3-HYDROXYETHYL GLUCOSE

Creamer

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A Thesis

by

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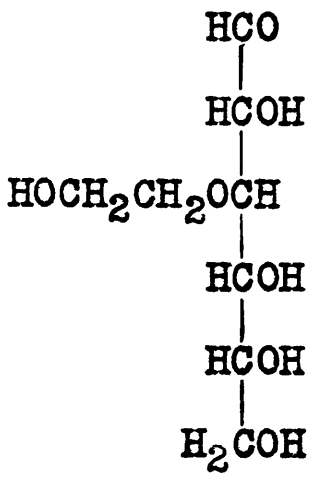
GENERAL INTRODUCTION

In a Ph.D. Thesis submitted in 1946 from this Laboratory, Tasker prepared in pure form the series of the monoethyl ethers of the polyethylene glycols, $R(OCH_2CH_2)_nOH$, where n was 1, 2 or 3. The tendency of several of these compounds to form peroxides when exposed to light and air was noted, the esters made with p-toluenesulfonyl chloride (tosyl chloride) and pyridine were prepared, and the replacement by iodine atoms of the tosyloxy groups in the products was studied. Tasker then applied the tosylation-iodination technique to a commercial hydroxyethyl ether of cellulose, but his results made it clear that side-reactions of an unexpected nature were occurring. In the light of the knowledge gained from his studies in the polyethylene oxide series, Tasker put forward suggestions concerning the possible nature of the side-reactions. These suggestions, however, were only tentative, because at that time the literature contained no reference to the existence of an hydroxyethyl derivative of a simple sugar, the chemical behavior of which would serve as a model for the probable behavior of an hydroxyethylcellulose.

The present research is particularly concerned with the preparation and properties of 3-hydroxyethyl glucose (I) and seventeen of its derivatives. Suitable derivatives were then submitted to the tosylation-iodination technique with



I

the result that Tasker's tentative explanation of the anomalies he observed with hydroxyethylcellulose were shown to be in part less probable than he had supposed.

Tasker's observations on the apparent lack of peroxide formation in hydroxyethylcelluloses were briefly extended.

HISTORICAL INTRODUCTION

In order to orient the reader, it will be helpful to summarize the information available concerning the hydroxyethylation of hydroxy compounds, the chemical and thermal stability of hydroxyethyl ethers and their behavior during tosylation and subsequent iodination. Tasker's thesis (1) discussed the relevant literature up to 1946 in great detail; his list of references appears to be complete, and his review was published in abbreviated form in the articles by Tasker and Purves (2)(3). The present summary, therefore, need only be very brief and of necessity has been based on Tasker's review. Tasker's own experimental work, and that of several other very recent authors, is discussed in greater detail.

The observation by Wurtz (4) in 1859 that ethylene oxide slowly condensed with alcohols led later investigators (5)(6)(7) to introduce catalysts for the condensation and so to develop a general method for the preparation of the monoalkyl ethers of ethylene glycol (Cellosolves). Conditions

$$ROH + \underset{\diagdown\,O\,\diagup}{CH_2\text{-}CH_2} \longrightarrow ROCH_2CH_2OH$$

ranging from eight hours at 100° to three hours at 200° with sulfuric acid or an inorganic sulfate as catalyst were used by Zimakov and Churakov (7). The product usually contains appreciable amounts of ethylene glycol as well as the monoether

of diethyleneglycol.

The same series of monoalkyl ethers could also be obtained by condensing a sodium alcoholate with ethylene chlorohydrin (8)(9)(10)(11). Ethylene chlorohydrin has the advantage

$$RONa + ClCH_2CH_2OH \longrightarrow ROCH_2CH_2OH + NaCl$$

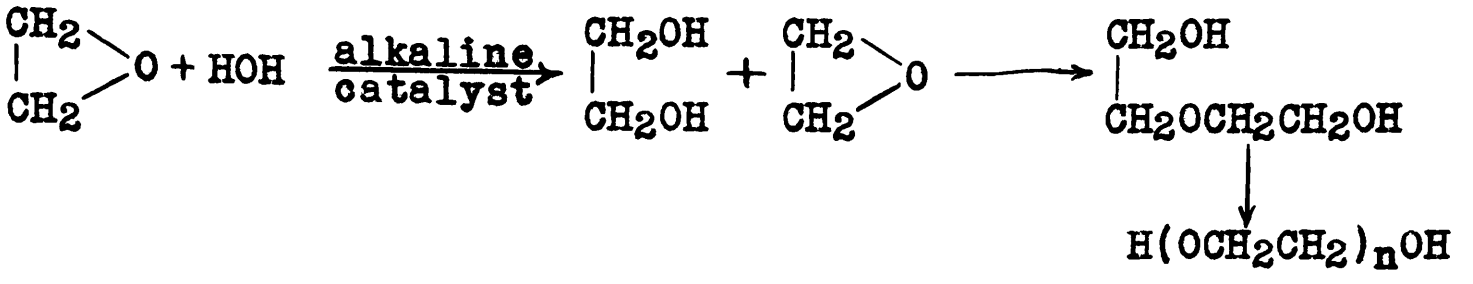
of reacting only with the alcoholate and not with itself thus avoiding the formation of polyethylene glycol derivatives as by-products.

In 1948 a third general method was claimed by Carlson (12) who found that alcohols and phenols, as well as thiols, thiophenols, amines and carboxylic acids, when treated with ethylene carbonate or ethylene sulfite, had their active hydrogen atoms replaced by $-CH_2CH_2OH$. Use was made of an inert solvent, with or without a catalyst, which might be acidic, basic or an alkyl sulfate. With alcohols and phenols for example the reaction took place as follows:

$$ROH + O{=}\overline{X\text{-}OCH_2CH_2O} \longrightarrow ROCH_2CH_2OH + XO_2$$

where X was a carbon or sulfur atom.

The polymerization of ethylene oxide in presence of an alkaline catalyst to form polyethylene glycols was thoroughly investigated by Hibbert and co-workers (11)(13)(14)(15)(16)(17) who proposed the Stepwise Addition Theory to account for the formation of both high and low polymers.

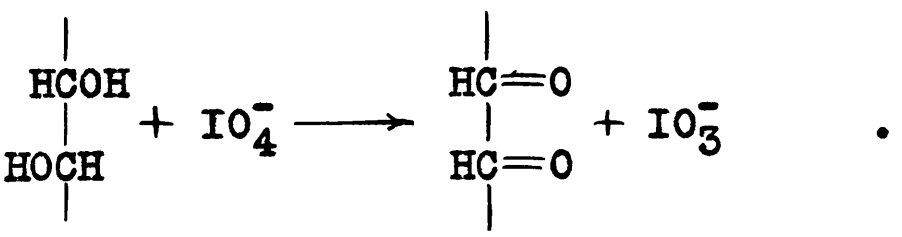


The Hibbert school (16)(17)(18)(19)(20) also studied the physical properties of an homologous series of polyethylene glycols $H(OCH_2CH_2)_nOH$, prepared by the chlorohydrin route, in which n varied from one to one hundred and eighty-six. The results indicated that the polyethylene glycols existed as zig-zag molecules which apparently were highly convoluted in solution. There also appeared to be quite noticeable intermolecular forces operating between the molecules in the undiluted state. The unique behavior of diethylene glycol, the second member of the series, was attributed to an ability to assume a structure similar to that of 1,4-dioxane, perhaps because of some sort of intramolecular coordination of the polar hydroxyl groups.

Many other authors, carefully catalogued by Tasker and Purves (1)(2), employed either the ethylene oxide or the ethylene chlorohydrin route with many different simple alcohols to obtain the corresponding monoethers of ethylene and diethylene glycol, the products usually being oils that were obtained in twenty-five to sixty per cent yields and in varying states of purity by fractional distillation. The same general methods, when applied to cellulose suspended in dilute caustic soda or to alkali cellulose, produced a series of hydroxyethylcelluloses whose substitution ranged from a low figure to four or even six, hydroxyethyl groups per glucose residue (21)(22). Since each

of these residues contained only three hydroxy groups, an hydroxyethyl substitution greater than three clearly indicated that some of the substituent consisted of polyethylene oxide chains. The hydroxyethylcelluloses were in general more reactive than cellulose itself and it was easy to prepare a variety of esters, xanthates and ethers from them. Lack of reliable analytical methods, however, made it impossible for Sönnerskog (23) to correlate their physical properties with their chemical nature.

Sönnerskog's latest article (24) in 1948 attempted to mitigate this deficiency by estimating the number of unsubstituted 2,3-glycol units in an hydroxyethylcellulose by oxidation with potassium periodate, the observed amount of periodate reduced to iodate being taken as the number of such units:



His hydroxyethylcellulose, of substitution 0.54, consumed 1.12 moles of periodate per glucose unit. Since the theoretical periodate consumption would be 1.0 mole in the case of unsubstituted cellulose or of a derivative substituted only in position 6, and less than 1.0 mole for derivatives substituted in either or both positions of the 2,3-glycol units, the high result seemed to indicate that the hydroxyethyl group was not stable to periodate under the conditions used. This conclusion is rendered extremely probable by Tasker and Purves' observation (1)(2) that simple

hydroxyethyl monoethers were stable neither to lead tetra-acetate nor to alkaline hypoiodite solutions. Sönnerskog, however, ignored this possibility of over-oxidation and concluded that ethylene oxide reacted preferentially with the primary hydroxy group at position 6.

Hydroxyethyl derivatives of starch, although not discussed by Tasker and Purves, were mentioned in several patents (25)(26)(27)(28) primarily concerned with hydroxyethylcellulose and were also prepared by Zeise (29) and by Clemens (30). Zeise treated a solution of starch in dilute caustic soda with ethylene oxide at room temperature for two hours. After neutralization and purification by dialysis, the water-soluble product no longer gave a blue color with aqueous iodine-potassium iodide, but in sufficient concentration gave a dark brown color. No published work was found concerning the degree, uniformity or location of substituents in the starch derivatives.

A thorough search of the literature revealed no mention of hydroxyethyl ether derivatives of glucose or glucosides; the only reference to the preparation of an hydroxyethyl ether of a sugar was the work, in 1948, of Le Maistre and Seymour (31). These authors found that sucrose and ethylene oxide did not react in neutral solution, but did so readily in aqueous sodium hydroxide at room temperature. After removal of the sodium hydroxide by passing the solution through a column of the ion-exchange resin, Amberlite IR-100H, and after evaporation of the water in vacuo, sirupy hydroxyethyl ethers of sucrose were ob-

tained. By varying the amount of ethylene oxide used, the products had molar ratios of ethylene oxide to sucrose ranging from 1:1 to 11:1. About three per cent of the product from 0.1 mole of sucrose and 0.4 mole of ethylene oxide crystallized as white needles melting at 215° and having a specific rotation of $[\alpha]_D^{25}$ in water -38.7°. The elementary composition of this material agreed essentially with that calculated for bis-(β - hydroxyethyl) sucrose, $C_{12}H_{22}O_{11} \cdot 2C_2H_4O$, but the exact structure was not determined.

A major reason for the lack of accurate published data concerning the degree of substitution of hydroxyethylcellulose and starch derivatives was the lack of a reliable method for estimating the hydroxyethyl group. The only methods available were conventional alkoxyl estimations which gave anomalous results; elementary analyses for carbon and hydrogen and the increase in weight caused by the substitution. Neither of the last named methods were very sensitive.

In 1946 Morgan (21) showed that during the reduction of an hydroxyethyl ether with constant boiling hydriodic acid as in the conventional Zeisel method for alkoxyl the following reactions occurred:

$$ROCH_2CH_2OH + 3HI \longrightarrow RI + ICH_2CH_2I + 2H_2O$$

$$ICH_2CH_2I \longrightarrow CH_2{=}CH_2 + I_2$$

$$ICH_2CH_2I + HI \longrightarrow CH_3CH_2I + I_2$$

$$CH_2{=}CH_2 + HI \longrightarrow CH_3CH_2I$$

or in total,

$$ROCH_2CH_2OH + (3 + x)HI \longrightarrow RI + (x)CH_3CH_2I + (1 - x)CH_2{=}CH_2 + I_2 + 2H_2O \quad .$$

On this basis, the ethyl iodide and ethylene together accounted quantitatively for every alkoxyl and every hydroxyethyl group in the molecule. By estimating both the ethyl iodide and the ethylene in a modified Zeisel apparatus, Morgan developed the first trustworthy estimation for the hydroxyethyl group and so made possible Tasker's research (1)(3) on hydroxyethylcellulose.

As already mentioned, simple hydroxyethyl ethers reduced alkaline hypoiodite, and in consequence this reagent is of little value in estimating the reducing power of hydroxyethylcelluloses, starches or sugars. The rather ready oxidizability of these ethers was also illustrated by the great tendency shown by some of them to form peroxides when stored, even for brief periods, in light and air. Tasker (1)(2) stressed the fact that this tendency had to be counteracted by rigorous precautions if pure preparations were to be obtained. For unknown reasons, the monoethyl ether of triethylene glycol and several commercial hydroxyethylcelluloses gave negative tests for peroxide in all conditions tried.

Turning now to the tosyl esters of hydroxyethyl derivatives, Tipson (32) discussed in considerable detail the side reactions that might take place during the esterification with pyridine and tosyl chloride. The first was the formation of an ether,

$$ROSO_2C_6H_4CH_3 + ROH \longrightarrow ROR + HOSO_2C_6H_4CH_3 \quad ;$$

the second the formation of quaternary salts with the pyridine reaction medium,

$$ROSO_2C_6H_4CH_3 + C_5H_5N \longrightarrow RCl + C_5H_5N\begin{matrix} R \\ OSO_2C_6H_4CH_3 \end{matrix}$$

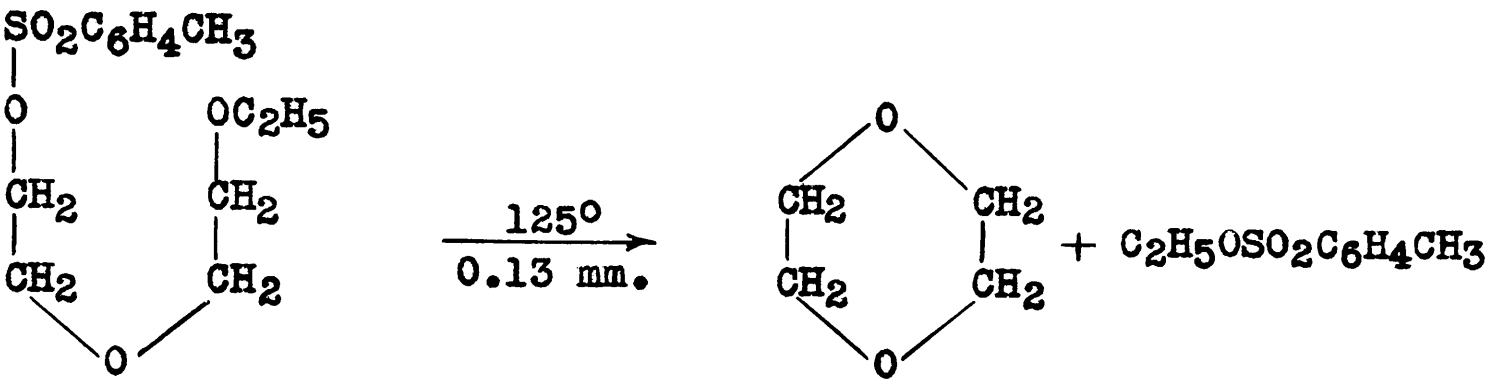
and the third was chlorination by by-product pyridine hydrochloride,

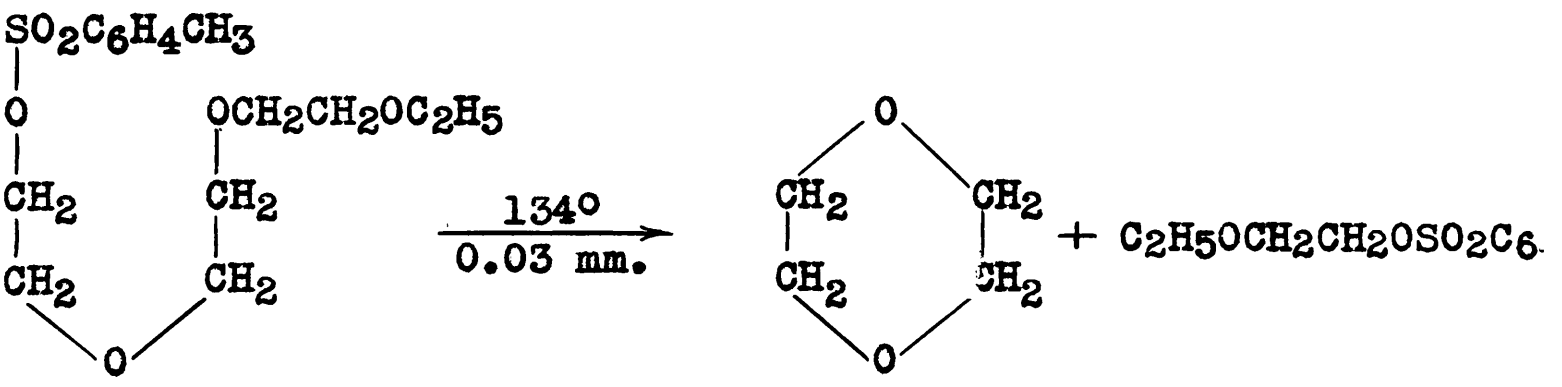
$$ROSO_2C_6H_4CH_3 + C_5H_5N\cdot HCl \longrightarrow RCl + C_5H_5N\begin{matrix} H \\ OSO_2C_6H_4CH_3 \end{matrix} .$$

He described a tosylation procedure for cellosolves using a molar equivalent of tosyl chloride in pyridine at zero degrees for two hours. This procedure gave good results, and kept the above side reactions to a minimum.

Tasker (1)(2) showed that simple hydroxyethyl ethers tosylated at a rate similar to that characteristic of primary alcohol groups in carbohydrates, and much greater than the rates pertaining to secondary alcohol units. He prepared the esters of the diethylene and triethylene glycol monoethyl ethers for the first time in a pure state. Both esters, when attempts

were made to purify them by distillation in the region of 125-135° at 0.03-0.13 mm., decomposed to give high yields of 1,4-dioxane together with nearly quantitative yields of ethyl p-toluenesulfonate in the first case and of cellosolve p-toluenesulfonate in the second.





