

SELECTIVE SUBSTITUTION OF SUCROSE

by

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ABSTRACT

Detritylation of tri-O-trityl-penta-O-acetyl sucrose with catalytic hydrogenolysis or graded hydrolysis with aqueous acetic acid gave in yields up to 60% a new crystalline penta-O-acetyl sucrose derivative. Methylation of the pentaacetate with the Purdie reagents, followed by deacetylation and chromatographic purification gave a sirupy tri-O-methyl sucrose which was shown to be 1', 4, 6' -tri-O-methyl sucrose by periodate oxidation and by hydrolysis to equal parts of 4-O-methyl-D-glucose and 1, 6-di-O-methyl-D-fructose. The glucose derivative was identified by paper chromatography, specific rotation and by conversion to the known, crystalline osazone, and the structure of the new sirupy 1, 6-di-O-methyl-D-fructose was established by analysis, periodate oxidation, paper chromatographic behavior and the specific rotation.

Deacetylation of tri-O-trityl-penta-O-acetyl sucrose gave an amorphous tri-O-trityl sucrose and methylation of this compound with the Purdie reagents, followed by detritylation with aqueous acetic acid gave a sirupy penta-O-methyl sucrose derivative, which was identified as 2, 3, 3', 4, 4' -penta-O-methyl sucrose by hydrolysis to equal parts of the known 2, 3, 4 -tri-O-methyl-D-glucose and 3, 4 -di-O-methyl-D-fructose.

It was therefore established that the trityl groups in the original tri-O-trityl-penta-O-acetyl sucrose

occupied the three primary positions (1', 6 and 6') in the sucrose molecule and that acetyl migration from C₄ to C₆ in the glucose moiety had occurred during the synthesis of the tri-O-methyl sucrose.

Vinylation of 1: 2 -3: 4-di-O-isopropylidene-D-galactose with vinyl acetate after the method of Adelman gave after catalytic hydrogenation followed by removal of the acetone groups a 0.7% yield of sirupy 6-O-ethyl-D-galactose. The new galactose derivative was identified by comparison with an authentic sample synthesized by direct ethylation of 1; 2 -3: 4 -di-O-isopropylidene-D-galactose. Preliminary studies of the vinylation of the new crystalline penta-O-acetyl sucrose are reported.

The action of Dowex I on several acetates of non-reducing carbohydrates was found to result in deacetylation in nearly quantitative yields.

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GEORGE GORDON McKEOWN

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The action of Dowex I. on several acetates of non-reducing carbohydrates was found to result in deacetylation in nearly quantitative yields.

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INTRODUCTION

The object of this research was, in the larger view, to contribute toward the bringing together of sucrose as an inexpensive, abundantly available, pure organic chemical, and the vigorously expanding chemical industry as a potentially vast consumer. Sucrose is produced on a scale of tens of millions of tons per year in a crystalline form of unrivalled purity for an industrial product. It has been calculated that the production could be practically trebled in a relatively short period of time if the occasion demanded and indeed international agreement has been necessary to curtail production in order to avoid the economic difficulties resulting from a surplus. After many years of research no outlet of any importance other than its use as a food has been discovered for sucrose. If such an outlet could be developed the world's supply of utilizable carbon could be vastly increased. Our present source of utilizable carbon is lodged primarily in the diminishing assets, coal and oil. As these resources become exhausted, the perennially renewed products of plants such as sucrose will inevitably rise to prime importance.

In particular, two objectives were proposed for this research. The first of these was to carry out a precise study of the chemistry of sucrose: to prepare by unequivocal methods specifically substituted derivatives of sucrose and to thoroughly characterize such derivatives. Most of the previously

reported derivatives of sucrose have been mixtures of sometimes highly doubtful composition. The second objective was to investigate the usefulness of a new method of preparing vinyl ethers as applied to the carbohydrate field. The standard method for preparing vinyl ethers involves harsh reaction conditions not compatible with sensitive, complex substances such as carbohydrates. The new method on the other hand offered the promise of a mild route to a vinyl ether. It was desired to test the value of the new method and if possible to prepare a selectively substituted vinyl ether of sucrose.

Since the eight reactive centers on the sucrose molecule are hydroxyl groups, three of which are primary, the proposed plan for preparing partially substituted derivatives was to first block the primary positions with trityl groups (trityl chloride(triphenylmethyl chloride) has been shown to react preferentially with primary hydroxyl groups), then acetylate or etherify the remaining positions and finally to remove the trityl blocking group. By this route, one could theoretically prepare numerous selectively substituted penta-O-acyl-and alkyl - sucrose derivatives.

The project was begun in this laboratory in 1953, under the direction of Dr. L.D. Hayward, by another worker, Mr. R.S.E. Serenius, who succeeded in preparing a key derivative,

tri-O-trityl-penta-O-acetyl sucrose in a pure, crystalline form.

Serenius also initiated studies on the detritylation of this compound.

HISTORICAL INTRODUCTION

The sugar cane seems to have originated in North East India, in particular Bengal (1). Probably sugar was first consumed by chewing the canes or drinking the pressed juice (2), however, it was known around 300 A.D. in certain parts of India, how to prepare solid cane sugar, at least for medical purposes (3). The Arabs on conquering Iraq around 640 A.D. were introduced to sugar and planted cane in Egypt (4) and later over North Africa, Sicily and Spain (5). In 1493, Columbus brought sugar cane from the Canary Islands to San Domingo (6). In America, because of favorable climatic conditions, the cultivation of cane spread rapidly and sugar grew into a world-wide commercial article (7).

Sucrose has been found to occur almost universally throughout the plant kingdom in the leaves, roots, seeds, juices, flowers and fruits of plants. Sucrose was reported in all of the 281 species of phanerogams studied by Bourquelot and his associates (8). Commercially, the principal sources are the sugar cane which contains about 12 - 18% sucrose and the sugar beet which contains about 12 - 17%.

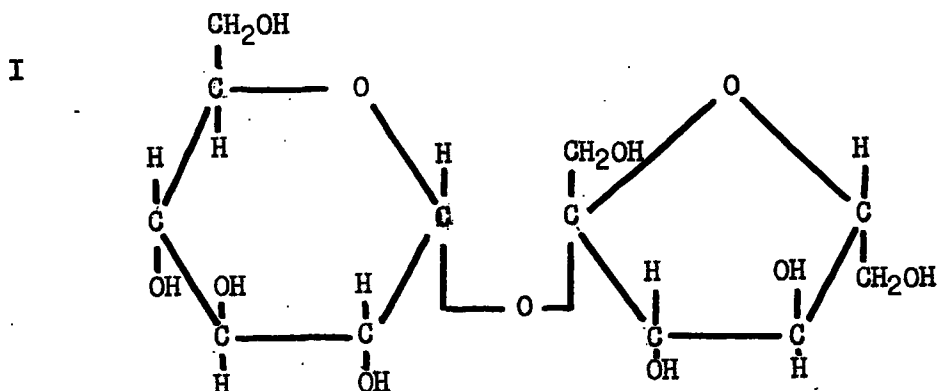
Sucrose is the most abundant fine organic chemical produced today, on a scale of tens of millions of tons

per year (9). In 1948, the world's production was 32 million long tons of which approximately two-thirds came from sugar cane and the remainder from sugar beets. The Americas produced more than a third of this total (10).

The consumption of sucrose is unfortunately limited almost entirely to its use as a food (11) and as the per capita consumption (about 100 pounds per year) is surprisingly constant production must be curtailed to just meet the demand. In recent years there have been increasing efforts to find and develop new uses for this abundant natural product. A few of the types of investigation now in progress are : the transformation of sucrose into useful products by the chemical processes of oxidation, reduction, acid transformation and alkaline degradation; the production of useful derivatives of sucrose itself; and the conversion of sucrose into other products by fermentation processes (12).

The determination of the structure and configuration of sucrose (I) was a monumental task which extended over more than a century and involved contributions from such noted workers as Lavoisier, Dumas, Gay-Lussac, Liebig, Fischer, Raoult, Kiliani, Hudson, Haworth, Purdie, Irvine, Hirst, Purves and many others. Although the structure and configuration of sucrose was

established with considerable certainty by 1934 (13), it was not until 1953 that the first chemical synthesis of sucrose was achieved by Lemieux and Huber (14). Their accomplishment marked a milestone in the history of carbohydrate chemistry.



Sucrose is a non-reducing disaccharide composed of an α -D-glucopyranose residue and a β -D-fructofuranose residue united through a double glycosidic linkage. The compound possesses eight reactive centers; the three primary and five secondary hydroxyl groups. As a consequence of the double glycosidic linkage and the lability of the furanose ring structure of the D-fructose moiety, sucrose is highly sensitive towards acid hydrolysis. Thus the ease of acid hydrolysis is approximately 1500 times greater for sucrose than for any other disaccharide (15, 16). This fact may well account for the scarcity of derivatives of sucrose. The molecule is very stable to alkali as is shown by

the fact that methylation of sucrose takes place in good yield in a solution of 40% sodium hydroxide (17). Since sucrose contains only hydroxyl groups as reactive centers, the only possible derivatives are esters, ethers and (perhaps) acetals.

A list of the reported derivatives of sucrose is given in TABLE I. From a consideration of the methods of preparation (non-selective partial acylation, non-selective partial etherification) of the majority of the partially substituted derivatives it becomes obvious the products are of necessity complex mixtures. Furthermore, doubt must shadow the authenticity of any derivative prepared by means of acid catalysis in view of the known sensitivity of sucrose toward acid hydrolysis. Some examples are the preparation of the diethylidene derivative by the action of acetaldehyde and sulfuric acid on sucrose, and of the octanitrate derivative by mixed nitric and sulfuric acids. In all fairness, however, it should be pointed out that in most cases the authors neither claimed nor implied homogeneity for their products. Of the total number of derivatives, possibly only four can be described as being adequately characterized homogeneous substances: the octamethyl, the octaacetyl, the trimethylpentaacetyl and the tritritylpentaacetyl derivatives. The preparation of the two last mentioned derivatives along with tritrityl sucrose will be described below in some detail as they have a direct bearing on the present research.

TABLE IFUNCTIONAL DERIVATIVES OF SUCROSE

<u>Derivative</u>	<u>m.p.</u>	$\left[\alpha\right]_{\text{D}}^{\text{T}}$	<u>Analytical data</u>
diethylidene (18)	sirup		
octamethyl (17)	sirup;b.p. 115°C/ 10 ⁻³ mm.	$\left[\alpha\right]_{\text{D}}^{+70.1^{\circ}}$	Calc. C,52.85, H,8.43; found C,52.76, H,8.55; Calc. OCH ₃ , 54.62; found 54.78; acetyl content after acety- lation 0.07
heptamethyl (19)			
trimethylpenta- acetyl (20)	glass	$\left[\alpha\right]_{\text{D}}^{28} + 52^{\circ}$	
dibenzyl (21)	amorphous		(Calc. C,59.77, H,6.51; found C, 59.73, H,6.14
pentabenzyl (21)	oil		Calc. C,71.21, H,6.56; found C,70.09, H,6.53
Hexabenzyl (22)	oil		
heptabenzyl (22)	oil		
octabenzyl (22)			
benzyl- acetyl (22)			

<u>Derivative</u>	<u>m.p.</u>	$\left[\alpha \right]_D^T$	<u>Analytical data</u>
pentabenzoyl (23)	amorphous		
hexabenzoyl (23)	amorphous		
octabenzoyl (24)	60-63°C (+2 moles of CCl ₄) crystalline	$\left[\alpha \right]_D^{+32.6^\circ}$ with 2 CCl ₄ $\left[\alpha \right]_D^{+40.6^\circ}$ without CCl ₄	CCl ₄ in crystals cont'g 2 moles of CCl ₄ : Calc. 20.75, found 22.56, 18.83. In solvent free material, calc. C69.50, H, 4.63; found C69.57, H, 4.90
octakis- (4-bromo- benzoyl) (25)	114-117°C amorphous		
octakis- (4-nitro- benzoyl) (26)	decomp. 150°C amorphous		
octacinnamoyl (27)	87-88°C amorphous		
octanitrate (28)	85.5°C crystalline	$\left[\alpha \right]_D^{20} +55.9^\circ\text{C}$	
sulfuric acid (29)	amorphous		
phosphoric acid (30)	amorphous		
monacetyl (31)	amorphous		
tetraacetyl (31)	amorphous		
heptaacetyl (31)	amorphous		

<u>Derivative</u>	<u>m.p.</u>	<u>$[\alpha]_D^T$</u>	<u>Analytical data</u>
octaacetyl (32)	69-70°C; 75°C; 87°C; poly-morphous, crystalline	$[\alpha]_D^{+59.5^\circ\text{C}}$	
pentaallyl (33)	oil		calc. C59.59, H 7.74; found C59.21, H 7.58.
heptaallyl (34)	oil bip. 190-92°C/5u		calc. allyl 46.2 found allyl 44.3
octallyl (34)	oil		calc. allyl 49.6; found allyl 48.5
-methallyl (34)			
-chloroallyl (34)			
acetyl- allyl (35)			
ethyl- allyl (35)			
bis-(2-hydroxy- ethyl) (36)	215°C crystalline	$[\alpha]_D^{25+38.7^\circ}$	
octamesyl (37)	86-94°C amorphous	$[\alpha]_D^{30+43.7^\circ}$	calc. C24.8, H 3.93S26.5; found C24.7, H 3.92, S26.2
octatosyl (37)	82-86°C amorphous	$[\alpha]_D^{25.9+41.78^\circ}$	calc. C51.84, H4.45, S 16.27; found C51.4, H 4.49, S 16.2
1',6', 6'- tritosyl- 2,3,3',4,4'- pentaacetyl (37)	58.5-61°C amorphous	$[\alpha]_D^{24.9+53.3^\circ}$	calc C50.86, H4.93, S 9.46; found C51.0, H 5.24, S 9.35

<u>Derivative</u>	<u>m.p.</u>	<u>$[\alpha]_D^T$</u>	<u>Analytical data</u>
tritrityl (38)	127-29°C amorphous	$[\alpha]_D^{23+43.9^\circ}$	calc. C 77.49, H 6.04; found C 77.07, H 6.19
tritrityl- pentaacetyl (39)	232.5-234. 5°C crystalline	$[\alpha]_D^{17+68.9^\circ}$	calc. trityl 56.6; found trityl 56.7; calc. acetyl 16.8; found acetyl 16.8
1', 6, 6'- tritosyl (37)	66-69°C amorphous		calc. C 49.2 H 4.97 S 11.94; found C 48.8, H 4.89, S 12.4

In 1935, E.G.W. Percival reported the preparation of 1', 6, 6' -tri-O-methyl-penta-O-acetyl sucrose (20). An addition compound of sucrose and potassium hydroxide was prepared ($C_{12}H_{22}O_{11} \cdot 3KOH$) which was methylated with dimethyl sulfate and then acetylated to give a non-reducing colorless glass, $[\alpha]_D^{20} = +52^\circ$ ($c = 1$ in acetone) which analysed correctly for a tri-O-methyl-penta-O-acetyl sucrose. After deacetylation and hydrolysis, a sirupy mixture of methylated sugars was obtained, $[\alpha]_D^{20} = +19^\circ$ ($c = 1$ in water). The mixture was treated with methanol and hydrogen chloride and the product acetylated and distilled. Two apparently homogeneous fractions were obtained: (a) bath temperature 146°/0.04 mm., $n_D^{18} 1.4475$, $[\alpha]_D^{21} = +24^\circ$ ($c = 1$ in chloroform) which

analysed correctly for a dimethyl methyl glycoside diacetate, and
 (b) bath temperature 170-180°/0.03 mm., n_D^{20} 1.4510, $[\alpha]^{21}_D$ = +33.0°
 (c = 1.5 in chloroform) which analysed correctly for a mono methyl
 methyl glycoside triacetate.

A portion of (a) was deacetylated and hydrolysed, during which period the optical rotation of the solution fell only slightly, to give a product which failed to give a crystalline osazone on treatment with phenylhydrazine and acetic acid. Another sample of fraction (a) was methylated with dimethyl sulfate and alkali to give tetra-O-methyl-methyl-D-fructofuranoside which was characterized by conversion by direct oxidation with nitric acid into crystalline, 2, 3, 4, 6-tetra-O-methyl-D-fructofuronamide.

