
<td>0.195</td>
</tr>
<tr>
<td>Ethyl (Run 3)</td>
<td>--</td>
<td>0.000</td>
<td>0.196</td>
</tr>
<tr>
<td>Ethyl (Run 1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
<td>0.000</td>
<td>0.191</td>
</tr>
<tr>
<td>Ethyl (Run 2)</td>
<td>--</td>
<td>id</td>
<td>id</td>
</tr>
<tr>
<td>Ethyl (Run 4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>--</td>
<td>id</td>
<td>id</td>
</tr>
<tr>
<td>Ethyl</td>
<td>0.062</td>
<td>0.004</td>
<td>0.159</td>
</tr>
<tr>
<td>LiOTs</td>
<td>0.062</td>
<td>0.009</td>
<td>0.185</td>
</tr>
</tbody>
</table>

LiOTs = lithium p-toluenesulfonate.
id = insufficient data for accurate calculation.
<sup>a</sup>All data obtained at 25.0°C. with 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoester)-α-D-glucose concentration of approximately 2% (w/v) catalyzed with 0.00517-0.00526N 2,6-dichlorobenzoic acid.
<sup>b</sup>Water scavenging was noted accounting for 7-9% of reactant.
<sup>c</sup>Weighted average values for reactant and products by graphical testing of Equations (1) and (2).
<sup>d</sup>Based on value of 0.795 mole fraction ester at infinite time. The Σ k<sub>i</sub> values are probably high due to water scavenging by triethyl orthoacetate.
<sup>e</sup>Appendix III. The isomerization of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose and mutarotation of 3,4,6-tri-O-methyl-α-D-glucose were corrected for.
<sup>f</sup>Calculated using values of X<sub>1,∞</sub> from Run 3 and measured X<sub>1,411</sub> values at 411 minutes in Equations (1) and (2).
form 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose*. The isopropanol in the ethanolic medium would reduce the acid dissociation constant of the 2,6-dichloro-benzoic acid and hence decrease the ethanolysis rate constant. Isopropyl glucosides, which were not detected, would be expected to be insignificant because of the low concentration of isopropanol and the probable decreased effectiveness (18) of isopropanol compared to ethanol in glycoside formation reactions with sugar 1,2-orthoesters.

In the two ethanolyses where hydrolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose was noted (footnote b of Table III) the rate constants were obtained using the assumption that hydrolysis was a parallel first-order reaction independent of the ethanolyses reactions. The values of \( X_{i,\infty} \) were calculated from Equation (3) as if hydrolysis was not present. This is reasonable since the values of \( X_{i,\infty} \) and \( \sum k_i \) in Run 1 in which hydrolysis was noted were in good agreement with those of Run 3 where no hydrolysis was noted of the reactant.

The source of the water in the ethanolysis with added lithium bromide may have been from the reaction flask which was not dried over potassium hydroxide pellets before use and/or from partially hydrated lithium bromide. If the source of water was from the lithium bromide the normality of the salt would have been lower than indicated because of gravimetric solution preparation. This will not affect the conclusions reached.

Classification of Salt Effects

The salt effects on the ethanolysis are of mechanistic importance. These salt effects are exhibited by the variations of rate constants and product distributions

*The molar concentration of 1,2-orthoesters being approximately the same in the runs discussed.
given in Table III. The theory of primary and secondary salt effects has been discussed in detail by Bell (38).

Secondary salt effects occur only when weak acid catalysts are used. 2,6-Dichlorobenzoic acid is undoubtedly a weak acid in ethanol. The secondary salt effect increases the concentration of protons by virtue of increasing the apparent acid dissociation constant. In theory, this should not change the product distribution of the reaction assuming that protons are the only significant catalytic species. The expected increase in ethanolation rate with salt addition can be estimated from published data on the variation of the apparent acid dissociation constant of benzoic acid in ethanolic lithium chloride solutions (32). Assuming parallel behavior of benzoic acid and 2,6-dichlorobenzoic acid, the addition of salt corresponding to 0.062N should increase $\Sigma k_i$ about 5 times compared to that with no salt present. This is approximately the total salt effect resulting (Table III).

The primary salt effect arises because of a change in the ground state to transition state energy difference due to the ionic atmosphere provided by the salt. Primary salt effects in acid-catalyzed reactions are invariably (38) found to be positive (rate enhancement). These primary salt effects must be minor compared to secondary salt effect since approximately the total increase in rate can be accounted for on the basis of secondary salt effects. However, the presence of primary salt effects is visible by virtue of the fact that the product distribution changes upon salt addition. This is an expected result since it must be true that ethanolation products are being formed by two or more mechanisms and it would be extremely fortuitous that the primary salt effect would result in the same rate enhancement in each mechanism.

The major primary salt effect exhibited is the large increase in the amounts of $\alpha$-glucosides formed. The decrease in the amounts of $3,4,6$-tri-$\beta$-methyl-$\alpha$-D-glucose
formed in the ethanolysis with added lithium p-toluenesulfonate must be due to a primary salt effect while the lack of change with lithium bromide is due to both a primary salt effect and a probable participation of bromide ion in the reaction. Lithium p-toluenesulfonate, because of the weakly nucleophilic anion* should not exhibit any noticeable nucleophilic participation which would affect the product distribution. Thus, the results with this salt should be considered close to the true primary salt effect. An important result with this salt is the small quantity of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside formed which was not previously detected in measurable amounts without the addition of salt to the ethanolysis medium. The amount of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside measured is probably due to a rate enhancement in the formation of this product by a primary salt effect.

Lithium bromide, because of the strongly nucleophilic bromide ion (39) may exhibit additional salt effects, which would be due to nucleophilic participation of bromide ion. These effects would be in addition to the effects noticed with lithium p-toluenesulfonate. The most noticeable effect is the increase of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-D-glucosides and decrease in ethyl 3,4,6-tri-O-methyl-D-glucosides in comparison to the lithium p-toluenesulfonate data. There is also a slight increase in 3,4,6-tri-O-methyl-α-D-glucose formation compared to the ethanolysis containing added lithium p-toluenesulfonate.

The salt effects described above will be discussed later in terms of their mechanistic significance.

*Nucleophilicity is between perchlorate and nitrate (39) which are both considered to be weak nucleophiles.
DISAPPEARANCE OF 3,4,6-TRI-O-METHYL-D-GLUCOSE

After the disappearance of 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-a-D-glucose is nearly complete, the disappearance of the 3,4,6-tri-O-methyl-a-D-glucose product becomes the major reaction in the ethanolysis. In the parallel-first-order kinetic treatment of ethanolyses data, the 3,4,6-tri-O-methyl-D-glucose product was considered to be unreactive because of the slow disappearance.

The disappearance of 3,4,6-tri-O-methyl-D-glucose appeared to result in formation of glucosides. The product distribution of small amounts of glucosides which evidently were formed could not be measured with any degree of accuracy because of the presence of much larger amounts of glucosides formed during the disappearance of 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-a-D-glucose. Thus, the best way to study the 3,4,6-tri-O-methyl-D-glucose disappearance was by isolation of the possibilities for this reaction from the ethanolysis of 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-a-D-glucose. The two possibilities for the disappearance of 3,4,6-tri-O-methyl-D-glucose are (1) acid-catalyzed Fisher glycosidation, and (2) the reversible formation of 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-a-D-glucose or other glucose orthoesters which subsequently undergo ethanolysis to glucosides. The former possibility was eliminated since 3,4,6-tri-O-methyl-D-glucose in 25.0°C, ethanolic 0.0052N 2,6-dichlorobenzoic acid did not form detectable amounts of glucosides (GLC detection limits < 0.5%) after 16,000 minutes. This leaves the latter possibility for the disappearance of 3,4,6-tri-O-methyl-D-glucose which was investigated and is discussed below.

GENERAL REACTION SCHEME AND PRODUCTS

The postulate that 3,4,6-tri-O-methyl-D-glucose reacts to form glucose orthoesters by transorthoesterification with triethyl orthoacetate and that these
intermediates subsequently undergo ethanolysis to glucosides was tested using the pure α-anomer of 3,4,6-tri-O-methyl-D-glucose and an approximately twofold excess of triethyl orthoacetate in ethanolic 0.00529N 2,6-dichlorobenzoic acid. The products of this reaction were ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside, ethyl 3,4,6-tri-O-methyl-α-D-glucoside and ethyl 3,4,6-tri-O-methyl-β-D-glucoside. However, product formation was considerably slower than that exhibited by the 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose ethanolysis. The intermediate glucose orthoesters were estimated by the measurement of mono-O-acetyl-3,4,6-tri-O-methyl-D-glucoses after sample hydrolysis. The data are given in Table IV as a function of time. The identification and analysis procedures are described in the Experimental section.

**Glucose Orthoester Intermediates.**

Initially there are two possible glucose orthoester intermediates, II and III, which may form by one transorthoesterification step by reaction of the 3,4,6-tri-O-methyl-α-D-glucose with the 1,1-diethoxyethyl cation (14) which forms from the triethyl orthoacetate.
TABLE IV

ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-α-D-GLUCOSE IN 0.00529N 2,6-DICHLOROBENZOIC ACID AT 25.0°C. IN THE PRESENCE OF TRIETHYL ORTHOACETATEa

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Products b X1,t</th>
<th>Intermediates b,c</th>
<th>Reactant b,c</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3</td>
<td>0.000 (1)</td>
<td>0.002 (2)</td>
<td>0.013 (2)</td>
<td>0.992 (24)</td>
</tr>
<tr>
<td>75.5</td>
<td>0.001 (1)</td>
<td>0.002 (0)</td>
<td>0.024 (3)</td>
<td>0.980 (33)</td>
</tr>
<tr>
<td>151.4</td>
<td>0.001 (1)</td>
<td>0.002 (1)</td>
<td>0.034 (4)</td>
<td>0.950 (20)</td>
</tr>
<tr>
<td>287.5</td>
<td>0.002 (1)</td>
<td>0.003 (1)</td>
<td>0.046 (1)</td>
<td>0.925 (18)</td>
</tr>
<tr>
<td>538.0</td>
<td>0.003 (1)</td>
<td>0.005 (1)</td>
<td>0.068 (4)</td>
<td>0.857 (29)</td>
</tr>
<tr>
<td>840.0</td>
<td>0.006 (1)</td>
<td>0.010 (1)</td>
<td>0.086 (4)</td>
<td>0.802 (13)</td>
</tr>
<tr>
<td>1273.0</td>
<td>0.008 (0)</td>
<td>0.014 (2)</td>
<td>0.101 (0)</td>
<td>0.726 (22)</td>
</tr>
<tr>
<td>1948.0</td>
<td>0.012 (1)</td>
<td>0.022 (1)</td>
<td>0.117 (3)</td>
<td>0.665 (15)</td>
</tr>
<tr>
<td>2859.0</td>
<td>0.018 (1)</td>
<td>0.032 (2)</td>
<td>0.264 (16)</td>
<td>0.551 (22)</td>
</tr>
<tr>
<td>4409.0</td>
<td>0.027 (1)</td>
<td>0.049 (3)</td>
<td>0.339 (15)</td>
<td>0.467 (9)</td>
</tr>
<tr>
<td>6469.0</td>
<td>0.036 (1)</td>
<td>0.064 (2)</td>
<td>0.412 (9)</td>
<td>0.374 (10)</td>
</tr>
<tr>
<td>9000.0</td>
<td>0.047 (2)</td>
<td>0.078 (3)</td>
<td>0.476 (15)</td>
<td>0.069 (1)</td>
</tr>
<tr>
<td>14619.0</td>
<td>0.057 (4)</td>
<td>0.100 (3)</td>
<td>0.572 (22)</td>
<td>0.039 (4)</td>
</tr>
<tr>
<td>22149.0</td>
<td>0.068 (2)</td>
<td>0.117 (2)</td>
<td>0.636 (19)</td>
<td>0.021 (1)</td>
</tr>
<tr>
<td>33375.0</td>
<td>0.074 (3)</td>
<td>0.132 (6)</td>
<td>0.682 (19)</td>
<td>0.010 (1)</td>
</tr>
</tbody>
</table>

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a0.6229 g. 3,4,6-Tri-O-methyl-α-D-glucose/25 ml., 0.581 = moles 3,4,6-tri-O-methyl-α-D-glucose/moles triethyl orthoacetate initially.

bFigures in parentheses are the range of three trials on the same sample multiplied by 10³.

cIntermediate and reactant values are minimum and maximum values, respectively, as explained in the text.
Both II and III may undergo a further transorthooesterification step (intramolecular) to form the endo and exo forms of 3,4,6-tri-O-methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\alpha\)-D-glucose (I). The slow mutarotation (Appendix V, Table XVII) of the 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose eventually results in appreciable quantities of 3,4,6-tri-O-methyl-\(\beta\)-D-glucose which may also form glucose orthoester intermediates IV and V by transorthoesterification. However, further intramolecular transorthoesterification of IV or V to yield 3,4,6-tri-O-methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\beta\)-D-glucose (VI) is not likely as the only 1,2-orthoesters of sugars which have been made have a cis relationship between the C-1 and C-2 oxygens (1, 5). The absence of detectable amounts of ethyl 2-\(\text{O-}\)acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucoside in the ethanolysis (Table IV), which would be a reasonable ethanolysis product of VI, further indicates the unimportance of VI. Thus, there are five possible glucose orthoester intermediates if both isomers of 3,4,6-tri-O-methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\alpha\)-D-glucose are considered to be one possibility.

Since the sum of glucose orthoester intermediates was estimated by the amount of mono-\(\text{O-}\)acetyl-3,4,6-tri-O-methyl-D-glucose present after a hydrolysis step, the measurement results in minimum values. Although 3,4,6-tri-O-methyl-1,2-\(\text{O-}(\text{ethyl orthoacetyl})\)-\(\alpha\)-D-glucose hydrolysis results completely in mono-\(\text{O-}\)acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucoses, the other intermediates (II, III, IV, and V) probably result
in some 3,4,6-tri-O-methyl-D-glucose also.* Thus, the measurement of 3,4,6-tri-O-
methyl-D-glucose is also affected and yields a maximum value.

The glucose orthoester intermediate estimates in Table IV clearly show the
behavior expected for intermediates in that the measurement first shows increasing
mole fraction values with time to a maximum of about 0.12 at about 2000 minutes and
a decline thereafter to about 0.01 at 33375 minutes. The fact that glucose ortho-
esters are readily measured by the analysis procedure is due to the high concentra-
tion of triethyl orthoacetate used (4%, v/v) in the experiment. However, not all
the possible intermediates need contribute significantly to the estimated values
since some intermediates may be extremely reactive and hence present only in low
concentrations. These same intermediates are not readily visible in the 3,4,6-tri-
O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose ethanolyses because of much lower
concentrations (15 times approximately) of triethyl orthoacetate which forms con-
currently with 3,4,6-tri-O-methyl-α-D-glucose.

Ester Formation

The further reaction of the glucose orthoester intermediates results in gluco-
side formation as seen by the results in Table IV. The total orthoester concen-
tration decreases because of the ester formed concurrently with the glucoside formation.
The amount of ester formed should be similar (or related) to that calculated for
the measured amounts of glucosides. The measured amount of ester formed was 3.40
millimoles per 25 ml. of reaction solution at 33375 minutes. Part was due to water
scavenging by triethyl orthoacetate, and this part was estimated by the measurement

*A compound similar to II, 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-
glucose, on hydrolysis yields approximately half 2,3,4,6-tetra-O-methyl-D-glucose
and half 1-O-acetyl-2,3,4,6-tetra-O-methyl-α-D-glucose (Table XXXIV, Appendix XII).
of 1.09 millimoles ester formed in a blank without added 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose. The difference between these two values, 3.40-1.09 = 2.31 millimoles ester, should represent the ester formed during glucoside formation. Experimentally, 2.49 millimoles of glucoside formed in 33375 minutes ethanolysis. Thus, glucosides and ester were formed in equivalent proportions within fair experimental accuracy.

**Implications from Glucose Product Distribution**

3,4,6-Tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose intermediate cannot account for the observed product distribution alone (Table IV). Had 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose been the only intermediate resulting in glucosides by ethanolyses, the glucoside product distribution would have been the same or very similar to that found for the parallel first-order appearance of glucosides from 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose previously discussed (Table III, see Run 3). This is illustrated graphically in Fig. 10 where the proportion of each individual glucoside formed \(\left(\frac{X_{i,t}}{\sum X_{i,t}}\right)\)** is plotted against the mole fraction sum of glucosides formed \(\left(\sum X_{i,t}\right)\). The proportion of each individual glucoside expected from intermediate 3,4,6-tri-O-methyl-1,2-\(\alpha\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose ethanolysis*** is represented by the dotted horizontal lines. The product distribution predicted on the basis of only the 3,4,6-tri-O-methyl-1,2-\(\alpha\)-

---

* The blank was the same solution which was used as the 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose reaction medium. The calculation of ester formed due to 3,4,6-tri-O-methyl-D-glucose reaction to glucosides assumes the same or complete water scavenging by both the blank and the reaction solution.

** The 90% confidence limits are approximately \(\left(\frac{X_{i,t}}{\sum X_{i,t}} + \text{Range}\right)/\sum X_{i,t}\) and are plotted in this manner.

***From Run 3, Table III the expected values of \(\frac{X_{i,t}}{\sum X_{i,t}}\) are calculated to be: ethyl 2-\(\alpha\)-acetyl-3,4,6-tri-O-methyl-\(\beta\)-D-glucoside (0.247), ethyl 3,4,6-tri-O-methyl-\(\beta\)-D-glucoside (0.718), and ethyl 3,4,6-tri-O-methyl-\(\alpha\)-D-glucoside (0.035).
Figure 10. Glucoside Distribution as a Function of Total Mole Fraction of Glucosides Formed from 3,4,6-Tri-O-methyl-α-D-glucose by Ethanolysis in the Presence of Triethyl Orthoacetate (Table IV)
(ethyl orthoacetyl)-α-D-glucose intermediate gives higher values of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside and lower values of both ethyl 3,4,6-tri-O-methyl-β-D-glucoside and ethyl 3,4,6-tri-O-methyl-β-D-glucoside than those experimentally measured. Also the product distribution changes with time (or \( \sum X'_{1,\infty} \)).

The only intermediate which can directly account for the ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside formation is 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. Thus, the quantity of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside formed is an indication of the fraction of glucosides formed via 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. Ethyl 3,4,6-tri-O-methyl-β-D-glucoside and ethyl 3,4,6-tri-O-methyl-α-D-glucoside must be formed from 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in constant proportion (2.91 and 0.143, respectively*) to the measured ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside (Table IV). The sum of the ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside and the calculated ethyl 3,4,6-tri-O-methyl-D-glucosides represent the quantity of glucosides formed from intermediate 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. Examples of the calculated fractions of the glucosides formed via 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose at different sample times are: 287 min. 17%; 1948 min. 20%; 14409 min. 27%; and 33375 min. 33%. These calculations assume that the presence of the high (4% v/v) and changing concentration of triethyl orthoacetate does not cause a significant change in the product distribution from the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose.

Thus, glucose orthoester intermediates other than 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose must account for the major proportion of glucosides formed during the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl

*These factors are calculated from Table III, Run 3 data, for the parallel-first-order kinetic constants, \( X'_{1,\infty} \). The calculations are described fully in Appendix VII.
orthoacetate. Clearly, the glucose orthoester intermediate possibilities, 3,4,6-tri-O-methyl-2-O-(diethyl orthoacetyl)-α-D-glucose (III) and 3,4,6-tri-O-methyl-2-O-(diethyl orthoacetyl)-β-D-glucose (V) are not likely to form glucosides by ethanolysis directly because the C-1 oxygen is not bonded to the orthoester group. Hence, the two remaining glucose orthoester intermediates, 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose (II) and 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-β-D-glucose (IV) must collectively account for the major proportion of glucosides formed in the ethanolysis of 3,4,6-tri-O-methyl-D-glucose in the presence of triethyl orthoacetate.

THE 3,4,6-TRI-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-D-GLUCOSE INTERMEDIATES

Although from previous discussion it is reasonably certain that 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucoses (II and IV) form glucosides by ethanolysis, the glucoside product distribution expected from these intermediates presents an interesting question. The glucoside product distribution can be estimated for II by the analysis below.

Initially only the α form (II) of 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucose can be an intermediate in glucoside formation of either II or IV in the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate. Because of the slow mutarotation of 3,4,6-tri-O-methyl-α-D-glucose (Table XVIII, Appendix V) appreciable quantities of glucosides are formed via II before IV can become an important intermediate in glucoside formation. Only ethyl 3,4,6-tri-O-methyl-β-D-glucoside, ethyl 3,4,6-tri-O-methyl-α-D-glucoside, and 3,4,6-tri-O-methyl-D-glucoses* are likely to form directly from either II or IV by ethanolysis.

*The formation of 3,4,6-tri-O-methyl-D-glucoses are expected on the basis of the reversibility of transorthoesterifications although that resulting cannot be determined in this system.
The estimated values for the total mole fractions each of these glucosides \( X''_{i,t} \) forming directly from both II and IV can be calculated from the product distribution given in Table IV (tabulated values and calculations are in Appendix VII). The results of the reaction, \( I \rightarrow II \rightarrow \text{glucosides} \), are eliminated from the values of \( X''_{i,t} \) by the method of calculation as this reaction is an integral part of the 3,4,6-tri-0-methyl-1,2-O-(ethyl orthoacetyl)-\( \alpha \)-D-glucose (I) intermediate ethanolysis.

Now the glucoside product distribution from the intermediate 3,4,6-tri-0-methyl-1-0-(diethyl orthoacetyl)-\( \alpha \)-D-glucose (II) can be estimated. This was accomplished by plotting the calculated \( X''_{i,t} \) values divided by \( \sum X''_{i,t} \) versus \( \sum X''_{i,t} \) in Fig. 11. The extrapolated values of \( \frac{X''_{i,t}}{\sum X''_{i,t}} \) at \( \sum X''_{i,t} = 0 \) (time = 0) are then reasonable estimates of the relative proportions of ethyl 3,4,6-tri-0-methyl-\( \beta \)-D-glucoside (0.94) and ethyl 3,4,6-tri-0-methyl-\( \alpha \)-D-glucoside (0.06) which result via II.

Unfortunately, a similar type of estimate for the intermediate 3,4,6-tri-0-methyl-1-0-(diethyl orthoacetyl)-\( \beta \)-D-glucose (IV) ethanolysis cannot be made with the data available. IV would be expected to show stereoselectivity for the \( \alpha \)-anomer of ethyl 3,4,6-tri-0-methyl-D-glucoside. The slopes of the plots in Fig. 11 are consistent with this belief but do not prove it.

ETHANOLYSES OF 2,3,4,6-TETRA-O-METHYL-1-0-(DIETHYL ORTHOACETYL)-\( \alpha \)-D-GLUCOSE

The ethanolysis behavior of 2,3,4,6-tetra-0-methyl-1-0-(diethyl orthoacetyl)-\( \alpha \)-D-glucose should approximate the ethanolysis behavior discussed for 3,4,6-tri-0-methyl-1-0-(diethyl orthoacetyl)-\( \alpha \)-D-glucose (II). The 2,3,4,6-tetra-0-methyl substitution of 2,3,4,6-tetra-0-methyl-1-0-(diethyl orthoacetyl)-\( \alpha \)-D-glucose precludes the formation of an 1,2-orthoester by transorthoesterification which is a
Figure 11. Ethyl 3,4,6-Tri-O-methyl-α- and β-D-glucosides Formed from Glucose Orthoester Intermediates Other than 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose as a Function of Total Mole Fraction of Glucosides Resulting from the Same Sources.
complication involved in the discussion of 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose ethanolysis behavior. Because of the probable mechanistic significance of 1-orthoesters in 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose ethanolyses, the ethanolysis was studied under the same conditions, utilizing a similar analysis procedure, as previously described for other ethanolyses.

Based on previous discussion, the predictions for the ethanolysis behavior of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose are: (1) the products; ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside, ethyl 2,3,4,6-tetra-O-methyl-α-D-glucoside, and 2,3,4,6-tetra-O-methyl-D-glucose; and (2) high stereoselective formation of β-glucoside compared to α-glucoside.

Glucose Moieties

Both of the above predictions for the ethanolysis behavior of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose were found to be true. Table V gives the parallel-first-order constants $\Sigma k_i$ and $x_{\alpha,\infty}$ as described by Equations (1)-(4) for this kinetic form with and without addition of lithium p-toluenesulfonate. A parallel-first-order kinetic plot is given in Fig. 12 for the data (Appendix VIII) in the absence of added salt.

**TABLE V**

RATE CONSTANTS, MOLE FRACTION SUMMARY, AND SALT EFFECTS FOR THE DISAPPEARANCE OF 2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE DURING ETHANOLYSIS AT 25.0°C.

| Run Conditions | Mole Fraction Product ($X_{\alpha,\infty}$) | $10^5 \Sigma k_i$ | $c,d$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T4MG-Et(β)</td>
<td>T4MG-Et(α)</td>
<td>T4MG-OH</td>
</tr>
<tr>
<td>0.00525N 2,6-DCBa</td>
<td>0.354</td>
<td>0.012</td>
<td>0.633</td>
</tr>
<tr>
<td>0.00522N 2,6-DCBa</td>
<td>0.440</td>
<td>0.212</td>
<td>0.348</td>
</tr>
<tr>
<td>0.063N LiOTs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a 2,6-Dichlorobenzoic acid.
bLithium p-toluenesulfonate.
cMinimum values explained in text.
dCalculated on the basis of the average $X_{\alpha,\infty}$ values (from all samples), and $X_{\alpha,t}$ and $X_{\beta}$ values at 2.7 min. ethanolysis.
Figure 12. Parallel-First-Order Kinetic Plot of 2,3,4,6-Tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose Ethanolysis Data (Table XXII)
The values of $\Sigma k_i$ in Table V should be considered minimum values as traces of pyridine in the 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-\(\alpha\)-D-glucose may not have been completely removed. The buffering effect of probable traces of pyridine on the 2,6-dichlorobenzoic acid was discussed previously (p. 29) with respect to the rate reduction observed with the ethanolysis of a mixture of isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose from which the residual pyridine from the purification procedure was removed in the same manner. Even with this possible complication the ethanolysis of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-\(\alpha\)-D-glucose exhibits rate constants ($\Sigma k_i$) over 20 times greater than those for the disappearance of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose (Table III).