A side reaction in the decomposition of the triethylene glycol monoethyl ether tosylate, indicated by the development of acidity and by unsaturation in the products, was assumed to proceed by a reaction such as,

$$C_2H_5(OCH_2CH_2)_3OSO_2C_6H_4CH_3 \longrightarrow C_2H_5(OCH_2CH_2)_2OCH{=}CH_2 + HOSO_2C_6H_4CH_3 \quad .$$

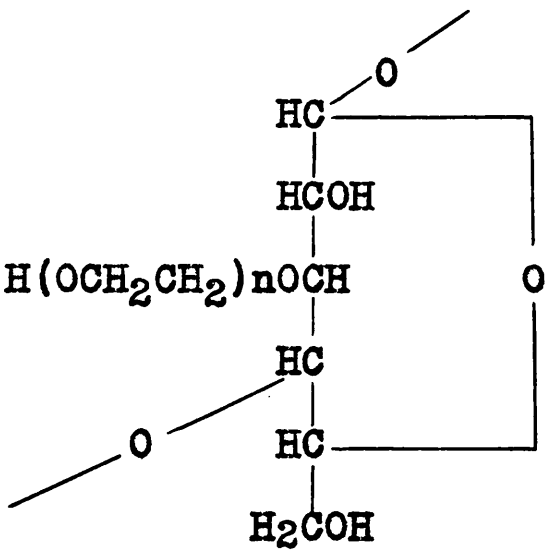
It was well established by workers in carbohydrate chemistry (33)(34)(35)(36) that the tosyl ester group could be

quantitatively replaced, except in a few special cases (37)(38) (39), from a primary alcohol unit ($-CH_2OTs$) by iodine. The necessary reagent was an alkali metal halide usually sodium iodide in acetone, acetonyl acetone or acetic anhydride solution. The usual treatment was for two hours at 110° to 120° but in the case of certain highly tosylated cellulose derivatives this treatment was drastic enough to extend the substitution of iodine for tosyloxy to tosylates of secondary alcohol units ($=CHOTs$) (40) (41). Realizing that the high temperature usually employed in these iodinations might promote the thermal decomposition of some hydroxyethyl tosylates, Tasker carried out the reaction at room temperature for periods ranging up to 120 hours. His rate plots revealed second order kinetics and he was successful in preparing pure β-ethoxy- β'-iododiethylether, $C_2H_5OC_2H_4OC_2H_4I$, from Carbitol-p-toluenesulfonate, and also β-ethoxyethoxy- β'-iododiethylether, $C_2H_5OC_2H_4OC_2H_4OC_2H_4I$, from the tosylate of triethylene glycol monoethylether. The iodine atoms in these ethers, as in other β-iodo ethers, were so stable that iodine analyses could not be carried out with alcoholic solutions of potassium ethylate or potassium hydroxide because such solutions often failed to displace the halogen completely. The Carius method, however, gave consistent and accurate results.

Although the number of hydroxyethyl groups in a cellulose ether could be estimated with some confidence by Morgan's (21) method, the task of determining the position and uniformity of the substitution still remained. There was also the problem of determining to what extent the condensation of ethylene oxide

occurred on a hydroxyethyl group giving polyethylene oxide side chains instead of simple hydroxyethyl groups directly attached to the cellulose.

In an attempt to answer the above questions, Tasker and Purves (1)(3) noted that the conversion of primary alcohol groups in the glucose residues of cellulose to hydroxyethyl ethers did not alter the total number of free primary alcohol units, but a similar conversion of secondary alcohol units replaced them with primary alcohol functions.



II

This consideration is illustrated in Structure II, in which both the length of the polyethylene oxide chain (n = 1 or an integer greater than 1) and its location in the glucose residue are arbitrary.

An hydroxyethylcellulose with a degree of substitution of 0.44, was converted to a uniform, highly swollen, completely translucent gel. This gel was tosylated with excess tosyl chloride in pyridine at 25° and the reaction was followed by

analyses of intermediate products for sulfur, chlorine and hydroxyethyl. From these data the corresponding changes in tosyl, chlorine and hydroxyethyl substitutions were calculated and are recorded in Figs. 1 and 2, which are reproduced from their article. Fig. 1, Plot B shows that nearly two-thirds of the original 0.44 hydroxyethyl groups were eliminated during the first four days, but that the remaining third were still intact after twenty days. Since the starting material was shown to be stable to the pyridine hydrochloride which was formed during the tosylation as a by-product, Tasker and Purves concluded that the loss of hydroxyethyl groups occurred after, and not before, their tosylation and that the groups consisted of two distinct kinds, about one-third yielding stable and the other two-thirds unstable tosylates. They also suggested that the unstable tosylates might be analogous to those of the monoethers of di- and triethylene glycol, which were quantitatively cleaved to 1,4-dioxane and a stable lower tosylate when vacuum distillation was attempted. A similar reaction could account for the loss of hydroxyethyl substituents from the hydroxyethylcellulose without loss of tosyl units. The hydroxyethyl groups which formed stable tosylates would on this assumption be those attached to the cellulose directly, either as a monomer or as the initial unit of an odd membered polyethylene glycol chain. The foregoing mechanism would require that at least two-thirds of the hydroxyethyl substituents existed as polyethylene glycol chains. This large fraction seems rather unlikely, especially in a derivative with a total degree of substitution of only 0.44,

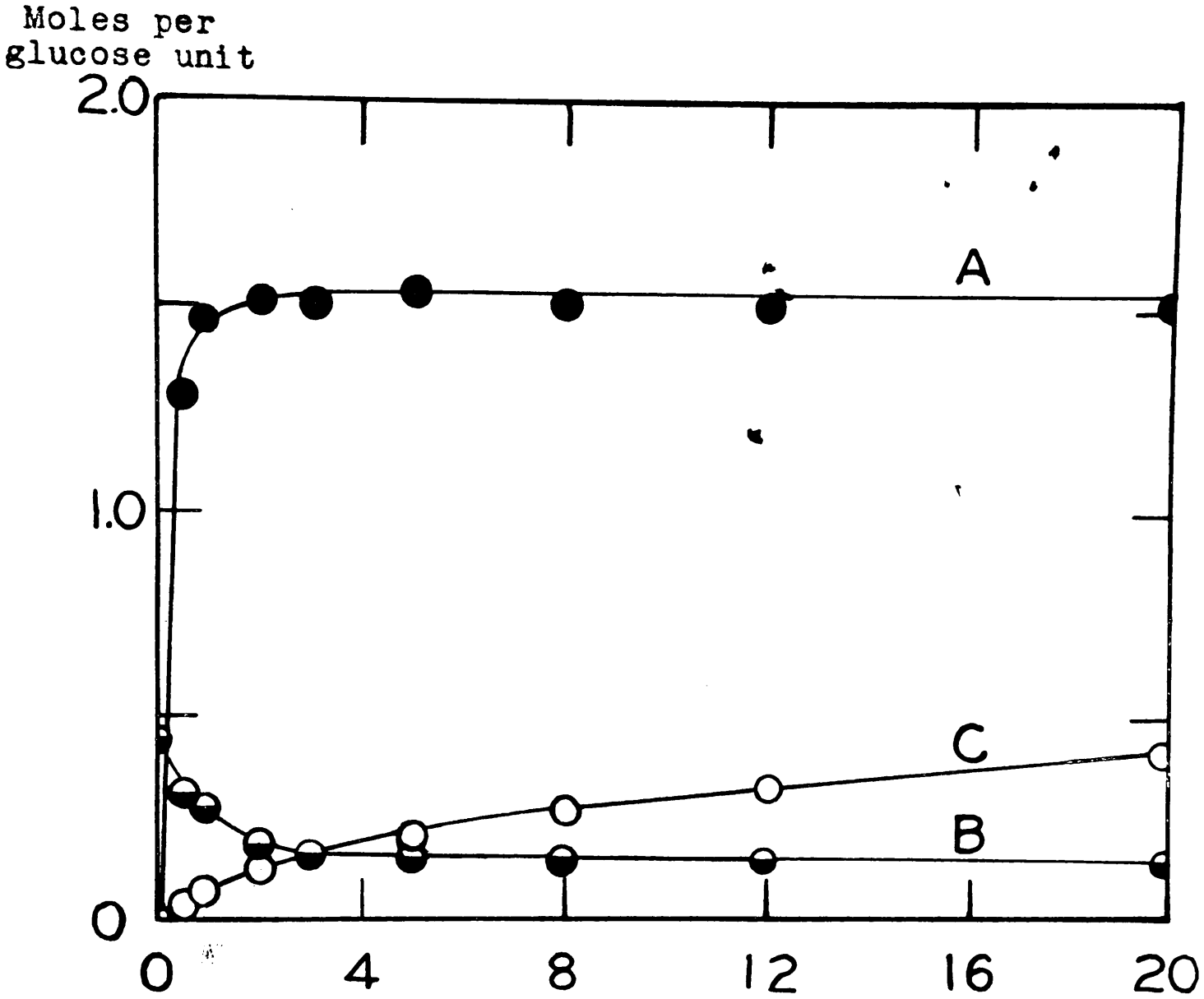


FIG. 1 Changes with Time in Days in the Substituent Groups during Tosylation of Hydroxyethylcellulose (Ceglin, E.S. Type H). Reproduced from (1).

Plot A ● Moles of Tosyl Groups
Plot B ◒ Moles of Ethylene Oxide Groups
Plot C ○ Moles of Chlorine Groups

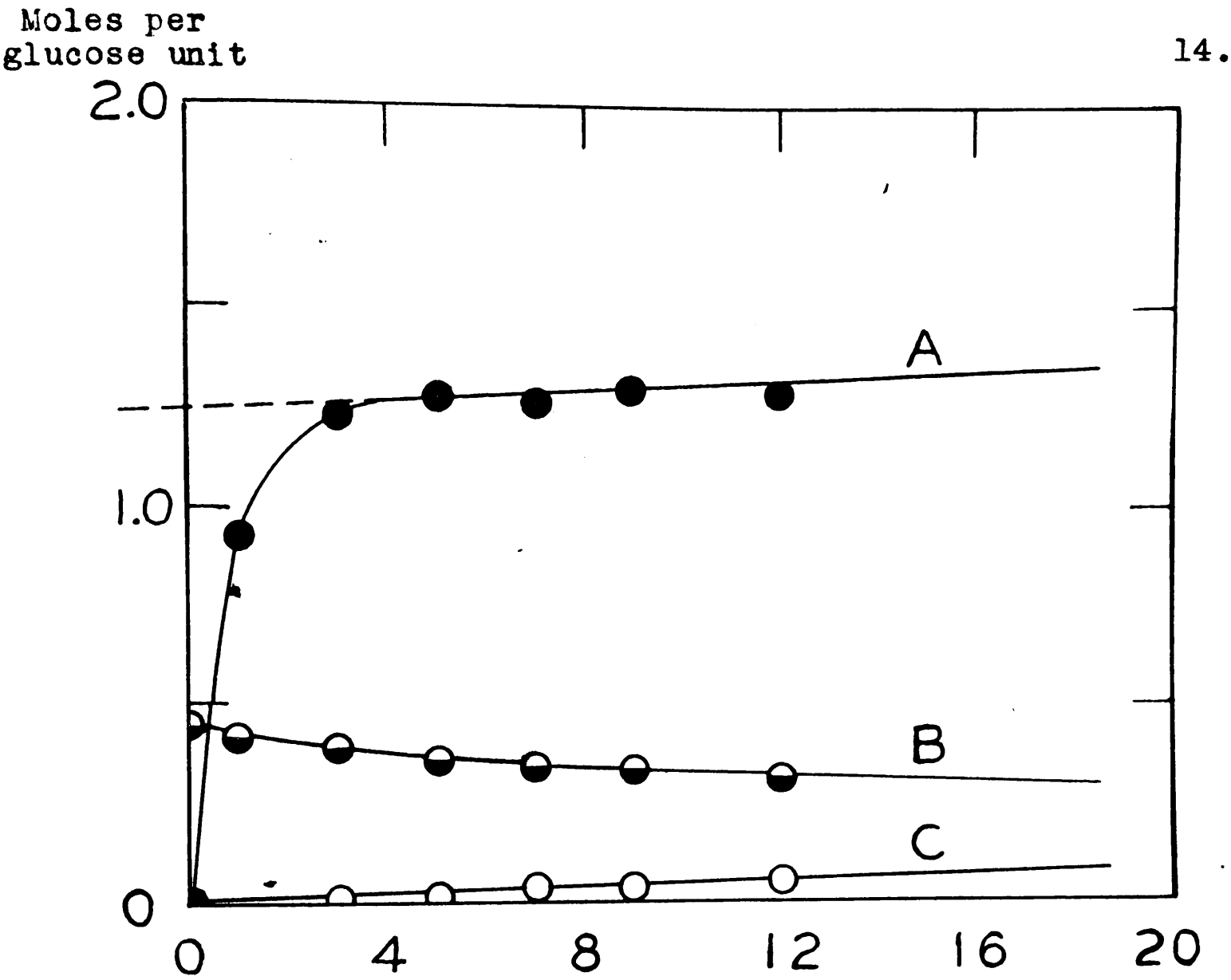


FIG. 2. Changes with Time in Hours in the Substituent Groups during Tosylation of Hydroxyethylcellulose (Ceglin, E.S. Type H). Reproduced from (1).

Plot A ● Moles of Tosyl Groups
Plot B ◒ Moles of Ethylene Oxide Groups
Plot C ○ Moles of Chlorine Groups

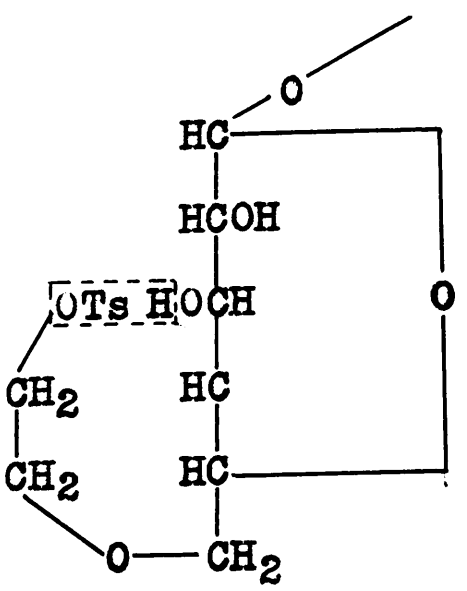
unless during preparation of the hydroxyethylcellulose ether the ethylene oxide reacted preferentially with hydroxyethyl groups already *in situ*.

Plot C records a rather rapid chlorination which probably resulted in the conventional way by the interaction of primary tosyl groups with by-product pyridine hydrochloride.

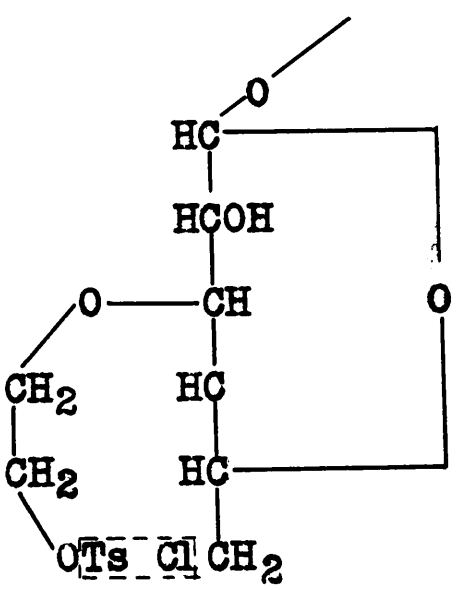
The extent of the initial rapid tosylation was determined by extrapolating the latter portion of Plot A (Fig. 2) to zero time, both the loss of alkoxyl and the appearance of chlorine being insignificant during the early hours of the tosylation (Fig. 2 Plots B and C). The result, 1.22 moles, was taken as equal to the number of primary alcohol groups in the original hydroxyethylcellulose because their rate of reaction was comparable to that displaced by primary alcohol groups in other cellulose derivatives (33)(35). At least 0.22 mole of the hydroxyethyl substituent was tentatively assigned to the secondary positions in the cellulose, since substitution in the primary alcohol positions would not change the primary alcohol substitution from the original figure of 1.0 (See Structure II).

Iodination of a sample tosylated for three hours introduced only 1.00 mole of iodine instead of the expected 1.22 moles, even under the rather extreme conditions of heating with sodium iodide in acetonylacetone for twelve hours at 115° to 120°. During the iodination the over-all substitution (tosyl plus halogen) unexpectedly decreased from 1.24 to 1.11 moles. A similar decrease in combined tosyl plus halogen substituents was noted during

chlorination of another tosylated sample with pyridine hydrochloride. Iodination revealed only 1.00 and chlorination 0.82 mole of primary hydroxyl groups, whereas the minimum number possible was 1.0 for cellulose, or any hydroxyethylcellulose (See Structure II), and the number probable in the present case was 1.22. This large discrepancy, which could not be attributed to inadequate conditions of halogenation, was tentatively attributed to the well-known ability of alkyl p-toluenesulfonates to act as alkylating agents in basic media (42). If the 0.15 mole of "stable" hydroxyethyl group quickly became tosylated or chlorinated and then slowly alkylated unsubstituted hydroxyl groups of the cellulose, structures such as III and IV might be produced, both of which are cyclic ethers of ethylene glycol. The ethylene oxide unit would be retained while 0.15 mole of primary alcohol group would be eliminated. The fact that the derivatives were soluble in some organic liquids made it improbable that the postulated ethylene glycol ethers formed cross-links between different glucose residues of the cellulose.



III



IV

With the ultimate objective of introducing amino groups into the cellulose molecule to make it sensitive to wool-type dyes, Champetier and Fournier (43) last year tosylated an hydroxyethylcellulose of degree of substitution 0.72. Assuming without proof that no loss of hydroxyethyl occurred, they found that 0.70 mole of tosyl groups could be introduced very rapidly by treatment with tosyl chloride in pyridine at room temperature for three hours, while under the same conditions native cellulose reacted only very slightly (See Fig. 3). These data seemed to indicate that the primary hydroxy groups of the hydroxyethyl substituents were much more reactive toward tosylation than the hydroxy groups of the cellulose itself. Plot A, Fig. 3 was taken to represent the preferential esterification of these hydroxyethyl groups. The hydroxyethylcellulose was more highly swollen by pyridine, and undoubtedly gave a more homogeneous reaction medium than the native cellulose under the same conditions. Although such differences in the physical condition of cellulose are known to have an enormous effect on its rate of reaction, the authors neglected to consider this difference as a factor contributing to the difference in esterification rates.