Another portion of fraction (a) was oxidized directly with nitric acid to yield a lactol acid containing only one methoxyl residue. Oxidation of this product yielded 5-methyl- γ -D-arabonolactone.

The identity of fraction (b) was established by methylation and hydrolysis to crystalline 2,3,4,5-tetra-O-methyl-D-glucose and by hydrolysis to 6-O-methyl-D-glucose which was identified as its crystalline osazone.

In 1929, K. Josephson reported the preparation of tri-O-trityl sucrose and tri-O-trityl-penta-O-acetyl sucrose (38).

Cane sugar, 3.4 g., and 8.4 g. trityl chloride in 50 ml. dried pyridine was heated for 2 hours on the steam bath. The solution was then poured into ice-water to precipitate a solid product which after drying weighed about 10 g. Purification was achieved by several precipitations from alcohol with water and finally by crystallization from ethyl acetate and petroleum ether: m.p. 127-129°; $[\alpha]_D^{23} = +43.4^\circ, +44.3^\circ$ (c = 2.44, 1.58 in alcohol); carbon hydrogen analysis, found c = 77.07, H = 6.19, calculated for $C_{69}H_{64}O_{11}$, c = 77.49, H = 6.04. Tritritylsucrose, 1 g., was dissolved in 4 ml. dried pyridine and 3 ml. acetic anhydride, let stand overnight at room temperature, then diluted with ice-water to yield a solid product which when air-dried weighed 1.05 g. This product was purified by a precipitation from alcohol with water and the dried product crystallized from absolute alcohol: the product "sintered at about 125-126°"; $[\alpha]_D^{23} = +57^\circ$ (c = 1.43 in chloroform); carbon hydrogen analysis, found c = 74.11, H = 5.91, calculated for $C_{19}H_{74}O_{16}$, c = 74.14, H = 5.83; trityl analysis, found 97% of theoretical.

In 1954, attempts to reproduce Josephson's results were made by R.S.E. Serenius and L.D. Hayward (39). These authors found that the tritylation of sucrose according to the method of Josephson gave an amorphous product which could not be crystallized. They succeeded, however, in preparing crystalline trityl-O-trityl-penta-O-acetyl sucrose by successive tritylation.

and acetylation in the same solution. A mixture of 1/10 mole of sucrose, 3/10 mole of trityl chloride and 50 g. Drierite in 6.4 moles of pyridine was heated with stirring for 3 hours at 75-80°C.

After standing overnight 3.2 moles acetic anhydride was added and the mixture again let stand overnight. Precipitation in ice-water gave an oil which was separated and washed then crystallized from tetrahydrofuran and ethanol: crude yield 30%; m.p. 215-217°C. After recrystallization to constant melting point, the compound which formed in colorless, hexagonal crystals melted at 232.5 - 234.5°C, $[\alpha]_D^{17} = +68.9^\circ$ (c = 2.449 in chloroform), showed on analysis an acetyl and trityl content correct for tri-O-trityl-penta-O-acetyl sucrose, and reduced Fehling's solution only after acid hydrolysis.

Serenius and Hayward found that detritylation of tri-O-trityl-penta-O-acetyl sucrose by the method of Helferich and Klein (40) caused extensive degradation of the parent molecule. Thus when 1 mole of tri-O-trityl-penta-O-acetyl sucrose in glacial acetic acid was treated with 3 moles of hydrogen bromide an immediate precipitation of trityl bromide occurred. The precipitate was filtered off, the filtrate diluted with chloroform and washed with water. Evaporation of the acid-free, dried organic layer yielded a brown sirup which was found to be strongly reducing toward Fehling's solution and which could not be induced to yield a crystalline non-reducing product.

More promising results were obtained by Serenius and Hayward with the catalytic detritylation technique of Micheel (41). Catalytic hydrogenolysis using platinum oxide or palladized charcoal catalyst was found to cause detritylation of tri-O-trityl-penta-O-acetyl sucrose with the formation of tri-cyclohexylmethane or tritane respectively. However, catalyst poisoning was found to be troublesome, causing the reaction to stop at a stage of partial detritylation.

To prepare a polymer of sucrose which is to contain the intact molecule, two general approaches are available. The first is condensation polymerization in which sucrose is either condensed with itself with loss of water or as is more feasible sucrose molecules are linked by means of an intermediate polyfunctional agent such as an aldehyde, or a polybasic acid. Numerous processes for preparing condensation polymers of sucrose are recorded in the literature (42) and according to the descriptions of the products in the patents, some were highly successful. However, commercial interests have apparently not been impressed since none of the processes has reached the production stage. The reason may be found in the fact that the sucrose molecule is highly sensitive to the action of heat and chemical reagents. Condensation polymerization is at best a vigorous process and would be certain to cause some degree of degradation with the inevitable consequence of discoloration and unpredictable variation in physical properties.

The second approach to the problem involves the preparation of a sucrose derivative substituted with groups capable of undergoing addition polymerization. This type of polymerization is a relatively mild process and should not cause any significant amount of undesirable side-reactions. Three types of suitable unsaturated sucrose derivatives would be: an acrylic ester, an allyl ether, or a vinyl ether. The preparation and polymerization of a pentamethacrylate of glucose (43) has been described but the methacrylation of sucrose has not yet been reported. Allyl and substituted allyl ethers of sucrose (33, 34, 35) were prepared and polymerized by Nichols and Yanovski of the Eastern Regional Research Laboratory of the United States Department of Agriculture. Tetra-O-vinyl- α -methyl-D-glucoside has been prepared (44) but no vinyl ether of sucrose has been reported.

Since 1937, the standard method of preparation of vinyl ethers has been that of Reppe (45). The method involves a reaction between an alcohol and acetylene under high pressure and high temperature under the influence of a strongly basic catalyst. The reaction has been applied with success to some of the more chemically-durable carbohydrate derivatives (46); for example, tetra-O-vinyl- α -methyl-D-glucoside mentioned above was prepared by this method.

A new method of vinylation which appeared to offer promise with alkali- and heat-sensitive compounds was

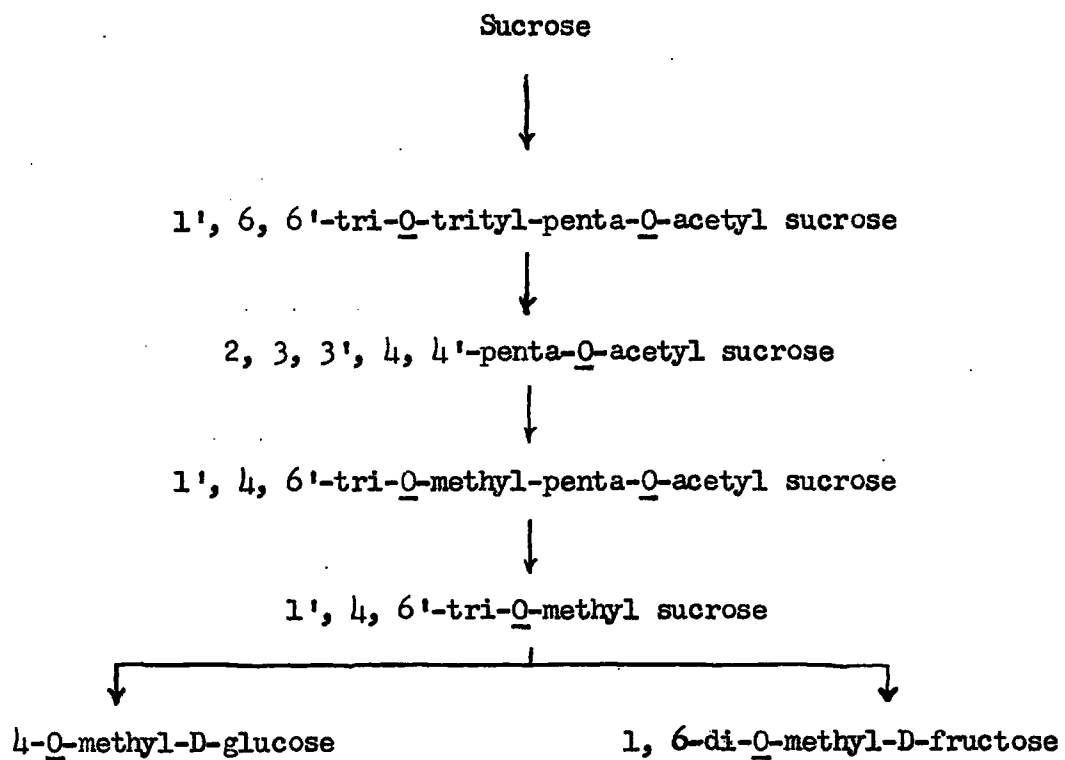
reported by Adelman in 1953 (47). He found that alcohols could be vinylated by treatment with vinyl acetate at low temperatures in the presence of catalytic amounts of mercuric acetate and sulfuric acid. A solution of methylglycolate in excess vinyl acetate was cooled to -22° and treated with a catalytic amounts of mercuric acetate and sulfuric acid for 2.5 hours. The reaction mixture was then neutralized, washed, dried and distilled to yield (40%) the vinyl ether of methyl glycolate. With other alcohols studied, the yields of the corresponding vinyl ethers were lower: ethanol 8%, tetrahydrofurfuryl alcohol 25%, 1,5-pentanediol 30%.

In 1955, Adelman reported on a similar type of vinyl ether preparation, transesterification between a vinyl ether and an alcohol occurring again at low temperature in the presence of mercuric acetate and sulfuric acid (48). For example, vinyl ethyl ether was prepared through transesterification between ethanol and vinyl butyl ether in 42% yield. Under similar conditions, however, reaction between tetrahydrofurfurylalcohol and vinyl ethyl ether yielded only 9% of the desired vinyl tetrahydrofurfuryl ether.

DISCUSSION OF RESULTS

The investigations in this thesis can be conveniently grouped into three phases: (i) the preparation of a penta-O-acetyl derivative of sucrose and subsequent transformations; (ii) the preparation of a penta-O-methyl derivative of sucrose and subsequent transformations; and (iii) a study of the Adelman reaction (47) as applied to partially substituted carbohydrate derivatives. In FIGURE I are presented the steps involved in the penta-O-acetyl **sucrose study**.

Attempts to reproduce Josephson's (38) reported synthesis of crystalline tri-O-trityl sucrose by direct tritylation of sucrose resulted in a colorless glass which was shown to be a complex mixture containing tri-O-trityl sucrose, products of lower trityl content, reducing sugar fragments and tritanol, from which the desired product could not be isolated. The dried mixture was of such high viscosity that it could be pulverized to a powder which had a softening point of about 125-30°C in the region of the melting point reported by Josephson for tri-O-trityl sucrose (127-129°C). Josephson reported an almost quantitative yield: in the many tritylations carried out in this research, hydrolysis of the glycosidic linkage was found to always accompany the substitution reaction and in no experiment was a yield higher

FIGURE I

than 50% achieved. Furthermore, 1', 6, 6'-tri-O-trityl sucrose has been prepared by an indirect route and the constants are not in agreement with those reported by Josephson.

Tri-O-trityl-penta-O-acetyl sucrose was prepared by successive tritylation and acetylation in the same solution (39, 40, 49). A 3:1 molar ratio of trityl chloride and sucrose was dissolved in anhydrous pyridine to give a colorless solution and heated to 65°C for 24 hours. Excess acetic anhydride was then added and the mixture let stand at room temperature for 7 hours. The now dark-red solution was poured into ice water causing the precipitation of a brown colored sirup which was separated, and crystallized from tetrahydrofuran-methanol to give a 50% yield of crude product. It was found that tritylation at a higher **temperature caused a** considerable degree of degradation; thus the reaction mixtures were dark colored, the mother liquors were strongly reducing toward Fehling's solution, the crude products had lower melting points and the crude yields varied from 10 to 50%.

A more convenient method of preparation was developed which gave consistently good yields of a high melting product. A 3:1 molar ratio of trityl chloride and sucrose in anhydrous pyridine was let stand at room temperature in a stoppered flask for 48 hours with occasional shaking. Excess acetic anhydride

was then added and the pale-yellow solution let stand overnight in the refrigerator. A quantity of crystalline material, m.p. 175-77°C, which separated out at this stage was shown to be the double salt of tritanol and pyridinium hydrochloride (50,51) (reported m.p. 172-4°C), and was removed by filtration. The pale-yellow filtrate was poured with stirring into ice water causing the precipitation of a colorless, amorphous solid which was recovered by filtration, washed, dried and crystallized from chloroform-methanol to give a 45% yield of colorless hexagonal crystals of tri-O-trityl-penta-O-acetyl sucrose of high purity. The mother liquor was shown to be reducing toward Fehling's solution.

Two methods of detritylating the tri-O-trityl-penta-O-acetyl sucrose were investigated: low pressure catalytic hydrogenolysis (39, 41) and graded hydrolysis with aqueous acetic acid (52, 53). Since the trityl ether (54) and the double glycosidic linkage of sucrose (15, 16) are both notably sensitive to acid hydrolysis it was expected that competitive reactions would occur.

In a series of runs, fairly pure tri-O-trityl-penta-O-acetyl sucrose (5 times recrystallized) in glacial acetic acid was hydrogenated in the presence of platinum oxide catalyst at 50°C. The reaction mixtures yielded varying quantities of tricyclohexylmethane melting at 57.5 - 58.0°C (55, 56),

partially detritylated starting material and a crystalline product melting at 218-19°C, $[\alpha]_D^{23} = +71.5^\circ$ ($c = 5.93$ in chloroform), which analysis indicated to be a partially saturated tri-O-trityl-penta-O-acetyl sucrose.

Under similar conditions, catalytic hydrogenolysis with palladized charcoal catalyst yielded varying quantities of partially detritylated material, unreacted tri-O-trityl-penta-O-acetyl sucrose and triphenylmethane.

Highly purified samples of tri-O-trityl-penta-O-acetyl sucrose which had been recrystallized 12 to 18 times alternately from chloroform - petroleum ether and chloroform-methanol were found to undergo complete detritylation giving yields of 27, 20, 38, 16, 23% (platinum oxide) and 20% (palladized charcoal) of crystalline penta-O-acetyl sucrose.

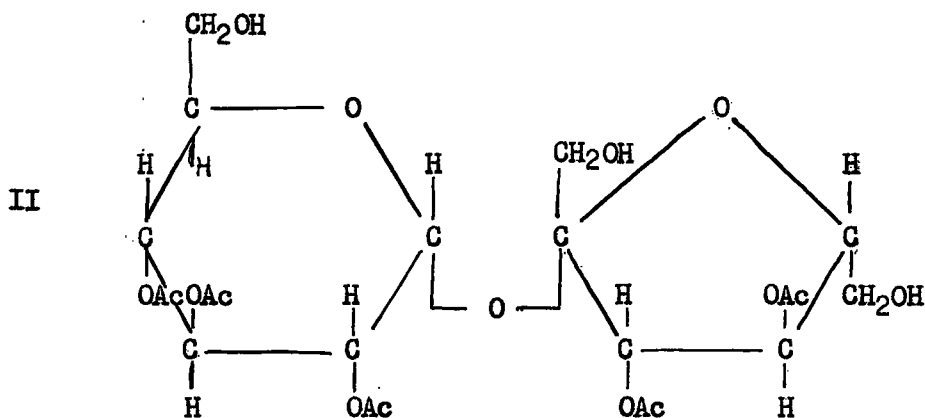
After recrystallization to constant melting point, the pure penta-O-acetyl sucrose which formed in colorless needle-like crystals melted sharply at 155-156°C, $[\alpha]_D^{22} = +22.0^\circ$ ($c = 3.1$ in chloroform), and showed on analysis the acetyl content of a dihydrate. The compound reduced Fehling's solution only after acid hydrolysis. Acetylation of the pentaacetate gave in good yield octa-O-acetyl sucrose which melted at 86-88°C and showed no depression in melting point on admixture with an authentic specimen.