**DISCUSSION OF ETHANOLYSIS MECHANISMS**

Two types of reactions, i.e., reversible transorthoesterification and irreversible glucoside formation, occur in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-\(\alpha\)-D-glucose in the absence of water. These two types of reactions, which may be broken down further into various individual reactions, cause the complexity of the overall reaction (Fig. 1). The probable reaction mechanisms involved and evidence for these mechanisms will be presented in the following pages.

**TRANSORTHOESTERIFICATION AND HYDROLYSIS MECHANISMS**

The mechanisms of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-\(\alpha\)-D-glucose alkoxy exchange (or transorthoesterification involving the ethanol solvent) and hydrolyses are related and best described together. The isomerization of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses can be visualized as an alkoxy exchange with solvent but can also be visualized to occur by mechanisms not involving alkoxy exchange. The formation of 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose was shown to
be due to transorthoesterification both by its anomeric configuration and by simultaneous formation of triethyl orthoacetate in the systems. However, 3,4,6-tri-O-methyl-α-D-glucose formation is much slower than alkoxy exchange.

The reaction mechanisms supported for these reactions have been postulated in the literature previously. However, these mechanisms have not been proven by elimination of other mechanistic possibilities nor have the essential products been demonstrated unequivocally. Some evidence cited for these mechanisms is not tenable in view of literature which has appeared later.

Transorthoesterifications and hydrolyses of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses must be visualized as beginning by protonation of one of the three orthoester oxygens and subsequent or simultaneous carbon-oxygen bond cleavage between the protonated oxygen and the orthoester carbon as shown in Fig. 13. The transition state cannot be defined because of uncertainty about the rate-controlling step, but the formation of carbonium ions in the reaction would seem certain on the basis of a large amount of data on acyclic orthoester hydrolyses (14).

In Fig. 13, the isomers of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose are not shown but it should be understood that I can be either isomer. Also, the scheme in Fig. 13 applies only to 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose but the extension to include 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucoses is obvious.

Mechanism of Alkoxy Exchange*

The alkoxy exchange reaction of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose and 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose would

*The part of the isomerization reaction not accounted for by alkoxy exchange could be accounted for by mechanisms such as I → VI → I and I → VIII → I. However, there is no evidence available that isomerization and alkoxy exchange occur at different rates so the importance of such mechanisms is subject to conjecture.
Figure 13. Mechanisms of Transorthoesterifications and Hydrolyses of 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucoses
be explained by one or a combination of mechanisms given by A, B, and C which refer to Fig. 13. Mechanism C is the mechanism

\[
A \quad I \rightarrow VII \rightarrow II \rightarrow VII \rightarrow I \\
B \quad I \rightarrow VIII \rightarrow III \rightarrow VIII \rightarrow I \\
C \quad I \rightarrow IX \rightarrow I
\]

postulated in the literature (13, 16); however, Mechanisms A and B have not been eliminated as possibilities.

In the first argument presented, Mechanisms A and B will be assessed on the basis that, experimentally, alkoxy exchange is a much faster reaction than 3,4,6-tri-\(\text{O}\)-methyl-D-glucose formation. Hence, any intermediate in the mechanism for alkoxy exchange must not predict significant amounts of 3,4,6-tri-\(\text{O}\)-methyl-\(\alpha\)-D-glucose.

Mechanism A can be eliminated as a likely mechanism for alkoxy exchange by 3,4,6-tri-\(\text{O}\)-methyl-1,2-\(\text{O}\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses by considering a part of Mechanism A (reaction scheme below) and comparing the necessary rate constants which must be exhibited for Mechanism A to explain experimental results.

\[
\text{VII} \xrightleftharpoons[k_1]{\text{slow}} \text{II} \xrightleftharpoons[k_2]{\text{slow}} \text{XIII}
\]

In the argument presented it will be assumed that Mechanism A is the important mechanism for alkoxy exchange until the argument yields an unreasonable result. The value of 300 is an approximate value for the number of alkoxy exchanges taking place for every reaction causing loss of 3,4,6-tri-\(\text{O}\)-methyl-1,2-\(\text{O}\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose. Hence, \(k_1 = 300\) in arbitrary units. The estimate of the value of \(k_2\) would be \(k_2 \leq 0.2\) in the same units since 3,4,6-tri-\(\text{O}\)-methyl-D-glucose formation,
probably by two mechanisms, one of which involves II, accounts for 20% of the ethanolysis products resulting by loss of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose.* Then $k_1 > 1500 k_2$ to explain the experimental results. Taking into account that II has two ethoxy oxygen-orthoester carbon bonds and only one C-1 oxygen-orthoester carbon bond, the former bonds would have to be at least 750 times more prone to cleave than the latter bond to rationalize the rate constants involved. This is not likely as both are acylic orthoester bonds and would not be expected to show this large difference in reactivity. Thus, Mechanism A is not likely to be important in alkoxy exchange by 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses.

A similar, but probably stronger argument may be constructed to show that Mechanism B is not a likely possibility either. The increased strength of the argument results from considerations of the expected relative basicities of the sugar oxygen-orthoester oxygens in II and III on the basis of inductive effects (electron withdrawing) of neighboring oxygens.

The second argument presented for elimination of Mechanisms A and B for alkoxy exchange involves the necessity that II and III, respectively, must rapidly form 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose without significant side reactions such as glucoside formation. This behavior must be exhibited to explain the fast alkoxy exchange compared to other reactions forming glucosides. This behavior is not exhibited with II as the results of the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate clearly show. The formation of glucosides from II was the major reaction while 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose accounted for a minor proportion of glucosides

*In the argument it is not necessary that 3,4,6-tri-O-methyl-D-glucose be formed via II at all since it is only necessary to be certain that $k_2 < 0.2$. 

formed. The minor amounts of glucosides which form from intermediate 3,4,6-tri-\(\beta\)-methyl-1,2-\(\beta\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose indicates that III also did not form 3,4,6-tri-\(\beta\)-methyl-1,2-\(\beta\)-(diethyl orthoacetyl)-\(\alpha\)-D-glucose significantly. However, no real proof can be presented to show that III was actually formed in significant quantities during this reaction. Thus, the argument does not rigorously eliminate Mechanism B.

Thus, Mechanism C is the likely mechanism for alkoxy exchange since Mechanisms A and B do not reasonably account for the experimental results obtained. Mechanism C is in good accord with experimental results. Mechanism C is also consistent with the observation that 2-ethoxy-2-methyl-1,3-dioxolane undergoes acid-catalyzed trans-orthoesterification in ethanol-\(d_6\) to result in 2-(ethoxy-\(d_5\))-2-methyl-1,3-dioxolane without detection of loss of ethylene glycol prior to equilibrium of ethoxy exchange (40). Similarly, dioxolane acetals also show resistance to ring opening as indicated by the order of magnitude slower rates of hydrolysis relative to the corresponding acyclic acetals (41). The existence of 1,2-acetoxonium ions similar to IX in Mechanism C has been demonstrated (42-44). This indicates strongly that IX may readily form in the ethanolyses of 3,4,6-tri-\(\beta\)-methyl-1,2-\(\beta\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucose.

**Mechanism of Hydrolysis**

The mechanism of hydrolysis of 3,4,6-tri-\(\beta\)-methyl-1,2-\(\beta\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses must account for the fact that the combined yield of 1-\(\beta\)-acetyl- and 2-\(\beta\)-acetyl-3,4,6-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose is quantitative. Acyl migrations are known to occur between the C-2 and C-1 oxygens of glucose (45) so the quantities of each monoacetate isolated does not necessarily represent the initial hydrolysis product distribution. Lemieux, et al. (46, 47) has claimed that hydrolyses of 1,2-orthoesters of glucose initially result in the 2-\(\beta\)-acetyl derivative yet later
claimed that the 1-0-acetyl isomer is formed first (3)*. However, the true identity of the 0-acetyl derivative(s) is unimportant for the present discussion.

The possible mechanisms for the hydrolyses of 3,4,6-tri-0-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucose from Fig. 13 are given below as Mechanisms D-H.

D  I + VII + X + XIV  
E  I + VII + X + XII + XIV  
F  I + VIII + XI + XIV  
G  I + VIII + XI + XII + XIV  
H  I + IX + XII + XIV

Pacu (1) favored Mechanism F while later, Lemieux and Cipera (46) argued that Mechanism H was the predominant mechanism based on expected carbonium ion stability. It is now known that expected carbonium ion stability does not correlate well with hydrolysis rates of acylic orthoesters (14). Thus, Lemieux's idea that the mechanism involving the most stable carbonium ion, if he has indeed made this assignment correctly, will result in the fastest rate of hydrolysis and hence the most important mechanism is not on a firm basis. In fact, a carbonium ion stability argument has been recently applied by DeWolfe (37) to favor Mechanism F originally favored by Pacsu (1).

The importance of Mechanisms D-G can be assessed on the basis of whether the intermediates involved can reasonably predict complete retention of resulting acetyl groups on the glucose moiety upon hydrolysis. The intermediates which are in question are X and XI. In order for these

*A personal communication cited as Ref. (12) of the indicated reference above.
intermediates to predict complete acetyl retention on the sugar (instead of ethyl acetate formation) it is necessary for the ethoxy group to be cleaved off selectively to retain the acetyl group on the sugar. This is not likely to occur selectively as the orthoacids (X and XI) are the same intermediates which would be expected in the corresponding reversible acid-catalyzed transesterification reactions (29, 39).

Thus, Mechanism H is supported by the elimination of Mechanisms D-G. Mechanism H does predict quantitative retention of acetyl groups on the sugar hydrolysis products of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose. In addition, Mechanism H for hydrolysis involves the same 1,2-acetoxonium ion (IX) which is supported for the alkoxy exchange mechanism. This similarity between mechanisms tends to strengthen the arguments for both mechanisms.

However, Mechanism H may not be the only mechanism of hydrolysis of 1,2-O-(benzyl orthoacetyl)-β-D-mannoses as these hydrolyses apparently do not result in complete retention of acetyl groups on the mannose moiety (2).

Mechanisms of 3,4,6-Tri-O-methyl-α-D-glucose Formation

The mechanisms of 3,4,6-tri-O-methyl-α-D-glucose formation from ethanolyses of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose must predict the α-anomer and an equivalent amount of triethyl orthoacetate. Two reaction mechanisms (I and J; refer to Fig. 13) which can be postulated (1, 7) are in accord with the experimental results obtained.

\[
\text{I} \quad I \xrightarrow{\text{VII}} \text{II} \xrightarrow{\text{XIII}} \\
\text{J} \quad I \xrightarrow{\text{VIII}} \text{III} \xrightarrow{\text{XIII}}
\]

Both mechanisms involve two transorthoesterification steps with the only difference between mechanisms being the order of the orthoester carbon-oxygen cleavages.
Hence, because of similarity it is probable that both mechanisms are of quantitative importance but the relative importance of each is difficult to assess. The two uncharged intermediates involved, II and III, must be of only transient existence because of the parallel-first-order kinetic requirement that the concentration of intermediates be approximately zero at any time during ethanolysis.

MECHANISMS OF GLUCOSIDE FORMATION

Complete glucoside and ester formation, as shown in Fig. 1, is the ultimate result of the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses in the absence of water scavenging by orthoesters. The reason for this is the reversibility of transorthoesterifications but irreversible glucoside formation.

Two mechanisms for glucoside formation, which are supported by this thesis work, and the mechanism usually postulated in the literature will be discussed at length. The mechanisms, in the order in which they are discussed, predict the following glucosidic products: (1) α- and β-glucosides with partial acetyl retention on the glucosides, (2) α- and β-glucosides with no retention of acetyl groups on the glucosides, and (3) β-glucosides with complete retention of acetyl group.

The relative importance of each mechanism, i.e., the proportions of glucosides formed via each mechanism, is a very difficult question to answer because in some cases the same product can be predicted by more than one mechanism. However, in certain cases, the product distributions can be used in an assessment of the mechanism's importance.

Glucoside Formation via Initial C-1 Carbon-Oxygen Cleavage

The small amount of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside formed in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in
the presence of lithium p-toluenesulfonate* (Table III), although of little quantitative importance, has considerable mechanistic significance. Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside very likely is formed by the mechanism described by the extreme left-hand arrows in Fig. 1**. An alternate possibility, readily eliminated, is acid-catalyzed anomerization of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside. The elimination of this possibility is due to the fact that ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside was not detected in ethanolyses without salt addition (Table III).

The formation of ion XV is necessary to account for the configurational retention in forming ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside. However, ion XV cannot be entirely specific for formation of α-glucosides so both α- and β-ethyl 3,4,6-tri-O-methyl-2-O-(ethyl orthoacetic acid)-D-glucosides must be formed. Generally, substitution at an asymmetric carbon atom involving carbonium-ion formation results in a predominance of inverted product (48). Thus, in the case being discussed, β-glucoside formation would be expected to predominate.

The α- and β-ethyl 3,4,6-tri-O-methyl-2-O-(ethyl orthoacetic acid)-D-glucosides would then quickly react forming the four glucosides shown and an equivalent amount of ester. The breakdown of the orthoacid group must be fast because of simultaneous glucoside and ester appearance which is found experimentally. The reason for expecting the breakdown of the orthoacid group to glucoside acetate or ethyl acetate (Fig. 1) is that orthoacids are intermediates in acid-catalyzed transesterifications (29, 39). The mechanism given in Fig. 1 has previously been postulated by Perlin (7) with the exception that the orthoacid group was shown forming only alkyl acetate.

*Salt effects were described in the pages near Table III.

**The possibility of a carbonium ion rearrangement was not considered for mechanisms of glucoside formation.
Ethyl 3,4,6-Tri-O-Methyl-2-O-(Ethyl orthoacetic Acid)-a, β-D glucosides

Figure 14. Glucoside Formation Mechanism by Initial C-1 Carbon-Dioxolane Ring Oxygen Cleavage
The primary salt effect on glucoside formation is perplexing but a reasonable interpretation is possible. Usually, it is assumed that the normal primary salt effect is an enhancement of the reaction rate by a reduction in the ground state to transition state energy difference. This does not appear to be the complete case for the primary salt effects noted because of the following reasoning. After correcting for secondary salt effects amounting to an estimated increase in rate of 5 times, there is no apparent increase in the rate of β-glucoside formation (Table III). However, the rate of α-glucoside formation increased 4-5 times even after the secondary-salt-effect correction. Because formation of α-glucosides by a necessary carbonium ion, e.g., ion XV, must also give β-glucosides the relative rate enhancement between α- and β-glucosides needs special interpretation.

The logical explanation would be that the stereoselectivity of β-glucoside formation compared to α-glucoside formation is altered by the ionic atmosphere provided by the added salts. The change in stereoselectivity may result by an increase in stability of ion XV* to further result in a longer average lifetime of ion XV*. The longer lifetime of ion XV would then allow the leaving orthoacid hydroxyl to move further away from the C-1 charge center to result in less shielding of the α-side of C-1 in ion XV. The final result on reaction with ethanol would be an increase in α-glucoside formation at the expense of β-glucoside formation without a large increase in the rate of formation of the combined glucosides (excluding secondary salt effects). This is the result experimentally obtained. The literature results for SN1 reactions at an asymmetric center lend support to this interpretation with respect to amounts of inversion expected compared to carbonium ion stability (48).

*Decreased energy of the transition state in the presence of salts would mean if ion XV is sufficiently close to the transition state on the reaction coordinate, the decreased transition state energy must also be reflected in a more stable ion XV.
The effect of added lithium bromide, which results in increased retention of acetyl groups on the C-2 oxygen of the glucosidic products as compared to the results with lithium p-toluenesulfonate, appears to be consistent with the mechanism given involving ion XV. The bromide ion being a strong nucleophile (39) should compete effectively with ethanol to react with ion XV to yield the α (XVI) and β (XVII) 3,4,6-tri-O-methyl-2-O-(ethyl orthoacetic acid)-D-glucosyl bromides.

The retention of an acetyl group at the C-2 oxygen by orthoacid breakdown would be enhanced by the presence of the bromo group at C-1 because of the electron-withdrawing effect of bromine. This electron-withdrawing effect would cause a decrease in the basicity of the C-2 oxygen and lessen the tendency for the orthoacid carbon-C-2 oxygen bond to cleave as compared to the more remote orthoacid carbon-ethoxy oxygen in an acid-catalyzed reaction. The glucosyl bromides would then undergo ethanolysis to form glucosides (33), or in the case of the 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucosyl bromide the original 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose might be reformulated also (49). The regeneration of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose from ion XV via 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucosyl bromide would be expected to cause: (1) decreased amounts of glucosides formed and hence an increase in the amount of 3,4,6-tri-O-methyl-α-D-glucose formed, and (2) a decrease in the rate constant, Σ k₁, for ethanolysis. Although both of these effects were noted (Table III) with lithium bromide compared to lithium p-toluenesulfonate addition, the increase in 3,4,6-tri-O-methyl-α-D-glucose was small and somewhat uncertain. Also, the rate constant, Σ k₁, should be affected by the
identity of the salt as salt effects are not usually identical beyond a first approxi-
mation of rate enhancement when two salts are compared (38). As mentioned previously,
there is also some uncertainty as to the concentration of lithium bromide because of
possible partial hydration of the salt used.

Additional support for the Fig. 14 mechanism will result from the discussion of
the Fig. 15 mechanism. The support results because of the similarity of the mechanisms
and the fact that experimentally observed salt effects can be attributed to similar
steps in both mechanisms.

**Glucoside Formation via Initial Transorthoesterification and Subsequent C-1 Carbon-Oxygen Cleavage**

At least two mechanisms must account for glucoside formation in the ethanolysis
of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose even though the Fig. 14
mechanism can account for all four glucosides formed (Table III). The evidence for
at least two mechanisms of glucoside formation comes from a comparison of the differ-
et glucoside product distributions of the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-
(ethyl orthoacetyl)-α-D-glucose (Tables II and III) and the ethanolysis of 3,4,6-
tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate (Table IV). The
glucoside product distributions in the two cases must result from the same inter-
mediates because of the reversibility of 3,4,6-tri-O-methyl-α-D-glucose formation.
The direction from which the intermediates are formed must be different and hence
the importance of each intermediate in glucoside formation is different in the two
cases.

The product distributions of the two ethanolyses indicated that 3,4,6-tri-O-
methyl-1-O-(diethyl orthoacetyl)-α-D-glucose (II) is a glucoside-forming inter-
mediate in the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of
Figure 15. Glucoside Formation Mechanism by Initial Transorthoesterification with Subsequent C-1 Carbon-Orthoacetate Oxygen Cleavage
triethyl orthoacetate and hence also an intermediate in the ethanolysis of $3,4,6$-tri-$\beta$-methyl-$1,2$-$\beta$-(ethyl orthoacetyl)-$\alpha$-$D$-glucose. The stereoselectivity of this intermediate for $\beta$-glucoside formation was estimated (curve intercepts, Fig. 11) to be $16:1::\beta:\alpha$ for ethyl $3,4,6$-tri-$\beta$-methyl-$D$-glucosides. A compound related to II, $2,3,4,6$-tetra-$\beta$-methyl-$1$-$\beta$-(diethyl orthoacetyl)-$\alpha$-$D$-glucose, was shown to yield considerable amounts of glucosides ($\beta:\alpha::29:1$) as well as $2,3,4,6$-tetra-$\beta$-methyl-$D$-glucose in ethanolysis (Table V). This further confirms the glucoside-forming ability of II. These results are summarized and interpreted as consistent with the mechanism given in Fig. 15.

There is little doubt that the ethanolysis mechanism of $3,4,6$-tri-$\beta$-methyl-$1$-$\beta$-(diethyl orthoacetyl)-$\alpha$-$D$-glucose (II) and $2,3,4,6$-tetra-$\beta$-methyl-$1$-$\beta$-(diethyl orthoacetyl)-$\alpha$-$D$-glucose are the same with the exception that II may form $3,4,6$-tri-$\beta$-methyl-$1,2$-$\beta$-(ethyl orthoacetyl)-$\alpha$-$D$-glucose by a reversible transorthoesterification. Postulation of the carbonium ion (XVIII) is necessary to account for $\alpha$-glucoside formation (Table V). An alternate possibility to the mechanism in Fig. 15 would involve reaction of ethanol on the $\beta$-side of VII to form the $\beta$-glucoside. This possibility does not explain the huge increase in the amount of ethyl $2,3,4,6$-tetra-$\beta$-methyl-$\alpha$-$D$-glucoside formed in the ethanolysis of $2,3,4,6$-tetra-$\beta$-methyl-$1$-$\beta$-(diethyl orthoacetyl)-$\alpha$-$D$-glucose with added salts. Hence, this possibility is eliminated.

The mechanisms given in Fig. 14 and 15 are similar with respect to carbonium ion formation at C-1 and formation of an orthoacid group prior to reaction with ethanol to form glucosides. Thus, for both mechanisms, the salt effects on stereoselectivity of glucoside formation should be similar.* The data in Table V show a

*An interpretation of the salt effect was given previously with respect to the Fig. 11 mechanism.
large increase in α-glucosides and should be indicative of the salt effect expected for the Fig. 15 mechanism. A similar salt effect should be reflected for products predicted only by the mechanism in Fig. 14, i.e., ethyl 2-O-acetyl-3,4,6-tri-O-methyl-D-glucosides. The formation of a measurable amount of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside (Table III) illustrates that this is the case. Thus, this strengthens the probability that both mechanisms are significant in glucoside formation during ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose.

A further argument for the Fig. 15 mechanism can be based on the product distribution observed (Table III). The major proportion of the observed products are predicted by the Fig. 15 mechanism. This mechanism is also consistent, as is the Fig. 14 mechanism, with equivalent amounts of glucosides and ester being formed.

Literature Mechanism for Ethyl 2-O-Acetyl-3,4,6-tri-O-methyl-β-D-glucoside Formation

The mechanism postulated in the literature (7, 13, 16, 20, 49) for the formation of 1,2-trans-2-O-acetyl glycosides from sugar 1,2-orthoester orthoesters involves attack by the alcohol at C-1 of an 1,2-acetoxonium ion (IX).

This mechanism, at most, can only be of minor importance, in ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose because of the product distributions observed. The 1,2-acetoxonium ion can lead only to one glucoside, i.e., ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside, so in the case of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose ethanolyses, the maximum possible proportion of glucosides which could be formed from the 1,2-acetoxonium ion would
be about 25%.* However, the Fig. 14 mechanism also predicts the formation of ethyl 2-\(\text{-O-}\)acetyl-3,4,6-tri-\(\text{-O-}\)methyl-\(\beta\)-D-glucoside and in addition explains the formation of other glucosidic products. In respect to this last point it should be noted that a 100% yield of a 1,2-trans-2-\(\text{-O-}\)acetyl glycoside has never been obtained from a sugar 1,2-orthoester. In fact, in all cases reported by Franks and Montgomery (12, 13),

more than one mannose was found even in the case of acid-catalyzed rearrangements.

A salt effect (16, 20) on glycoside formation has been proposed to cause an increased rate of formation of glycosides by shielding the charge center of the 1,2-acetoxonium ion by ion pair formation and thus directing the attack of the hydroxyl compound to specific formation of 1,2-trans-2-\(\text{-O-}\)acetyl glycosides. The addition of lithium \(p\)-toluenesulfonate to the ethanolysis of 3,4,6-tri-\(\text{-O-}\)methyl-1,2-\(\text{-O-}\)(ethyl orthoacetyl)-\(\alpha\)-D-glucose actually decreased the proportion of ethyl 2-\(\text{-O-}\)acetyl-3,4,6-tri-\(\text{-O-}\)methyl-\(\beta\)-D-glucoside formed (Table III) while an increase would be expected from Kochetkov's mechanistic interpretation (20). Thus, on this basis, the 1,2-acetoxonium ion mechanism, as interpreted by Kochetkov, is unlikely to be important in glycoside formation in ethanolyses of 3,4,6-tri-\(\text{-O-}\)methyl-1,2-\(\text{-O-}\)(ethyl orthoacetyl)-\(\alpha\)-D-glucose. Perhaps the rate increases noted by Kochetkov (20) are due to secondary salt effects.

In this author's opinion the Fig. 14 mechanism constitutes a better explanation for the formation of 2-\(\text{-O-}\)acyl glycosides from sugar 1,2-orthoesters than the 1,2-acetoxonium ion mechanism for any results ever reported.

*In the case of no added salts the maximum estimate based on data in Table III is: \((0.196/0.795)(100\%) = 25\%\).
EXPERIMENTAL

GENERAL

Melting points were determined on a Thomas Hoover unimelt apparatus which had been calibrated against known compounds.

Elemental analyses were performed by either Chemalytics, Inc., 2330 S. Industrial Park Drive, Tempe, Arizona, or Geller Microanalytical Laboratories, P.O. Box 423, Saddle River, N.J.

NMR spectra were determined with a Varian A-60A spectrometer using tetramethylsilane (TMS) as an internal standard. All spectra were determined at normal probe temperature.