Champetier and Fournier attempted to prepare aminoethylcellulose by the action of concentrated ammonium hydroxide on their tosylated hydroxyethylcellulose in an autoclave at 100°. Only a very slight amount of nitrogen remained in the insoluble product, and the principal reaction was postulated as being an elimination of tosyl groups with the formation of cyclic anhydrides or connecting bridges. This concept was similar to

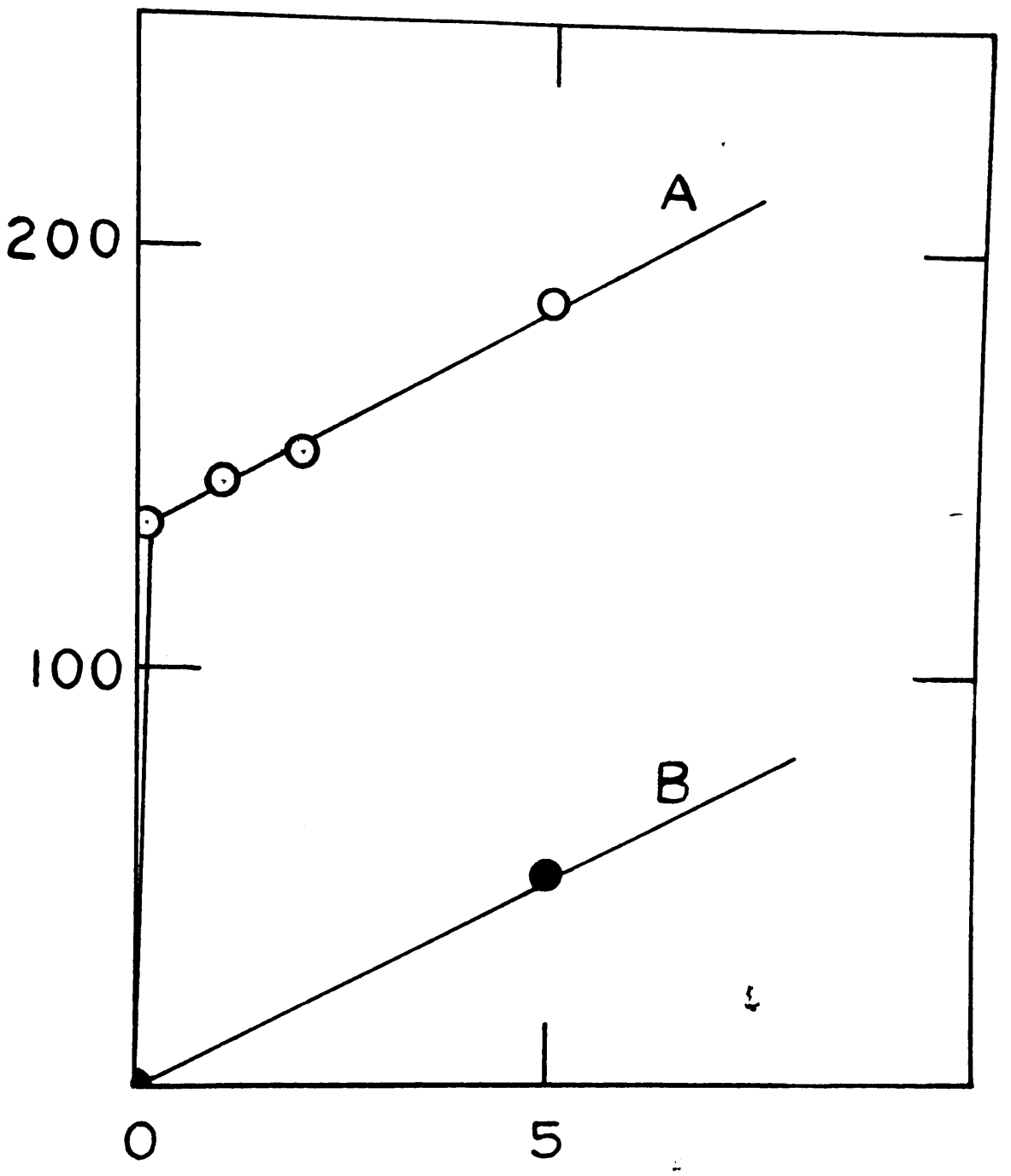


FIG. 3. Changes with Time in the Saponification Equivalents during Tosylation of Cellulose and Hydroxyethylcellulose. Reproduced from (43).

Plot A ○ Hydroxyethylcellulose

Plot B ● Cellulose

that suggested by Tasker and Purves (Structure III) to explain the loss of tosyl groups in a pyridine medium. Champetier and Fournier supported their anhydro hypothesis by showing that their product, when acetylated, gave only a monoacetate, instead of an acetate of substitution 2.28 to 3.0 required by other possible products.

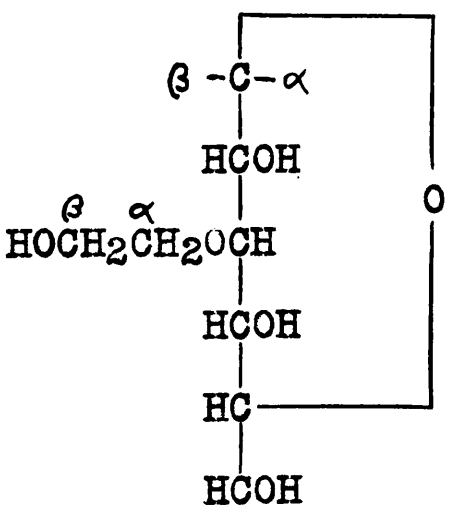
The double decomposition of the tosyl esters with alkaline iodides, sulfides and thiocyanates produced iodoethyl- , thioethyl- , thiocyanoethylcelluloses whose insolubility was probably attributable to the formation of intermolecular as well as intramolecular bridges.

The results of Champetier and Fournier differed from those of Tasker and Purves only in that the latter workers obtained soluble tosylated and iodinated products and thus ruled out the possibility of intermolecular bridges.

DISCUSSION

I. Introduction

All of the compounds discussed in this research were derivatives of β-hydroxyethyl-D-glucoses, the β indicating that the hydroxy group was on the β-carbon atom of the ethyl ether unit. It is also conventional to use the symbols α and β to denote the configuration of the substituents on carbon atom number one in the glucose molecule (Structure V).



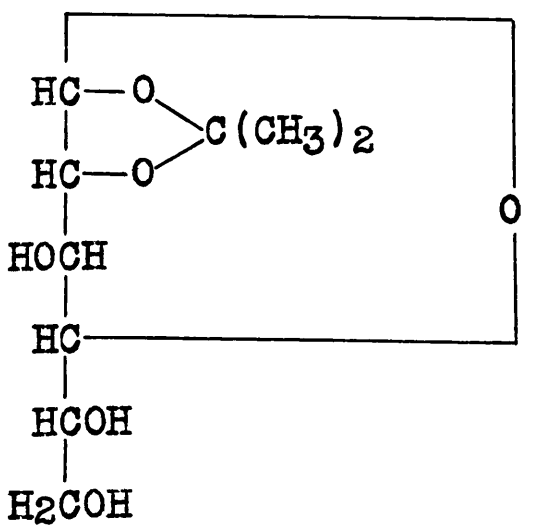
V

In order to prevent confusion, the use of α and β has been confined to the latter sense, with the understanding that substituents on the ethyl group are in the β position in all cases.

Several attempts were made to introduce one or more hydroxyethyl groups into the glucose molecule, the objective being to obtain a pure compound, the chemical behavior of which would be analogous to that of hydroxyethylcellulose. The minimum

requirements for such a compound were considered to be: (1) it must be a derivative of D-glucose containing at least one hydroxyethyl ether group; (2) its structure must be definitely determined, and (3) the compound must have no free reducing group, a β-glucoside analogous to the interunit linkage in cellulose being preferable. A few abortive initial attempts were based on the possibility that under suitable conditions a selective etherification either of an exposed primary or secondary alcoholic unit might obtained.

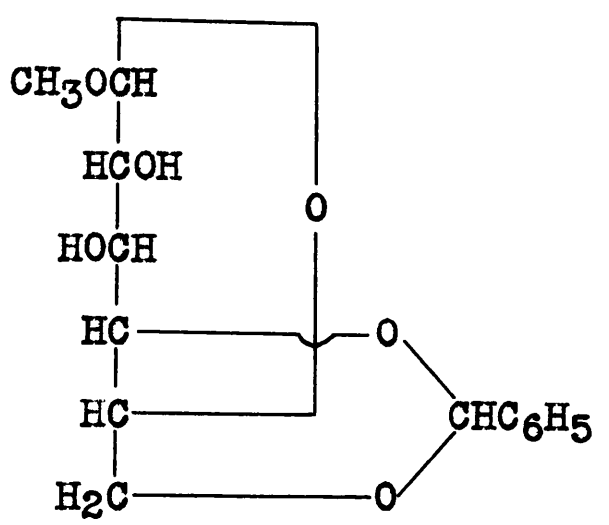
In an adaption of the general reaction,
$RONa + ClCH_2CH_2OH \longrightarrow ROCH_2CH_2OH + NaCl$ (8)(9)(10)(11) the amorphous trisodium derivative of monoacetoneglucose (1,2-isopropylidene-D-glucofuranose, Structure VI) was heated under re-



VI

flux with ethylene chlorohydrin in benzene solution for 30 minutes. Nearly 70 per cent of the monoacetoneglucose was recovered unchanged together with a small amount of colorless sirup. Similar results were obtained when monoacetoneglucose was treated with

ethylene oxide in aqueous 5 per cent caustic soda according to a second general method of introducing the hydroxyethyl group. In this case nearly 60 per cent of the starting material was recovered unchanged and a clear colorless sirup accounted for the remainder. Likewise a solution of methyl-4,6-benzylidene-β-D-glucoside (Structure VII) in a mixture of acetone and 5 per cent aqueous caustic soda was treated with ethylene oxide.

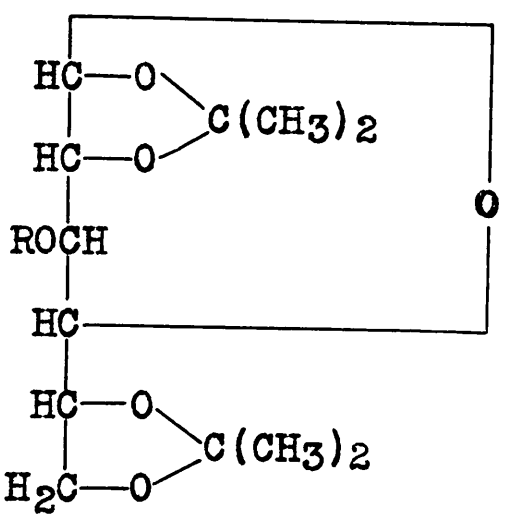


VII

Slightly more than 50 per cent of the starting material was recovered unchanged, together with a clear amber sirup.

All of these sirups, which failed to crystallize on standing, were probably complex mixtures of the several possible hydroxyethyl derivatives. They also decomposed when attempts were made to distill them in vacuo. Low yields and the lack of suitable methods of purification led to the decision to abandon attempts to prepare hydroxyethyl derivatives from monoacetoneglucose and methyl-4,6-benzylidene-β-D-glucoside.

In order to limit the possible complexity of the reaction, and to obtain products that might be stable to vacuum distillation, the use of starting materials containing more than one kind of hydroxy group was abandoned. Diacetoneglucose (1,2:5,6-diisopropylidene-D-glucofuranose, Structure VIII, R = H) appeared to be a suitable substance for the conditions in view since it had only one available hydroxy group, was readily dis-



VIII

R = H, or $-CH_2CH_2OH$

tillable <u>in vacuo</u> and was stable to the alkaline conditions usually employed in hydroxyethylation reactions.

When diacetoneglucose in pyridine solution was treated with ethylene oxide the substance was recovered unchanged; likewise when the sodium alcoholate of diacetoneglucose in benzene solution was warmed either with ethylene chlorohydrin or with ethylene oxide. Although no appreciable reaction took place under the conditions employed, it is possible that a thorough study of the experimental variables would have led to a positive

result. The discovery that diacetoneglucose condensed readily with an excess of ethylene oxide in 5 per cent aqueous caustic soda at room temperature made such a study unnecessary.

The amount of the product, a colorless oil, corresponded to a practically quantitative yield of a monohydroxyethyl derivative. When fractionally distilled (Table VI) this viscous oil yielded 15 per cent of a fore-run which crystallized and was shown to be unchanged diacetoneglucose, 68 per cent as the main fraction and 17 per cent of high boiling residue. The main fraction, after a second distillation (Table VII), was found by combustion analyses and molecular weight determinations (Table I) to have the empirical formula of $C_{14}H_{24}O_7$ required for a monohydroxyethyl diacetoneglucose. The product from its method of preparation then had to be the 3-derivative (Structure VIII, $R = CH_2CH_2OH$). A direct Zeisel-type analysis for the hydroxyethyl group was not carried out on this compound because of the interference of the isopropylidene (acetone) groups which would undoubtedly produce isopropyl iodide and perhaps also propene during the hydriodic acid reduction. The still residue when fractionated (Table VIII) appeared to be a mixture of analogous derivatives of diacetoneglucose containing polyethylene oxide substituents of varying length in position number 3. This inference was supported by high and changing temperatures of distillation as well as by changing refractive indices during distillation.

TABLE I

SUMMARY OF ANALYTICAL DATA CONCERNING
3-HYDROXYETHYL GLUCOSE AND SEVERAL DERIVATIVES

Substance		C (%)	H (%)	Acetyl (%)	Alkoxyl (%)	Mol. Wt.	$[\alpha]_D^{20}$
3-Hydroxyethyl Diacetoneglucose	Calcd.	55.25	8.0	...	...	304	
	Found	55.1	7.9	...	...	305	-32.4
3-Acetoxyethyl Diacetoneglucose	Calcd.	55.5	7.6	12.4	...	346	
	Found	55.6	7.5	12.5	...	341	-28.0
3-Benzoxyethyl Diacetoneglucose	Calcd.	61.8	6.9	...	...	408	
	Found	61.8	6.9	...	...	393	-24.4
3-Hydroxyethyl Glucose	Calcd.	42.9	7.2	...	19.6	...	
	Found	42.6	7.2	...	19.2	...	+46.8
							Nitrogen
3-Hydroxyethyl Glucosazone	Calcd.	59.7	6.5	...	11.0	402	13.9
	Found	59.9	6.5	...	11.2	395	14.0
3-Hydroxyethyl Glucosyl Bromide	Calcd.	...	...	37.8	...	...	
	Found	...	...	37.7	...	...	+13.0
Methyl tetraacetyl 3-Hydroxyethyl- β -D-Glucoside	Calcd.	...	...	42.4	21.7	...	
	Found	...	...	42.0	20.5	...	-21.8
Methyl 3-Hydroxyethyl Glucoside	Calcd.	...	...	...	37.0	...	
	Found	...	...	...	37.1	...	-14.7
Benzyl Tetraacetyl 3-Hydroxyethyl- β -D-Glucoside	Calcd.	57.3	6.3	35.7	9.14	483	
	Found	57.5	6.3	35.8	9.30	471	-57.4
Benzyl 3-Hydroxyethyl Glucoside	Calcd.	...	...	...	14.0	...	
	Found	...	...	...	14.4	...	-44.9

II. 3-Hydroxyethyl Glucose and Several Derivatives

It was considered desirable to obtain 3-hydroxyethyl diacetoneglucose in crystalline form in order that its purity might be checked by recrystallization to constant melting point or rotation. However all attempts to obtain it in crystalline form from various solvents failed. The acetate and benzoate were then prepared in the hope that one or both of these derivatives might be crystalline. Like the parent compound, neither of these esters was ever crystallized but both remained as clear, colorless, viscous sirups readily purified by distillation *in vacuo*. Their molecular weights and analyses agreed very well with theory (See Table I).

Removal of the acetone groups from 3-hydroxyethyl diacetoneglucose (Structure VIII, R=CH_2CH_2OH) by mild acid hydrolysis gave 3-hydroxyethyl glucose (Structure I) as a clear, pale amber sirup which was strongly reducing to Fehling's solution. Alkoxyl analyses indicated 19.0 per cent of hydroxyethyl groups while the theoretical value was 19.65 per cent (Table I). The discrepancy could be accounted for by the presence of approximately 3 per cent of glucose arising from a little diacetoneglucose that had not been removed during the fractional distillation of the 3-hydroxyethyl derivative.

Since glucose is readily fermentable while substituted glucoses are usually stable to the action of yeast enzymes, an attempt was made to remove the suspected glucose impurity by fermentation. Although the impurity was estimated at 3 ± 2 per

cent by the hydroxyethyl analysis, it was found that no less than 26.5 per cent of the reducing power was destroyed by fermentation under normal conditions, and that an additional 8.1 per cent was eliminated by a second fermentation. The total of 34.6 per cent of fermentable material was far more than could be accounted for by the analytical discrepancy and showed that 3-hydroxyethyl glucose was unstable to the enzymes in yeast. The remaining sugar, presumably undestroyed 3-hydroxyethyl glucose, was isolated after fermentation as a clear, amber sirup which did not crystallized as was hoped.

Although the crystallization of 3-hydroxyethyl glucose was attained by a very indirect route toward the end of the research, for nearly two years all attempts at direct crystallization from various solvents failed. It was, however, easily possible to prepare a crystalline phenylosazone from the 3-hydroxyethyl glucose sirup. This was the first crystalline compound containing the hydroxyethyl group encountered in this research. The osazone when purified melted at 163° with decomposition and its analyses agreed very well with those calculated (Table I).