A more convenient method of preparing the penta-
O-acetyl sucrose was found in a graded hydrolysis of the tri-O-
trityl-penta-O-acetyl sucrose with aqueous acetic acid. After
(52)
optimum conditions of acid concentration and reaction time had been
established, yields of 43-60% of crystalline penta-O-acetyl sucrose
which was identical with that obtained by the catalytic detrity-
lation were readily obtained. Tri-O-trityl-penta-O-acetyl sucrose
was dissolved in glacial acetic acid, the solution heated to boiling
and a small quantity of water introduced. After 30 minutes refluxing
the solution was cooled, the solvent evaporated and the residue
crystallized from chloroform-petroleum ether to give the desired
pentaacetate. Tritanol was recovered from the mother liquor.
That hydrolysis of the sucrose derivatives took place simultaneously
with the detritylation is shown by the facts that the mother
liquors were strongly reducing toward Fehling's solution, and the
yields of the pentaacetate depended markedly on the length of
reflux time. After 120 minutes of refluxing no pentaacetate could
be isolated from the reaction mixture. The graded hydrolysis
method was preferred over the catalytic detritylation since a
relatively less pure sample of starting material could be used,
the hydrolysis required but a fraction of the time needed for a
hydrogenation, and the use of an expensive catalyst was avoided.

A sample of the pentaacetate after being repeatedly

recrystallized from neutral solvents showed a double melting point of 152-3° and 155-6°. It is believed that some acetyl migration took place during the purification, since other samples when recrystallized from solvents acidified with a trace of glacial acetic acid did not show the double melting point.

If the two assumptions are made: (i) that tri-tylation took place at the primary hydroxyl groups of sucrose according to Helferich's Rule (57) which in fact has been demonstrated in this research and is described below, and (ii) that no acetyl migration took place during the detritylation, then the structure of the pentaacetate can be designated as 2, 3, 3', 4, 4',-penta-O-acetyl sucrose (II).



The Purdie methylation of the penta-O-acetyl sucrose was undertaken for several reasons. At the time, the vinylation of penta-O-acetyl sucrose was being studied and it was desired to find some means of determining the extent of vinylation, if any. It was tentatively planned to hydrogenate the vinylation product, deacetylate and analyse the product for O-ethyl sucroses by paper chromatography. The extent of the vinylation could then

qualitatively determined from the relative intensities of the spots for sucrose, mono-, di-, and tri-O-ethyl sucrose. However, since no information on the chromatographic behavior of any partially alkylated sucrose derivative was reported in the literature, it was planned to use the R_f values of the mono-, di-, and tri-O-methyl sucroses, which would be formed in the methylation, to serve as a guide.

The penta-O-acetyl sucrose also offered an opportunity to study acetyl migration which has been reported to occur during Purdie methylations (58, 59, 60, 61, 62, 63, 64, 65). From the preferred conformation of the sucrose molecule (66), it was predicted that migration would not occur in the nearly planar fructofuranose ring and therefore 1', 6' -O-methylation should occur in the fructose moiety whereas in the glucopyranose ring, acetyl migration was to be expected, either of the type C2→C6 or C4→C6 both having been reported in structurally analogous glucopyranose compounds (61, 62, 67, 68).

A third reason for the methylation was that it offered an excellent opportunity to prepare a new tri-O-methyl sucrose and, if the above predictions held, the previously unknown 1, 6-di-O-methyl-D-fructose.

The progress of the methylation was followed by deacetylating a portion of the product after each treatment with the reagents and analysing by means of paper chromatography. When

the paper chromatograms were developed with butanol-ethanol-water (5:1:4) (69) and sprayed with p-anisidine hydrochloride reagent (70), sucrose and its methyl ethers showed as bright yellow, U.V. fluorescent spots. The course of the methylation reaction is shown in TABLE II.

TABLE II

Progress of methylation of Penta-O-acetyl Sucrose as followed by
Paper Chromatography

No. of Methylations	Sucrose, R _F 0.04	Mono-O-methyl Sucrose, R _F 0.08	Di-O-methyl Sucrose, R _F 0.20	Tri-O-methyl Sucrose, R _F 0.40
1	distinct	distinct	-	-
2	faint	very distinct	distinct	-
3	-	distinct	distinct	faint
5	-	-	faint	distinct

After 5 treatments with the reagents, the product obtained was a colorless, viscous glass, $[\alpha]_D^{17} = +57.7^\circ$ (c= 3.72 in chloroform) which showed approximately the methoxyl and acetyl content of a tri-O-methyl-penta-O-acetyl sucrose. It was interesting to note that the rotation was in reasonable agreement with that reported by Percival for his 1', 6, 6' -tri-O-methyl-penta-O-acetyl sucrose (20). Despite repeated attempts over a period of six months, the product could not be induced to crystallize and no convenient chromatographic procedure could be found for further

purifying the high molecular weight, hydrophobic compound.

The methylated pentaacetate was therefore deacetylated in 90% aqueous methanol with Dowex I anion exchange resin to give a quantitative yield of a colorless, viscous sirup which was indicated by paper chromatography to be a mixture containing approximately 75% tri-O-methyl sucrose, 25% di-O-methyl sucrose and a trace of mono-O-methyl sucrose.

The mixture of sucrose-O-methyl ethers was separated by partition chromatography on a column of powdered cellulose using butanol-water as developer. The appropriate fractions were combined and evaporated to give 193 mg. of a di-O-methyl sucrose as a colorless, viscous glass and 472 mg. of a tri-O-methyl sucrose as a colorless viscous sirup. The latter compound, $[\alpha]_D^{24} = +67.6^\circ$ ($c = 1.74$ in water), on analysis showed the correct methoxyl content for a tri-O-methyl sucrose.

From the known preferred conformation of the sucrose molecule (66) it was predicted that methylation and deacetylation of penta-O-acetyl sucrose should give either 1', 2, 6' -, or 1', 4, 6' -, but not 1', 3, 6' - or 1', 6, 6' - tri-O-methyl sucrose. Confirmation of the prediction was provided by periodate oxidation of the tri-O-methyl compound. Whereas sucrose or 1', 6, 6' - tri-O-methyl sucrose should consume 3 moles of periodate with a production of 1 mole of formic acid, 1', 2, 6' - or

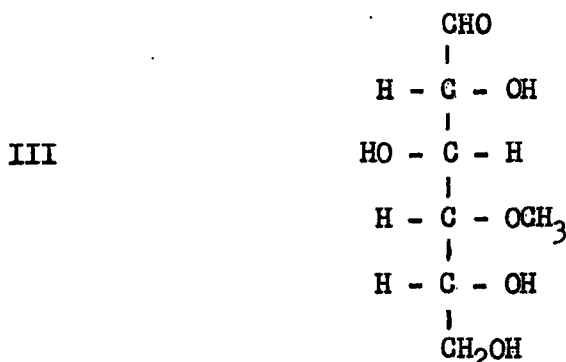
1', 4, 6'- tri-O-methyl sucrose should consume only 2 moles of periodate with no formic acid production and the 1', 3, 6' tri-O-methyl sucrose should consume only one mole of periodate with no formic acid.

A periodate oxidation was carried out on sucrose and after 24 hours, 3.1 moles of periodate were consumed with the formation of 0.61 moles of formic acid. These results are in good agreement with those of Flaury and Courtois (71). The tri-O-methyl sucrose, on the other hand consumed after 24 hours only 1.8 moles of periodate with the formation of no formic acid. These results indicate a 1', 2, 6', - or 1', 4, 6' - structure for the tri-O-methyl sucrose.

A sample of the sirupy tri-O-methyl sucrose was hydrolysed in aqueous acetic acid and the product separated on a cellulose column into two paper chromatographically homogeneous fractions which analysed correctly for a mono-O-methyl and a di-O-methyl hexose derivative.

The sirupy mono-O-methyl hexose was identified as 4-O-methyl-D-glucose (III) by the following evidence: The specific rotation, $[\alpha]_D^{24} = +61.2^\circ$ ($c = 1.428$ in water, equilibrium value), was in good agreement with previously reported values (72, 73). Paper chromatography revealed a single spot of hue and R_f value identical to that obtained with an authentic sample of 4-O-methyl-

D-glucose. The sirup did not crystallize on nucleation with 2-*, 3-, or 6-^{*}O-methyl-D-glucose. On treatment with phenylhydrazine and acetic acid the sugar yielded a crystalline osazone which melted correctly for 4-O-methyl-D-glucosazone and showed no depression in melting point on admixture with an authentic sample.

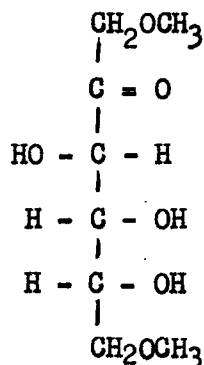


The structure of the liquid di-O-methyl hexose was established as that of the previously unreported 1, 6-di-O-methyl-D-fructose (IV) by the following evidence: substitution on the 6-position was indicated by the positive specific rotation, $[\alpha]_{\text{D}}^{24} = +17.4^\circ$ ($c = 1.843$ in water, equilibrium value). (All known 6-O-methyl fructose and therefore fructofuranose derivatives show a positive rotation (74) whereas fructose derivatives with a free 6-position show high negative rotations (74)). The

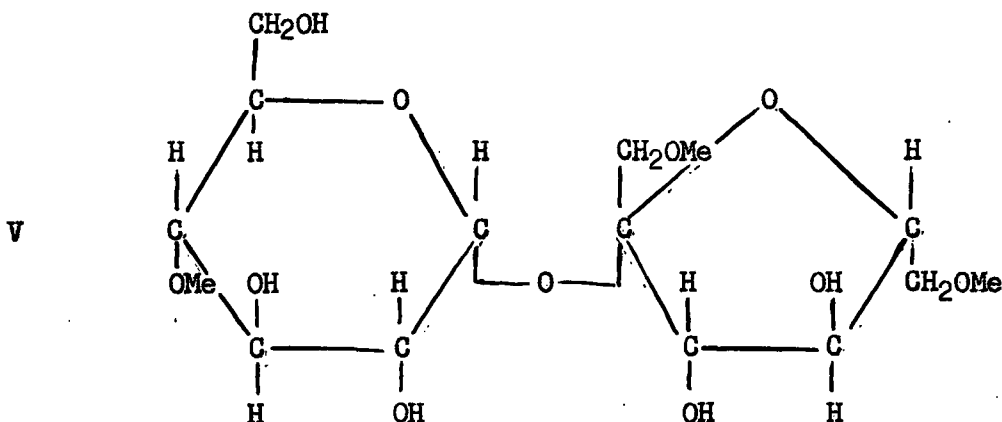
* Seed crystals of 2-O-methyl-D-glucose were supplied by Dr. M.L. Wolfrom of Ohio State University, and seed crystals of 6-O-methyl-D-glucose were supplied by Dr. Tore Timell, of McGill University. The author is appreciative of this courtesy.

sugar on treatment with phenylhydrazine and acetic acid in the usual manner failed to form an osazone. Paper chromatography (butanol-ethanol-water (5:1:4)) revealed a single spot of high R_f value (0.57) the color of which was characteristic of a ketose (70). (The R_f value found for 3, 4,-di-O-methyl-D-fructose was 0.51). A periodate oxidation of the sugar derivative revealed after 58 hours, a consumption of 3.2 moles of periodate, and the production of 1.71 moles of formic acid and no formaldehyde. These results are in harmony with the predicted behavior of 1, 6-di-O-methyl-D-fructose toward periodate oxidation.

IV

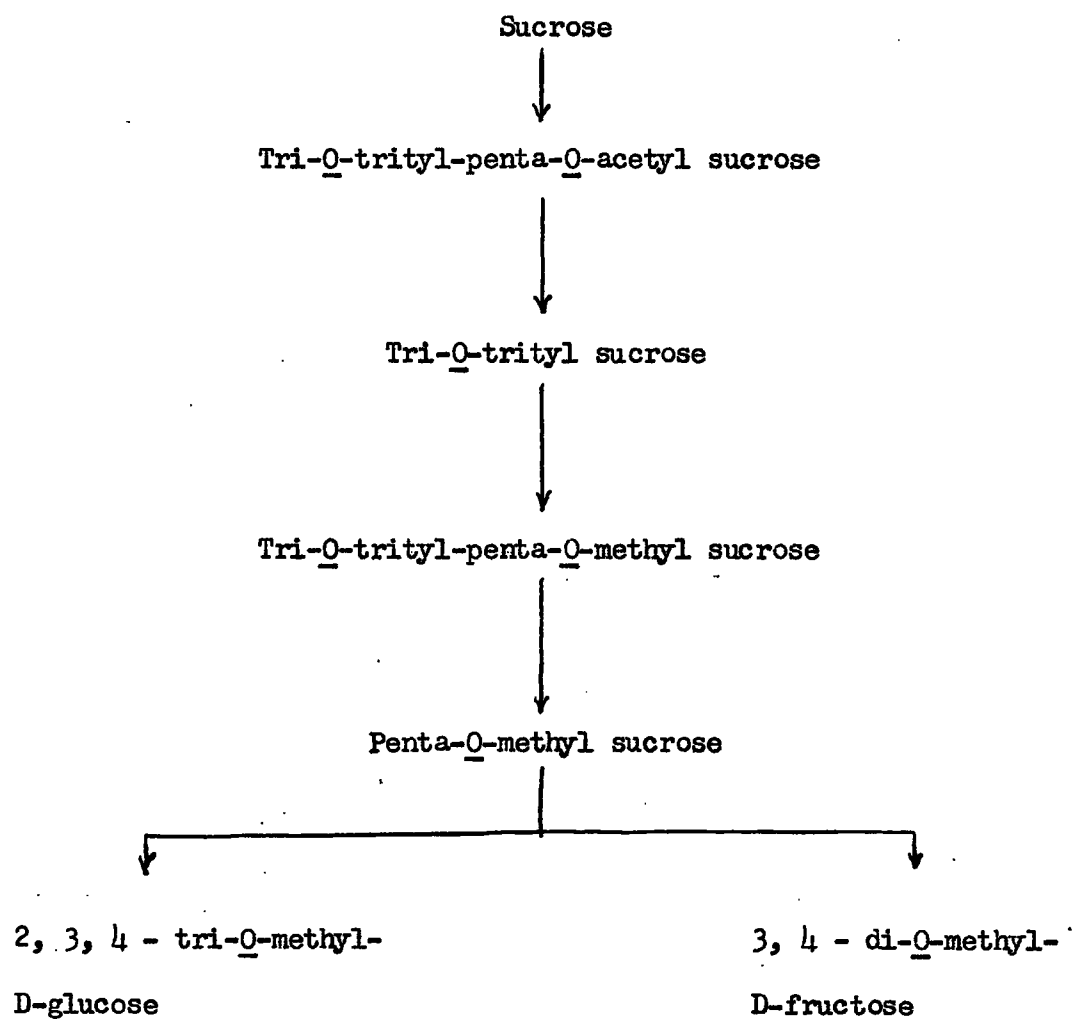


The foregoing evidence conclusively established the structure of the parent sucrose derivative as 1', 4, 6'-tri-O-methyl sucrose (V). Acetyl migration from C₄ to C₆ had occurred during the synthesis as predicted above.



In the second phase of this research a new penta-O-methyl sucrose was prepared and its structure established as outlined in FIGURE II.

The difficulties encountered in attempts to prepare tri-O-trityl sucrose by direct tritylation of sucrose have already been discussed. A convenient route to tri-O-trityl sucrose was found in the deacetylation of tri-O-trityl-penta-O-acetyl sucrose. The latter was prepared in pure crystalline form and deacetylated with sodium methoxide. The product obtained was a colorless glass, $[\alpha]_D^{22} = +14.7$ ($c = 3.3$ in chloroform), which was so viscous that it could be pulverized to a fine, white powder. The substance showed on analysis a trityl content which corresponded approximately to that calculated for a tetrahydrate of tri-O-trityl sucrose. It reduced Fehling's solution only after acid hydrolysis. Acetylation gave back tri-O-trityl-penta-O-acetyl sucrose in good yield. An attempt to detritylate a sample of the product by catalytic hydrogenolysis was unsuccessful. Catalyst poisoning as encountered in the tri-O-trityl-penta-O-acetyl sucrose study halted

FIGURE II

the reaction at an intermediate stage. Thus only a trace of sucrose was detected by paper chromatography of the reaction mixture.

Methylation of tri-O-trityl sucrose was undertaken for two principal reasons. A characterized, partially substituted sucrose derivative was desired which would be stable to alkali and hence suitable for future vinylation studies using the Reppe method; a penta-O-methyl sucrose possessing free primary hydroxyl groups should serve admirably for this purpose. Furthermore a tri-O-vinyl-penta-O-methyl sucrose **would be distillable and therefore easily purified**. The second objective was to establish unequivocally the structure of the tri-O-trityl sucrose and therefore also the tri-O-trityl-penta-O-acetyl sucrose. Because of the insolubility of the derivative in water the Purdie method of methylation rather than that of Haworth was employed.