Polarimetry measurements were made on a Zeiss-Winkel visual polarimeter capable of being read to 0.01°.

TLC was conducted on glass plates, 200 x 100 mm., or microscope slides using silica gel G (Brinkman Instruments, Westbury, L.I., N.Y.). Spot visualization was accomplished by spraying the chromatograms with methanolic sulfuric acid (20% w/w) and heating.

GLC was conducted on a Varian Aerograph Model 1200-1 Hy Fi III gas chromatograph equipped with a hydrogen flame ionization detector (50). Recording and integration of the chromatograph response was with a Honeywell Electronic 16 recorder equipped with a model 227 Disc Chart integrator. Prepurified nitrogen was used as the carrier gas. All columns were housed in 1/8 O.D. stainless steel. The conditions used are listed below.

Conditions A: column, 5% S E 30 on 60/80 mesh Chrom. W (10 ft.); nitrogen press. = 45 p.s.i.g.; hydrogen press. = 12.3 p.s.i.g.; column temp. = 162°C.; injector temp. = 205°C., detector temp. = 265°C.
Conditions B: same as conditions A except; column temp. = 130° + 162°C. at 1° min.⁻¹.

Conditions C: column, 80/100-mesh Porapak P (5 ft.); nitrogen press. = 25.5 p.s.i.g.; hydrogen press. = 12.3 p.s.i.g.; column temp. = 110° + 165°C. at 2 min.⁻¹; injector temp. = 180°C.; detector temp. = 265°C.

Conditions D: column, 1:1 w/w mixture of 20% Apiezon M grease on Chrom. W, 60/80 mesh, Chrom. W and 20% butanediol succinate polyester on Chrom. W, 60/80 mesh (5 ft.); nitrogen press. = 44.5 p.s.i.g.; hydrogen press. = 12.3 p.s.i.g.; column temp. = 168°C.; injector temp. = 204°C.; detector temp. = 265°C.

REAGENT PURIFICATION

ETHANOL

The purification method used is a modification of that of Lund and Bjerrum (51).

Absolute ethanol (1000 ml.), magnesium turnings (10 g.), and iodine (1 g.) were added to a 2000-ml. roundbottom flask. After the iodine color disappeared, the mixture was refluxed gently with the exclusion of moisture until the magnesium turnings were converted to magnesium ethoxide (a translucent material which retains the shape of the original turnings). The ethanol was then fractionally distilled (40 cm. Vigreux column) into 500-ml. bottles which had been previously dried by storage over potassium hydroxide or by rinsing with fresh distillate. The middle 600 ml. of distillate was retained and stored by sealing the glass-stoppered bottles with parafilm*.

Ethanol for kinetic runs was usually subjected to the drying procedure twice, the second time just prior to the kinetic run.

ISOPROPA NOL

Isopropanol (1000 ml. reagent grade) and sodium (5 g.) were reacted with the exclusion of moisture until the system was homogeneous. The isopropanol was fractionally distilled (40 cm. Vigreux column) with the exclusion of moisture. The middle 500 ml. was retained and stored in sealed glass ampules.

*Product of American Can Company.
CHLOROFORM

Chloroform (N.F. grade) was purified by the method of Reynolds and Evans (52).

GLYCEROL

Glycerol (J. T. Baker, U.S.P.) (300 ml.) was stored over activated alumina for 48 hours, decanted, and distilled at reduced pressure at about 130°C. The first 150 ml. of distillate was discarded and the second 100 ml. was retained.

2,6-LUTIDINE

2,6-Lutidine (Eastman Organic Chemicals, Practical grade) (1000 ml.) was fractionally distilled (40 cm. Vigreux column) with retention of the middle 700 ml.

PROPAANOIC ANHYDRIDE

Propanoic anhydride (Aldrich Chem. Co., Inc.) (1000 g.) was fractionally distilled (100 cm. Raschig ring column) from phosphorous pentoxide (20 g.). The middle 500 ml. of distillate was retained.

PICRIC ACID

Picric acid (Merck, m.p. 121°-123°C.) was recrystallized from methanol twice and dried in vacuo over potassium hydroxide. M.p. 121.3°-121.8°C. in agreement with the literature.

ETHANOLIC p-TOLUENESULFONIC ACID

p-Toluenesulfonic acid monohydrate (Mallinckrodt Chem. Works, m.p. 104°-106°C.) was dried in vacuo at 100°C. for 4 hours. The dried acid was dissolved in anhydrous ethanol and standardized with sodium hydroxide using phenolphthalein indicator.
PREPARATION OF COMPOUNDS AND PROOF OF STRUCTURE

**EXO-OR 3,4,6-TRI-O-ACETYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE**

The method of preparation is a modification of Schroeder's (53). Tetraethyl ammonium bromide (164 g.), sym-collidine (46.2 g.) and ethanol (28.5 g.) were dissolved in absolute chloroform (1200 ml.). The solution was added to 2,3,4,6-tetra-O-acetyl-α-D-glucosyl bromide (120 g.), and the resulting solution was refluxed for one hour with the exclusion of moisture. After cooling to 0°C., the chloroform solution was washed with ice water (3 x 800 ml.), dried over sodium sulfate, filtered, and concentrated in vacuo to a thick syrup. The syrup was dissolved in 150 ml. of hot isopropyl ether containing 1 ml. of pyridine and allowed to crystallize at room temperature (yield 94 g., 85%). Recrystallizations were from 3:1 (v/v) isopropyl ether-ethanol containing a trace of pyridine. The physical constants were: m.p. 95°-96°C.; [α]_D +29.5° (c, 4.0, chloroform). Literature (46): m.p. 97°-97.5°C.; [α]_D +31° (c, 1.0, chloroform).

**EXO-OR 3,4,6-TRI-O-ACETYL-1,2-O-(ISOPROPYL ORTHOACETYL)-α-D-GLUCOSE**

The preparation of 3,4,6-tri-O-acetyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose is similar to the preceding synthesis. Isopropanol was used in place of ethanol in the recrystallization solvent. The quantities, tetraethyl ammonium bromide (164 g.), sym-collidine (140 ml.), isopropanol (112 ml.), purified chloroform (1200 ml.), and 2,3,4,6-tetra-O-acetyl-α-D-glucosyl bromide (359 g.) resulted in 293 g. (86%) of the isopropyl orthoester. Physical constants after recrystallization were: m.p. 119.5°-120.5°C.; [α]_D +26.9° (c, 5.7, chloroform). Literature (3): m.p. 120°-121°C.; [α]_D +30° (c, 2.4, chloroform).
EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE

Powdered sodium hydroxide (120-130 g.) and 3,4,6-tri-O-acetyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose (40 g.) were added to tetrahydrofuran (650 ml.) in a 2000 ml., three-necked, roundbottom flask fitted with a dropping funnel and an efficient stirrer. The reaction system was partially immersed in a water bath at 24°-28°C. Dimethyl sulfate (65 ml.) was added dropwise over 2.5 hr. with vigorous stirring. After an additional 2.5 hr., triethylamine (200 ml.), benzene (473 ml.), and enough water to dissolve all solids were added. The bath temperature was raised to 60°C. for 1.0 hr., cooled to 0°C., and the stirrer stopped. The usually-encountered, three-phase (liquid) systems were broken by adding water and benzene. The benzene phase was washed with 1% aqueous potassium iodide (1 x 400 ml.), 1% aqueous sodium thiosulfate (1 x 400 ml.), and water (2 x 600 ml.); dried with sodium sulfate; and concentrated in vacuo to yield an oil (av. yield, ca. 90%).

The oil was purified by distillation at reduced pressure (0.05 mm. Hg) in a Kontes short path still fitted with a seven-inch Vigreux column. A small amount of barium oxide (0.5 g.) was added to act as an acid scavenger. A small, magnetic stirring bar prevented bumping in the pot which was heated by an oil bath on a magnetic stirring hot plate. Pot temperatures near 135°C. gave satisfactory distillation rates. The purest distillate, [α]D +45° (c, 1.5, chloroform), was found by TLC to be the last one-third to one-half of the still charge (Appendix IX). The purified oil was stored in a desiccator over sodium hydroxide pellets at -15°C. (Found C, 53.7; H, 8.3. C13H24O7 requires C, 53.4; H, 8.3.)

Acid hydrolysis of the O-methylated orthoester yielded crystalline 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucose which on prolonged hydrolysis gave both known (35) crystalline 3,4,6-tri-O-methyl-D-glucoses thus demonstrating the 3,4,6-tri-O-methyl substitution of the title compound. Another demonstration of
3,4,6-tri-O-methyl substitution resulted from the methanolysis of the title compound to known [35] crystalline methyl 3,4,6-tri-O-methyl-β-D-glucoside. The stability of the 1,2-0-(ethyl orthoacetyl) group during methylation and subsequent work up was readily demonstrated by comparison of NMR data (chloroform-d) before and after methylation. The anomic proton doublet; δ = 5.67 p.p.m., J = 5 c.p.s.; and orthoacetyl methyl singlet; δ = 1.67 p.p.m.; of exo-OR 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose (Fig. 2b, Spectrum C) are in close agreement with the corresponding chemical shifts of the 3,4,6-tri-0-acetyl derivative; δ = 5.72 p.p.m., J = 5 c.p.s., and δ = 1.71 p.p.m., respectively.

**EXO-OR 3,4,6-TRI-O-METHYL-1,2-0-(ETHYL-d5 ORTHOACETYL)-α-D-GLUCOSE**

The following preparation of the 3,4,6-tri-O-acetyl-1,2-0-(ethyl-d5 orthoacetyl)-α-D-glucose is a modification of Schroeder's method [53].

Anhydrous ethanol-d₅ (2 g., lot 2908A from Stohler Isotope), chloroform (100 ml., absolute), 2,6-lutidine (5.1 ml.) and tetraethylammonium bromide (15 g.) were mixed until homogeneous. 2,3,4,6-Tetra-O-acetyl-α-D-glucosyl bromide (11.8 g.) was added, and the resulting solution was refluxed 1 hour with the exclusion of moisture. After cooling to 0°C. the solution was diluted with 150 ml. absolute chloroform, washed with ice water (3 x 250 ml.), dried with sodium sulfate, concentrated in vacuo, and crystallized from isopropyl ether (20 ml.) containing pyridine (0.2 ml.) to yield 10.1 g. (92%) of material.

After recrystallization from a minimum of isopropyl ether containing a trace of pyridine, the m.p. was 95°-96°C. which is in agreement with 3,4,6-tri-O-acetyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose. The NMR spectrum showed no triplet for an ethoxy methyl group. Methylation, on a reduced scale, as described for 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose synthesis yielded the title compound.
Methylation of exo-OR 3,4,6-tri-O-acetyl-1,2-O-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose and subsequent purification of the resulting oil was in the same manner as described for the preparation of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose. The pure oil had \([\alpha]_D^{+42}° (c, 2.3, \text{chloroform}). (\text{Found} \ C, 55.0; \ H, 8.6. \ C_{14}H_{26}O_7 \text{requires} \ C, 54.9; \ H, 8.6.)

The 3,4,6-tri-O-methyl substitution of the title compound was shown by hydrolysis to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucose which had both been prepared previously by hydrolysis of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose. The stability of the 1,2-O-(isopropyl orthoacetyl) group during methylation and subsequent work-up was demonstrated by comparison of NMR data (chloroform-d) before and after methylation. The anomeric proton doublet: \(\delta = 5.65 \text{ p.p.m.}, \ J = 5 \text{ c.p.s.}; \) and orthoacetyl methyl singlet: \(\delta = 1.68 \text{ p.p.m.}, \) of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose (Fig. 2a, Spectrum B) are in close agreement with the corresponding chemical shifts of the 3,4,6-tri-O-acetyl derivative: \(\delta = 5.70 \text{ p.p.m.}, \ J = 5 \text{ c.p.s.}, \) and \(\delta = 1.72 \text{ p.p.m.}, \) respectively.

1-O-ACETYL- AND 2-O-ACETYL-3,4,6-TRI-O-METHYL-\(\alpha\)-D-GLUCOSE

Short-duration, acid-catalyzed hydrolyses of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose and 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose yield two monoacetates of 3,4,6-tri-O-methyl-\(\alpha\)-D-glucose. Separation of these compounds is facilitated if the orthoester hydrolyzed contains some colored materials. An example of a hydrolysis is described below.

Crude 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose (29 g.) was shaken with 200 ml. of 0.1N sulfuric acid at room temperature for 4 minutes, neutralized with aqueous sodium hydrogen carbonate, and extracted repeatedly with
chloroform (5 x 100 ml.). The chloroform extracts were washed with water (100 ml.), and the water phase was back-extracted with chloroform (100 ml.). The combined chloroform extracts were concentrated in vacuo to a yellow sirup which crystallized spontaneously to give 25.2 g. of pale yellow crystals. Recrystallization from isopropyl ether-petroleum ether (30°-60°C.) (5/1, v/v), yielded 20.5 g. (77%) of colorless needles; m.p. 102.5°-105°C. After several recrystallizations from isopropyl ether, this compound (A) had: m.p. 103.5°-105°C.; [α]_D +116° (c, 1.7, chloroform). (Found C, 50.3; H, 7.8. C_{11}H_{20}O_{7} requires C, 50.0; H, 7.6.)

Usually, the above crystallization yields two distinct crystalline materials. The product in greatest quantity (A above) crystallizes as nearly colorless needles from a colored mother liquor while the second product crystallizes as highly colored needles (yellow-orange). Physical separation of the colored crystals and recrystallization from isopropyl ether with decolorization yields B: m.p. 107.5°-108.5°C., [α]_D +146° (c, 1.1, chloroform). (Found C, 50.0, H, 7.7. C_{11}H_{20}O_{7} requires C, 50.0; H, 7.6.)

A mixed melting point of A and B gave a depression of 20°C. A and B both gave positive ferric hydroxamate ester tests. The NMR spectra (chloroform-d) are dissimilar. However, both compounds have three O-methyl singlets near δ = 3.5 p.p.m., an O-acetyl methyl singlet near δ = 2.1 p.p.m., and lose a proton signal upon the addition of D_2O to the NMR sample tubes. Acetylation of A and B with acetic anhydride in pyridine at 0°C. yielded the same crystalline compound as that obtained upon a similar acetylation of known 3,4,6-tri-O-methyl-α-D-glucose. Thus, both A and B must have 3,4,6-tri-O-methyl substitution, contain one unsubstituted hydroxyl and one O-acetyl at C-1 or C-2, and have α-configuration.

The α-configuration of A and B are further confirmed by the high positive specific optical rotations and the coupling constants of the anomeric protons:
A, $\delta = 5.33$ p.p.m. (1:2:1 triplet); $J = 3.5$ c.p.s.; and B, $\delta = 6.20$ p.p.m. (doublet), $J = 3.5$ c.p.s.; which are typical of the $\alpha$-configuration (54-56):

The anomeric proton triplet of A changes to a doublet upon deuterium oxide addition indicating that it is coupled with a hydroxyl proton. Hence, the unsubstituted hydroxyl of A is at C-1 and the O-acetyl group is at C-2. Thus, B should have an unsubstituted hydroxyl group at C-2 and an O-acetyl group at C-1. Confirming evidence of O-acetyl substitution at C-1 in B is obtained by comparing the chemical shifts of the anomeric protons of A ($\delta = 5.33$ p.p.m.), B ($\delta = 6.20$ p.p.m.), and penta-O-acetyl-\(\alpha\)-D-glucopyranose ($\delta = 6.34$ p.p.m.). The chemical shifts for the anomeric protons of the compound with the 1-O-acetyl group and penta-O-acetyl-\(\alpha\)-D-glucopyranose would be expected to be in close agreement and at lower field than the chemical shift of the anomeric proton of the derivative with the C-1 hydroxyl unsubstituted. On this basis B must have the O-acetyl group on C-1.

On the basis of the above evidence, A is 2-O-acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucose and B is 1-O-acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucose.

3,4,6-TRI-O-METHYL-\(\alpha\)-D-GLUCOSES

A mixture of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-\(\alpha\)-D-glucose (16 g.) was dissolved in 250 ml. 0.1N $\text{H}_2\text{SO}_4$. After refluxing for 24 hours, the reaction solution was cooled, deionized with Amberlite MB-3 resin, concentrated in vacuo to a thick sirup, and dissolved in hot isopropyl ether (100 ml.). Upon cooling to room temperature and the addition of seed crystals (needles from a previous preparation which crystallized from the sirup) the solution set "solid" with extremely fine needles. Yield 4.6 g. Upon cooling the mother liquor in a refrigerator and subsequently in a freezer, two additional crops of crystals were obtained totaling 4.9 g. for an overall crystalline yield of 71%. Recrystallization of the first crop of
crystals to constant melting point gave: m.p. 80.5°-81.5°C.; \([\alpha]_D^{22}\) approximately +120° + 77° (c, 1.6, water). Reported for the \(\alpha\) form (35): m.p. 76°-77°C., 78°-80°C.; \([\alpha]_D^{25}\) +91.9° + 77.4° (c, 1.6, water). The literature data for the mutarotation of 3,4,6-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose is questionable since material melting at 64°-67°C. was used. Evidently the literature material initially contained some of the \(\beta\)-form as the equilibrium rotation agrees with the present work.

Recrystallizations of the second and third crops of crystals from isopropyl ether gave prisms: m.p. 102°-103°C.; \([\alpha]_D^{25}\) +41° + 76° (c, 1.3, water). Reported for \(\beta\)-form (35): m.p. 97°-98°C., \([\alpha]_D^{25}\) +41.1° + 78° (c, 1.6, water).

1,2-DI-\(\beta\)-ACETYL-3,4,6-TRI-\(\beta\)-METHYL-\(\alpha\)-D-GLUCOSE

To a mixture of 1-\(\beta\)-acetyl- and 2-\(\beta\)-acetyl-3,4,6-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose (46 g.), a solution of acetic anhydride (92 ml.) and pyridine (184 ml.) at 0°C. was added. After 16 hours at 0°C., the reaction solution was poured into 400 ml. of stirred ice water. After 0.5 hour, the product was extracted with chloroform (2 x 300 ml.); washed successively with N sulfuric acid, saturated sodium hydrogen carbonate and water; and concentrated in vacuo to a pale yellow sirup. The sirup was dissolved in an equal volume of hot isopropyl ether and crystallized at -15°C. to yield 48.5 g. (91%) of prisms: m.p. 60°-64°C. Several recrystallizations from isopropyl ether yielded prisms: m.p. 64°-65°C.; \([\alpha]_D^{22}\) +122° (c, 1.9, chloroform). (Found C, 51.1, H, 7.2. \(C_{13}H_{22}O_8\) requires C, 51.0, H, 7.2.)

The assignment of \(\alpha\)-configuration is indicated by the high positive specific optical rotation, a coupling constant of 3 c.p.s. (54-56) for the anomeric proton at \(\delta = 6.25\) p.p.m. (chloroform-d), and by the fact that acetylation under these conditions generally yields the anomeric configuration of the reactant (57). The title compound was also obtained when pure 3,4,6-tri-\(\beta\)-methyl-\(\alpha\)-D-glucose,
l-0-acetyl-3,4,6-tri-0-methyl-α-D-glucose, or 2-0-acetyl-3,4,6-tri-0-methyl-α-D-glucose were acetylated by the above procedure.

ETHYL 3,4,6-TRI-O-METHYL-β-D-GLUCOSIDE

Method A, Koenigs-Knorr Synthesis

1,2-Di-0-acetyl-3,4,6-tri-0-methyl-α-D-glucose (15 g.) was dissolved in hydrobromic acid (30-32%) in acetic acid (20 ml.) with occasional stirring over 15 min. After 2 hr. at room temperature, the reaction solution was diluted with chloroform (200 ml.) and washed with ice water (200 ml.). The water phase was back-extracted with chloroform (75 ml.). The combined chloroform extracts were washed with ice water (2 x 200 ml.), dried over calcium chloride, and concentrated in vacuo to yield 16.3 g. crude 2-0-acetyl-3,4,6-tri-0-methyl-D-glucosyl bromide as a pale yellow sirup. Attempts to crystallize the crude bromide failed so it was employed in a modified Koenigs-Knorr synthesis (58) without further purification.

Drierite (8 mesh, 27.4 g.), yellow mercuric oxide (8.9 g.), mercuric bromide (0.5 g.), and anhydrous ethanol (137 ml.) were stirred in a stoppered flask for 0.5 hr. A solution of 2-0-acetyl-3,4,6-tri-0-methyl-D-glucosyl bromide (16.3 g., from above) in dry chloroform (137 ml.) was added and stirring was continued for 15 hr. The solids were removed by filtration through Celite, and the filtrate was concentrated in vacuo to a sirup. The sirup was dissolved in ethanol (150 ml.) and sodium hydroxide (150 ml., 0.75N aqueous) was added. After refluxing for 2 hr., the mixture was filtered through Celite and the filtrate was refluxed for 1 hr. longer. After cooling to room temperature, sulfuric acid was added to pH ~ 8 and the product was extracted repeatedly* with chloroform (1/4 x 100 ml.) to give chloroform extracts A. Chloroform extracts A were washed with water (3 x 100 ml.). These

*The water washing of the chloroform extracts serves to remove impurities which probably result from a small amount of demethylation of the sugar during preparation of the 2-0-acetyl-3,1,6-tri-0-methyl-D-glucosyl bromide.
combined water washings were back extracted with chloroform (200 ml.) to give chloro-
form extracts B. Chloroform extracts B were washed with water (4 x 75 ml.). The
combined chloroform extracts (A + B) were concentrated in vacuo to a pale yellow oil.
Crystallization from hexane (50 ml.) at -15°C. gave 7.9 g. (64%) of needles. Several
recrystallizations from hexane gave colorless needles: m.p. 51.5°-53°C.; [α]$_D^{22}$
-23.8° (c, 2.7, chloroform).

Method B. Orthoester Ethanolyses

Anhydrous ethanol (250 ml.) and 0.192N ethanolic p-toluenesulfonic acid (25 ml.)
were added to crude 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose (30.3 g.).
After 0.5 hr. at room temperature, aqueous 1.17N sodium hydroxide (200 ml.) was added.
The resulting solution was refluxed for 3 hours, cooled, and sulfuric acid was added
to pH ~ 8. The dark brown solution was treated with carbon, filtered, and concen-
trated in vacuo. The oil was dissolved in hot chloroform (500 ml.), filtered to
remove insoluble salts, and concentrated in vacuo to 23.2 g. of yellow oil. Crystal-
lization from petroleum ether (100 ml., 60°-90°C.) at -15°C. gave 20.3 g. (78%) of
colorless needles. Several recrystallizations from hexane gave colorless needles:
m.p. 52°-53.5°C.; [α]$_D^{22}$ -23.8° (c, 2.5, chloroform). (Found C, 52.9; H, 8.9.
C$_{11}$H$_{22}$O$_6$ requires C, 52.8; H, 8.9.)

Use of 3,4,6-tri-O-methyl-1,2-0-(isopropyl orthoacetyl)-α-D-glucose in a similar
preparation gave a 72% yield of crystals which did not exhibit a depression of the
melting point on admixture with crystals obtained from the above 3,4,6-tri-O-methyl-
1,2-0-(ethyl orthoacetyl)-α-D-glucose ethanolysis.

The physical constants of the products obtained via the Koenigs-Knorr synthesis
and orthoester ethanolysis agree very well. A mixed melting point shows no depres-
sion. The negative specific optical rotation and the anomeric proton coupling
constant of 7 c.p.s. (δ = 4.22 p.p.m., chloroform-d) (54-56) are evidence of the
B-configuration. Also the Koenigs-Knorr synthesis is known to yield predominantly the β-glucoside (58). By analogy, the synthesis of known methyl 3,4,6-tri-O-methyl-β-D-glucoside by orthoester methanolysis described below is further proof of the β-configuration of the glucoside formed in orthoester ethanolysis.

METHYL 3,4,6-TRI-O-METHYL-β-D-GLUCOSIDE

Methanol* (150 ml.) was added to 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose (3.44 g.) at room temperature. No reaction was detected by TLC up to 0.5 hr., but after 11 hours the reaction was apparently complete. Three drops of sulfuric acid (98%) were added to insure completion. After 0.5 hr., 0.65N sodium hydroxide (100 ml.) was added. The resulting solution was refluxed for 0.75 hr., cooled, neutralized to pH ν 8 with sulfuric acid, treated with carbon, filtered, and concentrated in vacuo. The product was extracted with chloroform (400 ml.), filtered to remove suspended salts, and concentrated in vacuo to 1.96 g. of oil which crystallized spontaneously (71%). Recrystallization from hexane to constant melting point gave 1.72 g. of colorless needles: m.p. 51.5°-52°C.; [α]$_D^{22}$ -17.1° (c, 1.4, chloroform). Reported (35): m.p. 51.5°-52.5°C.; [α]$_D^{25}$ -16.4° (c, 2, chloroform). A mixed melting point of these crystals with the ethyl 3,4,6-tri-O-methyl-α-D-glucoside above was depressed to 38°-46°C.

ETHYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-β-D-GLUCOSIDE

At 0°C., a solution of pyridine (20 ml.) and acetic anhydride (10 ml.) was added to ethyl 3,4,6-tri-O-methyl-β-D-glucoside (5 g.). After 16 hours at 0°C., the acetylation solution was poured into 100 ml. of ice water. After stirring 0.5 hr., the product was extracted with chloroform (1 x 100 ml., 1 x 50 ml.). The chloroform extracts were washed with N sulfuric acid, sodium hydrogen carbonate, water, and

*Reagent grade without further drying.
concentrated in vacuo to a sirup which crystallized on cooling (5.8 g., 99%).