The 3-hydroxyethyl glucose sirup was probably a mixture of α and β isomers in which the α isomer predominated, since it was observed to mutarotate in aqueous solution from $+51.4$ to $+46.8^{\circ}$ (44). For each of these isomers (Structure V) a distinct pentaacetate was possible, the two pentaacetates likewise differing only in the configuration of the substituents on

carbon atom number one (45). According to Hudson (46) an equilibrium mixture of α and β isomers of a reducing aldose could be acetylated with acetic anhydride in the presence of pyridine at a low temperature without isomerization to give a similar mixture of α and β pentaacetates. When sodium acetate was used as the catalyst however the production of the β pentaacetate was favored but the reverse was true with an acidic catalyst like anhydrous zinc chloride. Portions of the 3-hydroxyethyl glucose sirup were acetylated using various catalysts and the results are recorded in Table II. The presence of pyridine gave a product with a specific rotation of $+33.3^{\circ}$, which by analogy was considered to be a mixture of α and β pentaacetates in the same ratio as the isomers in the original reducing sugar. Since the α isomer is by Hudson's definition (44) the more dextrorotatory one in the D series of sugars, the results indicated that the sodium acetate catalyzed product ($[\alpha]_D^{20}$ $+9.9^{\circ}$) was a β-rich mixture of pentaacetates, while that with zinc chloride ($[\alpha]_D^{20}$ $+43.4^{\circ}$) was an α-rich mixture. Although behavior was quite analogous to that of glucose and other aldoses and acetyl analyses were satisfactory, neither isomer was obtained in crystalline form in spite of prolonged attemps. All of the acetylation products remained as sirups; those prepared in the presence of pyridine or sodium acetate were clear and light amber in color, while those prepared with acid catalysts, either zinc chloride or sulfuric acid, were darker. During these acid catalyzed acetylations the reaction mixture always turned black within a very few minutes, but the

TABLE II

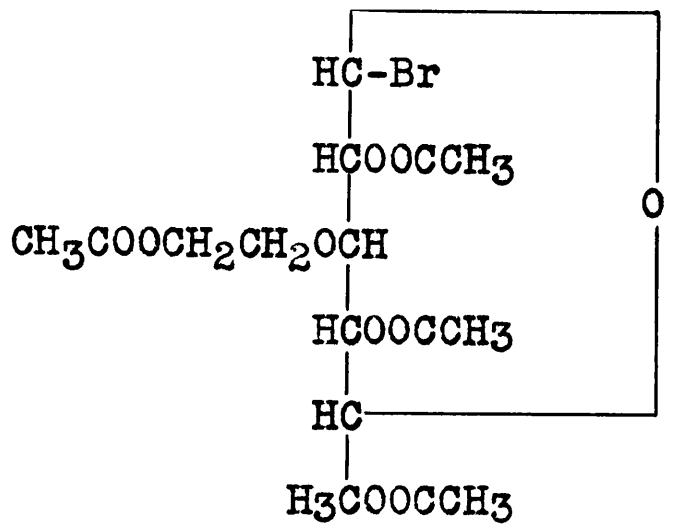
PENTAACETATES OF 3-HYDROXYETHYL-D-GLUCOPYRANOSE

Catalyst	Temp. (°C.)	Time (mins.)	Yield (%)	Acetyl Content (%)	$[\alpha]_D^{20}$	Color of Product
Sodium acetate	135-140	10	92.8	49.9 49.4	+9.9	clear amber
Sodium acetate	80-90	90	89.0	49.0 49.4	+12.4	clear, almost colorless
Zinc chloride	135-140	10	90.2	48.8 49.2	+43.4	dark red-brown
Zinc chloride	80-90	90	83.0	48.9 49.3	+42.5	dark red-brown
Pyridine	25	overnight	95.2	49.9 49.2	+33.3	clear amber
Sulfuric acid	80-90	120	...	...	...	black

Calculated acetyl content: 49.5%

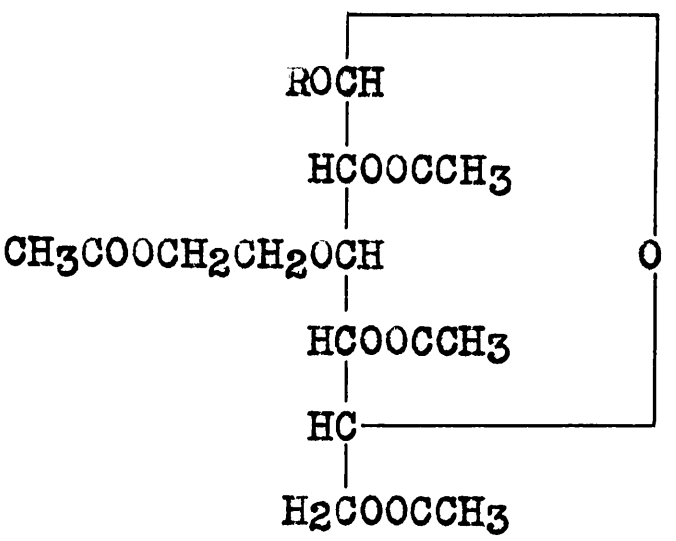
products could be isolated in good yield and by treatment with charcoal could be purified to clear red-brown sirups which gave good acetyl analyses. The dark color developed in these acetylations indicated unknown side-reactions leading to decomposition of either the 3-hydroxyethyl glucose or its pentaacetates. The high yields of pentaacetate, however, suggested that these side-reactions were either very slow or involved the decomposition of the unacetylated material only. Comparison with the ease with which glucose itself can be acetylated suggested that the cause of the difficulty was associated with the hydroxyethyl group.

As is well known, the acetoxy group on the reducing carbon atom of acetylated sugars can be replaced by halogen atoms. The resulting compounds, the acetyl glucosyl halides, are usually of the α configuration and are very useful intermediatesfor the synthesis of β-glucosides. When pentaacetyl 3-hydroxyethyl glucose was treated with dry hydrogen bromide in glacial acetic acid, the mixture turned black as during the acid catalyzed acetylations. The tetraacetyl 3-hydroxyethyl glycosyl bromide (Structure IX) when isolated, however, could be purified to a clear amber sirup which rapidly darkened on standing. Immediately after purification acetyl analyses on the sirup agreed with theory and the specific rotation of $+130^{\circ}$ was dextrorotatory enough to indicate that the product was the expected α isomer.



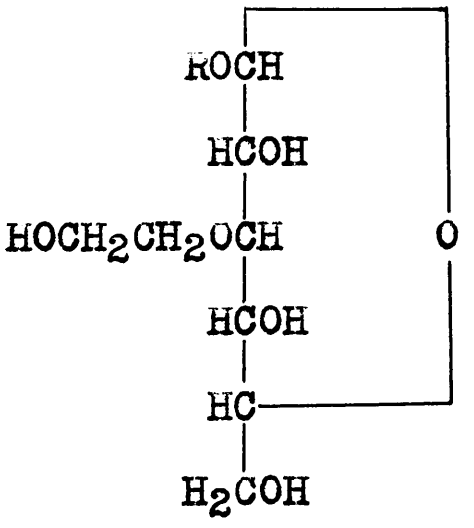
IX

The Königs-Knorr synthesis of β-glucosides (47) involves a Walden inversion at carbon atom number one during the reaction of acetyl α-glucosyl halides with hydroxy compounds in the presence of silver carbonate. The unstable tetraacetyl 3-hydroxyethyl- α -glucosyl bromide (Structure IX) was accordingly treated in separate experiments with methanol and benzyl alcohol. The former reaction gave a clear, non-reducing sirup, the analyses of which agreed with those expected for methyl tetraacetyl 3-hydroxyethyl- β -D-glucoside (Structure X, R = CH_3), while the latter reaction gave a non-reducing crystalline compound, benzyl tetraacetyl 3-hydroxyethyl- β -D-glucoside (Structure X, R = $CH_2C_6H_5$), (Table I). Careful deacetylation of these products gave the corresponding, non-reducing glucosides (Structure XI), the methyl compound being a slightly straw-colored sirup while the benzyl compound was a very clear colorless glass. Since reacetylation of the glass-like benzyl glucoside gave a 93.2 per cent yield of the original crystalline tetraacetate, the only change involved in the saponification was the removal of the acetyl groups.



X

R = CH_3 or $CH_2C_6H_5$



XI

R = CH_3 or $CH_2C_6H_5$

The benzyl tetraacetate (Structure X, R = $CH_2C_6H_5$), was the first crystalline substance encountered in the series of preparations from diacetone glucose and it was rigorously purified by repeated recrystallization. This tetraacetate and the benzyl 3-hydroxyethyl glucoside prepared from it were therefore free of impurities which might have arisen from the

suspected 3 ± 2 per cent of unsubstituted glucose in the original 3-hydroxyethyl glucose sirup. Taking advantage of the fact, discovered by Freudenberg and associates (48), that benzyl glucosides are readily cleaved by catalytic hydrogenation, pure 3-hydroxyethyl glucose was prepared by the hydrogenation of the uncrystallized but pure benzyl 3-hydroxyethyl glucoside. The compound was isolated as a strongly reducing, colorless sirup which crystallized on standing. After careful recrystallizations from ethanol, the product melted at 134-135° and gave an alkoxyl analysis of 19.5 per cent, in agreement with the calculated value of 19.64 per cent. This crystalline compound was observed to mutarotate in aqueous solution and the course of the mutarotation is plotted in Figure 4. The initial high dextrorotation and laevo direction of mutarotation indicated by Hudson's Rule that the crystalline compound was the α isomer.

The mutarotation of glucose is best explained when it is considered as two opposing first order reactions,

$$\alpha \text{ isomer} \underset{\xrightarrow{k_1}}{\xleftarrow{k_2}} \beta \text{ isomer} \quad .$$

The over-all rate of mutarotation ($k_1 + k_2$) is therefore expressed as follows:

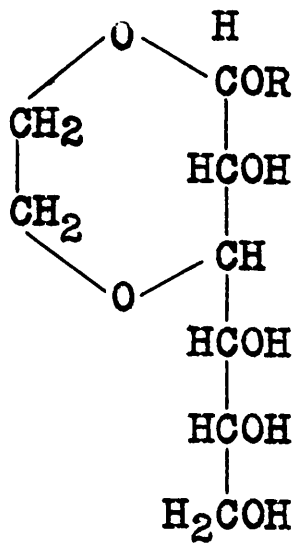
$$k_1 + k_2 = \frac{1}{T} \log \left[\frac{r_0 - r_\infty}{r - r_\infty} \right]$$

Rate constants were calculated for the mutarotation

of 3-hydroxyethyl glucose at various times using the above equation (Table X). Although lack of material rendered the solution too dilute for polarimetric observations of the highest accuracy ($k_1 + k_2$) was found to be fairly constant at an average value of 0.0050 min.$^{-1}$. This value was of the same order of magnitude as that of 0.0069 calculated for glucose under similar conditions (i.e. 20°C. at pH 7.4). Since the course of the mutarotation of 3-hydroxyethyl glucose was similar to that for glucose, it was very probable that only the normal pyranose type of mutarotation was involved. The extrapolated initial specific rotation of 3-hydroxyethyl- α -glucose was +87.9°, and the equilibrium rotation, +48.8°, whereas the values for α-glucose itself are +110° and+52.5° respectively.

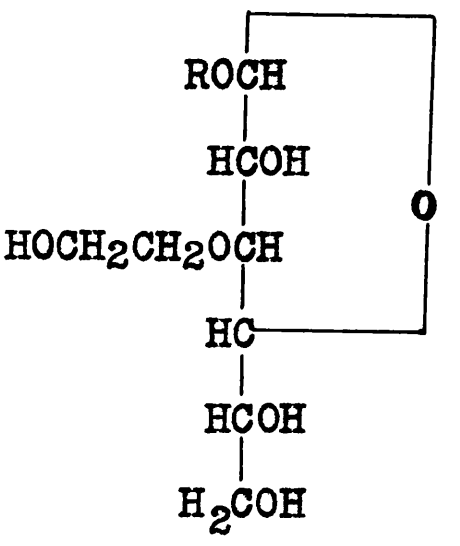
Although the mutarotation data indicate a normal pyranose ring, the possibility of structures such as XII involving a seven membered hemi-acetal ring and XIII with a furanose ring must also be considered since they could account very well for the analytical data for hydroxyethyl glucose and some derivatives (Table I). Each of these possible structures, however, would be expected to consume different amounts of oxidant during a glycol-cleaving periodate oxidation (49)(50).

The methyl 3-hydroxyethyl- β -D-glucoside sirup when treated with aqueous sodium periodate (Fig. 5) rapidly consumed approximately 0.4 mole of oxidant per mole of glucoside. The reaction continued at a much slower rate until, after 23 hours, 0.94 mole had been consumed. Slight impurities of methyl- β -



XII

R = H, CH_3 or $CH_2C_6H_5$



XIII

R = H, CH_3 or $CH_2C_6H_5$

D-glucoside, as well as the previously observed (1)(2) instability of hydroxyethyl compounds to glycol cleaving agents can probably be held accountable for the periodate consumed. These results seem to rule out the possibility of Structures XII and XIII since the former would be expected to consume in less than one hour two moles of periodate and the latter one mole.

III. Tosylation and Iodination of Derivatives of 3-Hydroxyethyl Glucose

Of the several derivatives prepared, three appeared to be suitable for tosylation-iodination studies. These three were, 3-hydroxyethyl diacetoneglucose (Structure VIII, R = CH_2CH_2OH), methyl 3-hydroxyethyl-β-D-glucoside (Structure X R = CH_3), and benzyl 3-hydroxyethyl-β-D-glucoside (Structure XI R = $CH_2C_6H_5$). The fact that all three of these compounds were sirups and therefore not rigorously purified was regrettable, nevertheless the tosylation-iodination investigations were begun in the hope of obtaining crystalline products at later stages from starting materials that at least analyzed correctly.

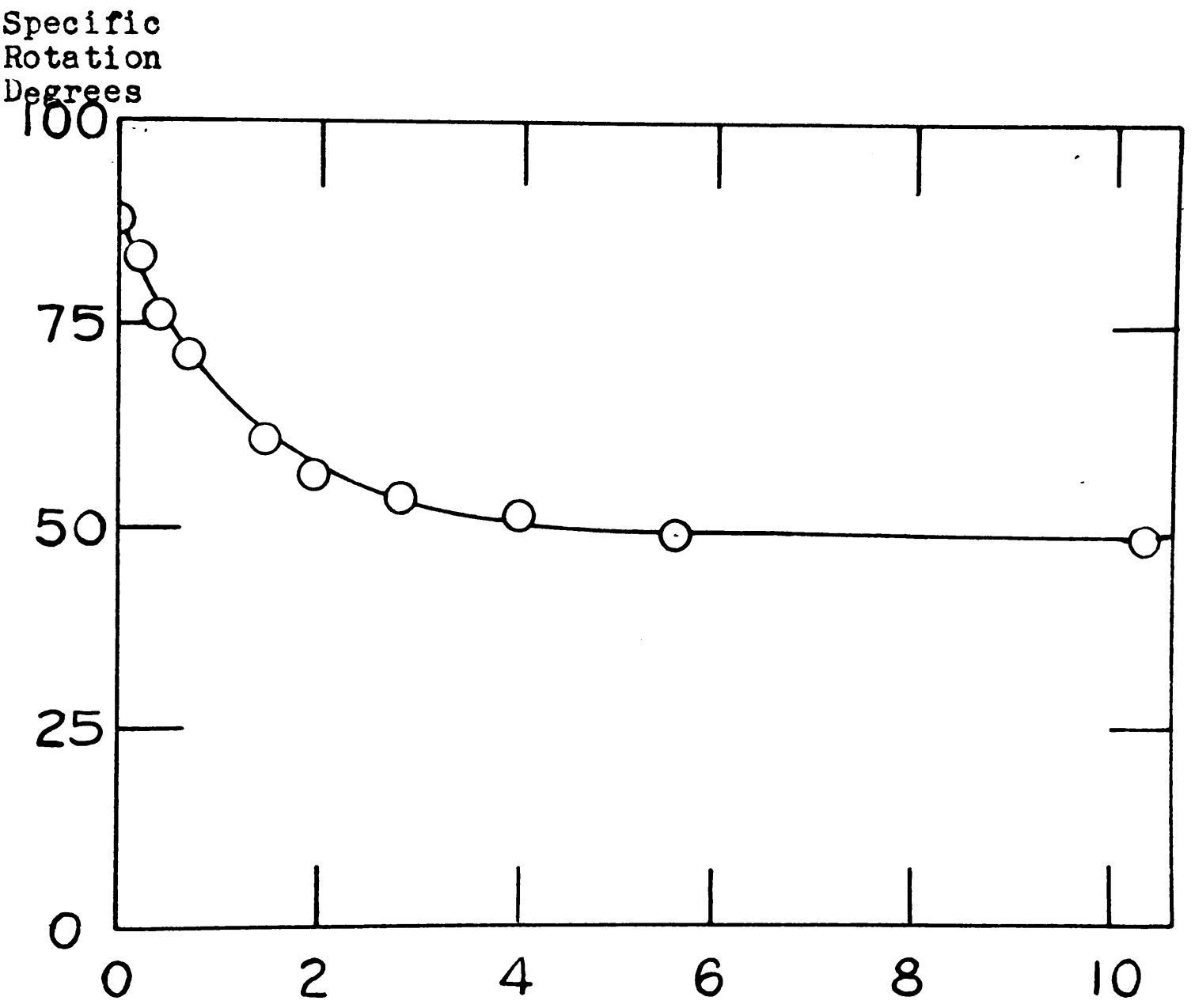


FIG. 4. Mutarotation of 3-Hydroxyethyl- ∝ -D-glucose (Table X)

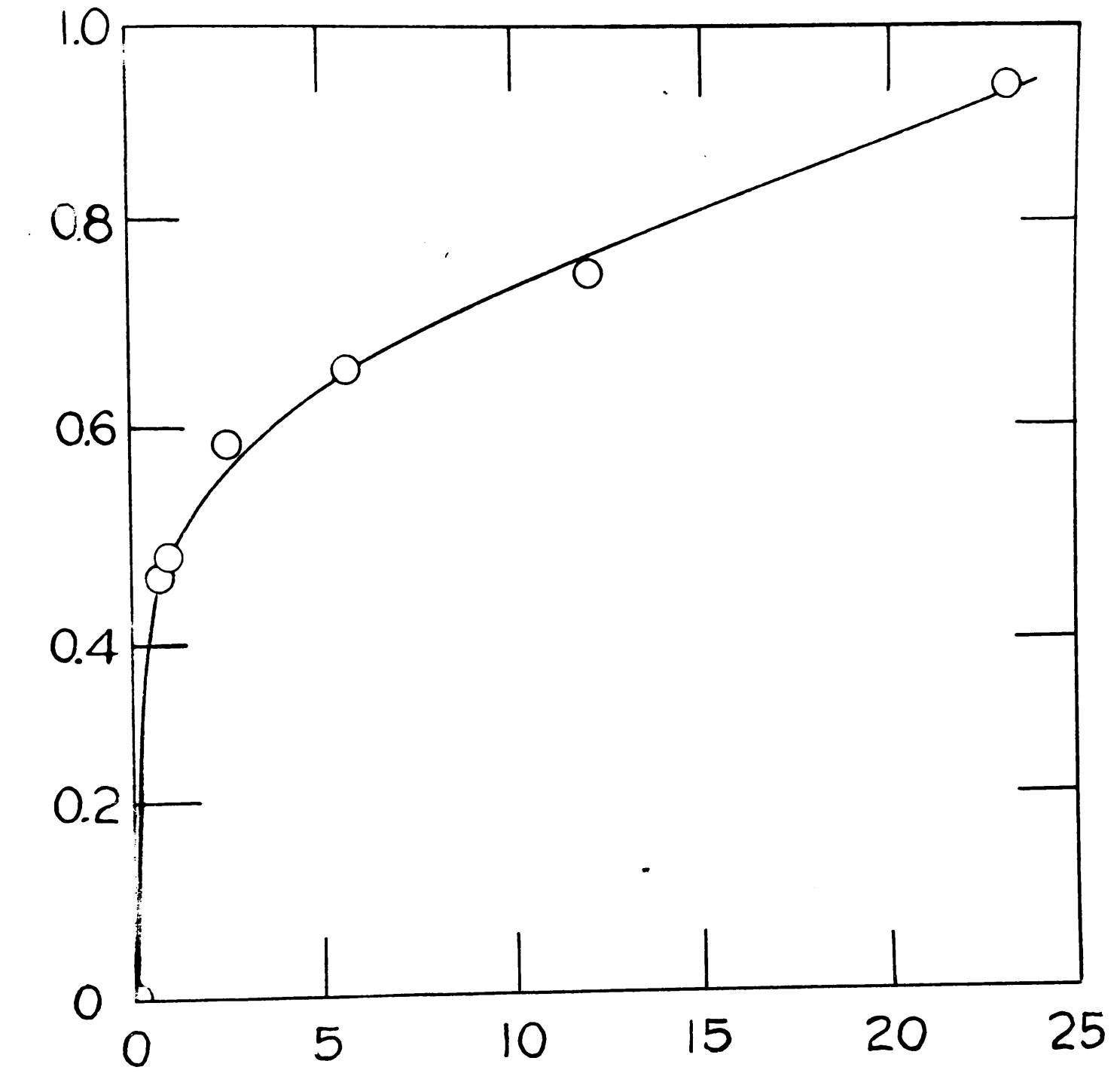


FIG. 5. Periodate Consumption by Methyl 3-hydroxyethyl-β -D-glucoside (Table IX)