The course of the methylation of tri-O-trityl sucrose was followed by detritylating and hydrolysing a sample after each methylation with aqueous acetic acid and chromatographing the hydrolysate on paper. The reaction was found to proceed very slowly and eleven treatments with the reagents were necessary to achieve a satisfactory degree of methylation. The final product was a colorless glass, $[\alpha]_D^{17} = +32.4^\circ$ ($c = 6.14$ in chloroform) which showed on analysis a trityl and methoxyl content approximating that of a tri-O-trityl-penta-O-methyl sucrose.

Paper chromatography of a partially hydrolysed sample showed a number of spots which were tentatively identified as due to penta-O-methyl sucrose, tetra-O-methyl sucrose, tri-O-methyl-D-glucose, di-O-methyl-D-fructose and mono-O-methyl-D-fructose (the latter spot was somewhat elongated and probably represented a mixture of 3- and 4-O-methyl-D-fructose).

The problem of effecting a detritylation of the methylated tri-O-trityl sucrose had now to be solved. The previous experiences with catalytic hydrogenation did not recommend this method. A graded hydrolysis seemed to offer more promise. Here a difficulty arose in the question of how to determine the optimum conditions for obtaining in good yield the desired penta-O-methyl sucrose. The arbitrary assumption could be made that tri-O-trityl-penta-O-methyl sucrose and tri-O-trityl-penta-O-acetyl sucrose hydrolyse and detritylate at about the same rates. However, such an assumption did not seem to be justified in view of the results of preliminary experiments. A more precise method was finally devised. The specific rotation of the methylated tri-O-trityl sucrose in glacial acetic acid was known to be about $+50^\circ$, and if the assumption was made that the specific rotation of the penta-O-methyl sucrose was about $+65^\circ$ (this seemed a reasonable assumption since sucrose, tri-O-methyl sucrose, and octa-O-methyl sucrose all show specific rotations of about this value), then a detritylation reaction should cause a decrease in specific rotation from

+50° to about +18° when a correction was made for the loss in molecular weight accompanying detritylation. On the other hand, complete hydrolysis to D-glucose and D-fructose fragments should cause a decrease in rotation to about 0°.

A sample of the methylated tri-O-trityl sucrose was dissolved in 98% aqueous acetic acid (initial rotation + 48.8°) and heated on the steam bath and the specific rotation rapidly decreased: after ten minutes, +35°; after 20 minutes, 28.2°; after 30 minutes, 24.2°; after 40 minutes, +22.0; and after 50 minutes, +19.8°. The rate of decrease of the optical rotation had begun to level off as predicted so the reaction was stopped at this point and the reaction mixture was then evaporated to yield a partly crystalline (tritanol) sirupy residue from which the detritylated products were extracted with water.

The next problem was to isolate the desired penta-O-methyl sucrose from the mixture. If the reducing sugars could be removed, then the separation of the methyl sucroses could be easily achieved by chromatography. In a first attempt, a quantity of the detritylation product was dissolved in water and heated on the steam bath in the presence of excess barium hydroxide (75). The colorless mixture rapidly discolored to a dark brown. After 2 hours heating the mixture was filtered, the pale-yellow filtrate deionized by exchange resins and the eluate evaporated to give a colorless sirupy residue. A paper chromatogram (butanol-ethanol-

water (5:1:4) developer) showed two spots which appeared to represent penta- and tetra-O-methyl sucrose. Separation^{of} the supposed penta-O-methyl sucrose on a cellulose column gave a sirupy product, $[\alpha]_D^{23} = +64.1^\circ$ (c= 1.1 in water). However, when a sample, 68 mg., of this product was hydrolysed and the hydrolysis products separated by chromatography only 20 mg. of what was believed to be 3, 4-di-O-methyl-D-fructose was obtained, whereas 40 mg. of what was believed to be 2,3,4-tri-O-methyl-D-glucose was obtained. The results strongly indicated that the supposed penta-O-methyl sucrose was actually a mixture containing some 30% 2, 3, 4-tri-O-methyl-D-glucose. The latter was probably in the form of 2, 3, 4-tri-O-methyl-D-glucosan $\langle 1-5 \rangle / \beta \langle 1-6 \rangle$ which is known to be stable to alkali (76). This method of isolating the penta-O-methyl sucrose was clearly of little value.

A convenient means of isolating the desired penta-O-methyl sucrose was found in partition chromatography with methyl ethyl ketone-water azeotrope (77). This very useful developer not only gives clean separations of sugars and their derivatives of relatively low R_f values but also gives excellent separations of the higher methylated sugars. This feature makes the solvent an invaluable complement to the more commonly used developers, for example, butanol-water, which give poor separations of the highly methylated sugars.

A sample of the detritylation product was first

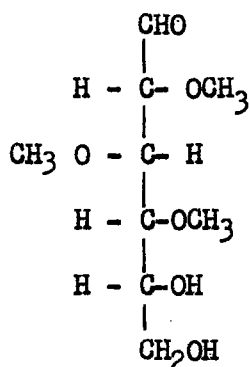
subjected to a preliminary purification by chromatography with butanol-water to remove the sugars of low methoxyl content, i.e., di-O-methyl-D-fructose, mono-O-methyl-D-fructose and traces of free sugars. This step was necessary as such substances would require up to a week's washing to be completely removed from a methyl ethyl ketone-water column of cellulose. After the preliminary separation the product, presumably now largely a mixture of penta-O-methyl sucrose and tri-O-methyl-D-glucose, was chromatographed twice on a cellulose column using methyl ethyl ketone-water. The appropriate fractions yielded a colorless viscous sirup, $[\alpha]_D^{23} = +64.3$ ($c = 1.46$ in water), which showed the methoxyl content calculated for a penta-O-methyl sucrose and reduced Fehling's solution only after acid hydrolysis.

A sample of the penta-O-methyl sucrose was subjected to acid hydrolysis and the product separated on a cellulose column into two paper chromatographically pure fractions which analysed correctly for a tri-O-methyl hexose and a di-O-methyl hexose.

The sirupy tri-O-methyl hexose was identified as the known 2, 3, 4-tri-O-methyl-D-glucose (VI) by the following evidence: The specific rotation $[\alpha]_D^{24} = +70.6$ ($c = 3.26$, equilibrium value in water), was in good agreement with previously reported values (76, 78). Paper chromatography using several

solvents gave a spot of hue and R_f value identical to that shown by an authentic sample of 2, 3, 4-tri-O-methyl-D-glucose. Treatment of the sugar with aniline gave in good yield a crystalline product melting at 127-8°C which showed no depression on admixture with an authentic sample of 2, 3, 4-tri-O-methyl-D-glucose anilide.*

VI

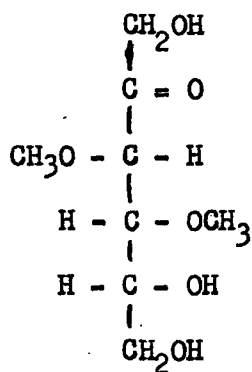


The sirupy di-O-methyl hexose was identified as the known 3, 4-di-O-methyl-D-fructose (VII) by the following evidence: The specific rotation, $[\alpha]_D^{24} = -58.5^\circ$ ($c = 2.0$ in water, equilibrium value), was in good agreement with previously reported values (79, 80). Paper chromatography using butanol-ethanol-water (5:1:4) revealed a single spot of the characteristic color of a ketose and an R_f value in agreement with the recorded value (69). Periodate oxidation of the sugar derivative showed, after 58 hours, a consumption of 1.8 moles of periodate, and a production of 1.53 moles of formaldehyde. Although the theoretical behavior of 3,4-di-O-methyl-D-fructose toward periodate calls for values of 2 and

*The sample of 2, 3, 4-tri-O-methyl-D-glucose anilide was supplied by Dr. G.G.S. Dutton of this University to whom the author is indebted.

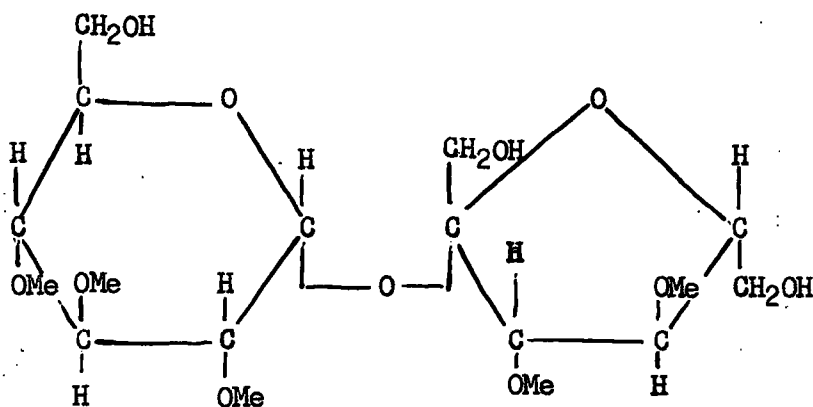
2 moles respectively, this sugar has been reported to give low yields of formaldehyde of the order of 1.5 moles (81).

VII



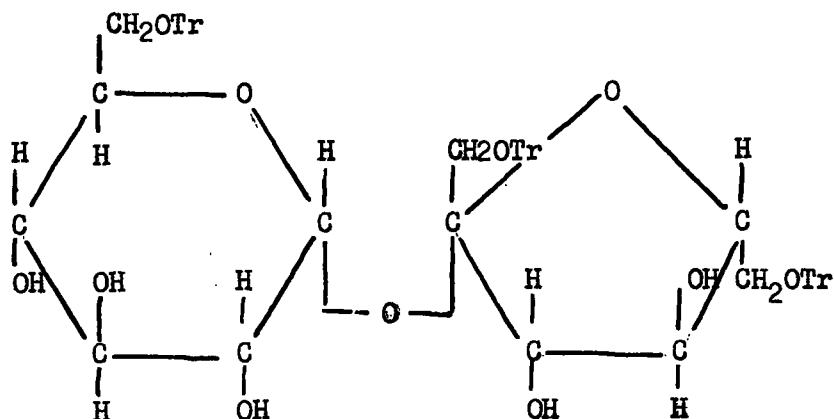
This evidence clearly established the structure of the parent sucrose derivative as the new 2, 3, 3', 4, 4' -penta-O-methyl sucrose (VIII).

VIII

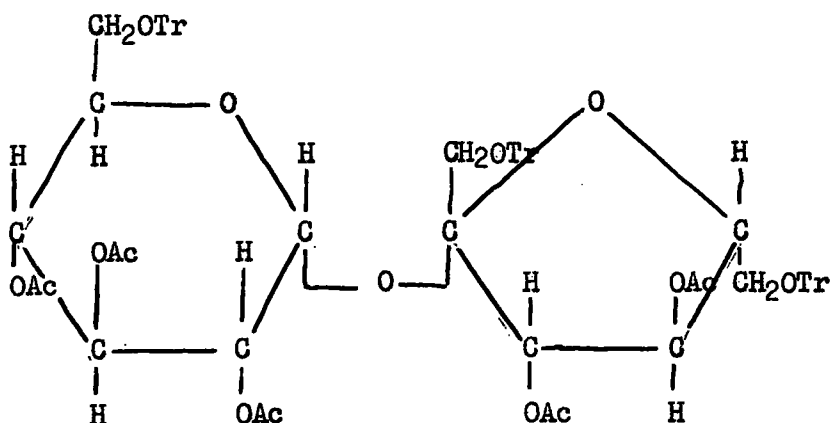


The structures of tri-O-trityl sucrose (IX) and tri-O-trityl-penta-O-acetyl sucrose (X) could now be designated.

IX



X



Attempts to vinylate the penta-O-acetyl sucrose by the method of Adelman (47) were begun shortly after the isolation of this compound was achieved.

A major obstacle was evident from the beginning. Adelman in his studies used a series of low molecular weight, relatively stable alcohols which gave easily distillable products. Thus the isolation and purification of the desired vinyl ethers presented no special problems. In this research, however, the

starting material was a non-volatile compound unstable toward both acids and bases. The desired product also possessed the same limitations and in addition a tendency toward polymer formation. The isolation process involved working up a residue, not a distillate. Furthermore, in view of well-known tendency of carbohydrates to form non-crystallizable sirups, fractional crystallization could not be depended upon as a means of isolating the desired product should the residues prove to be complex mixtures.

In a series of runs, with minor variations in temperature, reaction time and quantities of reagents, the penta-O-acetyl sucrose was treated with vinyl acetate according to Adelman's general method. The reaction mixtures were worked up by washing with cold aqueous sodium carbonate, followed by drying and evaporation of excess vinyl acetate. The composition of the residues varied considerably but in general, three products were obtained: a non-crystallizable colorless sirup, a crystalline product, and unchanged penta-O-acetyl sucrose.

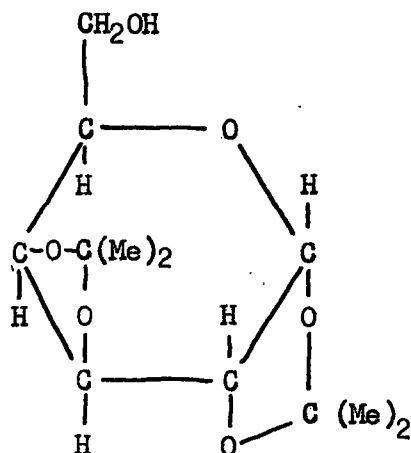
The sirupy material was identified as a partially vinylated penta-O-acetyl sucrose. Thus the substance decolorized bromine and on hydrogenation gave a sirupy product which analysed approximately as a mono-O-ethyl-penta-O-acetyl sucrose. Also the partially vinylated product slowly polymerized spontaneously to form a colorless, insoluble film.

The crystalline compound appeared to be a mole-

cular complex of mercuric acetate and vinyl acetate. The specific rotation was zero. Analyses for mercury and acetyl were variable as was the melting point (90-110°C).

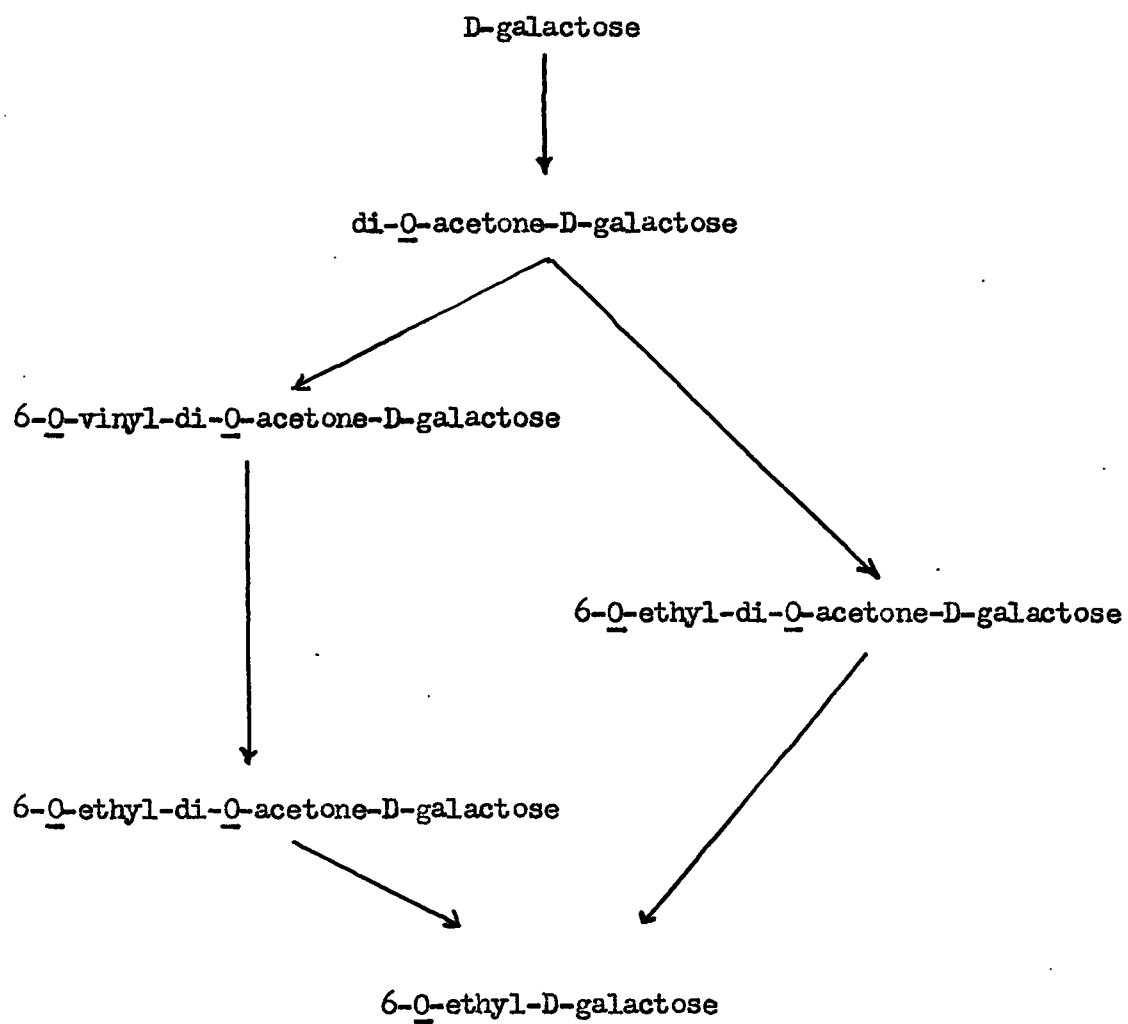
In view of these results, further work on the penta-O-acetyl sucrose was postponed and it was decided to study the vinylation of a model compound which did not possess the limitations and complexities of the disaccharide derivative. Di-O-acetone-D-galactose (1:2 -3 : 4-di-O-isopropylidene-D-galactose) (XI) was chosen for this purpose since the compound contained a free primary hydroxyl, could be distilled without decomposition and could be easily prepared from readily available starting materials.