Crystallization from isopropyl ether to constant melting point gave prisms: m.p. 36.5°-38.5°C., \([\alpha]_D^{25} = -22.6^\circ\) (c, 1.6, chloroform). (Found C, 53.2; H, 8.3. \(\text{C}_{13}\text{H}_{24}\text{O}_{7}\) requires C, 53.4; H, 8.3.)

The NMR spectrum run in chloroform-d shows an O-acetyl methyl singlet at \(\delta = 2.10\) p.p.m. and the anomeric proton doublet \(\delta = 4.34\) p.p.m. with the coupling constant, \(J = 8\) c.p.s., which is typical of the \(\beta\)-configuration (54-56).

ETHYL 2-0-ACETYL-3,4,6-TRI-0-METHYL-\(\alpha\)-D-GLUCOSIDE

A mixture of 1-0-acetyl- and 2-0-acetyl-3,4,6-tri-0-methyl-\(\alpha\)-D-glucose (6.8 g.) was dissolved in absolute ethanol (100 ml.), and acetyl chloride (5 ml.) was added with stirring. After 24 hours under reflux, with exclusion of moisture, the reaction was sampled and the optical activity was checked. An observed rotation of +16.5° in a 2-dm. tube using Hg green light indicated a large percentage of \(\alpha\)-glucoside. Sodium hydroxide (200 ml., 1.2N) was added and refluxing was continued for 1 hour. The resulting light yellow colored solution was cooled, neutralized to pH ~ 8 with sulfuric acid, concentrated in vacuo, and the residue was extracted with 400 ml. of hot chloroform. The filtered chloroform extract was concentrated in vacuo to a yellow oil (6.2 g.). Attempts to crystallize the oil failed.

A quantity of the above oil (26 g.) was acetylated with 60 ml. of pyridine and 30 ml. of acetic anhydride at room temperature for 48 hours. Work-up was as described under the preparation of ethyl 2-0-acetyl-3,4,6-tri-0-methyl-\(\beta\)-D-glucoside to give 30 g. of yellow oil. Distillation of the acetylated sirup in an annular-teflon-spinning band-distillation apparatus (Nester Faust Co.) at 0.06 mm. Hg, pot temperatures of 160°C., head temperature of 80°C., and reflux ratios of 7-25, gave about 4 ml. of colorless ethyl 2-0-acetyl-3,4,6-tri-0-methyl-\(\alpha\)-D-glucoside after
discarding an initial 1 ml. of distillate. Purity was checked by GLC (Conditions A) and the β-anomer was absent. The pure oil had $[\alpha]_D^{25} +158^\circ$ (c, 1.0, chloroform). (Found C, 53.3; H, 8.2. $C_{13}H_{24}O_7$ requires C, 53.4; H, 8.3.)

The α-configuration assignment was indicated by the high positive specific optical rotation. The NMR spectrum run in chloroform-d exhibits the typical anomeric proton coupling constant for α-configuration (54-56), $J = 3-4$ c.p.s., at $\delta = 4.97$ p.p.m.; an O-acetyl methyl singlet at $\delta = 2.11$ p.p.m.; and a triplet, $J = 7$ c.p.s., for the methyl protons of the ethoxy aglycon at $\delta = 1.20$ p.p.m.

ETHYL 3,4,6-TRI-O-METHYL-α-D-GLUCOSIDE

Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside (2.15 g.) was dissolved in acetone (20 ml.) and 0.3N sodium hydroxide (65 ml.) was added. After 15 minutes on a steam bath, the cooled solution was deionized with Amberlite MB-3 resin and concentrated in vacuo to an oil (1.81 g.). The oil failed to crystallize from hexane so the hexane solution was treated with carbon and concentrated in vacuo to a colorless oil with the final removal of hexane being at room temperature and 0.05 mm. Hg for 4 hours. The oil gave: $[\alpha]_D^{25} +165^\circ$ (c, 1.8, ethanol). (Found C, 52.8; H, 8.6. $C_{11}H_{22}O_6$ requires C, 52.8; H, 8.9.)

ISOPROPYL 3,4,6-TRI-O-METHYL-ß-D-GLUCOSIDE

The method of preparation is essentially the same as previously described for the preparation of ethyl 3,4,6-tri-O-methyl-ß-D-glucoside by a Koenigs-Knorr synthesis. A volume equivalent of dry isopropanol was used in place of the ethanol in the formation of the isopropyl glucoside from 2-O-acetyl-3,4,6-tri-O-methyl-D-glucosyl bromide.
The oily product was dissolved in petroleum ether (60°-110°C.) and cooled to -78°C. Crystals formed on warming to -15°C. The yield was 42% based on 1,2-di-0-acetyl-3,4,6-tri-0-methyl-α-D-glucose. Recrystallization from petroleum ether gave needles: m.p. 33.5°-36°C., [α]_D^0 -27° (c, 1.0, chloroform). (Found C, 54.3; H, 9.1. C₁₂H₂₄0₇ requires C, 54.6; H, 9.2.)

The β-configuration is confirmed by the negative specific optical rotation and the anomeric proton coupling constant of about 7 c.p.s. (δ = 4.27 p.p.m. in chloroform-d) typical (54-56) for β-configuration. Also the required doublet of doublets for the nonequivalent isopropoxy methyl groups are exhibited at δ = 1.20 p.p.m. and δ = 1.25 p.p.m. with J = 6 c.p.s. The C-2 hydroxyl proton doublet (δ = 2.52 p.p.m., J = 2 c.p.s.) disappears on addition of deuterium oxide.

ISOAMYL 3,4,6-TRI-0-METHYL-β-D-GLUCOSIDE

The method of synthesis was essentially the same as previously described for the preparation of ethyl 3,4,6-tri-0-methyl-β-D-glucoside by a Koenigs-Knorr synthesis. A volume equivalent of isoamyl alcohol was used in place of the ethanol in the formation of the isoamyl glucoside from 2-0-acetyl-3,4,6-tri-0-methyl-D-glucosyl bromide.

The resultant oil could not be crystallized and was acetylated with acetic anhydride in pyridine* as a prelude to purification by fractional distillation. The acetylated product mixture showed a predominant peak by GLC (Conditions A) which was assumed to be the desired 2-0-acetyl derivative of the title compound, and several other peaks. The mixture was distilled under reduced pressure (unknown) in a Kontes short path still fitted with a seven-inch Vigreux column at pot and head temperatures of 165° and 120°C., respectively. The first 20 ml. of distillate

*See the preparation of ethyl 2-0-acetyl-3,4,6-tri-0-methyl-β-D-glucoside.
was retained of a pot charge of 30 ml. A second distillation of this fraction was conducted in which the middle 10 ml. of distillate was retained. The oil was deacetylated with excess 0.2N sodium hydroxide in aqueous methanol (v 50%) at 70°C. for 1 hour. After removal of methanol by partial concentration in vacuo, the resulting solution was extracted with chloroform (2 x 200 ml.). The chloroform extracts were washed with water (4 x 200 ml.), treated with carbon, filtered, and concentrated in vacuo to an oil. The residual solvent was removed at 0.05 mm. Hg pressure and 75°C. for 2 hr. GLC analysis (Conditions A) of an O-propanoylated sample (propionic anhydride in pyridine) indicated about 1% of an impurity assumed to be the α-anomer and a smaller amount of an unidentified material. The constants of the title compound were: $[\alpha]_D^{25} -21.2^\circ$, $[\alpha]_{546}^{25}$ nm. -23.7° (c, 1.5, chloroform).

(Found C, 57.5; H, 9.7. C$_{14}$H$_{28}$O$_{6}$ requires C, 57.5; H, 9.7.)

The β-configuration is confirmed by the negative specific optical rotation and the anomic proton coupling constant of 7 c.p.s. ($\delta = 4.20$ p.p.m., chloroform-d). The required doublet ($J = 6$ c.p.s., 6 H) for the isoamyl methyl groups is exhibited at $\delta = 0.93$ p.p.m. The C-2 hydroxyl proton doublet ($J = 2$ c.p.s., $\delta = 2.73$ p.p.m.) disappears on addition of deuterium oxide.

**METHYL 2,3,4,6-TETRA-0-METHYL-β-D-GLUCOSIDE**

Methyl 2,3,4,6-tetra-O-acetyl-β-D-glucoside (74 g.), powdered sodium hydroxide (210 g.) and tetrahydrofuran (1150 ml.) were added to a 2000 ml., three-neck, round-bottom flask fitted with a dropping funnel and an efficient stirrer. The reaction system was partially immersed in a water bath at room temperature. Dimethyl sulfate (170 ml.) was added dropwise to the vigorously stirred reaction mixture over a period of 10 hr. After an additional 10 hr. of stirring, water (500 ml.) was added, and the water bath temperature was raised to 75°C. for 1 hour to destroy residual dimethyl sulfate and to remove most of the tetrahydrofuran. After cooling to room
temperature, the resulting solution was extracted with chloroform (1 x 750 ml., 
1 x 250 ml.). The chloroform extracts were washed with water (1 x 200 ml.) and 
concentrated in vacuo to a yellow oil (50 g., 97%) which crystallized on standing 
at -15°C. overnight. The crude product was crystallized once from ethyl ether at 
-15°C. and sublimed once at reduced pressure (ca. 0.05 mm. Hg) at 36°C. The puri-
Fied product had m.p. 37.5°-39°C.; [α] D 25 -19.4° (c, 1.0, water). Literature (59): 
m.p. 40°-41°C., [α] D 25 -17° (c, 4, water).

ETHYL 2,3,4,6-TETRA-O-METHYL-ß-D-GLUCOSIDE

Ethyl 2,3,4,6-tetra-O-acetyl-ß-D-glucoside (58) (42 g.) was methylated with 
dimethyl sulfate and powdered potassium hydroxide (in place of sodium hydroxide) 
in tetrahydrofuran according to the procedure given previously for methyl 2,3,4,6-
tetra-O-methyl-ß-D-glucoside.

The yield of oil was 30 g. The oil was distilled at reduced pressure (unknown*), 
a pot temperature of 100°C., and head temperature of 67°C. in a Kontes short path 
still fitted with a seven-inch Vigreux column. A middle fraction of 10 ml. was 
retained. GLC (Conditions B) showed the purity to be about 99%. Constants were: 
m.p. crystalline at less than 25°C.; [α] D 30 -18.7° (c, 29, ethanol). (Found C, 54.8; 
H, 9.0. C12H24O6 requires C, 54.5; H, 9.1.)

ETHYL 2,3,4,6-TETRA-O-METHYL-α,ß-D-GLUCOSIDE

Glucose (30 g.), ethanol (300 ml.), and acetyl chloride (15 ml.) were refluxed 
for 24 hours with the exclusion of moisture. The resulting solution was cooled, 
neutralized with solid sodium carbonate, filtered, and concentrated in vacuo. The 
thick sirup was acetylated with acetic anhydride (100 ml.) and pyridine (150 ml.) 
for 24 hours at room temperature. The resultant sirup (56 g.) was methylated using 

*The pressure usually was about 0.05 mm. Hg with this system.
-101-
dimethyl sulfate and powdered potassium hydroxide in tetrahydrofuran by the procedure
described for the preparation of methyl 2,3,4,6-tetra-O-methyl-β-D-glucoside.

The oil obtained (38 g.) was distilled at reduced pressure (unknown*), pot.
temperature of 120°C., and head temperature of 83°C. in a Kontes short path still
fitted with a seven-inch Vigreux column. A fraction of 10 ml. was collected after
discarding 1 ml. of forerun. GLC (Conditions B) showed two major components, one
of which corresponded to the β-anomer (~ 35%) and the other which must have been the
α-anomer (~ 65%). Trace impurities were also indicated. The α-anomer is the less
volatile anomer. The sample had a "specific" rotation of: [α] D 30° +92.5° (c, 2.7, 
ethanol) which also indicates a majority of the α-anomer. Elemental analysis
(found C, 54.7; H, 8.9. C12H24O6 requires C, 54.5; H, 9.1) is consistent with the
product being a mixture of the title compounds.

2,3,4,6-TETRA-O-METHYL-D-GLUCOSE

A mixture of anomers (~ 50/50) of ethyl 2,3,4,6-tetra-O-methyl-D-glucoside
(32 g.) was refluxed in 0.5N hydrochloric acid (300 ml.) for 48 hours. The solution
was cooled, neutralized with sodium hydrogen carbonate, and concentrated to dryness
in vacuo. The resulting mixture of salts and oil was extracted with chloroform
(500 ml.) with a little carbon added. The chloroform extracts were filtered through
Celite and concentrated in vacuo to an oil which crystallized spontaneously. After
one crystallization from petroleum ether (60°-110°C.), the yield was 20 g. or 70%.
Two recrystallizations from petroleum ether gave: m.p. 88°-98°C.; [α] D 30° +106 +
+78.5° (c, 2.8, water). Literature (60): m.p. 98° (α-anomer); [α] D 30° +79.4° (at
equilibrium in water).

*The pressure usually was about 0.05 mm. Hg with this system.
1-\text{O-ACETYL}-2,3,4,6-\text{TETRA-O-METHYL-D-GLUCOSE}

2,3,4,6-Tetra-\text{O-methyl-D-glucose} (3 g.) was acetylated at \(0°C\). with a solution of pyridine (12 ml.) and acetic anhydride (6 ml.). After 16 hours, the reaction solution was stirred with ice water (100 ml.) for 0.5 hr. and extracted with chloroform (2 x 100 ml.). The chloroform extracts were washed with sulfuric acid, saturated sodium hydrogen carbonate, water, treated with carbon, filtered, and concentrated in \text{vacuo} to a colorless oil. Residual chloroform was removed in \text{vacuo} (ca. 0.05 mm. Hg, room temperature, 3 hr.). GLC (Conditions B) showed no impurities. The oil had:

\([\alpha]_D^{21} +107\ (c, 1.9, \text{ethanol}).\) (Found C, 51.9; H, 8.0. \(\text{C}_{12}\text{H}_{22}\text{O}_7\) requires C, 51.8; H, 8.0.)

The oil is predominantly the \(\alpha\)-anomer as shown by the high positive specific optical rotation (+107°) which is similar to that obtained for 1,2-di-\text{O-acetyl}-3,4,6-tri-\text{O-methyl-\alpha-D-glucose} (+122°).

2,3,4,6-\text{TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-\alpha-D-GLUCOSE}

The following synthesis of the title compound is previously unreported work of Dr. Schroeder and F. C. Haigh to whom the author is grateful for a sample of this compound.

2,3,4,6-Tetra-\text{O-methyl-\alpha-D-glucose} (5 g.), triethyl orthoacetate (50 ml.), and 2,6-dichlorobenzoic acid (0.5 g.) were heated in a Kontes short-path still fitted with a seven-inch Vigreux column at reduced pressure (protected from water vapor). A small magnetic stirring bar prevented bumping during distillation. In a total time of 30 min. and at a maximum head temperature of 94°C. the following distillate was collected: 1.4 ml. (200 mm. Hg) and 3 ml. (105 mm. Hg). The reaction mixture was cooled, and chloroform (ethanol free, 50 ml.) was added. The chloroform solution
was washed with 0.1M sodium hydroxide (2 x 100 ml.), water (100 ml.), dried over sodium sulfate, and concentrated in vacuo after addition of several drops of pyridine to yield 6.5 g. of oil. The oil was purified by dry column chromatography on alumina (156 g. Alumin AR CC-10*, 25-mm. diameter column) by elution with 1/10, v/v, pyridine-isopropyl ether. Fractions 4-8 (15-ml. fractions) were combined and concentrated in vacuo to 2.1 g. of purified oil. A second column purification under the same conditions (Fractions 4-6) gave 1.4 g. of oil which was stored at 0°C. in a vacuum desiccator over sodium hydroxide pellets. The oil gave: \([\alpha]_D^{25} +115^0\) (c, 4.1, chloroform).

The purity of the oil was assessed by GLC (Conditions B) after hydrolysis and O-propanoylation (propanoic anhydride in pyridine). Ethyl 2,3,4,6-tetra-O-methyl-$$\beta$$-D-gluco-side was found in 2.4 mole % indicating a maximum purity of 97.6 mole % of the title compound (see Fig. 18b, Chromatogram D; or Appendix XII, Table XXXIV).

The $$\alpha$$-configuration of the title compound is indicated by the large positive specific optical rotation and the anomeric proton coupling constant of \(J_{1,2} = 3.5\) c.p.s. (\(\delta = 5.37\ p.p.m., \text{CDCl}_3\)). The 1-O-(diethyl orthoacetyl) group is verified by the relative integrals of the orthoacetyl methyl singlet (\(\delta = 1.52\ p.p.m., 3H\)) and the ethoxy methyl 1:2:1 triplet (\(J = 6.5\) c.p.s., \(\delta = 1.17\ p.p.m., 6H\)). 2,3,4,6-Tetra-O-methyl substitution is indicated by four O-methyl singlets (\(\delta = 3.3-3.7\ p.p.m.\)).

2,6-DICHLOROBENZOIC ACID

The title compound, 72 g. m.p. 143°-144°C., was prepared from 2,6-dichlorotoluene (94 g.) by a modification of the method given by Norris and Bearse (61). Literature (61): m.p. 143°-144°C.

The modification includes: (1) a prolonged (24-hour) alkaline hydrolysis of the $$\alpha$$-bromo-2,6-dichlorotoluene before addition of the permanganate for oxidation,

*Product of Mallinckrodt Chemical Works.
and (2) the removal of unreacted 2,6-dichlorotoluene and α-bromo-2,6-dichlorotoluene was by a chloroform extraction of the alkaline solution instead of the recommended steam distillation.

2,6-Dichlorobenzoic acid was sublimed before use in kinetics.

LITHIUM p-TOLUENESULFONATE

p-Toluenesulfonic acid (m.p. 104°-106°C. for monohydrate) in water was neutralized with lithium carbonate. Upon evaporation of the water, the salt crystallized and was dried at 100°C. in vacuo for 48 hours. A 5% aqueous solution of the salt was neutral.

d₅-ETHANOL-OH

Anhydrous d₅-ethanol (2 g., Stohler Isotope Chemicals, Lot 2910) was dissolved in anhydrous glycerol (20 g.) and several mg. of picric acid were added. After allowing 2 hr. for deuterium exchange, the ethanol was distilled from the glycerol with exclusion of moisture (Kontes short path still) at a maximum pot temperature of 170°C. The distillate receiver contained an additional 10 g. of glycerol and several mg. of picric acid. The receiver mixture was then distilled similarly to yield absolute d₅-ethanol-OH.

The d₅-ethanol-OH should contain less than 1% ethanol-d₆ assuming deuterium exchange resulted in equal distribution of deuterium between the ethanol and glycerol hydroxyls.

EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSE ETHANOLYSES

ETHANOLYSIS SOLUTION PREPARATION

Anhydrous conditions are imperative throughout the procedure given below because of the sensitivity of orthoesters to acid-catalyzed hydrolyses. To minimize
the introduction of moisture during solution preparation, the volumetric flasks were normally dried over potassium hydroxide pellets in a desiccator to remove most of the sorbed moisture before use.

Stock catalyst solutions were prepared by weighing 2,6-dichlorobenzoic acid into a volumetric flask and diluting with anhydrous ethanol at 25.0°C. The concentration of the stock catalyst solution was normally greater than 10 times the final acid concentration in the ethanolysis solution. A fresh catalyst solution was made up for each ethanolysis.

Stock salt solutions of lithium bromide and lithium p-toluenesulfonate were made up with anhydrous ethanol at 25.0°C. after drying the salts over phosphorous pentoxide in a vacuum desiccator for 5 days in tared volumetric flasks.

Sufficient 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose was weighed into a volumetric flask, to make a 2% (w/v) solution. The volumetric flask and contents, anhydrous ethanol, 2,6-dichlorobenzoic acid solution, and salt solution were thermostated at 25.0°C. in the bath for 15-30 min. Thermally equilibrated, anhydrous ethanol was added to the volumetric flask containing the orthoester to about 80% of the final intended volume. The orthoester was dissolved with the aid of swirling. If necessary, an aliquot of salt solution was added at this point to make a 0.062N solution upon final dilution. A portion of the 2,6-dichlorobenzoic acid solution was then added to make a 0.0052N solution on final dilution. Time zero was taken to be the point at which one half of the intended catalyst solution was added. The solution was then quickly diluted to volume, mixed thoroughly, and stored in the 25.0°C. bath. Contamination by water (atmospheric and sorbed moisture on sampling pipets) during sampling was minimized by utilization of the following apparatus.
The apparatus was attached to the volumetric flask containing the ethanolsis solution immediately after preparation. To remove a sample for analysis a pipet was placed in the rubber tube of the drying chamber and dry air was passed through the chamber for several minutes. The clamp was opened and the pipet was pushed down into the solution to withdraw an aliquot. The pipet was removed and the clamp closed until the next sample was taken.

The effect of water in ethanolses was studied by making up ethanolsis solutions containing known quantities of water. Standard ethanol-water solutions were made up by weighing water into a volumetric flask, adding an aliquot of a standard ethanolic solution of 2,6-dichlorobenzoic acid, diluting to volume with anhydrous ethanol, and reweighing. Exo-OR 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose was then weighed into a 10-ml. volumetric flask to make a 2% (w/v) solution. After thermosetting, the ethanol-water solutions were used to dilute the orthoester to 10 ml. In calculations, it was assumed that the density of exo-OR 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose is 1 g. ml.⁻¹ and that the volumes were additive.
KINETIC TECHNIQUES

Polarimetry

The constant temperature polarimetry system is the same as that used by Schroeder (62).

A sample of ethanolysis solution was added to a 2-dm., side-arm, water-jacketed polarimeter tube at 25.0°C. The side arm was sealed with a rubber stopper wrapped with Saran Wrap. Readings were begun about 3-4 minutes from time zero. Two readings, approximately one minute apart, were averaged for each reported value. A rotation blank was taken through the empty tube before adding the ethanolysis solution.

The anomer of 3,4,6-tri-O-methyl-D-glucose formed in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose was determined using the following procedure. An ethanolysis was stopped by neutralization of the 2,6-dichlorobenzoic acid catalyst with an 11-fold excess of triethylamine which also affected mutarotation of the 3,4,6-tri-O-methyl-D-glucose. The amount of triethylamine added (0.10 ml.) was small compared to the volume of ethanolysis solution (about 12 ml.) in the polarimeter tube. Thus, the rotation correction for dilution on addition of triethylamine was small and not affected appreciably by the assumption that the volumes were additive. The observed rotation decreased to a constant value after approximately 500 min. under the above conditions. This result, indicating the 3,4,6-tri-O-methyl-D-glucose is the α-anomer, is discussed more completely in the text.

Glucose Moiety

Product Identification

GLC provides the most important tool for the identification of glucose moieties and their quantitative measurement in the ethanolyses of exo-OR 3,4,6-tri-O-methyl-
1,2-\(\text{Q}\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses. However, quantitative chemical modifications of the components in the ethanolysis samples were necessary prior to GLC analysis. These chemical modifications, which are useful for GLC separation, are also necessary to change unreacted orthoesters and nonglucosidic components to derivatives which do not decompose under GLC conditions. The chemical modifications include,

(1) hydrolysis of unreacted 3,4,6-tri-\(\text{Q}\)-methyl-1,2-\(\text{Q}\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucose quantitatively to 1-\(\text{Q}\)-acetyl- and 2-\(\text{Q}\)-acetyl-3,4,6-tri-\(\text{Q}\)-methyl-\(\alpha\)-D-glucose, and

(2) subsequent \(\text{Q}\)-propanoylation of free hydroxyl groups on the glucose moieties.

(The exact procedure is given under Quantitative Measurement Procedure.)

The utility of the analysis procedure is demonstrated by the four chromatograms in Fig. 16a and 16b. Chromatograms B, C, and D are copies of the actual chromatograms used for glucose moiety identifications and quantitative analysis of \(\text{exo-OR}\) 3,4,6-tri-\(\text{Q}\)-methyl-1,2-\(\text{Q}\)-(ethyl orthoacetyl)-\(\alpha\)-D-glucose ethanolyses. Similar chromatograms are obtained for \(\text{exo-OR}\) 3,4,6-tri-\(\text{Q}\)-methyl-1,2-\(\text{Q}\)-(isopropyl orthoacetyl)-\(\alpha\)-D-glucose ethanolyses.

Chromatogram A (Fig. 16a) illustrates the separation of a synthetic mixture of all the glucose moieties expected in an ethanolysis sample. The identities of the compounds are:

1. ethyl 2-\(\text{Q}\)-acetyl-3,4,6-tri-\(\text{Q}\)-methyl-\(\alpha\)-D-glucoside
2. ethyl 2-\(\text{Q}\)-acetyl-3,4,6-tri-\(\text{Q}\)-methyl-\(\beta\)-D-glucoside
3. ethyl 3,4,6-tri-\(\text{Q}\)-methyl-\(\alpha\)-D-glucoside (as the 2-\(\text{Q}\)-propanoyl derivative)
4. ethyl 3,4,6-tri-\(\text{Q}\)-methyl-\(\beta\)-D-glucoside (as the 2-\(\text{Q}\)-propanoyl derivative)
5. 1-\(\text{Q}\)-acetyl- and 2-\(\text{Q}\)-acetyl-3,4,6-tri-\(\text{Q}\)-methyl-\(\alpha\)-D-glucoses [as \(\text{Q}\)-propanoyl derivatives, these two compounds are the hydrolysis products of 3,4,6-tri-\(\text{Q}\)-methyl-1,2-\(\text{Q}\)-(alkyl orthoacetyl)-\(\alpha\)-D-glucoses]
6. 3,4,6-tri-\(\text{Q}\)-methyl-\(\alpha\)-D-glucose (as the 1,2-di-\(\text{Q}\)-propanoyl derivatives, anomers do not separate)
7. isoamyl 3,4,6-tri-\(\text{Q}\)-methyl-\(\beta\)-D-glucoside (as the 2-\(\text{Q}\)-propanoyl derivative, this compound is the internal standard added for quantitative analysis)
Chromatogram B (Fig. 16a) illustrated the quantitative conversion of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucose by acid hydrolysis. Very little ethanolysis products appear in this chromatogram because the sample was taken at a very short ethanolysis time. The very small peak for 3,4,6-tri-O-methyl-D-glucose (6) illustrates that the acid hydrolysis conditions were not drastic enough to cause any significant loss of O-acetyl group from the initial orthoester hydrolysis products. The small peaks at retention times of 27 and 33 minutes are due to impurities in the isoamyl 3,4,6-tri-O-methyl-β-D-glucoside used as an internal standard.