Three portions of 3-hydroxyethyl diacetoneglucose (Structure VIII, R = CH_2CH_2OH) were tosylated under various conditions and the results are recorded in Table III. Experiment A was carried out at 0° for 2 hours with 1.1 moles of tosyl chloride, or under the very mild conditions recommended by Tipson (32) for the successful tosylation of Carbitols and Cellosolves. Reactions B and C were under the more severe conditions usually employed for the tosylation of carbohydrates. The products of all three reactions, were isolated by precipitating the mixtures into water but were unfortunately sirups. Calculation on the basis of a monotosyl derivative showed that reaction A gave 96.9 per cent of the expected yield, while B and C gave 45.0 and 44.3 per cent yields respectively. Furthermore, Table III records that the sulfur content of Product A, 6.36 per cent, approximated the 6.99 per cent calculated for the monotosyl compound, but those for B and C were much lower. Product A contained considerably more chlorine (3.07 per cent) than the approximately 0.8 per cent necessary to account for the low sulfur analysis on the assumption that the action of by-product pyridine hydrochloride had replaced some of the tosyloxy group by chlorine. Although every effort was made to crystallize or otherwise purify the substance, the possibility remained that at least some of the excess halogen was contributed by traces of chloroform and possibly pyridine hydrochloride. It was also possible that an unknown side-reaction occurred. The results seemed to indicate that product A consisted primarily of 3-tosyloxyethyl diacetoneglucose (Structure

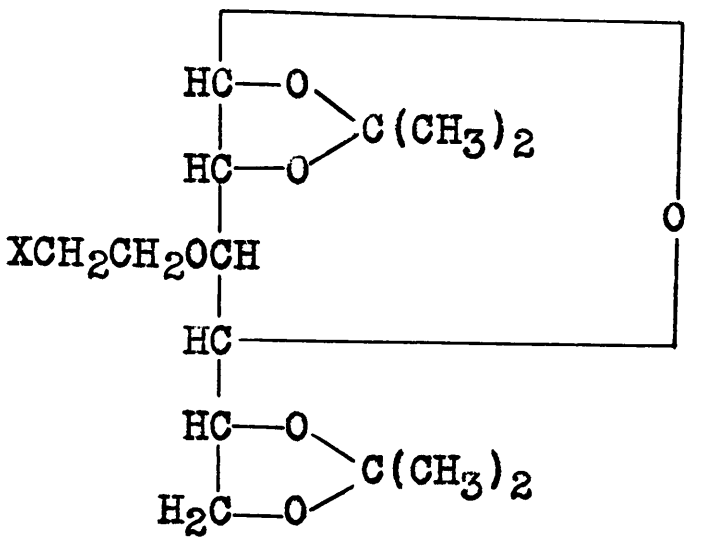
TABLE III

TOSYLATION OF 3-HYDROXYETHYL-1,2:5,6-DIISOPROPYLIDENE-D-GLUCOFURANOSE

	Reaction			
	A	B	C	Theory
Moles tosyl chloride/mole	1.1	1.5	2.1	...
Time (hrs.)	2	14	64	...
Temperature (°C.)	0	30	25	...
Yield (%)	96.9	45.0	44.3	...
Sulfur content (%)	6.34 6.38	4.01 3.95	3.44 3.63	6.99
Chlorine content (%)	3.05 3.09	5.92 6.05	7.64 7.54	0.00
$[\alpha]_D^{20}$ in chloroform	-16.0	....	-32.5*	...

* in acetylene tetrachloride

XIV, X = $C_7H_7SO_3$) together with perhaps 10 per cent of 3-chloroethyl diacetoneglucose (Structure XIV, X= Cl), and possibly other substances of an unknown nature. The tosylation probably proceeded normally at 0° with only a very slight excess of tosyl chloride, but even with these unusually mild conditions the replacement of tosyloxy by chlorine was marked. As for products B and C, their very low sulfur and high chlorine contents showed beyond dispute that conditions suitable for the tosylation of primary and secondary alcohol groups in carbohydrates led to



XIV

X = $C_7H_7SO_3$(tosyloxy) or Cl

serious chlorination. Moreover, the low yields indicate that other side-reactions leading to the formation of water-soluble substances, also occurred.

Preliminary experiments showed that when the methyl- and benzyl-3-hydroxyethyl-β-D-glucosides (Structure XI) were partially tosylated at room temperature, yields of only 45 to 55 per cent were obtained because the monotosyl products were water-soluble and could not be extracted efficiently from the aqueous liquors with chloroform. These products were therefore acetylated before isolation. Separate portions of each glycoside (Structure XI) were tosylated in pyridine for two hours at 0° and 21° with exactly one mole of tosyl chloride. All four products were isolated as straw colored sirups which defied all attempts at crystallization. Their analyses, recorded in Table IV, approximated those calculated for monotosyl triacetyl derivatives contaminated with varying amounts of monochloro triacetyl derivatives. Those tosylated at 21° had a higher pro-

TABLE IV

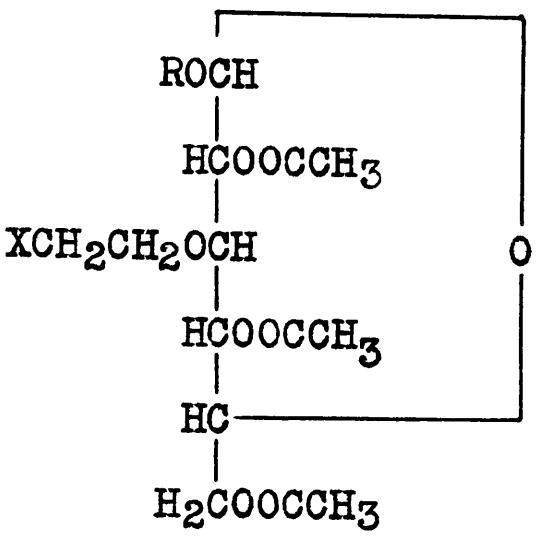
TOSYLATION PRODUCTS OF 3-HYDROXYETHYL- β -D-GLUCOSIDES

Product	Temp. (°C.)	Acetyl (%)	S (%)	Cl (%)	Alkoxyl (%)	$[\alpha]_D^{20}$
Methyl Glycoside						
D	0 (a)	26.0	5.71	1.80	17.9 (b)	-5.66
E	21 (a)	27.6	5.00	4.50	17.7 (b)	-5.41
Theory for monotosyl triacetyl derivative		24.9	6.19	0.00	17.0	...
F	20 (c)	...	13.6	1.99	4.38	0.00
Theory for tetratosyl derivative	...		15.0	0.00	10.3	...
Benzyl Glycoside						
G	0 (a)	22.0	5.02	1.55	7.80	-43.6
H	21 (a)	22.0	4.74	2.18	7.85	-44.1
Theory for monotosyl triacetyl derivative		22.0	5.40	0.00	7.41	...
I	20 (c)	...	12.2	1.92	1.57	-4.2
Theory for tetratosyl derivative	...		13.8	0.00	4.73	...

(a) tosylated for 2 hours with 1 mole tosyl chloride then acetylated
(b) total value including both methoxyl and hydroxyethyl groups as (CH_2CH_2O-)
(c) tosylated for 8 days with excess tosyl chloride

portion of the chloro-compound than those tosylated at 0°, indicating as before that the chlorination side-reaction was more severe at the higher temperature. The specific rotations of the preparations made at 0° and 21° agreed very well and this concordance suggested that any structural difference between them was restricted to the substitution in the hydroxyethyl unit, since a partial change from tosyloxy to chlorine substitution at an asymmetric carbon atom would probably have altered the rotation markedly. In all cases the alkoxyl analyses indicated that no hydroxyethyl groups were lost during tosylation either at 0° or 21° with the particular conditions used.

Compton (51) reported that the tosylation of methyl-β-D-glucoside in pyridine with 1.1 moles of tosyl chloride for 24 hours at room temperature, followed by acetylation, resulted in the formation of methyl 6-tosyl-triacetyl-β-D-glucoside in 41 per cent yield. By contrast, the present work shows that the analogous methyl-3-hydroxyethyl-β-D-glucoside gave more than 90 per cent of a monotosyl triacetyl derivative under the much milder conditions of 0° for 2 hours. The rate of tosylation in this case was much faster than would be expected if the primary hydroxyl group on position 6 of the glucose unit were involved. It is therefore probable that the tosylation took place on the primary hydroxyl group of the hydroxyethyl unit and that the tosylation-acetylation products were essentially 3-tosyloxyethyl-2,4,6-triacetyl-β-D-glucosides (Structure XV, X = $C_7H_7SO_3$).



XV

R = CH_3 or $C_6H_5CH_2$

X = $C_7H_7SO_3$(tosyloxy), Cl or I

The hydroxyethyl ethers of cellulose are known to be chemically more reactive than cellulose itself (1). Although this difference in reactivity might be accounted for by the increased solubility of hydroxyethylcelluloses in the reaction medium, it might also be caused by the greater chemical reactivity of the hydroxy group on the hydroxyethyl substituents.

Methyl-3-hydroxyethyl- β -D-glucoside (Structure XIII R = CH_3) was also tosylated with a large excess of tosyl chloride at room temperature for 8 days, or with conditions approximate to those used by Tasker and Purves (1)(3) for the tosylation of hydroxyethylcellulose. A small amount, 4.7 per cent, of crystalline methyl tetratosyl- β -glucoside, m.p. 182-183° was separated from the light amber glass that formed the main product of the reaction. The analyses of this glass (Table IV) showed that the chlorination side-reaction was evident. A very low alkoxyl content (hydroxyethyl plus methyl) of 4.38 per cent instead

of 10.3 per cent calculated as ethylene oxide for the tetratosyl derivative strongly suggested that hydroxyethyl units had been lost during the prolonged tosylation. Difficulty was encountered in the alkoxyl analysis owing to the high content of sulfur and for this reason the value is quoted with reserve. The true value was probably higher, because the alkoxyl content of methyl tetratosyl glucoside, the product corresponding to a complete elimination of hydroxyethyl, was 5.9 per cent. Since it was suspected that the original methyl-3-hydroxyethyl glucoside contained a small amount of methylglucoside derived from diacetoneglucose, the isolation of crystalline tetratosyl methyl glucoside could not be taken as an argument for the loss of hydroxyethyl groups during tosylation.

Decisive evidence concerning the loss of hydroxyethyl units was obtained from a parallel tosylation of benzyl-3-hydroxyethyl-β-glucoside, which, although uncrystallized, had been prepared from the pure, crystalline tetraacetate and was free of benzyl glucoside. After an 8-day tosylation at room temperature, the product was a clear, straw colored glass with the analyses given in Table IV. The sulfur plus chlorine contents were not excessive for benzyl tetratosyl-3-hydroxyethyl glucoside, but the alkoxyl (hydroxyethyl) percentage of 1.57 per cent was only about one-third of that expected. It was therefore obvious that hydroxyethyl groups were lost during the prolonged tosylation, although failure of the product to crystallize made it necessary to abandon efforts to determine the nature of the side-reaction involved. It will be remembered that Tasker (1)(3)

tentatively attributed a similar loss of hydroxyethyl units during the tosylation of an hydroxyethyl cellulose to the presence in the latter of polyethylene oxide chains, but assumed that a single hydroxyethyl unit directly substituted in cellulose would be stable. The present work shows that this assumption was not necessarily valid, and that single hydroxyethyl substituents might be unstable during tosylation as well as the polymeric variety.

When the crude methyl and benzyl tosyloxyethyl triacetyl-β-glucosides, (Table IV) (Structure XV, X = $C_7H_7SO_3$) were iodinated by boiling in acetone with excess sodium iodide for 5 hours, the sirupy products contained only about one-half of the amount of iodine calculated for iodoethyl triacetyl derivatives. (Structure XV, X = I). When the iodinations were repeated in acetonylacetone at 110 - 115° for 2 hours, however, the reaction appeared to be complete or nearly so. (Table V). These conditions of iodination are usually suitable for the replacement of the tosyloxy group from the primary alcohol position of carbohydrates and the above experiment shows that similar conditions are suitable for the tosyloxyethyl ether group substituted in glucose. Although the iodine content of the methyl 3-iodoethyl triacetyl-β-glucoside was 3% below theory and the substance persisted as an intractable amber sirup, the corresponding benzyl derivative eventually crystallized solidly. After thorough purification benzyl 3-iodoethyl, 2,4,6-triacetyl-β-D-glucoside (Structure XV, R = $C_6H_5CH_2$, X = I) was obtained with accurate analyses with a melting point of 114 - 115° and a specific rotation of -26.8°

TABLE V

ANALYSES OF IODINATION PRODUCTS

Starting Materials	Products of Iodination: Iodine (%) Calcd.	Iodine (%) Found	$[\alpha]_D^{20}$
Methyl tosyloxyethyl triacetyl glucoside			
D	26.8	23.6 (a) 15.3 (b)	+22.0
E	26.8	24.1 (a)	+20.2
Benzyl tosyloxyethyl triacetyl glucoside			
G, H (c)	23.1	22.8 (a) 10.9 (b)	-26.8
Tosylated glucosides			
F	...	26.2 (b)	...
I	...	38.8 (b)	...

(a) iodinated for 2 hours at 110-115°
(b) iodination for 5 hours in refluxing acetone
(c) G and H both gave the same crystalline iodination product under conditions a

---

in chloroform. The fortunate circumstance that this compound was obtained in a pure condition checked the reliability of the work throughout the benzyl 3-hydroxyethyl glucoside series.

As might be expected, iodinations of the products from the prolonged tosylations (Table V, F and I) which were deficient in hydroxyethyl units, gave dark yellow sirups whose composition offered no clear indication as to their structure.

IV. Study of Peroxide Formation in a Freshly Prepared Hydroxyethylcellulose

Tasker and Purves (1)(2) found that carefully purified Carbitol and Cellosolve, like many other ethers, formed peroxides during storage, and that the presence of light and air accelerated the formation. Carbitol was very much more liable than Cellosolve to peroxide formation and no peroxides were detected in the higher homologue, the monoethyl ether of triethylene glycol. The same authors (3) then investigated several hydroxyethylcelluloses and found no peroxides present in any case as judged by the failure of the samples to liberate iodine from an acidified solution of potassium iodide. Not even the minute amount of iodine liberated in the reagent blank was found in tests of cellulose derivatives. All the samples investigated by Tasker and Purves were commercial hydroxyethylcelluloses of unknown age and it was considered possible that peroxides might have formed at one time and later been consumed by reaction with reducing groups or other portions of the cellulose macromolecule.

An hydroxyethylcellulose of average substitution 0.85 was therefore prepared by condensing alkali cellulose with ethylene oxide and was analyzed for peroxides at intervals over a period of 5 months. The results agreed completely with those

of Tasker for commercial derivatives in that peroxides were absent in all cases and that the presence of the sample reduced the amount of iodine liberated below the level of the blank itself.

Freshly prepared hydroxyethylcellulose of average substitution 1.5 and a commercial derivative of substitution 1.44 were then treated with aqueous hydrogen peroxide. The rate of disappearance of the peroxide in each case was followed and the results are summarized in plots A and B of Figure 6, together with those representing the decomposition of hydrogen peroxide in water alone (Plot C). Plots A and B (Fig. 6) indicate that the hydroxyethylcelluloses consumed peroxide slowly, therefore any peroxides which might be formed by autooxidation of the hydroxyethyl ether linkages during storage of these derivatives would probably not accumulate to a detectable concentration. The apparent absence of peroxides in hydroxyethylcelluloses therefore could not be taken as evidence that autooxidation of the ether linkages did not take place.

It is apparent from Fig. 6 that the commercial derivative (Plot A) consumed peroxide at a much greater rate than the freshly prepared derivative (Plot B), although the hydroxyethyl substitutions were nearly the same. This difference might be caused by the presence of more readily oxidizable impurities, or more aldehyde groups in the commercial sample, but the investigation of such possibilities lay beyond the plan of the present research.