XI



The transformations involved in the vinylation study of di-O-acetone-D-galactose are outlined in FIGURE III.

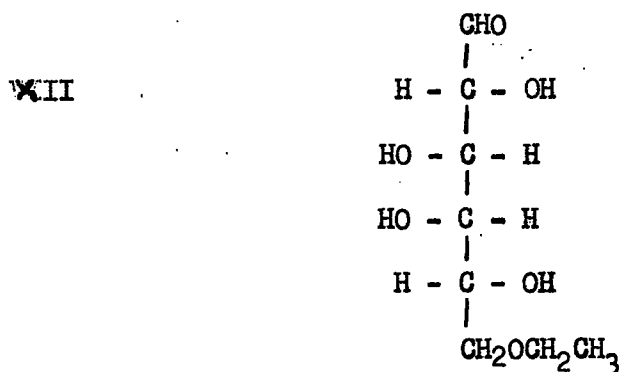
In a preliminary run, a 13.0 g. sample of di-O-acetone-D-galactose was treated with vinyl acetate according to Adelman's method for a period of 3 hours at -25°C. The reaction

FIGURE III

mixture was then washed with sodium carbonate solution, dried with anhydrous sodium carbonate and the solvent evaporated to yield a viscous, colorless sirup. The sirup was distilled under high vacuum to yield 3.5 g. of a colorless distillate which contained a considerable quantity of unchanged di-O-acetone-D-galactose. Redistillation from both sodium hydroxide and sodium failed to give a homogeneous product. A sample was then hydrogenated catalytically and the product hydrolysed. Chromatographic studies on the hydrolysate showed at least four substances to be present: D-galactose, 6-O-ethyl-D-galactose, and two unidentified products of R_f values similar to that of the mono-O-ethyl derivative. The 6-O-ethyl-D-galactose was easily recognized by its brown non-fluorescent spot (a feature seemingly characteristic of terminally substituted aldohexoses, e.g. 6-O-methyl-D-glucose and 6-O-methyl-D-galactose) whereas the unknown compounds gave yellow-brown fluorescent spots. The unknown compounds could conceivably be 3- and 4-O-isopropyl-D-galactose derivatives which could arise from ring opening of di-O-acetone-D-galactose during hydrogenation.

A second vinylation was carried out on di-O-acetone-D-galactose and the distilled product was hydrogenated directly and then hydrolysed. D-galactose was removed from the sirupy product by a preliminary purification on a cellulose column using butanol-water. The semi-purified product was then chromatographed twice on a column using methyl ethyl ketone-water as developer. A final

purification was achieved by preparative paper chromatography using the same solvent. Elution of the appropriate zones with water gave a 0.7% yield of sirupy product which was shown to be 6-O-ethyl-D-galactose (XII) by comparison of its specific rotation and paper chromatographic behavior with an authentic sample prepared by direct ethylation of di-O-acetone-D-galactose.



During the work with acetylated derivatives, some experiments were carried out to determine the effect of a strongly basic anion exchange resin on such compounds. Acidic resins have often been used as catalysts for hydrolysis and other reactions (82, 83, 84, 85, 86, 87, 88) in carbohydrate chemistry; it was reasoned that a basic resin might well cause deacetylation.

A solution of octa-O-acetyl sucrose in methanol was run onto a column of Dowex I strongly basic resin. After standing 24 hours at room temperature the column was washed with aqueous methanol and the eluate evaporated. Pure, crystalline

sucrose was obtained in 92% yield and identified by melting point, specific rotation, paper chromatography and the Raybin test (89). Other acetates of non-reducing carbohydrate derivatives were also tested and found to give the corresponding deacetylated products in yields up to 99%.

An interesting observation was made when a solution of octa-O-acetyl sucrose was passed rapidly through a column of Dowex I. The eluate yielded on evaporation a sirupy product which did not crystallize on nucleation with either sucrose or octa-O-acetyl sucrose. It gave however, crystalline sucrose on further treatment with the resin. It would appear that the original product was a partially deacetylated sucrose derivative.

The results of this research have shown that vinylation in the carbohydrate field by means of the Adelman reaction is not likely to prove of much value. As an exception however, one possible application should be noted. At present there is no reliable method for determining the precise structure of a partially acylated carbohydrate derivative (e.g. our penta-O-acetyl sucrose). The usual method of determining the location of free hydroxyl groups is by methylation and identification of the products. However, even under the mildest conditions of methylation acyl migration and even deacetylation have been shown to occur. The Adelman reaction on the other hand offers a means of alkylation under conditions (slightly acid and low temperature)

in which acyl migration is not likely to occur. The supposed 2, 3, 3', 4, 4'-penta-O-acetyl sucrose can serve as an illustration. This compound would be subjected to an Adelman vinylation and the product would then be hydrogenated, deacetylated and hydrolysed. Detection by chromatography of 6-O-ethyl-D-glucose and I, 6-di-O-ethyl-D-fructose even in low yields would establish the structure of the original disaccharide derivative.

At this stage, it would appear that the most profitable approach to a tri-O-vinyl sucrose would be through the 2, 3, 3', 4, 4'-penta-O-methyl derivative. This compound should be capable of withstanding the harsh reaction conditions of a Reppe vinylation and the completely vinylated product could be readily isolated and purified by distillation. Moreover, if such a product showed desirable properties on polymerization, commercial adaptation should be relatively straightforward. Sucrose could be partially methylated directly and a suitable starting material isolated by distillation.

EXPERIMENTAL

A. Materials

Silver Oxide

Silver oxide catalyst for the methylations was prepared according to a standard procedure (90). As the freshly prepared material did not seem to differ appreciably in activity as compared to the commercial product, both commercial and prepared samples were used.

Palladized charcoal catalyst

Palladized charcoal catalyst used for detritylations and hydrogenations was prepared after the method of Hartung (91).

Trityl chloride (Triphenylmethyl chloride)

Commercial samples of trityl chloride were found to be contaminated with considerable quantities of tritanol and other substances. The trityl chloride used in the tritylation reactions was freshly prepared according to the method of Bachmann (92).

Platinum oxide catalyst

The platinum oxide catalyst used in the hydrogenolyses and hydrogenations was the commercial product as supplied by Brickman and Company, Montreal.

Solvents and reagents

Solvents and reagents were purified by standard procedures; special purification methods are noted in the text.

B. Analytical Methods

Trityl

Trityl determinations were carried out according to the method of Helferich and Koester (93).

Acetyl

Acetyl determinations were carried out as described by Clark (94).

Alkoxy

Alkoxy (methoxy and ethoxy) determinations were carried out according to the method of Viebock and Schwappach as described by Clark (94).

Carbon and hydrogen

All carbon and hydrogen analyses were done by W. Manser, Zurich, Switzerland.

Periodate oxidations

The procedures described by several authors (73, 95, 96, 97) were adapted and combined so that a single 20 mg. sample revealed the consumption of periodate, the production of formic acid and the formation of formaldehyde.

A 20 mg. sample was dissolved in 20 ml. of 0.02 M sodium metaperiodate solution and let stand at room temperature in the dark. At suitable intervals 2 ml. aliquots were removed

and titrated with 0.01 N sodium hydroxide using methyl red indicator to determine the amount of formic acid produced. To the neutralized solution was then added 0.5 g. sodium bicarbonate, 0.25 g. potassium iodide and 2 ml. of 0.05 N sodium arsenite solution, and after standing 15 minutes, the solution was titrated with 0.05 N iodine solution in the presence of starch indicator to reveal the consumption of periodate ion. A 5 ml. aliquot of the oxidation solution was treated with 2.5 ml. N hydrochloric acid, 20 ml. 0.05 N sodium arsenite, 1 g. of solid sodium acetate and 2 ml. of an 8% solution of dimedone in ethanol, and after standing 24 hours at 0°C, the precipitate was recovered, dried and weighed to determine the amount of formaldehyde formed in the oxidation.

G. Tri-O-trityl-penta-O-acetyl Sucrose

Preparation at an elevated temperature

Into a 1 liter flask equipped with an mechanical stirrer and a reflux condenser was introduced 300 ml. of anhydrous pyridine, 17.1 g. (0.05 mole) of powdered sucrose and 50 g. (0.15 mole) of trityl chloride. The latter dissolved readily to give a pale-yellow solution. The reaction mixture was then heated to about 65°C and maintained at this temperature with constant stirring for 24 hours. After this period, all of the sucrose had dissolved. The now dark-red solution was cooled to 35°C and 50 ml. acetic anhydride was added which caused an immediate rise in temperature to 40°C. After standing 7 hours, the solution was

poured in a fine stream into ice water which caused the precipitation of a brown, viscous sirup. The product was recovered by decantation and crystallized from tetra hydrofuran-methanol. The crude product weighed 31.6 g., a yield of 49%. The mother liquors were found to be strongly reducing toward Fehling's solution and could not be induced to yield any additional crystalline product.

The yields obtained by this method varied considerably, from 10 to 49% and the crude products were of low purity, usually giving on recrystallization only about a 65% yield of the pure tri-O-trityl-penta-O-acetyl sucrose.

Preparation at room temperature

Into a 250 ml. flask was introduced 5.0 g. of powdered sucrose, 14.3 g. of trityl chloride and 100 ml. of anhydrous pyridine. The flask was tightly stoppered and allowed to stand with occasional shaking for 48 hours at room temperature. Acetic anhydride (20 ml.) was then added and the colorless solution was stored overnight in the refrigerator. During this interval, colorless crystals were deposited from the solution. This product was removed by filtration and dried in vacuo. The dried material weighed 6.7 g. and melted at $175\text{--}\overset{177}{77}^{\circ}\text{C}$. It was very hygroscopic, showed an acid reaction to pH paper and a positive test for chloride ion and gave tritanol (m.p. $160\text{--}\overset{161}{71}^{\circ}\text{C}$) on hydrolysis. The reported melting point of tritanol-

pyridinium hydrochloride is 172-174°C (50, 51).

The filtrate was poured with stirring into 1500 ml. of ice-water causing the precipitation of a colorless, amorphous solid which was recovered by filtration and washed thoroughly with water. Precipitation in water at 10°C gave a sticky mass which could not be filtered or washed efficiently. The solid product was dried in vacuo over phosphorus pentoxide and then crystallized from chloroform-methanol to give 8.5 g. (45% yield) of colorless tri-O-trityl-penta-O-acetyl sucrose of high purity judging by the melting point and color. Again the mother liquors were strongly reducing toward Fehling's solution.

On recrystallization to a constant melting point, the pure tri-O-trityl-penta-O-acetyl sucrose which formed in colorless hexagonal crystals melted at 235-236°C.(corr.); $[\alpha]_D^{17} + 68.9^\circ$ ($c = 2.45$ in chloroform). Analysis: calc. for $C_{79}H_{74}O_{16}$: C, 74.2%; H, 5.84%. Found: C, 73.7% H, 5.9%. The compound was soluble in chloroform, ether, tetrahydrofuran, ethyl acetate, insoluble in water, methanol, ethanol, petroleum ether and reduced Fehling's solution only after acid hydrolysis. The compound gave a negative Raybin test (89).

D. Tri-O-trityl sucrose

Direct tritylation of sucrose

Into a 1 liter flask equipped with a reflux

condenser and a mechanical stirrer was introduced 500 ml. of anhydrous pyridine, 34.2 g. (0.1 mole) of sucrose, 50 g. of Drierite and 85 g. (0.3 mole) of trityl chloride. The solution was heated to 80°C, maintained at this temperature for 3 hours and then allowed to cool to room temperature. The now dark-red colored reaction mixture was filtered free of solids and poured in a fine stream into ice water with stirring. The brown amorphous precipitate was purified by several precipitations from methanol with water.

During several unsuccessful attempts to crystallize the product from a variety of solvents, approximately 25 g. of tritanol (m.p. 159-61°) was isolated from the mixture. Also, from ethyl acetate and petroleum ether, 0.25 g. of colorless needle-like crystals were obtained which melted sharply at 146-7°C and gave a positive reaction with Fehling's solution only after acid hydrolysis. Trityl analysis: found, 57.2%; calculated for di-O-trityl sucrose, 58.8%.

The semi-purified tri-O-trityl sucrose was a colorless glass with a variable softening point around 125 to 130°C. Analysis: calc. for $C_{69}H_{64}O_{11}$: trityl, 68.3%. Found: 55.7%. The substance showed a slight reducing action toward Fehling's solution before and a strong reducing action after acid hydrolysis.

Deacetylation of tri-O-trityl-penta-O-acetyl sucrose

To a solution of 10.0 g. of pure tri-O-trityl-

penta-O-acetyl sucrose in 25 ml. of anhydrous tetrahydrofuran was added 100 ml. anhydrous methanol and 5 ml. of 0.1 N sodium methoxide solution. The solution was heated to reflux for 10 minutes, cooled to room temperature and let stand overnight. The solution was then evaporated to dryness under reduced pressure and the residue was taken up in ethyl acetate and washed with water. Evaporation of the organic layer yielded a colorless glass which was dried for 10 days in vacuo over phosphorus pentoxide. The dried product weighed 8.6 g. (yield 103%, calculated for anhydrous tri-O-trityl sucrose).

The product was a colorless glass of such high viscosity that it could be pulverized to a fine, white powder. It showed a softening point of about 125-30°C and was soluble in methanol, ethanol, ethyl acetate, insoluble in water and petroleum ether. Specific rotation: $[\alpha]_D^{22} = +14.7^\circ$ (c= 3.3 in chloroform). Analysis: calc. for $C_{69}H_{64}O_{11}$: trityl, 68.3% (tetrahydrate, 63.9%; pentahydrate, 63.0%); mol. wt., 1069. Found: trityl, 63.6, 63.5%, mol. wt., 950 (Rast method). The substance reduced Fehling's solution only after acid hydrolysis. After standing for more than a year, samples in various solvents failed to crystallize.

Acetylation of tri-O-trityl sucrose.

Tri-O-trityl sucrose, 71 mg., was dissolved in a mixture of 2 ml. pyridine, and 1 ml. acetic anhydride and let

stand for 24 hours. The solution was then diluted with 50 ml. of water and the resulting amorphous precipitate was recovered by filtration, washed with water and dried. Crystallization from chloroform and methanol yielded 66.2 mg. (78% yield) of colorless, hexagonal crystals melting correctly at 233-4°C and showing no depression in melting point on admixture with an authentic specimen of tri-O-trityl-penta-O-acetyl sucrose.