Chromatogram C (Fig. 16b) illustrates a product analysis for an ethanolysis (Run 3 ethanolysis, same as Chromatogram B) at long reaction times. The 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose has undergone ethanolysis almost to completion as indicated by the virtual absence of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucose [Peak (5)]. The almost complete disappearance of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucose [Peak (5)] also shows that no significant hydrolysis occurred during ethanolysis. In some runs Peak (5) remains after long ethanolysis time indicating a small amount of acid-catalyzed hydrolysis concurrent with ethanolysis. Thus, when quantitative measurement of 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucose remains unchanged with time at long ethanolysis times, this can be attributed to hydrolysis and can be described quantitatively.

Chromatogram D (Fig. 16b) illustrates an analysis of a partially completed ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in the presence of lithium bromide. The addition of salts causes noticeable changes in the product distribution. One very significant change is the detection of a small quantity of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside [Peak (1)].
Figure 16a. Sample Chromatograms of Glucose Moieties in the Ethanolysis of 3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucoses: A, Synthetic mixture; B, Run 3, 7 min.
Figure 16b. Sample Chromatograms of Glucose Moieties in the Ethanolysis of 3,4,6-Tri-$\beta$-methyl-1,2-$\alpha$-(ethyl orthoacetyl)-$\alpha$-D-glucoses: C, Run 3, 4920 min.; D, Added LiBr Run, 153 min.
The product identification and quantitative results obtained by GLC are in agreement with polarimetry results. The 3,4,6-tri-O-(ethyl orthoacetyl)-α-D-glucose ethanolysis sample at 3007 minutes (Table XIX, Appendix V) can be calculated to have an "observed" rotation of +0.48° (2-dm. tube, 546 nm. light) from the individual values of specific rotation (Table XI, Appendix III) for each measured component if the 3,4,6-tri-O-methyl-α-D-glucose has mutarotated to equilibrium. The actual observed rotation was found to be +0.44° for a sample at 3013 minutes (Table XVII, Appendix V) which was assured to be at equilibrium mutarotation by triethylamine addition. The two values of rotation, +0.48° and +0.44°, are in good agreement when one considers that the calculated value (+0.48°) is the sum of both positive and negative terms for the various measured components for which the sum of absolute values of the rotation contributions was 1.43°.

A further method for identification of ethanolysis products by TLC is given in Appendix IX.

Quantitative Measurement Procedure

A 1-ml. aliquot of an ethanolysis solution of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose was pipeted into 2 ml. of a standard solution of isoamyl 3,4,6-tri-O-methyl-β-D-glucoside (0.00874 g. ml. at 25°) in triethylamine-toluene (3/7, v/v). These samples can be stored for weeks in the refrigerator with no further reaction at this point.

A portion of the sample (1-2 ml.) was concentrated to an oil in vacuo (45°C. bath). Four ml. of a 1/9, v/v acetone-water solution of Universal Indicator* was added. One drop of N sulfuric acid was added. After 3 min., 0.01N sodium hydroxide was added dropwise with swirling until the solution was an orange to green color.

*50 ml. of Universal Indicator was concentrated to dryness to remove ethanol. The residue was taken up in 2 liters of 90% water 10% acetone.
(pH ~ 5-7). Eight drops of buffer (0.1M potassium monohydrogen orthophosphate and 0.1M potassium dihydrogen orthophosphate) were added, and the solution was concentrated to about 0.5 ml. *in vacuo* (45°C. bath). Drying of the sample was completed by storing the open flask in a vacuum desiccator over potassium hydroxide pellets for about 5 hr. at water pump vacuum. Propanoic anhydride-pyridine (3/5, v/v; ca. 1.5 ml.) was added to the dry sample, and the flask was stoppered and left standing (occasional swirling) at room temperature for a minimum of 24 hr. Water (12 ml.) was added, and after 15 min. the resulting solution was extracted with chloroform (3 x 15 ml.). The combined chloroform extracts were washed with 2N hydrochloric acid in saturated sodium chloride (6-7 ml.), and the aqueous phase was back-extracted with chloroform (5 ml.). The combined chloroform extracts were washed with saturated sodium bicarbonate in 10% sodium chloride (6-7 ml.), and the aqueous phase was back-extracted with chloroform (5 ml.). The combined chloroform phase was washed with water (10 ml.), and the water phase back-extracted with chloroform (10 ml.). The combined chloroform extracts were concentrated *in vacuo* to an oil. If any odor of propanoic acid was noted, several ml. of water were added, and the solution was reconcentrated to remove the propanoic acid as its water azeotrope. The oil was then dried over potassium hydroxide several hr. in a desiccator. The sample was dissolved in acetone (1-2 ml.) and chromatographed (three trials) using GLC Conditions A.

The required GLC response factors for each reaction component were determined by treatment of synthetic mixtures of these compounds in ethanol by the procedure given above. These response factors and their use in calculations of mole fraction of glucose moieties in ethanolysis samples are given in Appendix X.
**Ester Appearance**

**Method**

The disappearance of an 1,2-O-(ethyl orthoacetyl) group during ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose must be accompanied by the appearance of either ethyl acetate, a glucoside acetate, or triethyl orthoacetate. Since esters consume alkali by saponification while acylic orthoesters (14) and sugar 1,2-orthoesters (1) are reasonably stable under alkaline conditions, the saponification equivalent of a 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose ethanolysis sample should be a measurement of ester produced in the ethanolysis prior to sampling.* The difference between the initial concentration of exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose and the measured saponification equivalent is therefore the total concentration of orthoesters (cylic and acylic) remaining. The assumption involved, i.e., that the sum of ester and orthoester concentrations is a constant throughout the ethanolysis, is readily proved by subjecting an ethanolysis sample to acid hydrolysis to convert all remaining orthoester to ester before measurement of the saponification equivalent. Saponification equivalents obtained in this manner were in excellent agreement with the initial weighed concentration of sugar orthoester (see Appendix VI).

**Procedure**

Distilled water was boiled to remove dissolved carbon dioxide. Sodium hydroxide solutions were prepared by dilution of a 50% (w/w) aqueous sodium hydroxide solution and standardized against potassium acid phthalate using phenolphthalein indicator. Hydrochloric acid solutions were standardized against the standard

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*The accuracy of the analysis procedure depends upon minimizing alkali consumption via reaction with reducing sugars and ester generated by general-acid-catalyzed hydrolysis of orthoester. This is the subject of Appendix XI.*
sodium hydroxide solutions. Sodium hydroxide solutions were stored in paraffin-coated glass bottles.

An aliquot (5.0 ml.) of an ethanolysis solution was pipeted into a partially frozen mixture of standard 0.1N sodium hydroxide (10.0 ml.) and water (10.0 ml.). After 750-850 min. at 0°C., an aliquot of standard 0.1N hydrochloric acid (10.0 ml.) was added, and the cold sample was back-titrated quickly to a phenolphthalein end point with 0.03N standard sodium hydroxide.

To check the total amount of ester and orthoester present, an aliquot (5.0 ml.) of the ethanolysis solution was pipeted into water (10 ml.) and left standing for 80 min. at room temperature to hydrolyze all remaining orthoester to ester. After cooling to -15°C., an aliquot of standard 0.1N sodium hydroxide (10.0 ml.) was added. After 750-850 min. at 0°C., an aliquot of standard 0.1N hydrochloric acid was added, and the solution was titrated as before.

**Alkyl Acetate and Isopropanol**

**Identification**

GLC (Conditions C) provides a means of identification of ethyl acetate ($T_r = 9.3$ min.), isopropyl acetate ($T_r = 12.5$ min.), and isopropanol ($T_r = 4.1$ min.) formed in the ethanolysis of 3,4,6-tri-$O$-methyl-1,2-$O$-(alkyl orthoacetyl)-$\alpha$-D-glucose. Isopropyl acetate was not found in identifiable quantities in the ethanolysis of 3,4,6-tri-$O$-methyl-1,2-$O$-(isopropyl orthoacetyl)-$\alpha$-D-glucose. The isopropanol formed cannot be measured with any degree of accuracy because the isopropanol peak is on the shoulder of the ethanol peak ($T_r = 3.0$) and hence was partially obscured. Accurate quantitative estimates of ethyl acetate formed in the ethanolysis of 3,4,6-tri-$O$-methyl-1,2-$O$-(alkyl orthoacetyl)-$\alpha$-D-glucose could not be obtained because of continuing formation of ethyl acetate via water scavenging by triethyl orthoacetate in the ethanolysis sample even in the presence of 2,6-lutidine. Sample chromatograms (Fig. 3) have been discussed in the text.
The formation of ethyl acetate and triethyl orthoacetate were confirmed by NMR (Fig. 4).

Procedure

A 1-ml. aliquot of the 3,4,6-tri-0-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucose ethanolysis solution was pipeted into 1 ml. of a standard n-butyl acetate (T = 22.5 min.) solution in ethanol containing seven times the amount of 2,6-lutidine necessary to neutralize the 2,6-dichlorobenzoic acid. The samples were then analyzed by GLC (Conditions C).

TRANSORThOESTERIFICATION OF Exo-OR 3,4,6-TRI-0-METHYL-1,2-0-(ISOPROPYL ORTHOACETYL)-α-D-GLUCOSE

Exo-OR 3,4,6-tri-0-methyl-1,2-0-(isopropyl orthoacetyl)-α-D-glucose (1.14 g.) in ethanolic 2,6-dichlorobenzoic acid (50 ml., 0.00525N) was allowed to react for 15.0 min. at 25.0°C. The reaction was stopped by addition of triethylamine (30 ml.) and toluene (70 ml.). The solvent was removed by concentration in vacuo (45°C. bath). Traces of triethylamine remaining were removed by subsequent concentrations in vacuo after addition of benzene containing a trace of pyridine. The oil obtained was essentially a mixture of endo-OR and exo-OR 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose (Fig. 2a, Spectrum A).

TRANSORThOESTERIFICATION OF Exo-OR 3,4,6-TRI-0-METHYL-1,2-0-(ETHYL ORTHOACETYL)-α-D-GLUCOSE

An equilibrium mixture of endo-OR and exo-OR 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose was needed to determine the optical rotation of the endo-OR isomer and the polarimetric curve of the ethanolysis of the mixture. The isomeric mixture was prepared by an ethanolysis of exo-OR 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose to partial orthoester disappearance and subsequent
purification by column chromatography to remove ethanalyses products. The procedure is given below.

**Exo-OR** 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose (2.05 g.) in ethanolic 2,6-dichlorobenzoic acid (100 ml., 0.00525N) was allowed to undergo ethanolysis for 80 min. at 25.0°C. The ethanalyses solution was poured into 0.05N sodium hydroxide (400 ml.) at 0°C. After 750 min.* at 0°C., benzene (400 ml.) and triethylamine (100 ml.) were added, the mixture was shaken, and transferred to a separatory funnel. The benzene phase was washed with water (3 x 300 ml.), dried with sodium sulfate, filtered, and concentrated in vacuo to an oil. The oil was purified by dry column chromatography on alumina (170 g. Alumin AR CC-10**, 25-mm. diameter column) using benzene-pyridine (30/1, v/v) as the elution solvent. Fractions 15-35 (8 ml. each) were combined and concentrated to an oil. Residual pyridine was removed in vacuo at ca. 0.05 mm. Hg pressure and room temperature for 2 hr.

NMR in chloroform-d and benzene-6d indicated the isomeric percentages as 19.6% endo-OR (δ = 1.48 p.p.m., CDCl₃) and 80.4% exo-OR (δ = 1.67 p.p.m., CDCl₃) where the chemical shifts are given for the orthoacetyl methyl singlet. The pure exo-OR isomer and the mixture of endo-OR and exo-OR isomers gave, respectively: [α]⁰⁺二十五 nm. +67.0 and [α]⁰⁺二十五 nm. +71.5 [c, 2.0, toluene-triethylamine (4/1, v/v)]. Quantitative GLC (Conditions A, procedure similar to that for glucose moiety measurements in ethanalyses) showed the oil to be 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose (98.6 mole %), 3,4,6-tri-0-methyl-D-glucose (0.9 mole %) ethyl 3,4,6-tri-0-methyl-β-D-glucoside (0.4 mole %), and ethyl 3,4,6-tri-0-methyl-α-D-glucoside (0.1 mole %).

*Complete saponification occurs under these conditions. This facilitates later purification by column chromatography since each ethanalyses product now has at least one free hydroxyl group.

**Product of Mallinckrodt Chemical Works.
3,4,6-TRI-O-METHYL-α-D-GLUCOSE ETHANOLYSIS IN THE PRESENCE OF TRIETHYL ORTHOACETATE

ETHANOLYSIS SOLUTION PREPARATION

Sufficient 2,6-dichlorobenzoic acid to make a 0.0053N solution was weighed into a 100-ml. volumetric flask. Triethyl orthoacetate (4 ml., Eastman Organic Chemicals, practical grade) was added to the flask, and the contents were diluted to 100 ml. with anhydrous ethanol to make Solution B. 3,4,6-Tri-O-methyl-α-D-glucose, in a tared 25-ml. volumetric flask, was dried over phosphorous pentoxide in vacuo for 24 hr. and weighed. This flask with contents and Solution B were then thermostated at 25.0°C. for 24 hr. after attachment of a sampling apparatus* to each flask. A dry, 25-ml. pipet was filled with Solution B, and the 3,4,6-tri-O-methyl-α-D-glucose was dissolved and diluted to 25.0 ml. at time zero to make Solution A. The remaining portion of Solution B in the pipet was then weighed to determine, by difference, the volume of Solution B used to make up Solution A.

KINETIC TECHNIQUES

Glucose Moiety
Product Identification

The identification and subsequent quantitative analyses of glucose moieties were made by GLC using Conditions A. The expected products of the reaction are the same as those obtained in the ethanolyses of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose. Thus, similar sample work-up procedures involving orthoester hydrolysis and subsequent O-propanoylation were employed. Chromatogram A (Fig. 16a) illustrates the separation of all probable components of a worked up

*Described previously for sampling of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose ethanolysis solutions.
ethanolysis sample.* 1-O-Acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucoses [Peak (5)] result from hydrolysis of intermediate glucose orthoesters which form by transorthoesterification of triethyl orthoacetate by 3,4,6-tri-O-methyl-D-glucoses**. Intermediate glucose orthoesters, other than 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-D-glucose, may also result in 3,4,6-tri-O-methyl-D-glucose on hydrolysis. Therefore, measurement of the monoacetates results in a minimum value for intermediate glucose orthoesters. Also, for this reason, the measurement of 3,4,6-tri-O-methyl-D-glucose [Peak (6)] yields a maximum value.

Chromatograms A and B (Fig. 17) illustrate the glucose moiety identification and quantitative measurement as a function of time. In addition to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-D-glucose [Peak (5)] and 3,4,6-tri-O-methyl-D-glucose [Peak (6)], the ethanolysis products, ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside [Peak (2)], ethyl 3,4,6-tri-O-methyl-α-D-glucoside [Peak (3)], and ethyl 3,4,6-tri-O-methyl-β-D-glucose [Peak (4)] are evident. The internal standard was isoamyl 3,4,6-tri-O-methyl-β-D-glucoside [Peak (7)] which contained a small amount of impurity evident at about 33 minutes retention time.

Quantitative Measurement Procedure

An aliquot (2 ml.) of a standard solution of isoamyl 3,4,6-tri-O-methyl-β-D-glucoside (0.00874 g. ml.\(^{-1}\)) was carefully concentrated to an oil in a 50-ml. round-bottom flask in vacuo. Four ml. of a 1/9, acetone-water solution of Universal Indicator and a drop of N sulfuric acid were added. An aliquot (1 ml.) of the ethanolysis solution (Solution A) was added to the flask and the sample was worked

*Sample hydrolysis converts triethyl orthoacetate to ethyl acetate.

**The original configuration was α, however, mutarotation takes place concurrently with the ethanolysis.
Figure 17. Sample Chromatograms of Glucose Moieties in the Ethanolysis of 3,4,6-Tri-O-methyl-α-D-glucose in the Presence of Triethyl Orthoacetate: A, 1948 min.; B, 22149 min.
up as previously described for the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose starting with the sentence, "After 3 min., 0.01N sodium hydroxide....."

The response factors and calculations of glucose moiety mole fractions are given in Appendix X.

Orthoester Consumption

Method

The ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate should result in formation of either or both glucoside acetates and ethyl acetate. This reasoning follows from the consideration of possible ethanolysis mechanisms which can result in glucoside formation*. These mechanisms include formation of a glucose orthoester with the orthoacetyl group on C-1 or both C-1 and C-2 followed by subsequent cleavage of the C-1 carbon-oxygen bond to form glucosides. However, ethyl acetate formation via hydrolysis (water scavenging) of triethyl orthoacetate also must occur.

Both of these routes for ester formation (orthoester consumption) exist in the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate (Solution A). Only water scavenging by triethyl orthoacetate may occur in the ethanolic triethyl orthoacetate 2,6-dichlorobenzoic acid solution (Solution B) used to make up Solution A. The difference between the saponification equivalent of Solution B at time zero and the saponification equivalent of Solution B after hydrolysis gives the initial concentration of triethyl orthoacetate in Solution A after a small volume correction. The loss of orthoester in Solution A during ethanolysis can be calculated from a measured saponification equivalent of Solution B.

*Fisher type glycosidation was eliminated as a possibility for glucoside formation since without triethyl orthoacetate present no glucosides form under the conditions and time period studied.
A at any time. An estimate can be made of the extent of loss of triethyl ortho-
acetate by water scavenging in Solution A by measuring the saponification equiv-
alent of Solution B if it is assumed that water scavenging is equivalent in both
Solutions A and B at the time of measurement.

Quantitative Measurement Procedure

A procedure previously given for the quantitative measurement of ester in
3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose ethanolyses was followed.
Larger quantities of sodium hydroxide were used because of larger quantities of
ester and orthoester present.

2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL) -
α-D-GLUCOSE ETHANOLYSES

ETHANOLYSIS SOLUTION PREPARATION

Sufficient 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose to
make a 2% (w/v) solution was transferred to a tared volumetric flask. The pyridine
used as a stabilizer in the orthoester was removed in vacuo at about 0.05 mm. Hg
for 3 hours at room temperature, and the flask with contents was reweighed. The
orthoester, anhydrous ethanol, and ethanolic 2,6-dichlorobenzoic acid solution
were thermostated for 20 min. in the 25.0° bath. The ethanolysis solution was
prepared by adding anhydrous ethanol, sufficient 2,6-dichlorobenzoic acid solution
to prepare a 0.0052N solution on final dilution, and diluting to volume with an-
hydrous ethanol. Zero time was taken to be that time at which half of the acid
catalyst solution had been added. The special sampling apparatus* was attached
and sampling was begun.

*Described previously for sampling of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl) -
α-D-glucose ethanolysis solutions.
The ethanolysis with added salts was conducted by adding the lithium $p$-toluenesulfonate to the ethanolic 2,6-dichlorobenzoic acid solution and preparing the ethanolysis solution as above.

**KINETIC TECHNIQUES**

**Product Identification**

All probable ethanolysis products of 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose can be separated by GLC (Conditions C) for identification and quantitative measurement. Unreacted 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose was converted by hydrolysis to 1-O-acetyl-2,3,4,6-tetra-0-methyl-$\alpha$-D-glucose and 2,3,4,6-tetra-0-methyl-D-glucose. Since the latter compound is also an ethanolysis product, but the former is formed only by hydrolysis of remaining 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose, knowledge of the ratio of these two compounds formed by hydrolysis was necessary to calculate the amount of unreacted orthoester. 2,3,4,6-Tetra-0-methyl-D-glucose was measured as its 1-O-propanoyl derivative.

Chromatograms A, B, C, D, (Fig. 18a and 18b) illustrate the GLC separation of ethanolysis and hydrolysis products of 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose. Chromatogram A (Fig. 18a) is a synthetic mixture illustrating the GLC (Conditions B) separation of all probable glucose moieties which could be encountered in an analysis. The identities of the components are:

1. ethyl 2,3,4,6-tetra-0-methyl-$\beta$-D-glucoside
2. ethyl 2,3,4,6-tetra-0-methyl-$\alpha$-D-glucoside
3. 1-O-acetyl-2,3,4,6-tetra-0-methyl-$\alpha$-D-glucose [a hydrolysis product of 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose]
4. 2,3,4,6-tetra-0-methyl-D-glucose [ethanolysis and hydrolysis product of 2,3,4,6-tetra-0-methyl-1-O-(diethyl orthoacetyl)-$\alpha$-D-glucose as the 1-O-propanoyl derivatives]
5. isopropyl 3,4,6-tri-0-methyl-$\beta$-D-glucoside (internal standard for quantitative measurement as its 2-O-propanoyl derivative)
Figure 18a. Sample Chromatograms of Glucose Moieties in the Ethanolysis of 2,3,4,6-Tetra-O-methyl-1-O-(diethyl orthoacetate)-α-D-glucose: A, Synthetic Mixture; B, 121 min. Ethanolysis
Figure 18b. Sample Chromatograms of Glucose Moieties in the Ethanolysis and Hydrolysis of 2,3,4,6-Tetra- β-methyl-1- β-(diethyl orthoacetate)-α-D-glucose: C, 2.7 min. Ethanolysis with Added Salt; D, Hydrolysis
Chromatogram B (Fig. 18a) illustrates the ethanolysis products found: ethyl 2,3,4,6-tetra-O-methyl-\(\beta\)-D-glucoside, [Peak (1)] ethyl 2,3,4,6-tetra-O-methyl-\(\alpha\)-D-glucoside [Peak (2)], and 2,3,4,6-tetra-O-methyl-D-glucose [Peak (4)]. The very small peak for 1-O-acetyl-2,3,4,6-tetra-O-methyl-\(\alpha\)-D-glucose [Peak (3)] indicates that the ethanolysis is nearly complete for this sample.

Chromatogram C illustrates the products of a partial ethanolysis of 2,3,4,6-tetra-O-methyl-\(1-O\)-(diethyl orthoacetyl)-\(\alpha\)-D-glucose in the presence of lithium p-toluenesulfonate. The large increase in ethyl 2,3,4,6-tetra-O-methyl-\(\alpha\)-D-glucoside [Peak (2)] relative to the \(\beta\)-anomer [Peak (1)] is quite noticeable upon comparison to that obtained without salt addition (Chromatogram B, Fig. 18a).

Chromatogram D illustrates the hydrolysis product distribution from 2,3,4,6-tetra-O-methyl-\(1-O\)-(diethyl orthoacetyl)-\(\alpha\)-D-glucose. Ethyl 2,3,4,6-tetra-O-methyl-\(\beta\)-D-glucoside [Peak (1)] was an impurity in the 2,3,4,6-tetra-O-methyl-\(1-O\)-(diethyl orthoacetyl)-\(\alpha\)-D-glucose. The sample used to generate Chromatogram D was carried through the entire analysis procedure used for ethanolysis samples with the exception that no internal standard was used. Other samples which were hydrolyzed before treating as ethanolysis samples gave identical results showing that 2,3,4,6-tetra-O-methyl-\(1-O\)-(diethyl orthoacetyl)-\(\alpha\)-D-glucose was stable prior to hydrolysis in the ethanolysis sample work up.

Quantitative Measurement Procedures

The GLC response factors, hydrolysis data, and calculations for glucose moieties in hydrolyses and ethanolyses are given in Appendix XII.

**Ethanolysis sample procedure.** The procedure was the same as that used for measurement of glucose moieties in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-\(\alpha\)-D-glucose with the exception that isopropyl 3,4,6-tri-O-methyl-\(\beta\)-D-glucoside was used as the internal standard. GLC Conditions C were used for the analyses.
Hydrolysis sample procedure. Two samples were made up by adding 2 drops of 2,3,4,6-tetra-0-methyl-l-0-(diethyl orthoacetyl)-α-D-glucose to 2 ml. of triethyl-aminotoluene (3/7, v/v), then 1 ml. of ethanolic 0.005N 2,6-dichlorobenzoic acid was added. The sample was then treated as an ethanolsysis sample.

Two samples were made up by hydrolysis of two drops of 2,3,4,6-tetra-0-methyl-l-0-(diethyl orthoacetyl)-α-D-glucose in 4 ml. of a 1/9, v/v acetone-water solution of Universal Indicator and one drop of N sulfuric acid. These samples were hydrolyzed 3 and 6 minutes, respectively. Work up thereafter was the same as ethanolsysis samples beginning with the statement "0.01N sodium hydroxide was added dropwise...." 

The data from the two methods of hydrolysis is given in Appendix XII, Table XXXIV.
CONCLUSIONS

Reversible transorthoesterifications and glucoside formation are the only types of reactions found to occur in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses in the absence of water. Traces of water in the ethanolysis medium can result in large proportions of hydrolysis products relative to ethanolysis products. In the presence or absence of water the reaction should be considered to be complete only when the ester formed is equivalent to the amount of original 1,2-orthoester. In the absence of water, the quantities of glucoside and ester formed are equivalent.