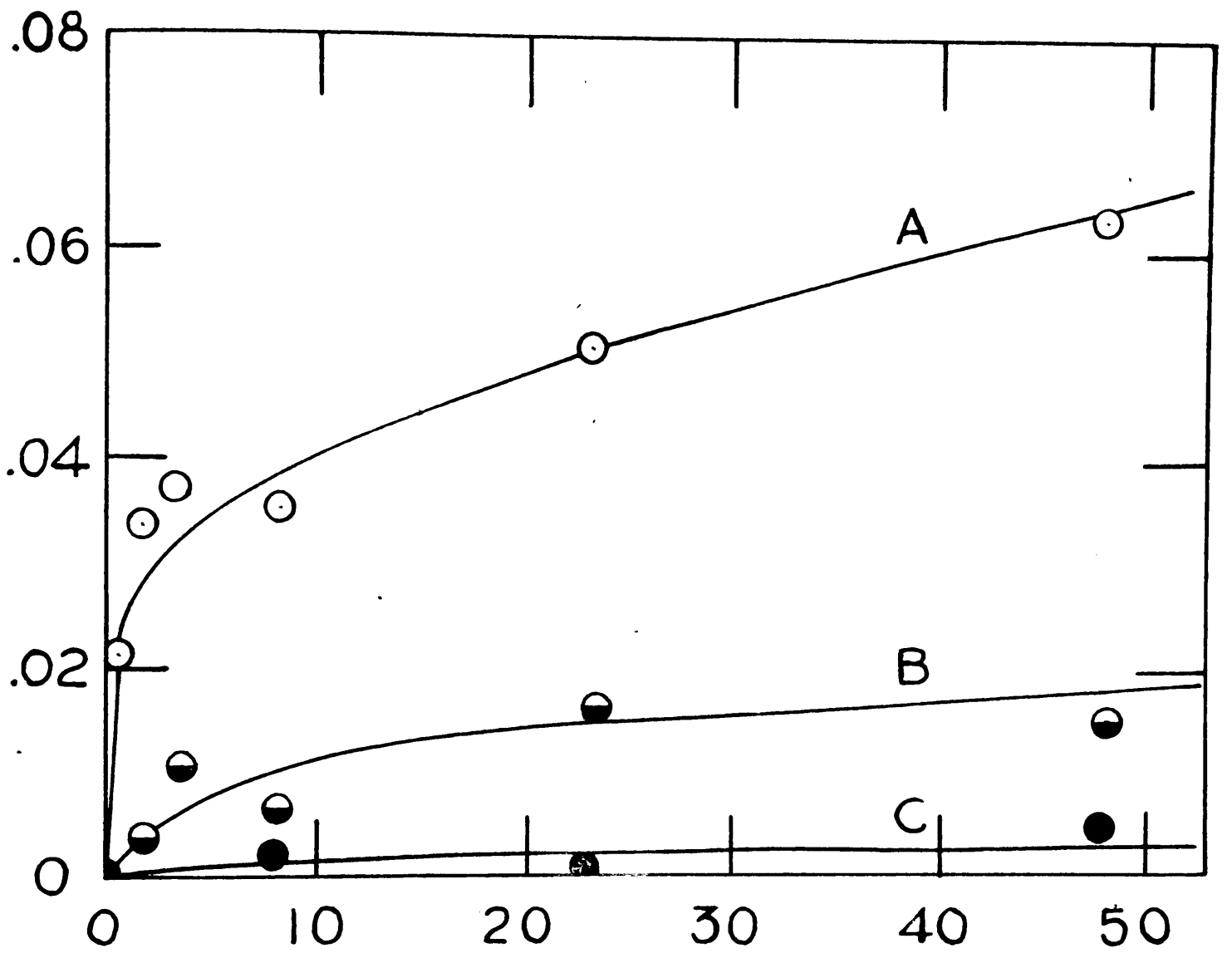


FIG. 6. Peroxide Consumption by Hydroxyethyl-celluloses (Table XIV)

Plot A ○ Cellosize WS-100 of unknown age
Plot B ◒ Freshly Prepared Hydroxyethylcellulose
Plot C ● Blank

EXPERIMENTAL

Note: All reported experimental melting points are uncorrected.

I. Materials and Reagents

Solvents

Since most products were isolated as sirups after distillation of the solvent, it was most important to purify, very carefully, all solvents employed in this research. Standard methods of purification were employed as described by Fieser (52) and by Weissberger and Proskauer (53).

Purification of p-Toluene Sulfonyl Chloride (tosyl chloride)

Technical grade tosyl chloride (100 g.) was dissolved in 300 cc. of benzene and the solution was washed free of acid with cold water, then dried over anhydrous sodium sulfate for several hours, decolorized with charcoal and the benzene removed under reduced pressure on a steam bath. The tosyl chloride residue, after two recrystallizations from ether, had a sharp melting point at 68.5-69°. The pure tosyl chloride was found to decompose slowly, liberating hydrochloric acid fumes, when stored without precaution, but when stored in a vacuum desiccator over phosphorus pentoxide it was quite stable for several months.

Anhydrous-D-glucose

Pure anhydrous glucose was prepared from Cerelose, a commercial glucose monohydrate, by a method described by Hudson and Dale (54) which involves crystallization from an acetic

acid - water (4:1) mixture. The resulting pure white crystals, which were predominantly the α-isomer, melted correctly at 146°.

1,2:5,6 Diisopropylidene-D-glucofuranose

This compound, also known as diacetoneglucose, was prepared by condensing finely divided anhydrous glucose with acetone in yields ranging from 55 to 75 per cent by the method of Van Gaunenberg, Bredt, and Freudenberg (55). After recrystallization from ligroin (b.p. 90-100°) and then from ethyl ether, the fine white needles melted correctly at 111° and had the correct specific rotation $[\alpha]_D^{20}$ in water, -18.7° (C = 2.11).

1,2 Isopropylidene-D-glucofuranose

This compound, otherwise known as monoacetoneglucose, was obtained from diacetoneglucose by a partial hydrolysis described by Irvine and MacDonald (56). After recrystallization from ethyl acetate, fine white crystals were obtained in 65 per cent yield. m.p. 158 - 159.5°. $[\alpha]_D^{20}$ in water -11.6° (C = 2.02). These values agreed well with those quoted (48).

Methyl- β -D-glucopyranoside

Two different procedures were employed for the preparation of methyl- β -D-glucoside. The first, originated by Königs and Knorr (47) and modified by Kreider and Evans (57) and by Levene and Tipson (58) gave an over-all yield of 57 per cent from Cerelose (commercial glucose monohydrate) via the penta-acetate, acetobromoglucose and methyl tetraacetyl- β -D-glucoside.

The second and much more convenient procedure, reported recently by Raymond and Schroeder (59), gave the glucoside in an over-all yield of 19 per cent. This method involved separating the methyl-α- and β-glucopyranoside mixture from glucose and methanolic hydrogen chloride by means of the crystalline potassium acetate complex formed by the β isomer. The product was obtained as the crystalline hemihydrate from both procedures and after recrystallization from ethanol melted correctly at 109-110° and had the correct specific rotation of $[\alpha]_D^{20}$ in water -32.6°, (C = 2.08).

Methyl 4,6-benzylidene-β-D-glucopyranoside

Methyl-β-D-glucoside was allowed to react with benzaldehyde in the presence of anhydrous zinc chloride following the method described by Freudenberg and co-workers (60) except that the time of reaction was extended to six days at room temperature. After recrystallization from water, long white needles were obtained in 74 per cent yield. These crystals melted correctly at 203 - 204.5° and had the correct specific rotation of $[\alpha]_D^{20}$ in methanol -74.2° (C = 2.42).

II. Methods of Analysis

Preparation of Materials for Analysis

A large majority of the compounds prepared and analyzed during this research did not crystallize, but remained as viscous sirups. It was very important to remove the last traces of solvent which were tenaciously held by these sirups prior to analysis. All sirups were therefore dried in vacuum

desiccators over phosphorus pentoxide until the weight became constant or the rate of loss in weight became constant, owing to vaporization of the sirup. A drying period of one to four weeks was usually required.

Carbon and Hydrogen Analyses

All of these analyses were carried out on a semimicro scale according to standard procedure as described in the text by Niederl and Niederl (61).

Sulfur Analysis

All sulfur analyses reported were obtained by the semimicro Carius method using barium chloride in the bomb tube. The method, as described by Clark (62) was followed carefully except that ceramic filter crucibles were used instead of platinum Gooch crucibles.

Chlorine and Iodine Analyses

The chlorine and iodine analyses were carried out by the semimicro Carius method using silver chloride in the bomb tube as described by Clark (63).

Alkoxyl Analysis

The alkoxyl analyses were carried out by the Morgan method (21), a recent modification of the Zeisel method which made it possible to determine hydroxyethyl groups for the first time with a reasonable degree of accuracy. The method involved the quantitative estimation of ethylene as well as alkyl iodide when the sample was boiled with hydriodic adid. Many of the

compounds analyzed in this research contained both methyl and hydroxyethyl ether groups. In such cases the Morgan method gave total moles of alkoxyl calculated as ($-OCH_2CH_2-$).

Acetyl Analysis

The acetyl content of acetate esters were determined by the semimicro method of Clark (64) and reported as per cent (CH_3CO-).

Active Hydrogen Analysis

Active hydrogen analyses were by the method of Zerewitinoff (65) using methyl magnesium iodide in butyl ether. Corrections for the vapor pressure of butyl ether were made according to the data of Fuchs and associates (66).

Molecular Weight Determination

The molecular weights of several products were determined by the Rast method as described by Clark (67). The cryoscopic constant for the camphor employed was found to be 40,500 by standardization against pure anthracene. The molecular weight of one product was obtained by the ebbuloscopic method of Menzies and Wright (68) using a differential thermometer.

Nitrogen Analysis

Osazone nitrogen was determined by the semimicro Kjeldahl method preceded by a hydriodic acid reduction as described by Clark (69).

Peroxide Analysis

A method based on that of Liebhafsky and Sharkey (70) was

used to estimate peroxides in hydroxyethylcelluloses. A one-gram sample of hydroxyethylcellulose, either dry or in aqueous solution, and one gram of sodium bicarbonate were placed in a 125 cc. glass stoppered Erlenmeyer flask, then 25 cc. of pure glacial acetic acid was added, followed by 1 cc. of potassium iodide solution (0.4 g KI/cc.). After washing down the sides with 5 cc. of distilled water, the flask was loosely stoppered and kept in the dark for 5 minutes together with a reagent blank. The iodine liberated was determined by titration with 0.01 N sodium thiosulfate.

III. Preliminary Investigations

Attempts to Prepare an Hydroxyethyl Derivative of Monoacetoneglucose

A. Pure monoacetoneglucose (4.7 g., 0.0214 mole) was dissolved in 100 cc. of liquid ammonia. To this solution 1.47 g. (0.064 mole) of sodium wire was added. The ammonia was allowed to evaporate at room temperature leaving what was presumed to be the trisodium alcoholate of monoacetoneglucose as a clear glass. This residue was dissolved in 100 cc. of anhydrous benzene, 10 cc. of pure ethylene chlorohydrin was added and the mixture was heated under reflux for 30 minutes. The reaction mixture solidified on cooling, but the organic material was redissolved by the addition of acetone. Solid sodium chloride was then removed by filtration. When the filtrate was cooled 3.2 g. of white crystals separated which was shown by melting point and mixed melting point to be unchanged monoacetoneglucose, representing a 68 per cent recovery of the start-

ing material. Evaporation of the mother liquor yielded a sirup weighing 1.1 g. Because of low yield, lack of crystalline products and decomposition during fractional distillation this preparation was abandoned.

B. In another experiment 5.0 g. (0.023 mole) of pure monoacetoneglucose was dissolved in 100 cc. of 5 per cent aqueous sodium hydroxide. Ethylene oxide was bubbled through the solution until 7.4 g. (0.168 mole) had been absorbed. During the absorption the temperature of the reaction mixture rose from that of the room to 43°. The solution was neutralized and evaporated to dryness under reduced pressure. Ethanol extraction of the residue yielded 2.9 g. of unchanged monoacetoneglucose m.p. 158 - 159°, mixed m.p. 158 - 159°, representing 62 per cent of the starting material, and 1.9 g. of a clear colorless sirup. Part of the sirup could be distilled in small amounts in a short-path still at bath temperatures of 180 to 210° at 0.10 mm. pressure, but effective fractionation was not possible. This preparation was also abandoned because of low yield and lack of suitable methods for purifying the product.

Attempted Preparation of an Hydroxyethyl Derivative of Methyl 4,6 benzylidene-β-D-glucoside

Since five grams of methyl 4,6-benzylidene- β -D-glucoside when mixed with 150 cc. of 5 per cent aqueous sodium hydroxide failed to dissolve, 75 cc. of acetone was added and the resulting mixture heated to 50° to promote the solubility of the sugar derivative. Ethylene oxide was bubbled through

the solution for 40 minutes, causing a further temperature rise to 60°. When the solution was neutralized and cooled 2.6 g. of unchanged reactant crystalized out, m.p. 203-204°, representing 52 per cent of the starting material. The aqueous mother liquor was extracted three times with ethyl acetate. The combined extracts, after drying and removal of the solvent in vacuo, yielded 4.68 g. of clear amber sirup. Since this sirup yielded no crystalline products and decomposed on distillation *in vacuo*, the preparation was abandoned.

Unsuccessful Attempts to Prepare 3-Hydroxyethyl diacetoneglucose

A. Diacetone glucose (5.0 g., 0.019 mole) was dissolved in 100 cc. of dry pyridine, and ethylene oxide gas was bubbled through the solution for 15 minutes until 5.3 g. of gas had been absorbed. After standing 4 hours at room temperature, the pyridine was removed by distillation *in vacuo* and practically all of the diacetoneglucose was recovered unchanged.

B. The sodium derivative was prepared by dissolving 5.0 g. (0.019 mole) of diacetoneglucose in 100 cc. of liquid ammonia, adding 0.442 g. (0.019 mole) of sodium wire and allowing the ammonia to evaporate at room temperature. The sodium alcoholate of diacetoneglucose which remained as a clear glass was dissolved in 50 cc. of anhydrous benzene and treated with 6.4 cc. (0.095 mole) of ethylene chlorohydrin. The resulting mixture was heated under reflux for 7 hours, filtered and distilled to dryness under reduced pressure. The residue yielded 4.0 g. of unchanged diacetoneglucose representing 80 per cent

of the starting material.

C. Another attempt involved treating a benzene solution of the sodium alcoholate of diacetoneglucose with ethylene oxide. The diacetoneglucose was recovered unchanged.

IV. Preparations

3-Hydroxyethyl-1,2:5,6-diisopropylidene-D-glucofuranose

Pure diacetoneglucose (20 g., 0.077 mole) was shaken with 300 cc. of 5 per cent aqueous sodium hydroxide at room temperature. A small amount (1-2 g.) of diacetoneglucose remained undissolved. Ethylene oxide gas was bubbled through the mixture rapidly for 45 minutes, during which time the temperature rose gradually to 90°. After about 20 minutes all the diacetoneglucose had dissolved leaving a clear solution, but after 25 minutes the solution became cloudy as the oily product began to separate. After 45 minutes 49 g. (1.1 moles) of ethylene oxide had been absorbed. Cooling to room temperature, followed by saturation with sodium sulfate caused 17.5 g. of an oil to separate from the reaction mixture. However, extraction of the entire mixture three times with chloroform was found to be of a more efficient method of isolation, since after washing the combined extracts free of alkali with water, drying over anhydrous sodium sulfate and removal of the chloroform *in vacuo*, 23.0 g. of an oil was obtained, representing a 98.5 per cent yield of crude product. All of this sirup was transferred to a 50 cc. still pot equipped with a Claisen head, 15 cm. vacuum

jacketed Vigreux type column and a vacuum adapter with two receivers. The still pot was packed with glass wool and heated in an oil bath. The sirup was fractionated as shown in Table VI. Fraction 1 crystallized and was identified by its melting point of 110-111° and by an undepressed mixed melting point to be unchanged diacetoneglucose. Most of the sirup was collected in the higher boiling fraction 2 which was refractionated as shown in Table VII. Fraction 2-B, which was obtained in over-all yield of 50 per cent, had a fairly constant boiling point, 140-145° at 0.025 mm. pressure, and therefore was considered to be a substantially pure compound, probably 3-hydroxyethyl diacetoneglucose. It was non-reducing toward Fehling's solution and had a specific rotation of $[\alpha]_D^{20}$ in water -32.5° (C = 2.42).

Anal. Calcd. for $C_{14}H_{24}O_7$; C, 55.2; H, 7.9; Mol. Wt. 304.4; Active H, 1.0.

Found: C, 55.1, 55.1; H, 7.9, 7.8; Mol. Wt. (Rast), 300, 310; Active H, 0.99, 0.99.

The still residue from the fractionation of the crude sirup (Table VI) could not be distilled through a column as the high bath temperature necessary caused decomposition. Distillation without a column, however, gave the three fractions described in Table VIII. The high distillation temperature, wide boiling range and changing refractive indices indicated that the residue was a mixture, probably consisting of analogous derivatives of diacetoneglucose with polyethyleneoxide substituents of varying length in position number 3.

TABLE VI

FRACTIONATION OF CRUDE 3-HYDROXYETHYL DIACETONEGLUCOSE*

Fraction	Bath Temp. (°C.)	Distillation Temp. (°C.)	Pressure (mm. Hg.)	Net Wt.	η_D^{20}
1	165-180	120-135	.025	3.6	crystallized m.p. 110-111°
2	180-205	135-150	.025	15.5	1.4617
still residue	...	...	...	3.9	...

* starting material 23.0 g. of crude sirup

TABLE VII

REFRACTIONATION OF FRACTION 2*, TABLE VI

Fraction	Bath Temp. (°C.)	Distillation Temp. (°C.)	Pressure (mm. Hg.)	Net Wt.	η_D^{20}
2-A	165-180	120-135	.025	3.2	1.4612
2-B	180-190	135-145	.025	11.6	1.4619

* starting material 15.0 g. of Fraction 2

TABLE VIII

FRACTIONATION OF STILL RESIDUE* (NO COLUMN)

Fraction	Bath Temp. (°C.)	Distillation Temp. (°C.)	Pressure (mm. Hg.)	Net Wt.	η_D^{20}
1	165-175	140-150	.025	1.87	1.4631
2	175-190	150-160	.025	1.01	1.4640
3	190-220	160-165	.025	0.20	1.4658

* starting material 3.9 g. of residue

3-Acetoxyethyl-1,2:5,6-diisopropylidene-D-glucofuranose

The acetate was prepared by dissolving 2.1 g. (0.0069 mole) of the twice fractionated 3-hydroxyethyl diacetoneglucose in 1.5 cc. of dry pyridine, cooling to 0° and adding 0.95 g. (0.0093 mole) of acetic anhydride. After standing at 0-5° for about 15 hours, the clear colorless solution was poured into 100 cc. of cold water. The product which separated as a sirup was purified by dissolving in ethyl ether and washing the solution successively with dilute aqueous sulfuric acid, dilute aqueous potassium carbonate and twice with water followed by drying over anhydrous sodium sulfate. Removal of the solvent by distillation *in vacuo* left the product as a clear colorless sirup having a slight odor of pyridine. The sirup was further purified by distillation *in vacuo* giving 1.5 g. (or 72 per cent yield) of

a clear, colorless, viscous distillate, which gave a negative test with Fehling's solution. B.P. 115-120°/0.09 mm. $\eta_D^{20} = 1.4553$. $[\alpha]_D^{20}$ in ethanol -28.0° (C = 2.16)

Anal. Calcd. for $C_{16}H_{26}O_8$: C, 55.5; H 7.6; (CH_3CO-), 12.4; Mol. Wt. 346.4

Found: C, 55.6, 55.6; H, 7.5, 7.6; (CH_3CO), 12.4, 12.5; Mol. Wt. (Rast), 334, 348.