Attempted catalytic detritylation of tri-O-trityl sucrose

Tri-O-trityl sucrose, 0.500 g. was dissolved in 25 ml. of ethyl acetate and shaken under 3 atmospheres pressure of hydrogen with 0.25 g. of palladized charcoal catalyst for 24 hours. The catalyst was then removed by filtration and the filtrate evaporated to yield a pale-yellow sirup. Even after nucleation, neither sucrose nor tritane could be induced to crystallize from the sirup. A paper chromatogram developed with butanol-ethanol-water (5:1:4) and sprayed with p-anisidine hydrochloride reagent (70) showed that only a trace of sucrose was present as evidenced by a faint yellow, fluorescent, spot of R_f 0.03.

E. Penta-O-acetyl Sucrose

Catalytic hydrogenation of tri-O-trityl-penta-O-acetyl sucrose

Tri-O-trityl-penta-O-acetyl sucrose, 10.0 g., melting at 229-32°C, was dissolved with warming in 200 ml. of

glacial acetic acid. Two g. of Adams platinum oxide catalyst was added and the mixture was shaken under 4 atmospheres pressure of hydrogen for 36 hours at 50°C. After recovery of the catalyst by filtration, the filtrate was evaporated under reduced pressure to yield a colorless sirup which was extracted with 600 ml. of hot petroleum ether (b.p. 100-120°C).

The residue, a colorless sirup (2.02 g.) which could not be induced to crystallize, reduced Fehling's solution only after acid hydrolysis; $[\alpha]_D^{22} = +53.3^\circ$ ($c = 15.08$ in chloroform). Analysis: calc. for di-O-trityl-penta-O-acetyl sucrose: acetyl, 20.8%. Found: acetyl, 21.9%. Acetylation of 240 mg. of the sirup using acetic anhydride in pyridine gave a sirupy product which yielded 87 mg. of colorless crystalline material melting at 100-120°. Analysis: calc. for di-O-trityl-hexa-O-acetyl sucrose: acetyl, 23.9%. Found: acetyl, 23.7%. Nucleation of the sirupy residue with octa-O-acetyl sucrose did not induce crystallization.

The petroleum ether extract was evaporated to dryness and the sirupy residue fractionally crystallized from methanol. Tricyclohexylmethane, 1.8 g., melting correctly at 57.5 - 58.0°C (55, 56) was obtained. Analysis: calc. for $C_{19}H_{34}$: C, 86.9%; H, 13.1%. Found: C, 86.3%; H, 13.0%. Also 0.98 g. of a crystalline material was obtained which formed in colorless, hexagonal crystals, m.p. 218-19°C, $[\alpha]_D^{20} = +71.5^\circ$ ($c = 5.93$ in chloroform), which was believed to be partially saturated starting

material. Analysis: calc. for $C_{79}H_{92}O_{16}$: C, 73.1%; H, 7.15%.

Found: C, 72.4%; H, 7.11%.

Another sample of tri-O-trityl-penta-O-acetyl sucrose when hydrogenated under similar conditions using palladized charcoal as catalyst, was also found to be partially detritylated yielding a glass of trityl content approximating that of a mono-O-trityl-penta-O-acetyl sucrose. Analysis: calc. for mono-trityl-penta-O-acetyl sucrose: trityl, 30.6%. Found: trityl, 26.8%. However, hydrogenation of the aromatic rings did not take place with the palladium catalyst; thus triphenyl-methane and some unreacted tri-O-trityl-penta-O-acetyl sucrose were recovered from the reaction mixtures but no tricyclohexylmethane or "reduced" tri-O-trityl-penta-O-acetyl sucrose.

A 5.0 g. sample of tri-O-trityl-penta-O-acetyl sucrose, m.p. $231-2^{\circ}C$, which had been purified by repeated recrystallization alternately from tetrahydrofuran-methanol and tetrahydrofuran-petroleum ether (b.p. $30-60^{\circ}C$) was dissolved on warming in 100 ml. of glacial acetic acid and shaken under 4 atmospheres pressure of hydrogen in the presence of 0.5 g. of platinum oxide catalyst at $50^{\circ}C$. After 34 hours the theoretical uptake of hydrogen had occurred and a colorless, crystalline material had deposited from solution. The crystalline material, tricyclohexylmethane, m.p. $57.5 - 58.0^{\circ}C$, weight 2.55 g. (83% yield), was filtered off. The filtrate was evaporated to dryness

and the residue crystallized from chloroform-petroleum ether (b.p. 30-60°C) to give 0.60 g. (27% yield) of colorless, needle-like crystals. This product was recrystallized to a constant melting point; m.p. 155-156°C; $[\alpha]_D^{22} = +22.0$ ($c = 3.1$ in chloroform). Analysis: calc. for $C_{22}H_{32}O_{16} \cdot 2H_2O$: acetyl, 36.6%. Found: acetyl, 36.6%, 36.6%. The compound was soluble in methanol, acetone, chloroform, insoluble in water, petroleum ether and reduced Fehling's solution only after acid hydrolysis. In subsequent hydrogenations using platinum oxide as catalyst, yields of 20, 38, 16 and 23% of the pentaacetate were obtained.

A highly purified sample of tri-O-trityl-penta-O-acetyl sucrose, 0.50g., in 50 ml. glacial acetic acid was shaken over 0.25 g. of palladized charcoal catalyst under 3 atmospheres pressure of hydrogen at 50°C for 64 hours. The reaction mixture was worked up in the above manner to yield 44 mg. (20% yield) of crystalline penta-O-acetyl sucrose.

A sample of crude penta-O-acetyl sucrose when repeatedly recrystallized from chloroform-petroleum ether (b.p. 30-60°C) exhibited the following progression in melting point: 138-43°; 154-54.5°; 155-55.5°; 155-155.5°; 152-53°; and 155-56°; 152-3° and 155-56°. Another sample when recrystallized from chloroform-petroleum ether acidified with a trace of glacial acetic acid did not show the double melting point.

Graded hydrolysis of tri-O-trityl-penta-O-acetyl sucrose

Tri-O-trityl-penta-O-acetyl sucrose, 2.0 g., was dissolved on warming in 50 ml. of glacial acetic acid, the solution was heated to reflux temperature and 1 ml. of water was introduced. After refluxing for 30 minutes the solution was cooled, the solvent evaporated and the partially crystalline residue dried in vacuo. Recrystallization from chloroform-petroleum ether acidified with acetic acid yielded 504 mg. (58% yield) of crystalline penta-O-acetyl sucrose. Reworking of the mother liquors which showed reducing activity toward Fehling's solution yielded tri-tanol. The yields of penta-O-acetyl sucrose obtained in subsequent runs varied between 43 and 60%. The effect of time of hydrolysis on the yield of penta-O-acetyl sucrose was as follows: 15 minutes, 23-31%; 30 minutes, 43-60%; 60 minutes, 35%; 120 minutes, 0%. Variation of the amount of water did not greatly influence the yield: 0.25 ml. water, 23%; 1.0 ml. water, 31%; 2.0 ml. water 26% (reaction time, 15 minutes).

Acetylation of penta-O-acetyl sucrose

Penta-O-acetyl sucrose, 100 mg., was dissolved in a mixture of 2 ml. pyridine and 1 ml. acetic anhydride and let stand at room temperature overnight. The colorless solution was then diluted with 50 ml. of water, seeded with octa-O-acetyl sucrose

and let stand in the refrigerator. After several hours, colorless, needle-like crystals had formed which were recovered by filtration, washed with water and dried in vacuo; weight 75 mg. (yield 65%); m.p. 83-87°. After recrystallization from ether-petroleum ether (b.p. 30-60°C), the product melted at 86-88°C and showed no depression in melting point on admixture with an authentic specimen of octa-O-acetyl sucrose.

F. Methylation of penta-O-acetyl sucrose

Penta-O-acetyl sucrose, 1.579 g., was dissolved in 25 ml. of dry acetone and 15 ml. freshly distilled methyl iodide, 5 g. freshly prepared silver oxide and 2 g. Drierite were added. After 15 hours refluxing, the reaction mixture was filtered, the solids washed with acetone and the combined filtrate and washings evaporated to yield a viscous, colorless sirup, weight 1.527g.

A few milligrams of the sirup was dissolved in aqueous methanol and heated with DowexI strongly basic ion exchange resin on the steam bath for 2 hours. A paper chromatogram was then run of the deacetylated product using butanol-ethanol-water (5:1:4) as developer. On treating the developed chromatogram with the p-anisidine hydrochloride spray reagent, two bright yellow, U.V. fluorescent spots appeared: R_f 0.04, distinct, for sucrose, and R_f 0.08, distinct for mono-O-methyl sucrose.

The main product was remethylated using 25 ml. of acetone, 25 ml. of methyl iodide, 5 g. of silver oxide and 2 g. of Drierite and a reflux time of 20 hours. A chromatogram of a deacetylated sample showed a faint spot for sucrose and a distinct spot for a mono-O-methyl sucrose.

A third methylation using 50 ml. methyl iodide, 10 g. silver oxide and 3 g. Drierite (no acetone was necessary to effect solution of the partially methylated sirup) was run for 24 hours. Chromatographic analysis showed a distinct spot, R_f 0.08, for mono-O-methyl sucrose, a distinct spot, R_f 0.20, for di-O-methyl sucrose, and a faint spot, R_f 0.40, for tri-O-methyl sucrose.

A fourth methylation using 40 ml. methyl iodide, 10 g. silver oxide and 3 g. Drierite was run for 48 hours. After working up the reaction mixture as described above, a colorless, viscous sirup was obtained which was analysed for methoxyl content; found 14.4%, calculated for tri-O-methyl-penta-O-acetyl sucrose, 15.7%.

A fifth methylation using 40 ml. methyl iodide, 5 g. silver oxide and 2 g. Drierite was run for 24 hours. A chromatogram on a deacetylated sample of the product showed a very distinct spot, R_f 0.40 for tri-O-methyl sucrose and a faint spot for di-O-methyl sucrose.

The methylated penta-O-acetyl sucrose, weight 1.55 g., was a colorless, viscous glass; $[\alpha]_D^{17} = +57.7^\circ$ ($c = 3.72$

in chloroform). Analysis: Calc. for tri-O-methyl-penta-O-acetyl sucrose, $C_{25}H_{38}O_{16}$: methoxyl, 15.7%; acetyl, 36.2%. Found: methoxyl, 15.5%, 15.8%; acetyl, 36.2%, 36.0%. After six months the product has not crystallized.

G. Tri-O-methyl sucrose

Deacetylation of methylated penta-O-acetyl sucrose

The methylated penta-O-acetyl sucrose, 1.30 g., was dissolved in 5 ml. methanol and run onto a 20 x 1.8 cm. column of 40-80 mesh Dowex I ion exchange resin. The solution was washed in with an additional 7 ml. of methanol. After standing 24 hours at room temperature, the column was eluted with 90% aqueous methanol. Fractions of 200 ml. were collected and evaporated to dryness. Fraction #1 yielded 776 mg., fraction #2 yielded 51 mg., and fraction #3 yielded 8 mg., of a colorless, viscous sirup (a total of 835 mg., 99% yield). Paper chromatography revealed that the product was a mixture containing 75% tri-O-methyl sucrose, 25% di-O-methyl sucrose and 1% mono-O-methyl sucrose.

Chromatographic purification of the tri-O-methyl sucrose

Approximately 650 mg. of the tri-O- and di-O-methyl sucrose mixture was dissolved in 2 ml. of butanol-water and run onto a 30 x 2.6 cm. column of cellulose which was then developed with the same solvent while ^{15 ml.} fractions were collected at one hour intervals. The fractions were qualitatively analysed by

spotting on paper and treating the paper with the p-anisidine hydrochloride reagents. The appropriate fractions were then combined and evaporated under reduced pressure to dryness. The di-O-methyl sucrose fractions⁽¹⁸⁻²²⁾ yielded 193 mg. of a colorless glass. The tri-O-methyl sucrose fractions⁽¹⁰⁻¹⁶⁾ yielded 472 mg. of a colorless, viscous sirup; $[\alpha]_D^{24} = +67.6^\circ$ ($c = 1.74$ in water). Analysis: calc. for tri-O-methyl sucrose, $C_{15}H_{28}O_{11}$: methoxyl, 24.2%. Found: methoxyl, 24.9%, 24.3%.

Periodate oxidation of tri-O-methyl sucrose

A sample of 19.2 mg. (0.05 milli mole) of the tri-O-methyl sucrose was oxidized with 10 ml. of 0.02 M sodium metaperiodate solution. The results are indicated in TABLE III.

TABLE III

Periodate Oxidation of Tri-O-methyl sucrose

<u>Reaction time</u>	<u>Periodate consumed</u>	<u>Formic acid</u>
3 hours	1.7 moles	0.025 moles
6 hours	1.8 moles	0.025 moles
24 hours	1.8 moles	0.025 moles

For comparison, a sample of sucrose, (166.27 mg.) was also oxidized with sodium meta-periodate (100 ml. 0.02M) under the same conditions. The results are listed in TABLE IV.

TABLE IVPeriodate Oxidation of Sucrose

<u>Reaction time</u>	<u>Periodate consumed</u>	<u>Formic acid</u>
1 hour	2.3 moles	0.26 moles
3 hours	2.7 moles	0.35 moles
6 hours	2.9 moles	0.47 moles
24 hours	3.1 moles	0.61 moles

Hydrolysis of tri-O-methyl sucrose

Tri-O-methyl sucrose, about 358 mg., was dissolved in 10 ml. of 1% aqueous acetic acid and heated to reflux temperature.

In order to follow the progress of the hydrolysis conveniently, 5 g. of sucrose, which should hydrolyse at approximately the same rate as a partially methylated sucrose, was treated similarly in 100 ml. of 1% aqueous acetic acid and the optical rotation was measured at one hour intervals. The change in specific rotation with time is shown in TABLE V.

TABLE VHydrolysis of Sucrose

<u>Reaction time (hours)</u>	<u>Specific rotation</u>
0	+66.5°
1	-16.2°
2	-17.7°
3	-18.7°
4	-18.8° constant value

After 5 hours, the hydrolysis of the tri-O-methyl sucrose was stopped, the hydrolysate filtered through Celite and evaporated to dryness under reduced pressure. A colorless sirup was obtained which was dried in vacuo to a constant weight of 342 mg.

Chromatographic separation of the tri-O-methyl sucrose hydrolysis products

The entire hydrolysis product of tri-O-methyl sucrose was dissolved in 2 ml. of the butanol-water solvent and run onto a 30 x 2.6 cm. cellulose column which was then developed with the same solvent while fractions ^(10 ml.) were collected at 30 minute intervals. The location of the sugars within the series of fractions was determined by spotting on paper and spraying with the p-anisidine hydrochloride reagent.

Fractions 15 - 19, which contained a di-O-methyl hexose were combined and evaporated. The sirupy residue was then taken up in water and filtered through Celite to remove colloidal particles of cellulose coming from the column and the filtrate was evaporated. After drying to constant weight in vacuo over phosphoruss pentoxide the colorless, sirupy residue weighed 161 mg.

Fractions 31 - 39, which contained a mono-O-methyl hexose, were combined and evaporated to yield a colorless

sirup which was then taken up in water, filtered through Celite and the filtrate again evaporated. After drying in vacuo over phosphoruss pentoxide, the residue, a colorless sirup, weighed 148 mg.

H. 4-O-methyl-D-glucose

The sirupy mono-O-methyl hexose isolated from the hydrolysis product of tri-O-methyl sucrose showed $[\alpha]_D^{24} = +61.2^\circ$ ($c = 1.428$ in water, equilibrium value). Analysis: calc. for mono-O-methyl hexose, $C_7H_{14}O_6$: methoxyl, 16.0%. Found: methoxyl, 15.5, 15.9%. Crystallization was not induced by nucleation with 2-O-methyl-D-glucose, 3-O-methyl-D-glucose or 6-O-methyl-D-glucose.

Paper chromatograms using the developers butanol-ethanol-water (5:1:4), and methyl ethyl ketone-water were run on the mono-O-methyl sugar along with authentic specimens of 2-, 3-, 4- and 6-O-methyl -D-glucose. The R_f value and color of the spot (p-anisidine hydrochloride spray reagent) for the mono-O-methyl hexose was found to be identical with that given by 4-O-methyl-D-glucose. The 2- and 6-O-methyl-D-glucose gave brown spots which did not fluoresce under U.V. light whereas the 3- and 4-O-methyl-D-glucose gave yellow-brown, fluorescent spots. The R_f values of 3- and 4-O-methyl-D-glucose differ considerably, the 3- isomer having the higher value.