The alkoxy exchange reaction of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose is approximately 300 times faster than disappearance of the 1,2-orthoester by ethanolysis. This rate difference between the two reactions could explain results obtained by Russian workers. These workers claim to have found acid catalysts or combinations and concentrations of acid catalysts for which alkoxy exchange occurs but not glycoside formation.

The 1,2-acetoxonium ion mechanism usually postulated for glucoside formation is, at most, of minor importance compared to other mechanisms of glucoside formation. The proof of this is: (1) ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside, which is the only readily predicted glucoside by the 1,2-acetoxonium ion mechanism, represents less than 25% of the glucosides formed; and (2) ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside can be readily predicted by another mechanism. Also, addition of salt to ethanolyses decreases the proportion of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside formed while according to the 1,2-acetoxonium ion, ion-pair mechanism postulated by Russian workers the rate of formation of this product should increase greatly upon salt addition.
Two similar mechanisms of glucoside formation which can collectively explain all glycosidic products involve formation of a carbonium ion at C-1 of the sugar concurrently with formation of an orthoacid group. This can occur as either, (1) the initial step, or (2) subsequent to a transorthoesterification step to form a 1-O-(diethyl orthoacetyl) group. Ethanol reacts at the C-1 carbonium ion to form α- and β-glucosides and the orthoacid group forms an ester and an alcohol. The evidence for these mechanisms includes: (1) there is no reasonable alternate mechanism to explain formation of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside, (2) the ethanolysis behavior of an analog of one of the proposed intermediates was demonstrated to be in agreement with the mechanism requirements, (3) the observed stereoselectivity for β-glucoside formation is consistent with the mechanisms, (4) equivalent amounts of glucoside and ester are formed in agreement with the postulated mechanisms, (5) the observed salt effects on β-glucoside stereoselectivity are in agreement with predictions based on the two mechanisms, and (6) it was demonstrated that two or more mechanisms must account for glucoside formation.

Two mechanisms supported for formation of 3,4,6-tri-O-methyl-α-D-glucose are in agreement with the literature. Both mechanisms involve two successive transorthoesterifications in which only the order of bond cleavages is different. The demonstrated formation of triethyl orthoacetate and the α-anomer of 3,4,6-tri-O-methyl-D-glucose are in agreement with both mechanisms.

Alkoxy exchange between 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose and ethanol, as well as hydrolyses of the orthoester were shown to proceed predominantly through the 1,2-acetoxonium ion. Those conclusions followed from: (1) the disparity between rates of alkoxy exchange and 3,4,6-tri-O-methyl-α-D-glucose formation although both are transorthoesterifications, and (2) hydrolysis results in quantitative retention of an acetyl group on the glucose moiety.
In glycoside syntheses with sugar 1,2-orthoesters water scavenging and electrolyte effects can be detrimental with respect to the yield and to the anomeric purity of the glycosides formed, respectively.

Sugar 1-orthoesters also form glucosides on ethanolysis. From limited data in this thesis it appears that 1-orthoesters are more reactive than 1,2-orthoesters. Also, sugar 1-orthoesters can be readily generated in situ in glycoside syntheses eliminating a considerable amount of synthesis work. The initial anomeric configuration of the hemiacetal sugar is the most important consideration since it is expected that the 1-orthoester will yield predominantly glycosides of opposite anomeric configuration. In demonstration of this type of synthesis, the ethanolysis of 3,4,6-tri-O-methyl-α-D-glucose in the presence of triethyl orthoacetate gave predominantly the β-glucosides under very mild conditions of temperature and acidity. This method of forming glycosides may be the mildest known, and as such may find use where other methods are not satisfactory.
NOMENCLATURE

GLC  Gas-liquid partition chromatography
TLC  Thin layer chromatography
NMR  Nuclear magnetic resonance spectroscopy
α Et 2-O-A  Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoside
β Et 2-O-A  Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside
α Et  Ethyl 3,4,6-tri-O-methyl-α-D-glucoside
β Et  Ethyl 3,4,6-tri-O-methyl-β-D-glucoside
TMG  3,4,6-Tri-O-methyl-D-glucose
2-O-A  2-O-Acetyl-3,4,6-tri-O-methyl-α-D-glucoside
M-O-A  Mono-O-acetyl-3,4,6-tri-O-methyl-D-glucose(s)
TM-Et-ortA  3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose
TM-ip-ortA  3,4,6-Tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose
T₄MG-Et(α)  Ethyl 2,3,4,6-tetra-O-methyl-α-D-glucoside
T₄MG-Et(β)  Ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside
T₄MG-OH  2,3,4,6-Tetra-O-methyl-D-glucose
T₄MG-O-Ac  1-O-Acetyl-2,3,4,6-tetra-O-methyl-α-D-glucoside

\( X_1 \)  Reactant mole fraction of original reactant remaining at time \( t \)
\( X_{1,t} \)  Glucose product mole fraction of original reactant which has appeared by time \( t \)
\( X_{E,t} \)  Ester mole fraction of original reactant which has appeared by time \( t \)
\( X_{1,\infty} \)  Glucose product mole fraction which has appeared by time infinity
\( k_i \)  Pseudo-parallel-first-order rate constant for the formation of product \( i \), time\(^{-1}\)
\( \Sigma k_i \)  Pseudo-first-order rate constant for the disappearance of reactant or the sum of \( k_i \)
\( X_{i,t} \)  Glucoside \( i \) mole fraction of original 3,4,6-tri-O-methyl-α-D-glucose appeared by time \( t \)
Glucoside mole fraction formed directly via 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetate)-D-glucose intermediates of total glucosides appeared by time $t$ from the ethanolysis of 3,4,6-tri-O-methyl-$\alpha$-D-glucose in the presence of triethyl orthoacetate.

Glucoside mole fraction formed via 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetate)-$\alpha$-D-glucose intermediate of total glucosides appeared by time $t$ from the ethanolysis of 3,4,6-tri-O-methyl-$\alpha$-D-glucose in the presence of triethyl orthoacetate.
ACKNOWLEDGMENTS

The author wishes to thank the thesis advisory committee; Drs. L. R. Schroeder, D. C. Johnson, and P. A. Seib, for assistance, constructive criticisms, and encouragement.

In particular, for the many times when Dr. Schroeder expressed helpful ideas; listened to my ideas; discussed and, or argued about ideas, the author is grateful. The author is indebted to Dr. Schroeder and F. C. Haigh for a sample of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose which they had prepared by the synthesis they developed which is given in this thesis. The time spent by Dr. Schroeder and L. O. Sell in using the NMR spectrometer is gratefully acknowledged.

Last, but not least, I am indebted to my wife, Linda, for continual encouragement and help in this manuscript preparation.


40. Schroeder, L. R., Submitted for publication.


53. Schroeder, L. R., Personal communication, 1967.
APPENDIX I

NMR ANALYSIS OF THE d5-ETHANOLYSIS OF EXO-OR 3,4,6-TRI-O-
METHYL-1,2-O-(ETHYL-d5 ORTHOACETYL)-α-D-GLUCOSE
CATALYZED BY PICRIC ACID

TABLE VI

RUN A\(^a\)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Singlet Signal Height</th>
<th>δ (p.p.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.04</td>
<td>1.98</td>
</tr>
<tr>
<td>Initial</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>1.8</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>4.7</td>
<td>1.3</td>
<td>3.6</td>
</tr>
<tr>
<td>8.2</td>
<td>2.3</td>
<td>7.2</td>
</tr>
<tr>
<td>11.5</td>
<td>3.1</td>
<td>9.4</td>
</tr>
<tr>
<td>16.0</td>
<td>4.0</td>
<td>12.3</td>
</tr>
<tr>
<td>21.0</td>
<td>4.8</td>
<td>14.8</td>
</tr>
<tr>
<td>26.0</td>
<td>5.3</td>
<td>16.4</td>
</tr>
<tr>
<td>30.7</td>
<td>5.8</td>
<td>17.8</td>
</tr>
<tr>
<td>38.4</td>
<td>6.1</td>
<td>18.7</td>
</tr>
<tr>
<td>47.5</td>
<td>6.5</td>
<td>19.9</td>
</tr>
<tr>
<td>55.3</td>
<td>6.8</td>
<td>20.8</td>
</tr>
<tr>
<td>64.6</td>
<td>7.0</td>
<td>20.7</td>
</tr>
<tr>
<td>D2O</td>
<td>6.3</td>
<td>21.2</td>
</tr>
</tbody>
</table>

\(^a\)Approximately 0.6 ml. CD3-CD2-OH, 0.4 ml. exo-OR 3,4,6-tri-O-methyl-1,2-O-
(ethyl-d5 orthoacetyl)-α-D-glucose, and several mg. picric acid. Temperature = 45°C.

\(^b\)Singlets due to orthoacetyl or acetyl methyl groups: ethyl 2-O-acetyl-3,4,6-
tri-O-methyl-β-D-glucoside (2.04), ethyl acetate (1.98), 3,4,6-tri-O-methyl-
1,2-O-(ethyl-d5 orthoacetyl)-α-D-glucose (exo-OR 1.60 and endo-OR 1.48),
triethyl orthoacetate and an impurity (1.41), and TMS (0.00).

\(^c\)Before adding picric acid.
TABLE VII

RUN B

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Singlet Signal Height, δ (p.p.m.) =</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.04</td>
</tr>
<tr>
<td>2.3</td>
<td>0.7</td>
</tr>
<tr>
<td>4.3</td>
<td>1.7</td>
</tr>
<tr>
<td>6.3</td>
<td>2.6</td>
</tr>
<tr>
<td>8.2</td>
<td>3.2</td>
</tr>
<tr>
<td>11.1</td>
<td>4.2</td>
</tr>
<tr>
<td>15.9</td>
<td>5.5</td>
</tr>
<tr>
<td>20.9</td>
<td>6.1</td>
</tr>
<tr>
<td>27.6</td>
<td>6.8</td>
</tr>
<tr>
<td>34.3</td>
<td>7.2</td>
</tr>
<tr>
<td>43.8</td>
<td>7.6</td>
</tr>
<tr>
<td>53.5</td>
<td>7.6</td>
</tr>
<tr>
<td>58.7</td>
<td>7.7</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>6.8</td>
</tr>
</tbody>
</table>

$^a$Approximately 0.6 ml. CD$_3$-CD$_2$-OH, 0.4 ml. exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl-d$_5$ orthoacetyl)-α-D-glucose, 0.2 ml. triethyl orthobenzoate, and several mg. picric acid. Temperature = 45°C.

$^b$See footnote b of Table VI.

These data are discussed on p. 23-26 and p. 40. The purpose of the trimethyl orthobenzoate (Run B) was to insure an anhydrous system before adding the 1,2-orthoester. This eliminates the possibility of water-scavenging by triethyl orthoacetate formed.
APPENDIX II

POLARIMETRIC DATA FOR THE ETHANOLYSES OF 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSES AT 25.0°C.

Appendix II contains all polarimetric ethanolyses data other than Run 4 which is given in Appendix V, Table XVII.

TABLE VIII

ETHANOLYSIS OF EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE AT 25.0°C. (RUN 2)a,c

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>α° b ob.</th>
<th>Time, min.</th>
<th>α° b ob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>+2.57</td>
<td>522</td>
<td>+1.46</td>
</tr>
<tr>
<td>7.5</td>
<td>2.59</td>
<td>575</td>
<td>1.40</td>
</tr>
<tr>
<td>9.7</td>
<td>2.60</td>
<td>755</td>
<td>1.21</td>
</tr>
<tr>
<td>15.6</td>
<td>2.62</td>
<td>842</td>
<td>1.13</td>
</tr>
<tr>
<td>24.0</td>
<td>2.60</td>
<td>941</td>
<td>1.04</td>
</tr>
<tr>
<td>30.0</td>
<td>2.61</td>
<td>1061</td>
<td>0.98</td>
</tr>
<tr>
<td>36.6</td>
<td>2.58</td>
<td>1185</td>
<td>0.92</td>
</tr>
<tr>
<td>43.7</td>
<td>2.55</td>
<td>1556</td>
<td>0.80</td>
</tr>
<tr>
<td>60.0</td>
<td>2.48</td>
<td>1870</td>
<td>0.72</td>
</tr>
<tr>
<td>75.4</td>
<td>2.44</td>
<td>2224</td>
<td>0.69</td>
</tr>
<tr>
<td>104.5</td>
<td>2.35</td>
<td>3470</td>
<td>0.55</td>
</tr>
<tr>
<td>135.9</td>
<td>2.26</td>
<td>4908</td>
<td>0.45</td>
</tr>
<tr>
<td>187.0</td>
<td>2.13</td>
<td>6651</td>
<td>0.44</td>
</tr>
<tr>
<td>270.0</td>
<td>1.91</td>
<td>7632</td>
<td>0.40</td>
</tr>
<tr>
<td>363.0</td>
<td>1.73</td>
<td>8608</td>
<td>0.41</td>
</tr>
<tr>
<td>442.0</td>
<td>1.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

a 2.090 g./100 ml., Exo-OR 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose in 0.00526N 2,6-dichlorobenzoic acid.
b 2-cm. tube, 546 nm. light.
c Glucose moiety data in Table XIII, ester data in Table XX.
**TABLE IX**

ETHANOLYSIS OF **EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ISOPROPYL ORTHOACETYL)-α-D-GLUCOSE**<sup>a</sup>,<sup>c</sup> AT 25.0°C.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>α&lt;sub&gt;obs.&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;°</th>
<th>Time, min.</th>
<th>α&lt;sub&gt;obs.&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;°</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td>+2.56</td>
<td>326</td>
<td>+1.91</td>
</tr>
<tr>
<td>6.6</td>
<td>2.60</td>
<td>400</td>
<td>1.77</td>
</tr>
<tr>
<td>9.8</td>
<td>2.61</td>
<td>437</td>
<td>1.71</td>
</tr>
<tr>
<td>17.7</td>
<td>2.63</td>
<td>528</td>
<td>1.61</td>
</tr>
<tr>
<td>25.5</td>
<td>2.62</td>
<td>673</td>
<td>1.43</td>
</tr>
<tr>
<td>37.7</td>
<td>2.58</td>
<td>709</td>
<td>1.39</td>
</tr>
<tr>
<td>50.2</td>
<td>2.55</td>
<td>1098</td>
<td>1.16</td>
</tr>
<tr>
<td>71.4</td>
<td>2.49</td>
<td>1262</td>
<td>1.10</td>
</tr>
<tr>
<td>98.2</td>
<td>2.42</td>
<td>1580</td>
<td>1.00</td>
</tr>
<tr>
<td>109.8</td>
<td>2.38</td>
<td>2083</td>
<td>0.94</td>
</tr>
<tr>
<td>140.0</td>
<td>2.32</td>
<td>2808</td>
<td>0.87</td>
</tr>
<tr>
<td>196.5</td>
<td>2.17</td>
<td>4380</td>
<td>0.84</td>
</tr>
<tr>
<td>252.0</td>
<td>2.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>2.175 g./100 ml., **EXO-OR 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose** in 0.00525N 2,6-dichlorobenzoic acid.

<sup>b</sup>2-dm. tube, 546 nm. light.

<sup>c</sup>Glucose moiety data in Table XVI.
## Table X

**Ethanolysis of an Endo-Exo Mixture of 3,4,6-Tri-O-Methyl-1,2-0-(Ethyl Orthoacetyl)-α-D-Glucose**

At 25.0°C.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>α&lt;sub&gt;obs.&lt;/sub&gt; °</th>
<th>Time, min.</th>
<th>α&lt;sub&gt;obs.&lt;/sub&gt; °</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>+3.07</td>
<td>342</td>
<td>+2.71</td>
</tr>
<tr>
<td>5.9</td>
<td>3.07</td>
<td>449</td>
<td>2.62</td>
</tr>
<tr>
<td>8.2</td>
<td>3.07</td>
<td>481</td>
<td>2.59</td>
</tr>
<tr>
<td>11.8</td>
<td>3.05</td>
<td>589</td>
<td>2.50</td>
</tr>
<tr>
<td>15.0</td>
<td>3.05</td>
<td>1043</td>
<td>2.17</td>
</tr>
<tr>
<td>19.4</td>
<td>3.04</td>
<td>1183</td>
<td>2.12</td>
</tr>
<tr>
<td>23.3</td>
<td>3.04</td>
<td>1339</td>
<td>2.04</td>
</tr>
<tr>
<td>25.5</td>
<td>3.03</td>
<td>1549</td>
<td>1.95</td>
</tr>
<tr>
<td>30.6</td>
<td>3.02</td>
<td>1815</td>
<td>1.83</td>
</tr>
<tr>
<td>36.7</td>
<td>3.01</td>
<td>2654</td>
<td>1.57</td>
</tr>
<tr>
<td>49.4</td>
<td>2.99</td>
<td>3005</td>
<td>1.44</td>
</tr>
<tr>
<td>62.6</td>
<td>2.97</td>
<td>4037</td>
<td>1.25</td>
</tr>
<tr>
<td>78.2</td>
<td>2.95</td>
<td>6851</td>
<td>1.01</td>
</tr>
<tr>
<td>107.0</td>
<td>2.92</td>
<td>7495</td>
<td>0.97</td>
</tr>
<tr>
<td>197.0</td>
<td>2.83</td>
<td>8315</td>
<td>0.94</td>
</tr>
<tr>
<td>300.0</td>
<td>2.74</td>
<td>10375</td>
<td>0.92</td>
</tr>
</tbody>
</table>

---

<sup>a</sup>2339 g./100 ml., 19.6% Endo-OR 80.4% exo-OR 3,4,6-tri-O-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose in 0.00530N 2,6-dichlorobenzoic acid.

<sup>b</sup>2-dm. tube, 546 nm. light.
POLARIMETRIC RATE CONSTANTS FOR THE ETHANOLYSIS OF \(3,4,6\)-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-\(\alpha\)-D-GLUCOSE

The integrated (parallel) first-order rate equation for an acid-catalyzed reaction of an optically active reactant and optically active products is given by Equation (5)

\[
\Sigma k_i = \ln \left( \frac{\alpha_o - \alpha_\infty}{\alpha_t - \alpha_\infty} \right) \frac{1}{t} \tag{5}
\]

where

- \(\Sigma k_i\) = the pseudo-first-order rate constant also given by Equations (1) and (2). (See Results and Discussion.) The term, \(k\), in the original equation given in a standard text (63) has been replaced by \(\Sigma k_i\) for nomenclature purposes,
- \(\alpha_o\) = optical rotation at time zero,
- \(\alpha_t\) = optical rotation at time \(t\),
- \(\alpha_\infty\) = optical rotation at time infinity.

The terms \(\alpha_o\), \(\alpha_t\), and \(\alpha_\infty\) may be expressed in any units which are self consistent; as a matter of choice this will be, \([\alpha]_{25}^{25}\) nm., the "specific" rotation in terms of original reactant weight.

The calculation of \(\Sigma k_i\) for Run 2 ethanolysis of \(3,4,6\)-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose will be demonstrated. There are two complications for determining \(\Sigma k_i\) by using Equation (5).

The first complication involves the initial isomerization of the \(3,4,6\)-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-\(\alpha\)-D-glucose to produce a maximum in optical rotation very early in the ethanolysis. To eliminate this complication the data in Fig. 6 were extrapolated to \(t=0\) to give a value of \([\alpha]_{546}^{25}\) nm., = +66 which is \(\alpha_o\). The extrapolation amounts to the good assumption that the equilibrium mixture of
endo-OR and exo-OR isomers of 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose is the reactant.

The second complication is the change in optical rotation due to acid-catalyzed mutarotation of 3,4,6-tri-0-methyl-α-D-glucose. This is in addition to the decrease in rotation caused by the ethanolysis of 3,4,6-tri-0-methyl-1,2-0-(ethyl orthoacetyl)-α-D-glucose. For Run 2, the value of -0.02° mutarotation prior to 408 min. ethanolysis (p. 36-37) is a good estimation of this complication. Then \[ \Delta [\alpha]^{25}_{546} \text{ nm. due to mutarotation is } -0.5°, \] and this value must be subtracted from the value of \[ [\alpha]^{25}_{546} \text{ nm. } = +39.2° \text{ at } 408 \text{ min. from Fig. 6} \text{ to give } \alpha_t = +39.7°. \]

The value of \( \alpha_\infty \) can be calculated from the values of \( \chi^{\infty}_{i,l} \) (Run 3, Table III) and the values of specific rotation for the ethanolysis products given in Table XI by

\[
\alpha_\infty = \alpha_1 + \alpha_2 + \alpha_3 + \alpha_4 = \sum_{i=1}^{4} \alpha
\]

or more specifically,

\[
\alpha_\infty = \sum_{i=1}^{4} (X_{i,\infty})(\text{mol. wt. } i/\text{mol. wt. reactant})([\alpha]^{25}_{546} \text{ nm. of } i) \] (6)

\[
= (-3.7°) + 4.7° + (-7.5°) + 24.6° = +18.1°.
\]

where the contributions to \( \alpha_\infty \) above are for ethyl 2-0-acetyl-3,4,6-tri-0-methyl-β-D-glucoside, ethyl 3,4,6-tri-0-methyl-α-D-glucoside, ethyl 3,4,6-tri-0-methyl-β-D-glucoside, and 3,4,6-tri-0-methyl-α-D-glucose, respectively.

Using the values \( \alpha_o = +66°, \alpha_t = +39.7°, \) and \( \alpha_\infty = +18.1° \) in Equation (5), the value of \( \Sigma k_j = 3.26 \times 10^{-5} \text{ sec}^{-1} \) for Run 2 ethanolysis. A similar ethanolysis (Run 4, Appendix V) yields \( \Sigma k_j = 3.39 \times 10^{-5} \text{ sec}^{-1} \) if the value of \( \alpha_o \) is assumed to be identical to that of Run 2 ethanolysis.
### TABLE XI
POLARIMETRIC CONSTANTS IN ETHANOL

<table>
<thead>
<tr>
<th>Compound</th>
<th>([\alpha]^{25}_{546}) nm (^o)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl 3,4,6-tri-O-methyl-(\beta)-D-glucoside</td>
<td>-15.3</td>
</tr>
<tr>
<td>Ethyl 3,4,6-tri-O-methyl-(\alpha)-D-glucoside</td>
<td>+194</td>
</tr>
<tr>
<td>Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-(\beta)-D-glucoside</td>
<td>-19.0</td>
</tr>
<tr>
<td>3,4,6-Tri-O-methyl-(\alpha)-D-glucose</td>
<td>+155 (\rightarrow) +116\textsuperscript{a}</td>
</tr>
<tr>
<td>3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-(\alpha)-D-glucose</td>
<td>+60</td>
</tr>
<tr>
<td><strong>exo</strong> isomer (pure)</td>
<td></td>
</tr>
<tr>
<td><strong>exo-OR</strong> isomer (80.4%) + <strong>endo-OR</strong> isomer (19.6%)</td>
<td>+66\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Mutarotation, 7.5 \(\times\) 10\(-6\) sec\(^{-1}\) = \(k\_\alpha + k\_\beta\) in 0.0052M 2,6-dichlorobenzoic acid, data in Table XVIII.

\textsuperscript{b} Extrapolated from data plotted in Fig. 6 with initial isomeric composition indicated.
APPENDIX IV

GLUCOSE MOIETY DATA FOR ETHANOLYSES OF 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSES

TABLE XII

ETHANOLYSIS OF EXO-OR. 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE\(^a\) AT 25.0°C. IN 0.00517 N 2,6-DICHLOROBENZOIC ACID (RUN 1)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Products (^b) ((X_{I,t}))</th>
<th>Reactant (^b,c) ((X_{I}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(9.6)</td>
<td>(\beta) Et 2-O-A</td>
<td>(\alpha) Et</td>
</tr>
<tr>
<td>37.0</td>
<td>0.011</td>
<td>0.003</td>
</tr>
<tr>
<td>77.2</td>
<td>0.024</td>
<td>0.005</td>
</tr>
<tr>
<td>150.8</td>
<td>0.045</td>
<td>0.007</td>
</tr>
<tr>
<td>320.0</td>
<td>0.079</td>
<td>0.011</td>
</tr>
<tr>
<td>631.0</td>
<td>0.123</td>
<td>0.017</td>
</tr>
<tr>
<td>980.0</td>
<td>0.156</td>
<td>0.019</td>
</tr>
<tr>
<td>1545.0</td>
<td>0.172</td>
<td>0.022</td>
</tr>
<tr>
<td>1948.0</td>
<td>0.179</td>
<td>0.023</td>
</tr>
<tr>
<td>(14439.0)</td>
<td>0.179</td>
<td>0.024</td>
</tr>
</tbody>
</table>

\(^a\)0.979 g./50 ml.

\(^b\)Values given are normalized with the exception of the values in parentheses which were measured using methyl tetra-O-methyl-α-D-glucoside as an internal standard. In the latter case, no sample work-up was involved and GLC conditions D were employed. The response factors (90% confidence limits) given by \(f_X = (\text{area X/area standard}) (\text{moles standard/moles X})\) are 1.256 ± 0.020 (\(\beta\) Et 2-O-A), 1.002 ± 0.033 (\(\alpha\) Et), and 1.039 ± 0.011 (\(\beta\) Et).

\(^c\)Hydrolysis due to water scavenging as indicated by the measurement of mono-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoses (7%) at long ethanolysis times.
<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Product(^c) ((X_{i,t}))</th>
<th>Reactant(^c) ((X_t))</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6520)</td>
<td>0.194 (9)</td>
<td>0.028 (2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

\(^a\)2.090 g./100 ml.