3-Benzoxyethyl-1,2:5,6-diisopropylidene-D-glucofuranose

The benzoate was prepared by treating 2.57 g. (0.0085 mole of carefully fractionated 3-hydroxyethyl diacetoneglucose with 1.0 cc. (0.0085 mole) of benzoyl chloride in 1.5 cc. of dry pyridine. Pyridine hydrochloride crystals began to separate immediately and the reaction mixture soon became a solid white mass. After standing at 45-50° overnight, the solid mass was dissolved by shaking with ether and water. The ether layer was washed successively with dilute aqueous solutions of sulfuric acid and potassium carbonate, then twice with water. After drying over anhydrous sodium sulfate and removal of the ether *in vacuo*, 3.3 g. of product representing a yield of 95.5 per cent remained as a clear, pale amber, viscous sirup. Distillation of the sirup *in vacuo* gave 2.9 g. of a clear, colorless sirup which was non-reducing to Fehling's solution. Over-all yield of pure product, 84 per cent. B.P. 135-140°/0.05 mm. $\eta_D^{20} = 1.4966$. $[\alpha]_D^{20}$ in ethanol -24.4° (C = 3.76).

Anal. Calcd. for $C_{21}H_{28}O_8$; C, 61.8; H, 6.9; Mol. Wt. 408.4

Found: C, 61.8, 61.8; H, 6.8, 7.0; Mol. Wt. (Rast) 395, 390.

Tosylation of 3-Hydroxyethyl-1,2:5,6-diisopropylidene-D-glucofuranose under Various Conditions

A. Following the method developed by Tipson (32) for the tosylation of Cellosolves and Carbitols, 3.2 g. (0.0105 mole) of 3-hydroxyethyl diacetoneglucose was dissolved in 10 cc. of anhydrous pyridine, cooled to 0° and treated with 2.2 g. (0.0115 mole) of tosyl chloride. The reaction mixture was kept at 0° for two hours, during which time crystals of pyridine hydrochloride separated, and was then poured into 200 cc. of ice water. The resulting aqueous mixture was extracted three times with chloroform. The combined extracts after washing successively with dilute aqueous sulfuric acid, water, aqueous sodium bicarbonate, and water, was dried over anhydrous sodium sulfate. Removal of the solvent by distillation under reduced pressure left 4.66 g., a 96.9 per cent yield, of product as a clear colorless sirup with a specific rotation of $[\alpha]_D^{20}$ in chloroform -16.0° (C = 5.14).

Anal. Calc'd for 3-tosyloxyethyl diacetone glucose $C_{21}H_{30}O_9S$;

S, 6.99; Cl, 0.00.

Found: S, 6.34, 6.38; Cl, 3.05, 3.09

B. Another tosylation was attempted with conditions employed by Freudenberg and Ivers (71) for the esterification of diacetoneglucose. In this experiment 2.01 g. (0.006 mole of 3-hydroxyethyl diacetoneglucose and 1.9 g. (0.01 mole) of tosyl chloride were dissolved in 4 cc. of dry pyridine and kept at 30° for 14 hours. Pyridine hydrochloride crystallized during the early hours of reaction but at the end of 14 hours the crystals had disappeared and

the solution was dark in color. The product, isolated by the method described in the preceding paragraph, was a clear amber sirup weighing 1.36 g. This amount represented a 45.0 per cent yield calculated on the basis of a monotosyl derivative.

$[\alpha]_D^{20}$ in acetylene tetrachloride -32.5^o (C = 2.05).

Anal. Found S, 4.01, 3.95; Cl, 5.92, 6.05.

C. A third tosylation was carried out under conditions approximating those used by Tasker (1)(3) for tosylation of hydroxyethylcellulose derivatives. 3-Hydroxyethyl diacetoneglucose (3.13 g., 0.097 mole) and 3.93 g. (0.0206 mole) of tosyl chloride were dissolved in 20 cc. of dry pyridine and kept at room temperature for 64 hours. Following the method described above, the product was isolated as a clear amber sirup weighing 2.09 g. representing a yield of 44.3 per cent when calculated as monotosyl derivative. $[\alpha]_D^{20}$ in chloroform 28.7^o (C = 2.84).

Anal. Found: S, 3.44, 3.63; Cl, 7.64, 7.54.

Iodination of the Product of the Tosylation of 3-Hydroxyethyl Diacetoneglucose

A mixture of 1.0 g. (0.0067 mole) of sodium iodide and 0.96 g. of the product from tosylation - A dissolved in 20 cc. of anhydrous acetone was heated under reflux for 5 hours with protection from moixture by a calcium chloride drying tube. During the reaction crystalline sodium p-toluenesulfonate separated. The mixture was poured into 200 cc. of water and the product was extracted three times with ethyl ether. The combined ether extracts were washed free of iodine with dilute aqueous sodium

thiosulfate, then twice with water and were dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the product remained as a clear, colorless, sirup weighing 0.70 g. The yield was 80.7 per cent of that calculated for a pure 3-iodoethyl diacetoneglucose from 3-tosyloxyethyl diacetoneglucose.

$[\alpha]_D^{20}$ in chloroform -20.7° (C = 3.04).

Anal. Calcd. for 3-iodoethyl diacetoneglucose, $C_{14}H_{23}O_6I$; I, 30.64

Found: I, 28.9, 29.3.

3-Hydroxyethyl-D-glucopyranose

Employing conditions known to remove the isopropylidene groups from diacetoneglucose (48), 5.8 g. (0.19 mole) of 3-hydroxyethyl diacetoneglucose was hydrolyzed by solution in 50 cc. of 0.1 per cent aqueous hydrochloric acid and heating on a steam bath for 3 hours. After neutralization with 0.65 g. of silver carbonate, the reaction mixture was filtered, saturated with hydrogen sulfide to precipitate the last traces of silver and again filtered. Removal of water from the filtrate in vacuo left a clear, pale amber, viscous sirup which was strongly reducing to Fehling's solution. After drying for 5 days in a vacuum desiccator over phosphorus pentoxide, the product weighed 4.3 g., indicating a quantitative yield. $\eta_D^{20} = 1.5005$.

$[\alpha]_D^{20}$ in water +51.4 ⟶ +46.8° (C = 2.72).

Anal. Calcd. for $C_8H_{16}O_7$; C, 42.8; H, 7.2; Alkoxyl as (OCH_2CH_2-) 19.65.

Found: C, 42.7, 42.4; H, 7.3, 7.1; Alkoxyl 18.9, 19.1.

A small amount of this compound was prepared in crystalline form by hydrogenation of pure benzyl 3-hydroxyethyl-β-D-glucoside

and is described in a later section.

Fermentation of 3-Hydroxyethyl-D-glucopyranose

Approximately 1.5 g. of 3-hydroxyethyl glucose sirup was dissolved in 100 cc. of water. The reducing power of the solution was estimated by the Schaffer-Somogyi method (72) and found to be 0.870 g. calculated as glucose. This solution was then fermented by adding 0.3 g. of baker's yeast, 0.05 g. of ammonium acetate and 0.05 g. of sodium dihydrogen phosphate and by keeping the mixture at 35° for three days. After removing the yeast with the aid of a centrifuge, the solution was found to contain 0.640 g. of reducing material as glucose. After a second fermentation under similar conditions only 0.571 g. of reducing power remained. The first fermentation had destroyed 26.5 per cent of the reducing sugar in the solution and the second fermentation had destroyed an additional 8.1 per cent making a total of 34.6 per cent fermented. The remaining sugar was isolated after fermentation as a clear amber sirup which did not crystallize as was hoped.

3-Hydroxyethyl-D-glucosazone

The osazone of 3-hydroxyethyl glucose was prepared by the method of Fischer (73). A solution of 1.0 g. (0.045 mole) of sirupy 3-hydroxyethyl glucose, 2.0 g. (0.014 mole) of phenylhydrazine hydrochloride and 3.0 g. (0.037 mole) of crystalline sodium acetate in 20 cc. of water was heated on a steam bath for 45 minutes. The osazone precipitated as an oily layer which solidified on cooling. After two recrystallizations from 20 per

cent aqueous ethanol the resulting yellow crystals were dried *in vacuo* at 56°. The pure derivative was obtained in 42 per cent yield and had m.p. 163° with decomposition.

Anal. Calcd. for $C_{20}H_{26}O_5N_4$; C, 59.7; H, 6.5; N, 13.9
Alkoxyl as ($-OCH_2CH_2-$), 11.0; Mol. Wt., 402.4.
Found: C, 59.9, 59.9; H, 6.6, 6.4; N, 13.9, 14.0;
Alkoxyl, 11.0, 11.3; Mol. Wt. (Rast), 410, 379.

Pentaacetates of 3-Hydroxyethyl-D-glucofuranose

A. Anhydrous pyridine (311 cc., 3.86 moles) was added to a flask containing 34.6 g. (.771 mole) of 3-hydroxyethylglucose sirup. When all the sirup had dissolved, the solution was cooled to 0° and 362 cc. (3.86 moles) of acetic anhydride was added. After standing overnight at room temperature, the reaction mixture was poured into 2 liters of ice water. The resulting mixture was extracted three times with chloroform. The combined extracts were washed successively with water, dilute aqueous sulfuric acid, water, saturated aqueous sodium bicarbonate and again with water. After drying the extract over anhydrous sodium sulfate, removal of the chloroform under diminished pressure and drying over phosphorus pentoxide *in vacuo*, 63.8 g. of product remained as a clear, amber sirup. Yield 95.2 per cent. $[\alpha]_D^{20}$ in ethanol $+33.3°$ (C = 2.40).

Anal. Calcd. for $C_{18}H_{26}O_{12}$; Alkoxyl, 10.2; Acetyl, 49.5.
Found: Alkoxyl, 9.7, 9.9; Acetyl, 49.9, 49.2.

B. Two grams (0.0066 mole) of 3-hydroxyethyl glucose sirup was dissolved in 20 cc. (0.211 mole) of acetic anhydride containing 2.0 g. of freshly fused sodium acetate. After heating under reflux for 10 minutes, the reaction mixture was poured into 200 cc. of ice water and allowed to stand for 2 hours. The mixture was then extracted three times with chloroform and the combined extracts were washed four times with water, dried over anhydrous sodium sulfate and the chloroform removed by distillation under reduced pressure. The product, a clear amber sirup, weighed 3.60 g. indicating a yield of 92.8 per cent of theory.

$[\alpha]_D^{20}$ in ethanol +9.9° (C = 2.42).

Anal. Calcd. Acetyl, 49.5;

Found: 49.9, 49.4.

When this preparation was repeated under the milder conditions of heating on a steam bath for 90 minutes the product was obtained in 89 per cent yield as an almost colorless sirup with a specific rotation of $[\alpha]_D^{20}$ in chloroform +12.4° (C = 3.71).

Anal. Calcd. Acetyl 49.5;

Found: 49.3, 48.9.

C. Two grams (0.0066 mole) of 3-hydroxyethyl glucose sirup and 2 g. of freshly fused zinc chloride were added to 20 cc. (0.211 mole) of acetic anhydride. The reaction mixture, which turned black almost immediately, was heated to reflux temperature for 10 minutes and thereafter treated in the same manner as described for the previous preparation. The product, a black sirup,

was dissolved in ethanol and decolorized twice with charcoal. After filtration and removal of the ethanol under reduced pressure, 3.5 g. of dark red brown sirup remained corresponding to a yield of 90.2 per cent. $[\alpha]_D^{20}$ in ethanol $+43.4^\circ$ (C = 3.09).

Anal. Calcd. Acetyl, 49.5;

Found: 48.8, 49.2.

A similar preparation was carried out by heating on a steam bath for 90 minutes. However, even under these milder conditions, the reaction mixture turned black. The product, a very dark sirup, was obtained in 83% yield. $[\alpha]_D^{20}$ in chloroform $+42.5^\circ$ (C = 2.32).

Anal. Calcd. Acetyl, 49.5;

Found: 49.0, 49.4.

D. Another acetylation of 3-hydroxyethyl glucose was carried out in acetic anhydride containing a trace of concentrated sulfuric acid at steam bath temperature for 2 hours. The mixture turned black within a few minutes and no attempt was made to isolate the product.

Pentaacetyl 3-Hydroxyethyl- α -D-glucopyranosyl Bromide

A solution of 38.8 g. of pentaacetyl 3-hydroxyethyl-D-glucose in 20 cc. of dry glacial acetic acid was mixed with 50 cc. of a glacial acetic acid solution containing 42 per cent of dry hydrogen bromide gas. After the mixture had been well shaken, an attempt was made to follow the reaction by optical rotations but

a dark color rapidly developed in the mixture. After one hour at room temperature, the mixture was poured into one liter of ice water, and was extracted three times with chloroform. The combined extracts were washed free of acid with saturated aqueous sodium bicarbonate, then were washed with water and dried over anhydrous sodium sulfate. Most of the chloroform was removed at room temperature under reduced pressure, leaving a residue of dark red-brown sirup weighing 45 g. and still containing a small amount of chloroform. No attempt was made to remove the last traces of solvent from this sirup which was quite unstable and decomposed with even gentle heating. A small portion (2 g.) was purified by dissolving in chloroform, passing the solution through a column of chromatographic grade alumina (1" x 1"), and removing the chloroform from the filtrate at room temperature in vacuo. The purified sample after drying in a vacuum desiccator over phosphorus pentoxide overnight was a clear amber sirup with a specific rotation of $[\alpha]_D^{20}$ in chloroform $+130^\circ$ (C = 1.58).

Anal. Calcd. Acetyl, 37.8;

Found: 37.9, 37.5.

Methyl Tetraacetyl-3-hydroxyethyl-β-D-glucopyranoside

Following the method devised by Königs and Knorr (47) as modified by Kreider and Evans (57) 20 g. of freshly regenerated Drierite and 6 g. of silver carbonate were added to 75 cc. of anhydrous methanol in a 500 cc. three necked flask equipped with a mercury sealed stirrer, a calcium chloride drying tube and a stopper. After stirring the mixture for 15 minutes to insure an-

hydrous conditions, approximately 15 g. of crude acetobromo derivative from the preceding preparation was added in three equal portions at 15 minute intervals. The reaction mixture was then stirred for 3 hours at room temperature and was then filtered. The methanol was removed from the filtrate by distillation on a steam bath under reduced pressure, leaving the product as a clear amber sirup. Most of the color was removed by heating an ethanol solution of the product with charcoal, filtering and removing the ethanol under reduced pressure. Assuming 80 per cent purity for the crude acetobromo derivative which served as starting material, the 9.7 g. of clear straw colored sirup represented a yield of approximately 90 per cent of theory. The purified sirup was non-reducing to Fehling's solution and had a specific rotation $[\alpha]_D^{20}$ in chloroform -21.8° (C = 2.47).

Anal. Calcd. Acetyl, 42.4; Alkoxyl, 21.7;

Found: Acetyl, 41.9, 42.1; Alkoxyl, 20.4, 20.5.

Benzyl Tetraacetyl 3-Hydroxyethyl-β-D-glucopyranoside

This compound was prepared from approximately 15 g. of the crude acetobromo derivative by the procedure just described for the analogous methyl-β-glucoside acetate, except that pure benzyl alcohol was used in place of methanol. Benzyl alcohol was removed from the filtrate from the reaction mixture by steam distillation, leaving the product as a water-insoluble sirup which crystallized on cooling. The crystalline material after being recrystallized three times from ethanol, had a melt-

ing point of 113-114°, unchanged after a fourth recrystallization. Assuming 80 per cent purity for the crude starting material, the 6.6 g. of pure product represented a yield of approximately 52 per cent. The product did not reduce Fehling's solution and had a specific rotation of $[\alpha]_D^{20}$ in chloroform -57.4° (C = 2.39).

Anal. Calcd. for $C_{23}H_{30}O_{11}$; C, 57.3; H, 6.3; Acetyl, 35.7; Alkoxyl, 9.14; Mol. Wt. 482.5.

Found: C, 57.5, 57.4; H, 6.3, 6.3; Acetyl, 35.7, 35.8; Alkoxyl, 9.26, 9.34; Mol. Wt., 480, 461. (Method of Menzies and Wright (68)).

Methyl 3-Hydroxyethyl- β -D-Glucopyranoside

Following the method devised by Isbel (74) as modified by Levene and Tipson (58) for deacetylation of sugar acetates, 8.9 g. (0.022 mole) of methyl tetraacetyl 3-hydroxyethyl- β -D-glucoside sirup was dissolved in 150 cc. of absolute methanol contained in a 500 cc. Erlenmeyer flask, protected from moisture by a calcium chloride drying tube. After cooling the solution to 0°, 5 cc. of a 0.228 M solution of barium methylate in anhydrous methanol was added and the mixture was kept at 0° for 24 hours. The clear amber solution was then saturated with carbon dioxide at 0°. After adding 30 cc. of water, the solution was again saturated with carbon dioxide and became cloudy with precipitated barium carbonate. Charcoal was added and the mixture was heated to boiling and filtered. The filtrate was distilled to dryness on a steam bath under reduced pressure to leave a residue of 5.25 g. of clear straw colored sirup, representing an

almost quantitative yield. The product did not reduce Fehling's solution and had a specific rotation of $[\alpha]_D^{20}$ in water -14.7° (C = 2.15).

Anal. Calcd. Alkoxyl, 37.0;

Found: Alkoxyl, 37.2, 36.9.

Benzyl 3-Hydroxyethyl- β -D-glucopyranoside

Ten grams (0.021 mole) of pure crystalline benzyl tetraacetyl 3-hydroxyethyl- β -D-glucoside was deacetylated by the procedure described above for the analogous methyl glucoside derivative. The product, a clear, colorless glass, weighed 6.5 g. representing a quantitative yield, was non-reducing to Fehling's solution and had a specific rotation of $[\alpha]_D^{20}$ in water -44.9° (C = 2.06).

Anal. Calcd. Alkoxyl, 14.01;

Found: Alkoxyl, 14.5, 14.2.

A portion of the above product was acetylated in an equimolar mixture of pyridine and acetic anhydride for 18 hours at room temperature. The crystalline product, obtained in 93.2 per cent yield, was shown to be benzyl tetraacetyl 3-hydroxyethyl- β -D-glucoside since its melting point of 113-114° was unchanged when the product was mixed with authentic material.

Periodate Oxidation of Methyl 3-Hydroxyethyl- β -D-glucoside

A sample of the methyl 3-hydroxyethyl- β -D-glucoside sirup weighing 0.1644 g. (0.00069 mole) was dissolved in 10 cc. of water in a 50 cc. volumetric flask. Fifteen cc. of a 0.11 M

solution of sodium metaperiodate was added and the solution was quickly made up to the mark with distilled water, shaken vigorously and kept at 25°. Aliquots (5 cc.) were removed from the flask at intervals, diluted to 10 cc. and mixed with 1.5 g. of sodium bicarbonate. Ten cc. of 0.1 N sodium arsenite and one cc. of 20 per cent potassium iodide solutions were added. After standing 10 minutes at room temperature the solutions were titrated with standard 0.0958 N iodine solution. From the iodine titre and a suitable blank, the amounts of periodate consumed were calculated and recorded in Table IX. This estimation is described in detail by Jackson (50).