The mono-O-methyl hexose, 27 mg., was heated for 1 hour on the steam bath in a mixture containing 0.35 ml. of freshly distilled phenylhydrazine (b.p. 115°C/0.3 mm), 0.30 ml. glacial acetic acid and 2.5 ml. water. The resulting yellow solution was diluted with 5 ml. of water and let stand at room temperature. A yellow crystalline precipitate formed which was recovered on a Pregl filter, washed with water and dried: weight of precipitate, 21 mg., yield 40%. Recrystallization twice from aqueous acetone gave 10 mg. of fine, yellow, needle-like crystals which melted at 156-8°C and showed no depression in melting point on admixture with an authentic sample of 4-O-methyl-D-glucose.

I. 1, 6-di-O-methyl-D-fructose

The liquid di-O-methyl hexose obtained from the hydrolysis of the tri-O-methyl sucrose showed a positive rotation $[\alpha]_D^{24} = +17.4^\circ$ ($c = 1.842$ in water, equilibrium value). Analysis: calc. for di-O-methyl hexose, $C_8H_{16}O_6$: methoxyl, 29.8%. Found: methoxyl, 29.8, 29.3%.

A paper chromatogram developed with butanol-ethanol-water (5:1:4) gave a single bright yellow, U.V. fluorescent spot of R_f 0.57 ($R_{TG}^* 0.69$) (3, 4 di-O-methyl-D-fructose has a considerably lower R_f value: 0.51, R_{TG} 0.61).

*
 R_{TG} represents travel on the chromatogram relative to tetra-O-methyl-D-glucose.

A sample of the di-O-methyl-D-fructose, 22 mg., was oxidized with 0.02 M sodium metaperiodate. The results are shown in TABLE VI.

TABLE VI

Periodate oxidation of 1,6-di-O-methyl-D-fructose

<u>Time</u>	<u>Consumption</u>	<u>Formic acid</u>	<u>Formaldehyde</u>
4 hours	3.1 moles	1.26 moles	
24 hours	3.2 moles	1.58 moles	0 moles
58 hours	3.2 moles	1.71 moles	

A 35 mg. sample of the di-O-methyl hexose was heated with a mixture of 3.5 ml. of phenylhydrazine, 0.3 ml. of glacial acetic acid and 5 ml. of water for one hour on the steam bath. A dark-red oil precipitated on cooling which partially crystallized. Repeated recrystallization from acetone/water gave an impure reddish-yellow crystalline product, 10 mg., which melted with decomposition at about 170-5°C.

J. Methylation of tri-O-trityl sucrose

Tri-O-trityl sucrose, 8.6 g., was dissolved in 50 ml. of methyl iodide and 10 g. of silver oxide and 15 g. of Drierite were added. The mixture was refluxed for 24 hours, then cooled and filtered through a sintered glass funnel. The solids were washed with 50 ml. of chloroform and the combined filtrate and washings evaporated to yield a colorless glass.

The dried product was remethylated using 25 ml. methyl iodide, 10 g. silver oxide and 10 g. Drierite for a reflux time of 24 hours. The reaction mixture was worked up as before to give a colorless glass. A sample of the product was hydrolysed and detritylated by heating for 3 hours on the steam bath in aqueous acetic acid and the hydrolysate was then chromatographed on paper using butanol-ethanol-water (5:1:4). The chromatogram indicated the hydrolysate to be a complex mixture containing D-fructose, mono-O-methyl-D-fructose, di-O-methyl-D-fructose, di-O-methyl-D-glucose and tri-O-methyl-D-glucose.

The product was subjected to a third methylation using 25 ml. methyl iodide, 10 g. silver oxide and 5 g. Drierite for a reflux time of 24 hours. The reaction mixture was worked as before to yield a colorless glass. A sample was again hydrolysed and detritylated with aqueous acetic acid and a paper chromatogram run on the hydrolysate. A very faint yellow spot, R_f 0.13, was

obtained for D-fructose; a very distinct yellow spot, R_f 0.28, for mono-O-methyl-D-fructose; a distinct yellow spot, R_f 0.51, for di-O-methyl-D-fructose and probably di-O-methyl-D-glucose; and a distinct red-brown spot, R_f 0.74 for tri-O-methyl-D-glucose.

The product was methylated a fourth time using 25 ml. methyl iodide and 5 g. silver oxide for a reflux time of 24 hours. After working up the mixture, paper chromatographic analysis was carried out as before. The chromatogram was similar to the previous one except that the D-fructose spot was less distinct while the tri-O-methyl-D-glucose spot was more pronounced.

The product was methylated a fifth time using 40 ml. methyl iodide and 5 g. of silver oxide with mechanical stirring. In this run the silver oxide catalyst was added in portions during the methylation. After 45 hours, the reaction mixture was worked up as before. A sample of the product was again hydrolysed and chromatographed. This paper chromatogram showed, a very distinct red-brown spot for tri-O-methyl-D-glucose, a very distinct yellow spot for di-O-methyl-D-fructose; and a distinct yellow spot for mono-O-methyl-D-fructose.

The product was methylated a sixth time using 25 ml. methyl iodide and 3 g. silver oxide for a reflux time of 48 hours with mechanical stirring. A paper chromatogram run on a hydrolysate showed distinct spots for tri-O-methyl-D-

glucose and di-O-methyl-D-fructose and a faint spot for mono-O-methyl-D-fructose.

The product was methylated a seventh time using 25 ml. methyl iodide, 5 g. silver oxide and 2 g. Drierite for a reflux time of 16 hours with mechanical stirring. The reaction mixture was worked up as before to yield a colorless glass which was pulverized to a fine, white, amorphous powder and dried in vacuo over phosphorus pentoxide to a constant weight of 8.64 g. Analysis: calc. for tri-O-trityl-penta-O-methyl sucrose: methoxyl, 13.6%. Found: methoxyl, 11.6, 11.8%.

The product was remethylated an eighth time using 50 ml. methyl iodide, 10 g. silver oxide and 3 g. Drierite with a reflux time of 48 hours. The reaction mixture was worked up as before and the product was dried in vacuo. Found: methoxyl, 12.6%.

A ninth methylation was carried out using 50 ml. methyl iodide, 10 g. silver oxide and 3 g. Drierite with a reflux time of 48 hours. The reaction mixture was worked up as before and a dried sample analysed. Found: methoxyl, 13.0%. Chromatographic analyses of a hydrolysed sample showed distinct spots for tri-O-methyl-D-glucose and di-O-methyl-D-fructose and a faint spot for mono-O-methyl-D-fructose .

The product was remethylated a tenth time using 40 ml. methyl iodide, 5 g. silver oxide and 2 g. Drierite with a

reflux time of 48 hours. Chromatographic analysis of a hydrolysed sample showed distinct spots for tri-O-methyl-D-glucose and di-O-methyl-D-fructose and a very faint spot for mono-O-methyl-D-fructose.

An eleventh and last methylation was carried out using 40 ml. methyl iodide, 10 g. silver oxide and 3 g. Drierite with a reflux time of 72 hours. The reaction mixture was worked up as before to yield a colorless glass which was pulverized to a fine, white powder and dried in vacuo over phosphorus pentoxide at 55°C; $[\alpha]_D^{17} = +32.4^\circ$ (c = 6.14 in chloroform). Analysis: calc. for tri-O-trityl-penta-O-methyl sucrose, $C_{74}H_{74}O_{11}$: trityl, 64.1%; methoxyl, 13.6%. Found: trityl, 63.9, 64.4%; methoxyl, 13.3, 13.4%.

K. Penta-O-methyl sucrose

Graded hydrolysis of methylated tri-O-trityl sucrose

1. Methylated tri-O-trityl sucrose, 1.00 g., was dissolved in 25 ml. glacial acetic acid and the solution heated to reflux. One ml. water was then added and the refluxing continued for 30 minutes. The solution was then cooled, the solvent evaporated under reduced pressure and the partly crystalline residue dried in vacuo. Extraction of the residue with four 10 ml. portions of water in the cold yielded a cloudy extract which was clarified by filtration through Celite and evaporated to yield a colorless sirup, 368 mg., $[\alpha]_D^{25} = +28.3$ (c = 7.36 in ethanol).

The product was studied by paper chromatography using butanol-ethanol-water (5:1:4) as solvent and the p-anisidine hydrochloride spray reagent. To detect ketose derivatives, the developed and sprayed chromatograms were heated only 1.5 minutes instead of the usual 10 minutes. This treatment caused a preferential development of fructose derivatives (including sucrose). A chromatogram developed in the usual manner showed five spots:

- (i) red-brown spot, very distinct, R_f 0.71, R_{TG} 0.85, probably represents 2,3,4-tri-O-methyl-D-glucose, reported value (69) R_{TG} 0.85;
- (ii) bright yellow U.V. fluorescent spot, very distinct, R_f 0.51, R_{TG} 0.61, probably represents 3,4-di-O-methyl-D-fructose, reported value (69) R_{TG} 0.61;
- (iii) bright yellow, U.V. fluorescent spot, faint, R_f 0.29, R_{TG} 0.35, somewhat elongated, probably represents mixture of 3- and 4-mono-O-methyl-D-fructose, no reported values available;
- (iv) bright yellow, U.V. fluorescent spot, very distinct, partially obscured by the tri-O-methyl-D-glucose spot, R_f and R_{TG} approximately 0.77 and 0.93, probably represents penta-O-methyl sucrose;
- (v) bright yellow, U.V. fluorescent, R_f 0.61, R_{TG} 0.73, faint, probably represents tetra-O-methyl sucrose. A developed and sprayed chromatogram was heated for only 1.5 minutes:

one very distinct, bright yellow, U.V. fluorescent spot appeared, R_f 0.75, R_{TG} 0.91, which probably represents penta-O-methyl sucrose. Since no other fructose derivative spots showed up on the chromatogram, e.g., tetra-O-methyl sucrose and di-O-methyl-D-fructose, it seemed reasonable to assume that the penta-O-methyl sucrose was in high concentration.

2. Methylated tri-O-trityl sucrose, 1.759 g., was dissolved in 24 ml. of glacial acetic acid and 1 ml. of water added and the solution was allowed to stand at room temperature. The specific rotation was determined at intervals: initial, $+48.0^\circ$; 3 hours, $+46.0^\circ$; 6 hours, $+44.0^\circ$; 24 hours, $+37.2^\circ$; 45 hours, $+30.3^\circ$; 73 hours, $+29.0^\circ$; 96 hours, $+27.7^\circ$. The solvent was evaporated and the partly crystalline residue dried in vacuo over sodium hydroxide. The dried residue was extracted with seven 15 ml. portions of water in the cold to give a cloudy extract which was clarified by filtration through Celite and evaporated to yield 312 mg. (yield of detritylated sugars, 47%) of colorless sirup; $[\alpha]_D^{20} = +58^\circ$ ($c = 2.30$ in water). A chromatogram run on this product indicated the presence of a considerable quantity of tri-O-methyl-D-glucose and di-O-methyl-D-fructose. The product was then worked up as will be described below to yield partially methylated sucrose.

3. Methylated tri-O-trityl sucrose, 2.28 g., was

dissolved in 50 ml. glacial acetic acid and 1 ml. of water added: initial rotation, $+48.8^\circ$. The solution was then heated on the steam bath for 5 minutes then cooled rapidly to room temperature; $[\alpha]_D = +38^\circ$. The solution was again heated for 5 minutes and then cooled; $[\alpha]_D = +35^\circ$. The solution was heated a third time for 10 minutes duration; $[\alpha]_D = +28.2^\circ$. After a fourth heating for 10 minutes duration, $[\alpha]_D = +24.2^\circ$. After a fifth heating of 10 minutes, $[\alpha]_D = +22.0^\circ$. After a final heating of 10 minutes, $[\alpha]_D = +19.8^\circ$. The reaction mixture was then evaporated and the partly crystalline residue dried in vacuo over sodium hydroxide. The residue was extracted with 20 ml. portions of water in the cold; the progress of the extraction was followed by measuring the optical rotation of the extracts. After 6 treatments, the extraction process appeared to be complete, and the combined extracts were evaporated and the residue dried in vacuo, weight 700 mg. (yield of detritylated sugars, 82%). As described below, penta-O-methyl sucrose was obtained from this product by chromatographic separation.

Isolation of penta-O-methyl sucrose

The sirupy mixture obtained as described under K, 2, was dissolved in 15 ml. of water, one g. of hydrated barium hydroxide was added, and the mixture was heated on the steam bath for 2 hours. The mixture rapidly discolored during the degradation to finally yield a dark-brown paste. The mixture was cooled, solid carbon dioxide was added and the solids were recovered on a

filter and washed with water. The combined pale-yellow filtrate and washings were passed through a 20 x 1.8 cm. column of Dowex I anion exchange resin and a similar column of Amberlite IR-C-50 cation exchange resin in that order followed by 350 ml. of wash water. The eluate was evaporated and the sirupy residue dried in vacuo, weight 172 mg. A paper chromatogram run on this product showed a very distinct spot for penta-O-methyl sucrose, a distinct spot for tetra-O-methyl sucrose and a faint spot for tri-O-methyl sucrose.

The product was chromatographed on a 30 x 2.6 cm. column of cellulose using butanol-~~water~~ as developer. The appropriate fractions were combined and evaporated to yield 41 mg. of tetra-O-methyl sucrose and 87 mg. of penta-O-methyl sucrose. The latter showed the specific rotation, $[\alpha]_D^{24} = +64.1^\circ$ (c= 1.1 in water). Analysis: calc. for penta-O-methyl sucrose, $C_{17}H_{32}O_{11}$: methoxyl, 37.6%. Found: methoxyl, 37.2, 37.5%.

A 68 mg. sample of the product was dissolved in 10 ml. of 1% aqueous acetic acid and refluxed for 6 hours. The hydrolysate was evaporated and the sirupy residue chromatographed on a cellulose column using butanol-~~water~~ as developer. The di-O-methyl hexose on evaporation yielded only 20 mg. of a colorless ~~liquid~~, whereas the tri-O-methyl hexose fractions yielded 40 mg. of colorless sirup. It is suspected that during the hexose

degradation with barium hydroxide, some 2,3,4-tri-O-methyl-D-glucosan $\langle 1-5 \rangle / \beta \langle 1-6 \rangle$ was formed which subsequently contaminated the penta-O-methyl sucrose fraction.

Chromatography appeared to offer the only means of isolating a pure sample of penta-O-methyl sucrose from the complex mixture obtained by the graded hydrolysis of the methylated tri-O-trityl sucrose. The major obstacle was to effect a separation of the desired product from the tri-O-methyl-D-glucose. The R_f values, 0.75 and 0.71 respectively, were so close a clean separation could not be expected using butanol-water. However, the methyl ethyl ketone-water azeotrope as developer was found to give better results. Paper chromatograms revealed the R_f values of the penta-O-methyl sucrose and the tri-O-methyl-D-glucose to be 0.60 and 0.52 using this solvent.

The sirupy mixture (700 mg.) obtained as described under K, 3, was dissolved in 2 ml. methyl ethyl ketone-water and run onto a 50 x 2.6 cm. column of cellulose and the chromatogram was developed with that solvent. Fractions of approximately 10 ml. volume were collected over 5 minute intervals. The highly diluted fractions were carefully examined by: (i) the usual spotting technique; (ii) by measuring the optical rotations and (iii) by paper chromatography. The bulk of the desired product was found to be concentrated in 4 fractions which were combined and evaporated

to yield 228 mg. of a colorless sirup. This product was rechromatographed and the fractions examined as described above. The bulk of the desired product was found to be contained in 3 fractions and to be free of the tri-O-methyl-D-glucose. The combined fractions were evaporated and the residue taken up in ethanol and filtered through Celite to remove colloidal particles of cellulose. The clear filtrate was evaporated and the residue dried in vacuo to a constant weight, 153 mg. (18% yield).

The pure penta-O-methyl sucrose was a colorless, viscous sirup, $[\alpha]_D^{23} = +64.3$ ($c = 1.46$ in water). Analysis: calc. for penta-O-methyl sucrose, $C_{17}H_{32}O_{11}$: methoxyl, 37.6%.