\(^b\)Polarimetric data Table VIII, ester data Table XX.

\(^c\)Figures in parentheses are the range of three GLC analyses on the same sample multiplied by 10\(^3\).
## TABLE XIV

ETHANOLYSIS OF EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-\(\alpha\)-D-GLUCOSE\(^a\) AT 25.0°C.
IN 0.062N LITHIUM \(\beta\)-TOLUENESULFONATE AND 0.00525N 2,6-DICHLOROBENZOIC ACID

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>(\alpha) Et 2-O-A</th>
<th>(\beta) Et 2-O-A</th>
<th>(\alpha) Et</th>
<th>(\beta) Et</th>
<th>TMG</th>
<th>TM-Et-ortA</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7</td>
<td>0.000 (0)</td>
<td>0.007 (1)(^b)</td>
<td>0.007 (1)</td>
<td>0.015 (8)</td>
<td>0.012 (2)</td>
<td>1.010 (25)</td>
<td>1.051</td>
</tr>
<tr>
<td>19.3</td>
<td>0.001 (1)</td>
<td>0.027 (3)</td>
<td>0.022 (1)</td>
<td>0.081 (5)</td>
<td>0.034 (5)</td>
<td>0.890 (28)</td>
<td>1.055</td>
</tr>
<tr>
<td>40.2</td>
<td>0.001 (1)</td>
<td>0.052 (7)</td>
<td>0.042 (2)</td>
<td>0.158 (6)</td>
<td>0.059 (3)</td>
<td>0.720 (16)</td>
<td>1.032</td>
</tr>
<tr>
<td>74.1</td>
<td>0.002 (2)</td>
<td>0.079 (5)</td>
<td>0.066 (5)</td>
<td>0.255 (14)</td>
<td>0.092 (3)</td>
<td>0.526 (18)</td>
<td>1.020</td>
</tr>
<tr>
<td>124.2</td>
<td>0.002 (2)</td>
<td>0.106 (1)</td>
<td>0.092 (2)</td>
<td>0.352 (6)</td>
<td>0.127 (3)</td>
<td>0.337 (2)</td>
<td>1.016</td>
</tr>
<tr>
<td>180.5</td>
<td>0.003 (2)</td>
<td>0.123 (4)</td>
<td>0.104 (6)</td>
<td>0.416 (9)</td>
<td>0.153 (4)</td>
<td>0.207 (22)</td>
<td>1.006</td>
</tr>
<tr>
<td>261.9</td>
<td>0.002 (1)</td>
<td>0.140 (4)</td>
<td>0.121 (2)</td>
<td>0.468 (10)</td>
<td>0.162 (1)</td>
<td>0.101 (4)</td>
<td>0.994</td>
</tr>
<tr>
<td>373.4</td>
<td>0.004 (1)</td>
<td>0.150 (2)</td>
<td>0.129 (1)</td>
<td>0.498 (13)</td>
<td>0.177 (4)</td>
<td>0.048 (6)</td>
<td>1.006</td>
</tr>
<tr>
<td>708.0</td>
<td>0.003 (1)</td>
<td>0.154 (11)</td>
<td>0.135 (10)</td>
<td>0.513 (23)</td>
<td>0.179 (10)</td>
<td>0.016 (3)</td>
<td>1.000</td>
</tr>
<tr>
<td>6122.0</td>
<td>0.003 (0)</td>
<td>0.158 (3)</td>
<td>0.138 (5)</td>
<td>0.526 (9)</td>
<td>0.172 (12)</td>
<td>0.012 (2)</td>
<td>1.009</td>
</tr>
</tbody>
</table>

\(^a\)0.5278 g./25 ml.

\(^b\)Figures in parentheses are the range of three GLC analyses multiplied by 10³.
TABLE XV

ETHANOLYSIS OF EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D GLUCOSE AT 25.0°C.
IN 0.062N LITHIUM BROMIDE AND 0.00525N 2,6-DICHLOROBENZOIC ACID

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>α Et 2-O-A</th>
<th>β Et 2-O-A</th>
<th>α Et</th>
<th>β Et</th>
<th>TMG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reactant</td>
<td>Total</td>
<td>Measured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1</td>
<td>0.000 (2)</td>
<td>0.014 (4)</td>
<td>0.011 (1)</td>
<td>0.031 (2)</td>
<td>0.018 (2)</td>
</tr>
<tr>
<td>19.9</td>
<td>0.001 (1)</td>
<td>0.028 (2)</td>
<td>0.018 (2)</td>
<td>0.067 (2)</td>
<td>0.032 (4)</td>
</tr>
<tr>
<td>39.7</td>
<td>0.002 (0)</td>
<td>0.047 (2)</td>
<td>0.030 (2)</td>
<td>0.118 (6)</td>
<td>0.051 (6)</td>
</tr>
<tr>
<td>68.2</td>
<td>0.004 (1)</td>
<td>0.070 (10)</td>
<td>0.047 (2)</td>
<td>0.185 (9)</td>
<td>0.080 (4)</td>
</tr>
<tr>
<td>100.5</td>
<td>0.005 (1)</td>
<td>0.094 (5)</td>
<td>0.061 (1)</td>
<td>0.243 (11)</td>
<td>0.107 (5)</td>
</tr>
<tr>
<td>153.0</td>
<td>0.006 (2)</td>
<td>0.119 (5)</td>
<td>0.076 (1)</td>
<td>0.310 (15)</td>
<td>0.135 (2)</td>
</tr>
<tr>
<td>236.7</td>
<td>0.007 (1)</td>
<td>0.144 (3)</td>
<td>0.092 (1)</td>
<td>0.374 (8)</td>
<td>0.162 (4)</td>
</tr>
<tr>
<td>383.0</td>
<td>0.009 (2)</td>
<td>0.166 (3)</td>
<td>0.108 (4)</td>
<td>0.423 (7)</td>
<td>0.185 (5)</td>
</tr>
<tr>
<td>1245.0</td>
<td>0.009 (1)</td>
<td>0.167 (7)</td>
<td>0.110 (2)</td>
<td>0.439 (4)</td>
<td>0.190 (6)</td>
</tr>
<tr>
<td>4616.0</td>
<td>0.009 (1)</td>
<td>0.171 (4)</td>
<td>0.116 (14)</td>
<td>0.442 (15)</td>
<td>0.197 (7)</td>
</tr>
</tbody>
</table>

\(^a\) 0.5271 g./25 ml.
\(^b\) Figures in parentheses are the range of three GLC analyses on the same sample multiplied by 10^3.
\(^c\) Hydrolysis due to water scavenging as indicated by the measurement of mono-O-acetyl-3,4,6-tri-O-methyl-α-D-glucoses (9%) at long ethanolysis times.
TABLE XVI

ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-1,2-O-(ISOPROPYL ORTHOACETYL)-α-D-GLUCOSE\textsuperscript{a,d} AT 25.0°C. IN 0.00525N 2,6-DICHLOROBENZOIC ACID

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>( \beta \text{ Et 2-O-A} )</th>
<th>( \alpha \text{ Et} )</th>
<th>( \beta \text{ Et} )</th>
<th>( \text{TMG} )</th>
<th>( \text{Reactant}\textsuperscript{b} (X_{1/2}) )</th>
<th>( \text{Total Measured} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.984 (2)</td>
<td>0.984</td>
</tr>
<tr>
<td>132.0</td>
<td>0.041 (2)</td>
<td>0.006 (1)</td>
<td>0.114 (2)</td>
<td>0.046 (11)</td>
<td>0.792 (19)</td>
<td>0.999</td>
</tr>
<tr>
<td>313.0</td>
<td>0.080 (1)</td>
<td>0.011 (1)</td>
<td>0.233 (12)</td>
<td>0.087 (6)</td>
<td>0.585 (16)</td>
<td>0.996</td>
</tr>
<tr>
<td>666.0</td>
<td>0.127 (2)</td>
<td>0.017 (1)</td>
<td>0.373 (5)</td>
<td>0.138 (9)</td>
<td>0.342 (15)</td>
<td>0.997</td>
</tr>
<tr>
<td>1126.0</td>
<td>0.157 (3)</td>
<td>0.020 (2)</td>
<td>0.467 (5)</td>
<td>0.163 (8)</td>
<td>0.157 (9)</td>
<td>0.964</td>
</tr>
<tr>
<td>2776.0</td>
<td>0.185 (3)</td>
<td>0.024 (2)</td>
<td>0.550 (2)</td>
<td>0.189 (10)</td>
<td>0.019 (2)</td>
<td>0.967</td>
</tr>
</tbody>
</table>

\textsuperscript{a}2.18 g./100 ml.

\textsuperscript{b}Figures in parentheses are the range of three trials on the same sample multiplied by 10\textsuperscript{3}.

\textsuperscript{c}The reactant is more correctly called 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose because of the rapid formation of this compound from 3,4,6-tri-O-methyl-1,2-O-(isopropyl orthoacetyl)-α-D-glucose.

\textsuperscript{d}Polarimetric data Table IX.
APPENDIX V

DATA ON THE QUANTITY, CONFIGURATION, AND RATE OF MUTAROTATION OF
3,4,6-TRI-O-METHYL-D-GLUCOSE FORMED IN THE ETHANOLYSIS OF EXO-OR
3,4,6-TRI-O-METHYL-1,2-0-(ETHYL ORTHOACETYL)-α-GLUCOSE

TABLE XVII

MUTAROTATION OF THE 3,4,6-TRI-O-METHYL-D-GLUCOSE FORMED IN THE
ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-GLUCOSE
AFTER ADDITION OF TRIETHYLAMINE (RUN 4)

<table>
<thead>
<tr>
<th>Time, a min.</th>
<th>α&lt;sub&gt;obs.&lt;/sub&gt; b°</th>
<th>Δα&lt;sub&gt;obs.&lt;/sub&gt; b° by mutarotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>380</td>
<td>+1.68</td>
<td>---</td>
</tr>
<tr>
<td>386</td>
<td>1.66</td>
<td>---</td>
</tr>
<tr>
<td>391</td>
<td>1.66</td>
<td>---</td>
</tr>
<tr>
<td>398</td>
<td>1.65</td>
<td>---</td>
</tr>
<tr>
<td>406</td>
<td>1.63</td>
<td>---</td>
</tr>
<tr>
<td>(408 triethylamine)</td>
<td>(+1.63°)</td>
<td>(0.00°)</td>
</tr>
<tr>
<td>415</td>
<td>1.59</td>
<td>-0.04</td>
</tr>
<tr>
<td>423</td>
<td>1.57</td>
<td>-0.06</td>
</tr>
<tr>
<td>435</td>
<td>1.55</td>
<td>-0.08</td>
</tr>
<tr>
<td>446</td>
<td>1.53</td>
<td>-0.10</td>
</tr>
<tr>
<td>471</td>
<td>1.52</td>
<td>-0.11</td>
</tr>
<tr>
<td>493</td>
<td>1.50</td>
<td>-0.13</td>
</tr>
<tr>
<td>517</td>
<td>1.50</td>
<td>-0.13</td>
</tr>
<tr>
<td>598</td>
<td>1.48</td>
<td>-0.13</td>
</tr>
<tr>
<td>652</td>
<td>1.47</td>
<td>-0.16</td>
</tr>
<tr>
<td>741</td>
<td>1.46</td>
<td>-0.17</td>
</tr>
<tr>
<td>815</td>
<td>1.48</td>
<td>-0.15</td>
</tr>
<tr>
<td>855</td>
<td>1.47</td>
<td>-0.16</td>
</tr>
<tr>
<td>1348</td>
<td>1.50</td>
<td>-0.13</td>
</tr>
<tr>
<td>1475</td>
<td>1.49</td>
<td>-0.14</td>
</tr>
<tr>
<td>1576</td>
<td>1.49</td>
<td>-0.14</td>
</tr>
<tr>
<td>1663</td>
<td>1.48</td>
<td>-0.15</td>
</tr>
<tr>
<td>1843</td>
<td>1.48</td>
<td>-0.15</td>
</tr>
<tr>
<td>2008</td>
<td>1.48</td>
<td>-0.15</td>
</tr>
<tr>
<td>2795</td>
<td>1.50</td>
<td>-0.13</td>
</tr>
<tr>
<td>3000</td>
<td>1.50</td>
<td>-0.13</td>
</tr>
<tr>
<td>fresh sample</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3014</td>
<td>+0.51</td>
<td>---</td>
</tr>
<tr>
<td>(3016 triethylamine)</td>
<td>(+0.51°)</td>
<td>(0.00°)</td>
</tr>
<tr>
<td>3021</td>
<td>0.52</td>
<td>+0.01</td>
</tr>
<tr>
<td>3082</td>
<td>0.49</td>
<td>-0.02</td>
</tr>
<tr>
<td>3268</td>
<td>0.45</td>
<td>-0.06</td>
</tr>
<tr>
<td>3543</td>
<td>0.44</td>
<td>-0.07</td>
</tr>
</tbody>
</table>

<sup>a</sup>Time from starting ethanolysis. Triethylamine stops the acid-catalyzed ethanolysis.

<sup>b</sup>2-dm. tube, 546 nm. light.
TABLE XVIII
MUTARotation of 3,4,6-tri-O-methyl-α-D-glucose\textsuperscript{a} IN ETHANOLIC 0.00517 N 2,6-DICHLOROBENZOIC ACID AT 25.0°C.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>$\alpha_{obs}^{b, c}$</th>
<th>Time, min.</th>
<th>$\alpha_{obs}^{b, c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>+1.49°</td>
<td>1777</td>
<td>+1.28°</td>
</tr>
<tr>
<td>15.0</td>
<td>1.50</td>
<td>2772</td>
<td>1.21</td>
</tr>
<tr>
<td>32.5</td>
<td>1.50</td>
<td>4428</td>
<td>1.17</td>
</tr>
<tr>
<td>69.7</td>
<td>1.49</td>
<td>6081</td>
<td>1.15</td>
</tr>
<tr>
<td>116.5</td>
<td>1.48</td>
<td>7553</td>
<td>1.12</td>
</tr>
<tr>
<td>206.0</td>
<td>1.46</td>
<td>9608</td>
<td>1.11</td>
</tr>
<tr>
<td>336.0</td>
<td>1.44</td>
<td>11803</td>
<td>1.12</td>
</tr>
<tr>
<td>500.0</td>
<td>1.46</td>
<td>14693</td>
<td>1.11</td>
</tr>
<tr>
<td>1264.0</td>
<td>1.35</td>
<td>17253</td>
<td>1.11</td>
</tr>
</tbody>
</table>

\textsuperscript{a}0.480 g./100 ml.

\textsuperscript{b}2-cm. tube, 546 nm. light.

The rate constants for the mutarotation of 3,4,6-tri-O-methyl-D-glucoside can be calculated from the data above to be $k_{\alpha \rightarrow \beta} + k_{\beta \rightarrow \alpha} = 7.5 \times 10^{-6}$ sec.\textsuperscript{-1} by graphically testing the mutarotation equation of Lowry (64).
TABLE XIX

ETHANOLYSIS of 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE\textsuperscript{a}
AT 25.0°C. IN 0.00525N 2,6-DICHLOROBENZOIC ACID (RUN 4)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Product\textsuperscript{b} (X_{i,t})</th>
<th>Reactant\textsuperscript{b} (X_{i})</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ Et 2-0-A</td>
<td>$\alpha$ Et</td>
<td>$\beta$ Et</td>
</tr>
<tr>
<td>411</td>
<td>0.107 (3)</td>
<td>0.013 (2)</td>
<td>0.315 (6)</td>
</tr>
<tr>
<td>3007\textsuperscript{c}</td>
<td>0.190 (2)</td>
<td>0.026 (1)</td>
<td>0.577 (8)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}2.121 g./100 ml.

\textsuperscript{b}Figures in parentheses are the range of three trials on the same sample multiplied by 10\textsuperscript{3}.

\textsuperscript{c}This sample can be calculated to have an optical rotation of +0.48° in a 2-dm. tube after mutarotation to equilibrium from the data in Table XI. The actual observed value is +0.44° in Table XVII.
APPENDIX VI.

ESTER FORMATION IN THE ETHANOLYSIS OF EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE AT 25.0°C.

TABLE XX

ESTER FORMATION DATA

<table>
<thead>
<tr>
<th>Run 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Run 3&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.0</td>
<td>0.000</td>
</tr>
<tr>
<td>48.5</td>
<td>0.039</td>
</tr>
<tr>
<td>109.7</td>
<td>0.064</td>
</tr>
<tr>
<td>190.0</td>
<td>0.104</td>
</tr>
<tr>
<td>276.0</td>
<td>0.135</td>
</tr>
<tr>
<td>407.0</td>
<td>0.175</td>
</tr>
<tr>
<td>577.0</td>
<td>0.215</td>
</tr>
<tr>
<td>766.0</td>
<td>0.244</td>
</tr>
<tr>
<td>989.0</td>
<td>0.267</td>
</tr>
<tr>
<td>1450.0</td>
<td>0.288</td>
</tr>
<tr>
<td>2186.0</td>
<td>0.305</td>
</tr>
<tr>
<td>3452.0</td>
<td>0.312</td>
</tr>
<tr>
<td>6514.0</td>
<td>0.324</td>
</tr>
<tr>
<td>4907.0</td>
<td>0.308</td>
</tr>
<tr>
<td>2025&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.358&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Glucose moiety data Table XIII. Polarimetric data Table VIII.

<sup>b</sup>Glucose moiety data Table II.

<sup>c</sup>These samples were allowed to hydrolyze to give complete conversion of orthoester remaining to ester before adding hydroxide. The calculated values of meq. ester/5 ml. are 0.357 (Run 2) and 0.358 (Run 3). The measured values of meq. ester/5 ml. were used to calculate the values of ester mole fraction.
APPENDIX VII

CALCULATION OF GLUCOSIDES FORMED FROM 3,4,6-TRI-O-METHYL-1,2-0-(ETHYL ORTHOACETYL)-α-D-GLUCOSE AND 3,4,6-TRI-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-D-GLUCOSES IN THE ETHANOLYSIS OF 3,4,6-TRI-O-METHYL-α-D-GLUCOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

3,4,6-Tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose produces glucosides in constant proportions by ethanolysis as exhibited by Run 3, Table III. Hence, the measured quantity of ethyl 2-O-acetyl-3,4,6-tri-O-methyl-β-D-glucoside (X' Et 2-O-At in Table IV), which is reasonably formed only via 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose, provides the basis for calculation of the quantities of ethyl 3,4,6-tri-O-methyl-α-D-glucoside [Equation (7)] and ethyl 3,4,6-tri-O-methyl-β-D-glucoside [Equation (8)] formed from 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucoses.

\[
X''_{\alpha \text{Et,t}} = X'_{\beta \text{Et,2-O-A,t}} (0.028/0.196)
\]  

\[
X''_{\beta \text{Et,t}} = X'_{\beta \text{Et,2-O-A,t}} (0.571/0.196)
\]

The values calculated are given in Table XXI.

The glucosides not formed via 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose must have been formed by ethanolysis of intermediate 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucoses. Thus, ethyl 3,4,6-tri-O-methyl-α-D-glucoside (X''_{\alpha \text{Et,t}}) and ethyl 3,4,6-tri-O-methyl-β-D-glucoside (X''_{\beta \text{Et,t}}) formed via ethanolysis of intermediate 3,4,6-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucoses are given by Equations (9) and (10), respectively (X'_{i,t}, values in Table IV) and are tabulated in Table XXI.

\[
X''_{\alpha \text{Et,t}} = X'_{\alpha \text{Et,t}} - X'''_{\alpha \text{Et,t}}
\]  

\[
X''_{\beta \text{Et,t}} = X'_{\beta \text{Et,t}} - X'''_{\beta \text{Et,t}}
\]
### TABLE XXI

MOLE FRACTIONS OF GLUCOSIDES ($X'''''_i,t$) FORMED VIA INTERMEDIATE
3,4,6-TRI-O-METHYL-1,2-$\beta$-(ETHYL ORTHOACETYL)-$\alpha$-D-GLUCOSE (I) AND
GLUCOSIDES ($X'''''_i,t$) FORMED VIA INTERMEDIATE
3,4,6-TRI-O-METHYL-1-$\alpha$-(DIETHYL ORTHOACETYL)-D-GLUCOSES (II' AND IV)$^a$

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>$X'''''_i,t$</th>
<th>$X''''_i,t$</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ Et 2-O-A</td>
<td>$\alpha$ Et</td>
<td>$\beta$ Et</td>
</tr>
<tr>
<td>8.3</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>75.5</td>
<td>0.001</td>
<td>0.000</td>
<td>0.003</td>
</tr>
<tr>
<td>151.4</td>
<td>0.001</td>
<td>0.000</td>
<td>0.003</td>
</tr>
<tr>
<td>287.5</td>
<td>0.002</td>
<td>0.000</td>
<td>0.006</td>
</tr>
<tr>
<td>538.0</td>
<td>0.003</td>
<td>0.000</td>
<td>0.008</td>
</tr>
<tr>
<td>840.0</td>
<td>0.006</td>
<td>0.001</td>
<td>0.017</td>
</tr>
<tr>
<td>1273.0</td>
<td>0.008</td>
<td>0.001</td>
<td>0.023</td>
</tr>
<tr>
<td>1948.0</td>
<td>0.012</td>
<td>0.002</td>
<td>0.035</td>
</tr>
<tr>
<td>2859.0</td>
<td>0.018</td>
<td>0.003</td>
<td>0.052</td>
</tr>
<tr>
<td>4409.0</td>
<td>0.027</td>
<td>0.004</td>
<td>0.079</td>
</tr>
<tr>
<td>6469.0</td>
<td>0.036</td>
<td>0.005</td>
<td>0.105</td>
</tr>
<tr>
<td>9000.0</td>
<td>0.047</td>
<td>0.007</td>
<td>0.137</td>
</tr>
<tr>
<td>14619.0</td>
<td>0.057</td>
<td>0.008</td>
<td>0.166</td>
</tr>
<tr>
<td>22149.0</td>
<td>0.068</td>
<td>0.010</td>
<td>0.198</td>
</tr>
<tr>
<td>33375.0</td>
<td>0.074</td>
<td>0.011</td>
<td>0.215</td>
</tr>
</tbody>
</table>

$^a$Glucosides formed by I $\rightarrow$ II $\rightarrow$ glucosides are included in $X'''''_i,t$ by the means of calculation.
From the values of $\Sigma X''_{i,t}$ and $\Sigma X'''_{i,t}$, the proportion of glucosides ($\% \Sigma X'''_{i,t}$) formed from ethanolysis of intermediate $3,4,6$-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-$\alpha$-D-glucose at any time are given by Equation (11).

$$\% \Sigma X'''_{i,t} = \left[ \frac{\Sigma X'''_{i,t}}{\Sigma X'''_{i,t} + \Sigma X''_{i,t}} \right] \times 100 \quad (11).$$

The proportions of glucosides formed from ethanolysis of intermediate $3,4,6$-tri-O-methyl-1-O-(diethyl orthoacetyl)-D-glucoses are then given by Equation (12).

$$\% \Sigma X''_{i,t} = 100\% - \% \Sigma X'''_{i,t} \quad (12).$$
**APPENDIX VIII**

PRODUCT ANALYSIS DATA FOR THE ETHANOLYSIS OF 2,3,4,6-TRI-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE

**TABLE XXII**

ETHANOLYSIS OF 2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE\(^a\) IN 0.00525N 2,6-DICHLOROBENZOIC ACID AT 25.0°C.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Product(^b) (X(_{i,t}))</th>
<th>Reactant(^b) (X(_{e}))</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T(_4)MG-Et (β)</td>
<td>T(_4)MG-Et (α)</td>
<td>T(_4)MG-OH</td>
</tr>
<tr>
<td>4.5</td>
<td>0.073 (2)</td>
<td>0.003 (0)</td>
<td>0.139 (20)</td>
</tr>
<tr>
<td>9.1</td>
<td>0.125 (2)</td>
<td>0.004 (1)</td>
<td>0.228 (4)</td>
</tr>
<tr>
<td>20.6</td>
<td>0.226 (11)</td>
<td>0.007 (3)</td>
<td>0.379 (2)</td>
</tr>
<tr>
<td>48.6(^c)</td>
<td>0.302 (8)</td>
<td>0.011 (2)</td>
<td>0.529 (2)</td>
</tr>
<tr>
<td>121.0</td>
<td>0.317 (4)</td>
<td>0.011 (2)</td>
<td>0.592 (9)</td>
</tr>
<tr>
<td>328.0</td>
<td>0.330 (8)</td>
<td>0.012 (2)</td>
<td>0.583 (3)</td>
</tr>
<tr>
<td>1145.0</td>
<td>0.342 (16)</td>
<td>0.011 (2)</td>
<td>0.589 (14)</td>
</tr>
<tr>
<td>4380.0</td>
<td>0.367 (6)</td>
<td>0.013 (1)</td>
<td>0.594 (4)</td>
</tr>
</tbody>
</table>

\(^a\)0.2271 g./10 ml.

\(^b\)Figures in parentheses are the range of three GLC analyses on the same sample multiplied by 10\(^3\).