TABLE IX

CONSUMPTION OF PERIODATE
BY METHYL 3-HYDROXYETHYL- β -D-GLUCOSIDE

Time (hrs.)	cc. of 0.0958 N Iodine Solution Consumed	Moles of Periodate Consumed per Mole of Glucoside
0	0	0
.75	0.63	0.438
1.10	0.66	0.458
2.55	0.83	0.575
5.67	0.93	0.645
12.0	1.08	0.749
23.0	1.36	0.944

Hydrogenation of Benzyl 3-Hydroxyethyl-β-D-glucopyranoside

A solution of 1.62 g. (0.00515 mole) of benzyl 3-hydroxyethyl-β-D-glucoside in 50 cc. of absolute ethanol containing 0.1 g. of palladium black, prepared according to Hartung (75), was shaken with hydrogen at 2 atmospheres pressure for 8 hours at room temperature (48)(76). During this time 0.0203 mole of hydrogen, equivalent to 3.96 moles of hydrogen per mole of glucoside, was absorbed while theory required 4.0 moles of hydrogen, one mole to cleave the glucoside and 3 moles to reduce the aromatic ring. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure, leaving 1.17 g. or a quantitative yield of a clear colorless sirup, 3-hydroxyethyl glucose. The sirup crystallized on standing, and after two recrystallizations from ethanol gave 0.1 g. of white cubes melting at 134-135° and strongly reducing to Fehling's solution.

Anal. Calcd. Alkoxyl, 19.64;

Found: Alkoxyl, 19.6, 19.4.

These pure crystals in aqueous solution exhibited mutarotation (Table X) from a calculated initial value of $[\alpha]_D^{20}$ +87.9 to an observed final value of +48.8° (C = 1.13). The high positive initial rotation indicated that the crystals were the α isomer (44). Rate constants were calculated from the mutarotation data using the equation

TABLE X

MUTAROTATION OF 3-HYDROXYETHYL- α -D-GLUCOPYRANOSIDE

T Time (mins.)	r Rotation (degrees)	$[\alpha]_D^{20}$ (degrees)	$k_1 + k_2$
0	1.984*	87.9*	...
12	1.87	83.0	.00507
17	1.78	79.0	.00316
25	1.71	75.9	.00404
34	1.64	72.8	.00453
42	1.61	71.5	.00426
57	1.49	66.2	.00520
91	1.37	60.8	.00501
116	1.29	57.2	.00523
169	1.20	53.2	.00525
240	1.15	51.2	.00495
335	1.11	49.2	.00562
620	1.10	48.8	...
1440	1.10	48.8	...

* extrapolated values

$k_1 + k_2 = \frac{1}{T} \log \left[\frac{r_o - r_\infty}{r - r_\infty} \right]$ which expressed the over-all rate of two opposing first order reactions as a function of r_o, the initial rotation; r_∞, the final rotation; and r, the rotation at any time T (77). The values of $k_1 + k_2$ calculated at various times were recorded in Table X.

V. Tosylation and Iodination of Methyl and Benzyl 3-Hydroxyethyl- β - D-glucopyranosides

Esterification with one Mole of Tosyl Chloride Followed by Acetylation

A solution of 1.90 g. (0.008 mole) of methyl 3-hydroxyethyl- β -D-glucoside in 9.0 cc. (0.112 mole) of dry pyridine, cooled to 0°, was mixed with 1.53 g. (0.008 mole) of pure tosyl chloride and the mixture was kept at 0° for 2 hours, being protected from moisture by a calcium chloride drying tube. An excess of acetic anhydride (10.5 cc., 0.112 mole) was added and the reaction mixture was allowed to stand at 21° overnight. The resulting mixture was then poured into 200 cc. of ice water and the water was extracted three times with chloroform. The combined extracts were washed successively with dilute aqueous sulfuric acid, aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. The chloroform was removed by distillation under reduced pressure, leaving the product as a straw colored sirup, (Product D, Table XI) weighing 3.80 g.

Another portion of methyl 3-hydroxyethyl- β -D-glucoside was tosylated and acetylated by the procedure just described except that the temperature during the 2-hour tosylation period was kept at 21°, (Product E, Table XI). Similar reactions were carried out on the corresponding benzyl glucoside derivative at tosyl-

ation temperatures of both 0 and 21° (Products G and H, Table XII). All products were clear straw colored sirups and their yields and their analyses, recorded in Tables XI and XII, approximate those calculated for the corresponding triacetyl tosyloxyethyl glucosides.

Iodination of Tosylation-Acetylation Products

One-gram samples of methyl triacetyl tosyloxyethyl glucoside (Product D, Table XI) and the corresponding benzyl derivative (Product H, Table XII) were iodinated by treating each with one gram of sodium iodide in 20 cc. of dry acetone for 5 hours at reflux temperature. In each case the reaction mixture was poured into 300 cc. of water and the water was extracted with ether. The ether extract was washed with dilute aqueous sodium thiosulfate to remove free iodine, then with water. After drying over anhydrous sodium sulfate the ether was evaporated under reduced pressure. The iodinated product from D was a clear straw colored sirup weighing 0.62 g.

Anal. Calcd. for methyl triacetyl 3-iodoethyl glucoside I, 26.8.

Found: I, 15.2, 15.3.

The product from H was a similar sirup weighing 0.89 g.

Anal. Calcd. for benzyl triacetyl 3-iodoethyl glucoside I, 23.1.

Found: I, 10.9, 10.9.

These preliminary experiments indicated that more severe conditions were necessary for complete iodination of

TABLE XI

DATA CONCERNING TOSYLATION-ACETYLATION OF METHYL 3-HYDROXYETHYL- β -D-GLUCOPYRANOSIDE

Product	Temp. (°C.)	Yield (%)	Acetyl (%)	S (%)	Cl (%)	Alkoxyl (%)	$[\alpha]_D^{20}$
D	0	91.9	26.1 25.8	5.55 5.83 5.76	1.68 1.89 1.82	17.9 17.8	-5.66
E	21	83.6	27.8 27.4	4.91 5.05 5.05	4.43 4.57	17.5 17.8	-5.41
Theory for monotosyl-triacetyl derivative			24.93	6.19	0.00	17.0	...

TABLE XII

DATA CONCERNING TOSYLATION-ACETYLATION OF BENZYL 3-HYDROXYETHYL- β -D-GLUCOPYRANOSIDE

Product	Temp. (°C.)	Yield (%)	Acetyl (%)	S (%)	Cl (%)	Alkoxyl (%)	$[\alpha]_D^{20}$
G	0	92.0	22.1 21.9	4.92 5.00 5.14	1.53 1.58 1.54	7.70 7.90	-43.6
H	21	87.0	21.8 22.1	4.66 4.82	2.14 2.30 2.09	7.88 7.82	-44.1
Theory for monotosyl triacetyl derivative			21.95	5.40	0.00	7.41	...

these compounds. One-gram portions of each of the methyl triacetyl tosyloxyethyl glucosides, D and E and the corresponding benzyl derivatives G and H were dissolved in separate 20 cc. portions of dry acetonylacetone with 1.0 g. of dry sodium iodide and kept at 110-115° for 2 hours. The products were isolated by the method just described. D and E gave clear amber sirups while G and H gave crystalline material which proved to be the same compound in both cases. After three recrystallizations from ethanol, the white needles melted sharply at 114-115°. Analyses of this crystalline compound agreed with those calculated for benzyl triacetyl 3-iodoethyl- β -D-glucoside and are recorded along with analyses of the other iodination products in Table XIII.

Esterifications Employing Excess Tosyl Chloride

Methyl 3-hydroxyethyl- β -D-glucoside (1.96 g.) (0.0082 mole) was dissolved in 26.45 cc. (0.328 mole) of anhydrous pyridine then 18.72 g. (0.098 mole of tosyl chloride was added. The resulting solution was kept at room temperature for 8 days, protected from moisture during this time by a calcium chloride drying tube. When the reaction mixture was poured into 200 cc. of ice water, the crude product separated as a tan semi-solid mass. The entire aqueous mixture was thrice extracted with chloroform and the combined extracts were washed thoroughly by shaking successively with dilute aqueous sulfuric acid, saturated aqueous sodium bicarbonate and twice with water. The chloroform solution was then decolorized with charcoal and dried

TABLE XIII

DATA CONCERNING IODINATION PRODUCTS

Starting Material	Time (hrs)	Temp. (°C.)	Yield (%)	$[\alpha]_D^{20}$	Iodine % Found	Iodine % Calcd.
Methyl triacetyl tosyloxyethyl glucosides						
D	2	110-115	66	+22.0	23.4 23.8	26.8
D	5	56-60	..	..	15.2 15.3	26.8
E	2	110-115	83	+20.2	23.4 24.3	26.8
Benzyl triacetyl tosyloxyethyl glucosides						
G(a)	2	110-115	90	-26.8	22.7	23.1
H(a)	2	110-115	98		22.8	
H	5	56-60	..	..	10.9 10.9	23.1

(a) G and H both gave the same crystalline product

over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure, leaving 4.5 g. of a viscous amber sirup containing a small amount of crystalline material. The product was dissolved in hot ethanol and seeded with some of the crystals. As the solution cooled 0.33 g. of white needles separated which were removed by filtration. The filtrate when evaporated to dryness <u>in vacuo</u> yielded 4.1 g. of a clear amber glass (Product F, Table IV) which was optically inactive and had the following analyses.

<u>Anal</u>. Calcd. for methyl tetratosyl 3-hydroxyethyl glucoside; S, 15.0; Cl, 0.00; Alkoxyl, 10.3.

Found: S, 13.5, 13.6, 13.6; Cl, 1.95, 2.02; Alkoxyl, 4.46, 4.30.

The crude crystalline fraction was found to melt at 175-178°. After recrystallization from ethanol the melting point was 182-183° and the specific rotation $[\alpha]_D^{20}$ in chloroform -7.8° (C = 1.59). Sulfur analyses on these crystals showed 15.9, 15.8 and 15.7 per cent sulfur, values which agreed very well with 15.8 per cent sulfur calculated for methyl tetratosyl β-D-glucoside. However the melting point of this compound is recorded (36) as 177-178° and the specific rotation as -6.6° in an unspecified solvent. An authentic sample of methyl tetratosyl β-D-glucoside was prepared by the method of Oldham and Rutherford (36) and found to melt at 177-178° after recrystallization from ethanol. Further recrystallization from an ethanol-chloroform (9:1) mixture, however, raised the melting point to 182-183° and the specific rotation of this purified material was

found to be $[\alpha]_D^{20}$ in chloroform -7.5° (C = 1.46). A mixed melting point of this authentic methyl tetratosyl β -D-glucoside with the unknown crystals showed no depression.

Benzyl 3-hydroxyethyl-β -D-glucoside (2.65 g., 0.0084 mole) was tosylated exactly as described above for the corresponding methyl derivative. The product was a clear straw colored glass (Product I, Table IV) weighing 5.96 g. and having a specific rotation $[\alpha]_D^{20}$ in chloroform -4.2° (C = 2.74).

Anal. Calcd. for benzyl tetratosyl 3-hydroxyethyl glucoside;
S, 13.8; Cl, 0.00; Alkoxyl, 4.73.

Found: S, 12.08, 12.24, 12.13; Cl, 1.88, 1.95; Alkoxyl, 1.57, 1.56.

Iodination of Tosylation Products

One-gram portions of the glassy products (F and I, Table IV) from the tosylation of the methyl and benzyl 3-hydroxyethyl- β -D-glucosides were iodinated by heating under reflux in 20 cc. of acetone with 1.0 g. of sodium iodide for 5 hours. The products, isolated by the method described for previous iodinations, yielded dark yellow viscous sirups. That from the methyl glucoside derivative weighed 0.75 g. and contained 26.2 per cent of iodine while the figures for the corresponding benzyl derivative were 0.93 g. and 38.8 per cent respectively.

VI. Investigation of the Stability of a Freshly Prepared Hydroxyethylcellulose

An hydroxyethylcellulose was prepared from extracted cotton linters by the method of Shorigin and Rymaschewskaja (78), involving the use of alkali cellulose and an acetone solution of ethylene oxide at 30°. The product contained 18.7 per cent of hydroxyethyl groups (analysis 18.7, 18.6) or an hydroxyethyl substitution of 0.85 per glucose residue. It was soluble in 2 per cent aqueous sodium hydroxide and was highly swollen by, but not completely soluble in, water even after several cycles of freezing and thawing. The derivative was stored at room temperature in a glass stoppered bottle in the presence of light and air. One-gram samples of this preparation were analyzed for peroxides at regular intervals according to the method of Liebhafsky and Sharkey (70) described in the section concerning analytical methods. The analyses were carried out over a period of 5 months and in all cases the test was negative. Not even the small amount of iodine liberated in the reagent blank was found in the hydroxyethylcellulose test.

VII. Peroxide Consumption by Hydroxyethylcelluloses

An hydroxyethylcellulose containing 29.0 per cent (Anal. 29.2, 28.8) of hydroxyethyl groups (substitution 1.5) was prepared by a slight modification of the method of Shorigin and Rymaschewskaja (78). In this case the alkali cellulose was treated with ethylene oxide in acetone solution for 118 hours at 5°. The product was soluble in a 2 per cent solution of sodium hydroxide and was very highly swollen by water. Ten grams of this freshly

prepared derivative was mixed with 390 cc. of water to form a very highly swollen transparent gel. Ten cc. of a dilute solution of hydrogen peroxide was added to this gel. Samples of the resulting mixture, each containing 1 g. of hydroxyethylcellulose, were analyzed at intervals by the method of Liebhafsky and Sharkey (70), the liberated iodine being titrated with 0.0102 N sodium thiosulphate. The results are recorded in Table XIV and Figure 6 together with those for a commercial water-soluble hydroxyethylcellulose (Cellosize WS-100) and a blank containing water and hydrogen peroxide only.

TABLE XIV

PEROXIDE CONSUMPTION BY HYDROXYETHYLCELLULOSES

Time (hrs.)	Milli-equivalents of Peroxide Consumed per Gram		
	Cellosize WS-100	Freshly Prepared Hydroxyethylcellulose	Blank
0	...	...	...
0.5	.0214	.00204	...
1.5	.0336	.00306	...
3.0	.0367	.0102	...
8.0	.0347	.0061	.0020
23.0	.0510	.0163	...
48.0	.0632	.0153	.0071
117.	.250	.0204	.0163
295.	.346	.149	.0224

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

All of the substances noted below, save the starting material diacetone-D-glucose, were new and all gave satisfactory analyses unless otherwise stated.

(1) Suitable conditions were eventually found to condense ethylene oxide with 1,2:5,6-diisopropylidene glucofuranose (diacetoneglucose) and to separate the resulting 3-hydroxyethyl derivative by fractional distillation. 3-Hydroxyethyl diacetone-glucose was a sirup, b.p. 135-140°/0.07 to 0.09 mm. which probably retained 2 or 3% of diacetoneglucose. The 3-acetoxyethyl and 3-benzoxyethyl derivatives were also sirups.

(2) Mild acid hydrolysis of 3-hydroxyethyl diacetoneglucose yielded an uncrystallized 3-hydroxyethyl glucose, but the phenylosazone was obtained crystalline, m.p. 163°. An indirect synthesis from the crystalline tetraacetate of benzyl 3-hydroxyethyl- β -glucopyranoside (see below) eventually yielded the α-isomer of 3-hydroxyethyl glucose in a crystalline condition, m.p. 134-135°. The substance had an initial rotation of approximately $[\alpha]_D^{20}$ +88° in water, and the kinetics of its mutarotation in water to the constant equilibrium value of $[\alpha]_D^{20}$ +49° resembled those of the mutarotation of glucose. A fermenting suspension of yeast appeared slowly to destroy 3-hydroxyethyl glucose.

(3) Acetylation of uncrystallized 3-hydroxyethyl glucose

with acidic catalysts produced more dextrorotatory, discolored liquid pentaacetates, but the more laevorotatory pentaacetates produced with basic catalysts were clear sirups. An uncrystallized, unstable, strongly dextrorotatory tetraacetyl -3-hydroxyethyl glucosyl bromide was produced from the last-named acetates by the action of hydrogen bromide in glacial acetic acid. Condensation of the glucosyl bromide with methanol and benzyl alcohol yielded a liquid acetylated methyl- β -glucoside, and a crystalline benzyl- β -glucoside acetate m.p. 113-114°. Deacetylation then gave the corresponding methyl and benzyl 3-hydroxyethyl glucosides but neither was obtained crystalline. The benzyl glucoside on hydrogenation over a palladium catalyst, however, yielded the crystalline sample of 3-hydroxyethyl glucose.

(4) Esterification with p-toluenesulfonyl chloride and pyridine tosylated the primary alcohol unit in 3-hydroxyethyl diacetoneglucose with unusual ease and speed, and the introduction of approximately one tosyloxy group into methyl or benzyl 3-hydroxyethyl- β -glucoside was likewise accomplished under unusually mild conditions. The latter compounds were not crystallized; neither were their triacetates, and analyses were lacking in accuracy. Drastic tosylations of the methyl and benzyl 3-hydroxyethyl glucosides, with excess reagent for days at room temperature as in tosylations of suitable cellulose derivatives yielded sirups whose analyses clearly showed that much of the hydroxyethyl units had been eliminated.

When heated with sodium iodide in a ketone solvent,

the primary toxyloxy groups in several of the above tosylated derivatives were replaced by iodine atoms in normal fashion and at rates in the expected range. One derivative, benzyl triacetyl -3-[illegible]iodoethyl- β -D-glucopyranoside, was obtained as pure crystals, m.p. 114-115°.

(5) The above work showed that the hydroxyethyl group in 3-hydroxyethyl glucose differed from most other substituents used in carbohydrate chemistry in that it was susceptible to the action of fermenting yeast, yielded black decomposition products with acidic reagents and was eliminated during prolonged tosylations. The latter observation rendered rather improbable an explanation advanced by an earlier worker for his observations on the tosylation of an hydroxyethyl cellulose. Although the spontaneous formation of peroxides was not observed in the present work, and the earlier observation to the same effect was confirmed for a specially prepared hydroxyethyl cellulose, the latter slowly consumed added hydrogen peroxide. The slight instability of the hydroxyethyl group toward another oxidizing agent, potassium periodate, was also noted.

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