\(^c\)A popcornlike odor similar to triethyl orthoacetate was noticed in this and subsequent samples.
TABLE XXIII

ETHANOLYSIS OF 2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE\(^a\) IN 0.063M LITHIUM 2-TOLUENESULFONATE AND 0.00522M 2,6-DICHLOROBENZOIC ACID AT 25.0°C.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>(X_{T_{4}MG-Et})</th>
<th>(X_{T_{4}MG-Et(a)})</th>
<th>(X_{T_{4}MG-OH})</th>
<th>(X_{T_{4}MG-ortA})</th>
<th>Total Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7</td>
<td>0.285 (3)</td>
<td>0.133 (1)</td>
<td>0.248 (2)</td>
<td>0.341 (7)</td>
<td>1.007</td>
</tr>
<tr>
<td>6.3</td>
<td>0.388 (4)</td>
<td>0.191 (3)</td>
<td>0.308 (3)</td>
<td>0.055 (0)</td>
<td>0.942</td>
</tr>
<tr>
<td>14.4</td>
<td>0.455 (7)</td>
<td>0.217 (12)</td>
<td>0.334 (7)</td>
<td>0.007 (4)</td>
<td>1.013</td>
</tr>
<tr>
<td>36.3</td>
<td>0.438 (8)</td>
<td>0.215 (5)</td>
<td>0.335 (4)</td>
<td>0.005 (2)</td>
<td>0.993</td>
</tr>
</tbody>
</table>

\(^a\)0.1040 g./5 ml.

\(^b\)Figures in parentheses are the range of three GLC analyses on the same sample multiplied by 10\(^3\).
APPENDIX IX

TLC METHOD OF IDENTIFYING ETHANOLYSIS PRODUCT AND CHECKING THE PURITY OF 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSE

TLC (Table XXIV, conditions in footnote a) provides a means of checking the purity of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucoses. The test(s) on a pure material must show: (1) one spot at $R_{2D}^* = 0.69$, and (2) one spot at $R_{2D} = 0.32$ after a mild hydrolysis to 1-O-acetyl- and 2-O-acetyl-3,4,6-tri-O-methyl-α-D-glucose. The hydrolysis of 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose (several drops) was conveniently carried out in water (3 ml.) with an acid catalyst (1 drop, $\text{N}_2\text{H}_2\text{SO}_4$) for five minutes at room temperature before spotting. TLC plates made from microscope slides were usually used.

The identification of ethanolysis products is illustrated in Table XXIV. Identifications were made by TLC on 100 mm. x 200 mm. glass plates by spotting the ethanolysis solution and the compounds listed in Table XXIV all on the same plate to eliminate variability between $R_{2D}$ values exhibited from plate to plate.

$^*_{R_{2D}}$ is defined as the $R_2$ value of a compound after two developments.
TABLE XXIV

$R_{2D}$ VALUES FOR TESTING FOR 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL
ORTHOACETYL-\(\alpha\)-D-GLUCOSE PURITY AND ETHANOLYSIS
PRODUCT IDENTITY BY TLC

<table>
<thead>
<tr>
<th>Compound</th>
<th>$R_{2D}^a$</th>
<th>Found for $b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4,6-Tri-O-methyl-1,2-O-(alkyl orthoacetyl)-(\alpha)-D-glucose</td>
<td>0.69</td>
<td>None (rxn complete)</td>
</tr>
<tr>
<td>Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-(\alpha)-D-glucoside</td>
<td>0.73</td>
<td>None</td>
</tr>
<tr>
<td>Ethyl 2-O-acetyl-3,4,6-tri-O-methyl-(\beta)-D-glucoside</td>
<td>0.59</td>
<td>Medium</td>
</tr>
<tr>
<td>Ethyl 3,4,6-tri-O-methyl-(\alpha)-D-glucoside</td>
<td>0.46</td>
<td>Dark</td>
</tr>
<tr>
<td>Ethyl 3,4,6-tri-O-methyl-(\beta)-D-glucoside</td>
<td>0.46</td>
<td>Light</td>
</tr>
<tr>
<td>1-O-Acetyl-3,4,6-tri-O-methyl-(\alpha)-D-glucose</td>
<td>0.32</td>
<td>Medium</td>
</tr>
<tr>
<td>2-O-Acetyl-3,4,6-tri-O-methyl-(\alpha)-D-glucose</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>3,4,6-Tri-O-methyl-D-glucose</td>
<td>0.17</td>
<td>Medium</td>
</tr>
</tbody>
</table>

$^a$Ratio of distance compound moved to solvent front. The TLC plates (silica gel G, Brinkmann Instruments) were developed twice in hexane-pyridine (4/1, v/v) (solvent evaporated from plate between developings). Spot detection was accomplished by spraying with sulfuric acid (1/5, w/w; $\text{H}_2\text{SO}_4$-methanol) and subsequent heating.

$^b$An ethanolysis sample which shows some hydrolysis (spot at $R_{2D} = 0.32$). Otherwise the sample is consistent with the ethanolysis products identified by GLC and polarimetry.
APPENDIX X

RESPONSE FACTORS FOR THE CALCULATION OF THE MOLE FRACTION OF GLUCOSE FOR THE ETHANOLYSES OF 3,4,6-TRI-O-METHYL-1,2-O-(ALKYL ORTHOACETYL)-α-D-GLUCOSES OR 3,4,6-TRI-O-METHYL-α-D-GLUCOSE IN THE PRESENCE OF TRIETHYL ORTHOACETATE

The solutions of the compounds in Table XXV were made up in ethanol and treated the same as 3,4,6-tri-O-methyl-1,2-O-(alkyl orthoacetyl)-α-D-glucose ethanolysis samples. GLC, Conditions A, resulted in the response factors in Table XXVI.

TABLE XXV

SOLUTION COMPOSITION FOR RESPONSE FACTOR DETERMINATIONS

<table>
<thead>
<tr>
<th>Soln. No.</th>
<th>Mole Ratio of Internal Standarda to</th>
<th>α Et 2-O-A</th>
<th>β Et 2-O-A</th>
<th>α Et</th>
<th>β Et</th>
<th>TMG</th>
<th>2-O-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>8.76</td>
<td>8.02</td>
<td>12.02</td>
<td>4.71</td>
<td>6.87</td>
<td>4.35</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>4.38</td>
<td>4.01</td>
<td>6.01</td>
<td>2.35</td>
<td>3.43</td>
<td>2.17</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2.92</td>
<td>2.67</td>
<td>4.01</td>
<td>1.57</td>
<td>2.29</td>
<td>1.45</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2.19</td>
<td>2.00</td>
<td>3.00</td>
<td>1.18</td>
<td>1.72</td>
<td>1.09</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1.46</td>
<td>1.34</td>
<td>2.01</td>
<td>0.79</td>
<td>1.15</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Internal standard: isoamyl 3,4,6-tri-O-methyl-β-D-glucoside.
TABLE XXVI
GLC RESPONSE FACTORS ($f^a_x$) RELATIVE TO ISOAMYL 3,4,6-TRI-0-METHYL-β-D-GLUCOSIDE

<table>
<thead>
<tr>
<th>Soln. No.</th>
<th>$\alpha$ Et 2-O-A</th>
<th>$\beta$ Et 2-O-A</th>
<th>$\alpha$ Et</th>
<th>$\beta$ Et</th>
<th>TMG</th>
<th>2-O-A $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.620</td>
<td>0.690</td>
<td>0.698</td>
<td>0.770</td>
<td>0.707</td>
<td>0.656</td>
</tr>
<tr>
<td></td>
<td>0.607</td>
<td>0.706</td>
<td>0.692</td>
<td>0.774</td>
<td>0.712</td>
<td>0.624</td>
</tr>
<tr>
<td>2</td>
<td>0.612</td>
<td>0.709</td>
<td>0.695</td>
<td>0.771</td>
<td>0.705</td>
<td>0.665</td>
</tr>
<tr>
<td></td>
<td>0.604</td>
<td>0.726</td>
<td>0.712</td>
<td>0.793</td>
<td>0.707</td>
<td>0.663</td>
</tr>
<tr>
<td>3</td>
<td>0.596</td>
<td>0.706</td>
<td>0.701</td>
<td>0.765</td>
<td>0.700</td>
<td>0.662</td>
</tr>
<tr>
<td></td>
<td>0.591</td>
<td>0.698</td>
<td>0.699</td>
<td>0.771</td>
<td>0.690</td>
<td>0.672</td>
</tr>
<tr>
<td>4</td>
<td>0.611</td>
<td>0.708</td>
<td>0.719</td>
<td>0.788</td>
<td>0.707</td>
<td>0.676</td>
</tr>
<tr>
<td></td>
<td>0.619</td>
<td>0.725</td>
<td>0.720</td>
<td>0.791</td>
<td>0.712</td>
<td>0.665</td>
</tr>
<tr>
<td>5</td>
<td>0.604</td>
<td>0.718</td>
<td>0.693</td>
<td>0.776</td>
<td>0.690</td>
<td>0.673</td>
</tr>
<tr>
<td></td>
<td>0.622</td>
<td>0.725</td>
<td>0.697</td>
<td>0.795</td>
<td>0.718</td>
<td>0.675</td>
</tr>
<tr>
<td>Av. $f^a_x$</td>
<td>0.609</td>
<td>0.711</td>
<td>0.703</td>
<td>0.779</td>
<td>0.705</td>
<td>0.664</td>
</tr>
</tbody>
</table>

$^a f^a_x = (\text{area } X/\text{area standard})(\text{moles standard/moles } X)$.  

$^b 2$-O-Acetyl-3,4,6-tri-0-methyl-α-D-glucose. This response factor was assumed to be the same as for 3,4,6-tri-0-methyl-1,2-0-(alkyl orthoacetyl)-α-D-glucose after hydrolysis. In the case of the 3,4,6-tri-0-methyl-D-glucose ethanolysis this response factor was assumed to be correct for any glucose orthoester intermediate.
The mole fraction of each component identified and measured by GLC is given by Equation (13) which is easily derived from the definition of the GLC response factor used.

\[ X_{i,\,t} \text{ or } X_t = \frac{1}{f_X} \left( \frac{\text{Area}_X}{\text{Area standard}} \right) \left( \frac{\text{Moles standard}}{\text{Moles reactant}} \right) \]  

(13)

where

- \( X_t \) = mole fraction of reactant remaining at time \( t \) in terms of original reactant,
- \( X_{i,\,t} \) = mole fraction of product at time \( t \) in terms of original reactant,
- \( \text{Area}_X \) = peak area of component \( X \) at time \( t \),
- \( \text{Area standard} \) = peak area of the internal standard on the same chromatogram,
- \( \text{Moles standard} \) = moles of internal standard in the sample, and
- \( \text{Moles reactant} \) = moles of reactant, equated at time zero, in the sample.

In the case of \( 3,4,6\)-tri-\( \beta \)-methyl-D-glucose measurements, a small amount of impurity in the isoamyl \( 3,4,6\)-tri-\( \beta \)-methyl-\( \beta \)-D-glucoside caused a small interference. This was corrected for by replacing \( \left( \frac{\text{Area}_X}{\text{Area standard}} \right) \) by \( \left( \frac{\text{Area}_X}{\text{Area standard}} - 0.009 \right) \) in Equation (13). The correction results because the peak area of the impurity was included in the \( 3,4,6\)-tri-\( \beta \)-methyl-D-glucose peak area upon integration and is a constant factor of 0.9% of the area of the internal standard peak.
APPENDIX XI

ESTER SAPONIFICATION AND STABILITY OF ORTHOESTERS IN ALKALI AT 0°C.

The conditions used for measurement of ester produced in the ethanolysis of 3,4,6-tri-O-methyl-1,2-O-(ethyl orthoacetyl)-α-D-glucose (p. 114) were decided upon by testing the rate of hydroxide consumption of pertinent compounds. The obvious requirement is that all esters undergo saponification completely while, during the same time period, orthoesters and reducing sugars do not consume appreciable alkali. Testing Procedure: The selected compounds (about 4.00 meq.) in 100 ml. of 20% ethanolic 0.06N sodium hydroxide (20 ml. ethanol diluted to 100 ml.) at 0°C. were sampled periodically. Samples (10 ml.) were diluted with standard 0.06N hydrochloric acid (10 ml.) and titrated to a phenolphthalein end point with 0.03N sodium hydroxide.

The results are given in Tables XXVII-XXXII. The calculated amounts of hydroxide consumed per 100 ml. of test solution are probably high by about 0.1 meq. (cf. Table XXVII or XXXI) because the acid and base reagents were not standardized against each other under the conditions in the procedure. However, the important point is that esters can be completely saponified before appreciable alkali is consumed by orthoesters or by alkaline degradation of reducing sugars.
### TABLE XXVII
ALKALI CONSUMPTION BY ETHYL ACETATE
(4.00 MEQ. ESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH⁻ Consumed/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>1.34</td>
</tr>
<tr>
<td>10.3</td>
<td>1.95</td>
</tr>
<tr>
<td>18.3</td>
<td>2.64</td>
</tr>
<tr>
<td>30.4</td>
<td>3.11</td>
</tr>
<tr>
<td>55.1</td>
<td>3.61</td>
</tr>
<tr>
<td>137.0</td>
<td>4.03</td>
</tr>
<tr>
<td>331.0</td>
<td>4.07</td>
</tr>
<tr>
<td>1385.0</td>
<td>4.09</td>
</tr>
<tr>
<td>1632.0</td>
<td>4.09</td>
</tr>
</tbody>
</table>

### TABLE XXVIII
ALKALI CONSUMPTION BY ETHYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-
β-D-GLUCOSIDE (3.89 MEQ. ESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH⁻ Consumed/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.7</td>
<td>1.31</td>
</tr>
<tr>
<td>14.7</td>
<td>2.08</td>
</tr>
<tr>
<td>35.0</td>
<td>2.99</td>
</tr>
<tr>
<td>71.0</td>
<td>3.51</td>
</tr>
<tr>
<td>166.0</td>
<td>3.82</td>
</tr>
<tr>
<td>274.0</td>
<td>3.89</td>
</tr>
<tr>
<td>523.0</td>
<td>3.89</td>
</tr>
<tr>
<td>637.0</td>
<td>3.94</td>
</tr>
</tbody>
</table>
TABLE XXIX

ALKALI CONSUMPTION BY ETHYL 2-O-ACETYL-3,4,6-TRI-O-METHYL-\(\alpha\)-D-GLUCOSIDE (3.89 MEQ. ESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH(^-) Consumed/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7</td>
<td>2.32</td>
</tr>
<tr>
<td>12.7</td>
<td>2.81</td>
</tr>
<tr>
<td>25.7</td>
<td>3.28</td>
</tr>
<tr>
<td>48.0</td>
<td>3.64</td>
</tr>
<tr>
<td>94.0</td>
<td>3.91</td>
</tr>
<tr>
<td>127.0</td>
<td>3.96</td>
</tr>
<tr>
<td>1538.0</td>
<td>3.93</td>
</tr>
<tr>
<td>1543.0</td>
<td>3.92</td>
</tr>
</tbody>
</table>

TABLE XXX

ALKALI CONSUMPTION BY 2-O-ACETYL-3,4,6-TRI-O-METHYL-\(\alpha\)-D-GLUCOSE (3.86 MEQ. ESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH(^-) Consumed/100 ml.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5</td>
<td>0.50</td>
</tr>
<tr>
<td>17.5</td>
<td>1.10</td>
</tr>
<tr>
<td>49.0</td>
<td>2.19</td>
</tr>
<tr>
<td>115.0</td>
<td>3.21</td>
</tr>
<tr>
<td>193.0</td>
<td>3.51</td>
</tr>
<tr>
<td>315.0</td>
<td>3.78</td>
</tr>
<tr>
<td>502.0</td>
<td>3.89</td>
</tr>
<tr>
<td>731.0</td>
<td>3.98</td>
</tr>
<tr>
<td>1502.0</td>
<td>4.13</td>
</tr>
</tbody>
</table>

\(^a\)The slow increase of OH\(^-\) consumed at long times is probably due to alkaline degradation of 3,4,6-tri-O-methyl-D-glucose.
TABLE XXXI
ALKALI CONSUMPTION BY EXO-OR 3,4,6-TRI-O-METHYL-1,2-O-(ETHYL ORTHOACETYL)-α-D-GLUCOSE (3.90 MEQ. ORTHOESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH⁻ Consumed/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5</td>
<td>0.10</td>
</tr>
<tr>
<td>31.0</td>
<td>0.11</td>
</tr>
<tr>
<td>94.0</td>
<td>0.10</td>
</tr>
<tr>
<td>252.0</td>
<td>0.11</td>
</tr>
<tr>
<td>461.0</td>
<td>0.09</td>
</tr>
<tr>
<td>1111.0</td>
<td>0.09</td>
</tr>
<tr>
<td>1771.0</td>
<td>0.10</td>
</tr>
<tr>
<td>2645.0</td>
<td>0.11</td>
</tr>
<tr>
<td>3243.0</td>
<td>0.10</td>
</tr>
</tbody>
</table>

TABLE XXXII
ALKALI CONSUMPTION BY TRIETHYL ORTHOACETATE (3.97 MEQ. ORTHOESTER/100 ML.)

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Meq. OH⁻ Consumed/100 ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.0</td>
<td>0.23</td>
</tr>
<tr>
<td>42.0</td>
<td>0.31</td>
</tr>
<tr>
<td>71.0</td>
<td>0.32</td>
</tr>
<tr>
<td>145.0</td>
<td>0.31</td>
</tr>
<tr>
<td>265.0</td>
<td>0.32</td>
</tr>
<tr>
<td>375.0</td>
<td>0.33</td>
</tr>
<tr>
<td>664.0</td>
<td>0.34</td>
</tr>
<tr>
<td>1164.0</td>
<td>0.38</td>
</tr>
<tr>
<td>2149.0</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*The initial fast OH⁻ consumption probably is due to an ethyl acetate impurity, and later OH⁻ consumption is probably due to ethyl acetate formed by acid-catalyzed triethyl orthoacetate hydrolysis by water or ethanol acting as the acid.*
The solutions of compounds listed in Table XXXIII were analyzed by GLC (Conditions C) to determine the necessary response factors for product analysis. The solutions were made up by weighing the individual compounds into volumetric flasks and diluting with ethanolic 0.005N 2,6-dichlorobenzoic acid. Treatment of these solutions was the same as actual samples of the ethanolysis of 2,3,4,6-tetra-O-methyl-β-0-(diethyl orthoacetyl)-α-D-glucose.

The data, Table XXXIV, calculated by a normalization method (50) using the response factor in Table XXXIII were necessary to determine the constant relative amounts of 1-O-acetyl-2,3,4,6-tetra-O-methyl-α-D-glucose and 2,3,4,6-tetra-O-methyl-D-glucose formed by hydrolysis of 2,3,4,6-tetra-O-methyl-β-0-(diethyl orthoacetyl)-α-D-glucose. This knowledge was necessary to determine the amounts of 2,3,4,6-tetra-O-methyl-D-glucose and 2,3,4,6-tetra-O-methyl-β-0-(diethyl orthoacetyl)-α-D-glucose in ethanolysis samples prior to the hydrolysis step in sample work up. The basis for this determination is the fact that 1-O-acetyl-2,3,4,6-tetra-O-methyl-α-D-glucose is formed by hydrolysis only.

In calculations of mole fractions of glucose moieties for ethanolysis samples, the factors 0.982 and 0.018, which appear in the equations, account for the purity of the 2,3,4,6-tetra-O-methyl-β-0-(diethyl orthoacetyl)-α-D-glucose employed. The factors 0.493 and 0.483 (from Table XXXIV) account for the deliberate hydrolysis of the unreacted 2,3,4,6-tetra-O-methyl-β-0-(diethyl orthoacetyl)-α-D-glucose prior to propanoylation and GLC analysis. Other terms in Equations (14)-(20) are defined in the same manner as similar terms in Equation (13) (Appendix X).
TABLE XXXIII
GLC RESPONSE FACTORS (f_X^a) RELATIVE TO ISOPROPYL 3,4,6-TRI-O-METHYL-β-D-GLUCOSIDE AT VARIOUS MOLE RATIOS^b

<table>
<thead>
<tr>
<th>Soln. No.</th>
<th>T₄MG-Et (β) Ratio</th>
<th>T₄MG-OH Ratio f_X</th>
<th>T₄MG-O-Ac Ratio f_X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.661</td>
<td>0.618</td>
<td>1.742</td>
</tr>
<tr>
<td></td>
<td>0.602</td>
<td>0.805</td>
<td>0.803</td>
</tr>
<tr>
<td></td>
<td>0.624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.961</td>
<td>0.594</td>
<td>1.238</td>
</tr>
<tr>
<td></td>
<td>0.607</td>
<td>0.810</td>
<td>0.806</td>
</tr>
<tr>
<td></td>
<td>0.613</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.424</td>
<td>0.610</td>
<td>0.872</td>
</tr>
<tr>
<td></td>
<td>0.605</td>
<td>0.824</td>
<td>0.808</td>
</tr>
<tr>
<td></td>
<td>0.594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.257</td>
<td>0.587</td>
<td>0.690</td>
</tr>
<tr>
<td></td>
<td>0.592</td>
<td>0.829</td>
<td>0.819</td>
</tr>
<tr>
<td></td>
<td>0.593</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Av.</td>
<td>0.603</td>
<td>0.812</td>
<td></td>
</tr>
</tbody>
</table>

^a f_X = (Area X/Area standard)(moles standard/moles X).

^b Moles X/moles standard.
TABLE XXXIV

HYDROLYSES OF 2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE AT ROOM TEMPERATURE

<table>
<thead>
<tr>
<th>Trial Conditions</th>
<th>Mole Fraction of a</th>
<th>( T_4 \text{MG-Et (β)} )</th>
<th>( T_4 \text{MG-OAc} )</th>
<th>( T_4 \text{MG-OH} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>0.024 (1)</td>
<td>0.472 (5)</td>
<td>0.505 (5)</td>
<td></td>
</tr>
<tr>
<td>1°</td>
<td>0.027 (1)</td>
<td>0.479 (1)</td>
<td>0.493 (0)</td>
<td></td>
</tr>
<tr>
<td>2°</td>
<td>0.025 (1)</td>
<td>0.487 (6)</td>
<td>0.488 (4)</td>
<td></td>
</tr>
<tr>
<td>2°</td>
<td>0.020 (1)</td>
<td>0.493 (5)</td>
<td>0.487 (5)</td>
<td></td>
</tr>
<tr>
<td>Av.</td>
<td>0.024</td>
<td>0.483</td>
<td>0.493</td>
<td></td>
</tr>
</tbody>
</table>

\[ a \text{Figures in parentheses are the range of three GLC analyses on the same sample times 10}^3. \]

\[ b \text{An impurity in the sample of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose which apparently is ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside (1.8% by weight).} \]

\[ c \text{Treated in an identical manner as an ethanolysis sample.} \]

\[ d \text{Hydrolyzed, then treated in an identical manner as an ethanolysis sample.} \]

ETHYL 2,3,4,6-TETRA-O-METHYL-α-D-GLUCOSIDE

Equation (14) gives the mole fraction ethyl 2,3,4,6-tetra-O-methyl-α-D-glucoside formed at time \( t \). The response factor for this compound was assumed to be the same as the \( β \)-anomer.

\[
X_{T_4 \text{MG-Et(α),}t} \approx \left( \frac{1}{f_{T_4 \text{MG-Et(β)}}} \right) \left( \frac{\text{Area} \ T_4 \text{MG-Et(α)}}{\text{Area standard}} \right) \left( \frac{\text{Moles standard}}{(0.982)\text{Moles reactant}} \right)
\]  

(14)
ETHYL 2,3,4,6-TETRA-O-METHYL-β-D-GLUCOSIDE

The correction factor, $Q$, given by Equation (15) is used to correct for the amount of ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside impurity in the reactant. Equation (16) gives the quantity of ethyl 2,3,4,6-tetra-O-methyl-β-D-glucoside formed only by ethanolysis.

$$Q = \left( \frac{\text{Moles reactant} \times 0.018}{\text{Moles standard}} \right) \left( \frac{f_{T_4MG-Et(\beta)}}{f_{T_4MG-Et(\beta)}} \right)$$  \hspace{1cm} (15)

$$X_{T_4MG-Et(\beta),t} = \left( \frac{1}{f_{T_4MG-Et(\beta)}} \right) \left( \frac{\text{Area } T_4MG-Et(\beta)}{\text{Area standard}} \right) \left( \frac{\text{Moles standard}}{0.982(\text{Moles reactant})} \right)$$  \hspace{1cm} (16)

2,3,4,6-TETRA-O-METHYL-1-O-(DIETHYL ORTHOACETYL)-α-D-GLUCOSE

The quantity of 1-O-acetyl-2,3,4,6-tetra-O-methyl-α-D-glucose measured [Equation (17)] is used to calculate the quantity of 2,3,4,6-tetra-O-methyl-1-O-(diethyl orthoacetyl)-α-D-glucose, $X_t$, present at time $t$ by Equation (18).

$$X_{T_4MG-O-Ac,t} = \left( \frac{1}{f_{T_4MG-O-Ac}} \right) \left( \frac{\text{Area } T_4MG-O-Ac}{\text{Area standard}} \right) \left( \frac{\text{Moles standard}}{0.982(\text{Moles reactant})} \right)$$  \hspace{1cm} (17)

$$X_t = \left( X_{T_4MG-O-Ac,t} \right) (1+0.493/0.483)$$  \hspace{1cm} (18)

2,3,4,6-TETRA-O-METHYL-D-GLUCOSE

The quantity of 2,3,4,6-tetra-O-methyl-D-glucose measured [Equation (19)] is used to calculate the quantity of 2,3,4,6-tetra-O-methyl-D-glucose formed by ethanolysis by Equation (20).

$$X_{T_4MG-OH,t} = \left( \frac{1}{f_{T_4MG-OH}} \right) \left( \frac{\text{Area } T_4MG-OH}{\text{Area standard}} \right) \left( \frac{\text{Moles standard}}{0.982(\text{Moles reactant})} \right)$$  \hspace{1cm} (19)

$$X_{T_4MG-OH,t} = "X_{T_4MG-OH,t} - X_t(0.493/0.483).$$  \hspace{1cm} (20)