Found: methoxyl, 37.7, 37.2%. The product reduced Fehling's solution only after acid hydrolysis.

Hydrolysis of penta-O-methyl sucrose

The sirupy penta-O-methyl sucrose, 146 mg., was dissolved in 10 ml. of 0.05 N sulfuric acid and heated under reflux on the steam bath for 2 hours. Barium carbonate, 500 mg., was then added and the mixture was stirred until neutral to pH paper. The mixture was then filtered, the solids were washed with water and the combined filtrate and washings were evaporated to dryness. The residue was extracted with acetone, and the extract was filtered through Celite and evaporated to yield a viscous sirup.

The sirupy hydrolysate was chromatographed on the methyl ethyl ketone-water column to yield on evaporation of the appropriate fractions, 70 mg. of a tri-O-methyl hexose and 55 mg. of a di-O-methyl hexose.

L. 2,3,4-Tri-O-methyl-D-glucose

The tri-O-methyl hexose was a colorless, viscous sirup, $[\alpha]_D^{24} = +70.6^\circ$ ($c = 3.26$ in water, equilibrium value).

Analysis: calc. for tri-O-methyl hexose, $C_9H_{18}O_6$: methoxyl, 41.8%. Found: methoxyl, 41.1, 41.5%.

Paper chromatography of the compound revealed a single spot of color and R_f value identical to that obtained with authentic 2,3,4-tri-O-methyl-D-glucose using both butanol-ethanol-water (5:1:4) and methyl ethyl ketone-water; red-brown spots (p-anisidine hydrochloride spray) were obtained of R_f values 0.71 and 0.52 respectively.

A 36 mg. sample of the tri-O-methyl sugar was heated on the steam bath under reflux with 70 mg. of freshly distilled aniline and 2 ml. of absolute ethanol for 6 hours. The volatile constituents were then removed in vacuo at $60^\circ C$ to yield 48 mg. of a viscous, yellow sirup. On seeding with authentic 2,3,4-tri-O-methyl-D-glucose anilide, the product crystallized in fine, colorless needles. After three recrystallizations

from ether-petroleum ether the derivative melted sharply at 127-8°C and showed no depression on admixture with the authentic sample.

M. 3,4-Di-O-methyl-D-fructose

The di-O-methyl hexose was a colorless, viscous liquid, $[\alpha]_D^{24} = -58.5^\circ$ ($c = 2.0$ in water, equilibrium value).

Analysis: calc. for di-O-methyl hexose, $C_8H_{16}O_6$: methoxyl, 29.8%

Found: methoxyl, 29.5, 29.6%.

A paper chromatogram of the compound using butanol-ethanol-water (5:1:4) and the p-anisidine hydrochloride spray reagent showed a single, bright yellow, U.V. fluorescent spot of R_f value 0.51 and R_{TG} 0.61.

A 20.8 mg. sample was oxidized with 20 ml. of 0.02M sodium metaperiodate at room temperature. The rate of consumption of periodate was as follows: after 6 hours, 1.5 moles; 24 hours, 1.7 moles; and 48 hours, 1.8 moles. After 48 hours 1.53 moles of formaldehyde were produced, as determined by the formation of the dimedone complex which melted sharply at 186-8°C.

N. Attempted vinylation of penta-O-acetyl sucrose

Penta-O-acetyl sucrose, 225 mg., was dissolved in 15 ml. of chloroform and 25 ml. of vinyl acetate (freshly distilled, b.p. 71-72°C) was added and the solution cooled to -25°C. One g. of mercuric acetate and one drop of concentrated sulfuric acid were added and the mixture stirred mechanically for 3 hours. The reaction mixture was then washed free of acid with 1% sodium carbonate, washed with water, dried with sodium sulfate and evaporated under reduced pressure to yield 192 mg. of a colorless sirupy residue; soluble in methanol and chloroform; insoluble in water and petroleum ether. The residue did not reduce Fehling's solution, yielded a dark-colored, insoluble residue on treatment with acid, and showed unsaturation toward bromine in carbon tetrachloride. On repeated attempts at crystallization, the substance gradually was transformed into an insoluble, hard, colorless film.

Another run, in which 167 mg. of penta-O-acetyl sucrose was treated with vinyl acetate at -30°C for 6 hours, was halted by the addition of 10 ml. of pyridine. The mixture was washed with water, then evaporated to yield a colorless sirup, 208 mg., which on drying in vacuo partially crystallized in needle-like crystals. Ethanol readily dissolved the sirup but not the crystalline material (m.p. 107-8°C). The ethanol extract was

hydrogenated over palladized charcoal to yield a colorless sirup which was purified by chromatography on alumina using chloroform as solvent and developer. The eluate (under the conditions of the purification, penta-O-acetyl sucrose would be retained on the column) on evaporation gave 72 mg. of a colorless sirup.

Analysis: calc. for a mono-O-ethyl-penta-O-acetyl sucrose, $C_{27}H_{42}O_{16}$: ethoxyl, 6.7%; acetyl, 34.5%. Found: ethoxyl, 5.0%; acetyl, 32.3%. This experiment and similar ones indicated that vinylation was not proceeding to any appreciable extent. In one experiment, unreacted penta-O-acetyl sucrose was recovered in 37% yield.

Penta-O-acetyl sucrose, 107 mg., dissolved in 10 ml. ethyl acetate and 20 ml. vinyl acetate, was treated at -30°C with mercuric acetate and sulfuric acid for 6 hours. The reaction mixture was then treated with 10 ml. pyridine, washed with water, dried, and evaporated to yield a partially crystalline residue. This product was purified by chromatography on alumina and recrystallized from chloroform-petroleum ether to yield 46 mg. of colorless crystals: m.p. $107-8^{\circ}\text{C}$; $[\alpha]_D^{23} = 0.00^{\circ}$ ($c = 4.7$ in chloroform); soluble in chloroform, ethyl acetate, ether, insoluble in water, methanol, petroleum ether. Found: acetyl, 38.1, 39.7%; mercury, 42.9, 43.2%. This crystalline product was also obtained when only vinyl acetate, mercuric sulfate and sulfuric acid were brought together. The substance was unstable,

on standing a gradual decomposition took place to yield dark-colored insoluble product. The melting point was variable ranging from 90 to 110°C. It was probable that the substance was a complex of vinyl acetate and mercuric acetate.

0. Preparation of 1:2-3:4-di-O-isopropylidene-D-galactose

Di-O-acetone-D-galactose was prepared according to the method of Van Grunenberg, Brecht and Freudenberg (98).

Anhydrous α -D-galactose, m.p. 160-3°C,
 $[\alpha]_D^{+130}$ (after 3 minutes) $\rightarrow +80^\circ$ (constant at 5 hours) ($c = 9.12$ in water), 100 g., was suspended in 2 liters of anhydrous acetone and 120 g. of zinc chloride and a mixture of 20 g. of phosphorus pentoxide and 40 g. of phosphoric acid added. The mixture was shaken mechanically for 48 hours at room temperature. A considerable quantity of the sugar did not dissolve. The solution was poured with vigorous stirring into a solution of 200 g. sodium carbonate in 500 ml. of water. After standing several hours the mixture was filtered, the solids washed with acetone, and the combined filtrate and washings evaporated under reduced pressure until most of the acetone was driven off. The aqueous solution was then extracted with three 150 ml. portions of ether and the combined ether extracts evaporated. Distillation of the sirupy residue yielded 49.6 g. (34% yield) of a colorless, viscous

sirup; $[\alpha]_D^{20} = -55.0^\circ$ ($c = 6.656$ in chloroform). A chromatogram using butanol-ethanol-water (5:1:4) and the p-anisidine hydrochloride reagent showed a single, yellow spot, R_f 0.88.

P. 6-O-Ethyl-1:2-3:4-di-O-isopropylidene-D-galactose

To 5.037 g. of di-O-acetone-D-galactose, in a 500 ml. flask equipped with a stirrer, reflux condenser and dropping funnel, was added 10 ml. of acetone and 10 g. sodium hydroxide dissolved in 25 ml. of water. The mixture was heated to 55°C and with vigorous stirring 13 ml. of diethyl sulfate was added dropwise over a period of 45 minutes. The temperature of the mixture was then raised to 85°C and maintained for 1 hour. The reaction mixture was cooled to room temperature and extracted with three 20 ml. portions of chloroform. The combined extracts were dried with anhydrous sodium carbonate, evaporated and the residual sirup distilled under high vacuum from sodium carbonate. A colorless, mobile sirup was obtained; weight 3.677 g. (yield 66%). A sample of the product was hydrolysed in boiling 70% aqueous acetic acid and the hydrolysate chromatographed using butanol-ethanol-water (5:1:4) as developer and the p-anisidine hydrochloride spray reagent. A distinct, brown, non-fluorescent spot, R_f 0.40, appeared for 6-O-ethyl-D-galactose plus a faint, yellow-brown, U.V. fluorescent spot, R_f 0.11 for D-galactose.

The sirup was redistilled under high vacuum

from sodium hydroxide to give 2.634 g. of a colorless, mobile sirup, b.p. 101-103°C/0.2 mm., $[\alpha]_D^{27} = -57.6^\circ$ (c= 4.895 in ethanol). After standing 5 months the product failed to crystallize.

Q. 6-O-Ethyl-D-galactose

A 783 mg. sample of 6-O-ethyl-di-O-acetone-D-galactose was dissolved in 10 ml. of 80% aqueous acetic acid and heated on the steam bath under reflux for 15 hours. The solution was then cooled and evaporated to dryness and the residue was refluxed in 10 ml. water for 5 hours in order to reverse any acetate formation. On evaporation, a viscous, colorless sirup was obtained which failed to crystallize on standing 3 months. A chromatogram showed the presence of a trace of D-galactose in the product.

The product was purified by chromatography on a cellulose column using butanol-water as developer. The appropriate fractions yielded on evaporation a colorless sirup which on drying to constant weight formed a hard glass, weight 358 mg., $[\alpha]_D^{25} = +74.2^\circ$ (c= 6.0 in water, equilibrium value). Analysis: calc. for mono-O-ethyl hexose, $C_8H_{16}O_6$: ethoxyl, 21.6%. Found: ethoxyl, 21.7, 21.5%. A paper chromatogram using butanol-ethanol-water (5:1:4) and the p-anisidine hydrochloride spray reagent revealed a single, brown, non-fluorescent spot of R_f 0.40.

R. Vinylation of 1:2-3:4-di-O-isopropylidene-D-galactose

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A solution of 13.0 g. (0.05 mole) of di-O-acetone-D-galactose in 96 ml. (1 mole) of vinyl acetate was mechanically stirred and cooled to -25°C and mercuric acetate, 0.5 g., and 2 drops of concentrated sulfuric acid were added. The mercuric acetate dissolved within a few minutes to give a slightly milky solution. After 3 hours, the reaction mixture was transferred to a separatory funnel and washed rapidly with three 25 ml. portions of a cold saturated solution of sodium carbonate. The organic layer was dried with anhydrous sodium carbonate and immediately evaporated under reduced pressure at a temperature less than 45°C to yield a colorless, mobile sirup, which was then distilled under high vacuum from sodium carbonate. At a bath temperature of 210°C, a colorless product began to come over (b.p. about 135°C/0.3 mm.). After about 5 ml. distillate had been collected, the still head temperature dropped rapidly. The holdup was a dark-colored, non-mobile substance which was discarded.

The distillate, weight 3.49 g., was a colorless sirup having a mobility intermediate between that of di-O-acetone-D-galactose (like liquid honey) and 6-O-ethyl-di-O-acetone-D-galactose (like glycerol). It decolorized bromine in carbon tetrachloride readily with the formation of a pale-yellow precipitate. Di-O-acetone-D-galactose also was found to decolorize

bromine in carbon tetrachloride with the formation of a precipitate but at a considerably slower rate.

A 637 mg., sample of the distillate was dissolved in 50 ml. of absolute methanol and shaken under 2 atmospheres pressure of hydrogen in the presence of palladized charcoal catalyst for 5 hours. The colorless sirup obtained after filtration and evaporation of the solvent was dissolved in 25 ml. of N sulfuric acid and heated on the steam bath for 16 hours. The hydrolysate was deionized by passage through a column of Amberlite IR-4B and evaporated to yield a colorless sirup. A chromatogram using butanol-ethanol-water (5:1:4) and the p-anisidine hydrochloride spray reagent showed (i) a very distinct, yellow-brown, U.V. fluorescent, spot, R_f 0.10 for D-galactose, and (ii) an elongated, diffuse, yellow-red-brown spot, R_f 0.38 (approximately). The latter represented a mixture.

The remainder of the distillate was redistilled from sodium hydroxide to yield 0.54 g. of a colorless, fairly mobile sirup boiling at 130°C/0.3 mm. This product was hydrogenated in dry ether in the presence of 100 mg. of platinum oxide catalyst for 24 hours. The product obtained after filtration and evaporation of the solvent was redistilled from sodium carbonate, then from sodium hydroxide, and finally from sodium to yield 68. mg. of a colorless, fairly mobile sirup boiling at 90°C at 0.3 mm. This product was hydrolysed with boiling 0.1 N sulfuric

acid for 19 hours, neutralized with barium carbonate, filtered and evaporated. The residue was taken up in methanol, filtered and evaporated to give a colorless sirup. On a chromatogram run for 40 hours using methyl ethyl ketone-water and the p-anisidine hydrochloride spray reagent, four spots were observed (i) a brown, non-fluorescent spot identical in color and R_f value with 6-O-ethyl-D-galactose, (ii) a yellow, U.V. fluorescent spot travelling slightly ahead of the 6-O-ethyl-D-galactose (iii) a yellow, U.V. fluorescent spot travelling slightly behind 6-O-ethyl-D-galactose, and (iv) a brown-yellow, U.V. fluorescent spot corresponding to D-galactose.

In a second run, 10 g. of di-O-acetone-D-galactose was treated with vinyl acetate, mercuric acetate and sulfuric acid at -25°C as described above. After a reaction time of 2 hours, the solution was washed with cold aqueous sodium carbonate, dried, evaporated and the colorless residue distilled. A fraction boiling at $114\text{--}116^{\circ}\text{C}$ at 0.3 mm. was obtained. After a redistillation from sodium hydroxide, the colorless, sirupy product was dissolved in 25 ml. anhydrous ether and shaken under 2 atmospheres pressure of hydrogen over 100 mg. platinum oxide catalyst for 6 hours at room temperature. Filtration and evaporation of the solvent yielded a clear sirup. The sirup was dissolved in 50% aqueous ethanol, the solution adjusted to 0.1 N with concentrated sulfuric acid and heated on the steam bath under reflux for $3\frac{1}{4}$ hours. The

hydrolysate was neutralized with barium carbonate, filtered and evaporated to yield a colorless sirup. A chromatogram developed with methyl ethyl ketone-water revealed four spots: (i) a yellow, fluorescent spot for D-galactose, (ii) a brown spot which corresponded with 6-O-ethyl-D-galactose, and (iii) (iv) two yellow, fluorescent spots of unknown identity in the neighbourhood of 6-O-ethyl-D-galactose.

A preliminary purification was carried out on a 30 x 2.6 cm. cellulose column using butanol-water. The fractions containing (ii) (iii) and (iv) were combined and evaporated to yield 311 mg. of colorless, viscous sirup. A second purification was carried out on a 50 x 2.8 cm. cellulose column using methyl ethyl ketone-water and collecting 10 minute fractions of about 20 ml. volume. To obtain the 6-O-ethyl-D-galactose, the appropriate fractions were combined and evaporated to yield 88.2 mg. of colorless sirup. Final purification was achieved by chromatographing 40 mg. of the sirup on paper (spots of about 2 mg. of sirup) and developing with methyl ethyl ketone-water. Extraction of the appropriate zones of the paper with cold water yielded 28.5 mg. of the desired product (0.7% yield).

Drying to constant weight gave the 6-B-ethyl-D-galactose as a colorless, hard glass, $[\alpha]_D^{25} = +76.5^\circ$ ($c = 1.4$ in water). Analysis: calc. for a mono-O-ethyl hexose, $C_8H_{16}O_6$:

ethoxyl, 21.6%. Found: ethoxyl, 21.4, 21.0%. The substance was chromatographed using butanol-ethanol-water (5:1:4) and methyl ethyl ketone-water: the spots obtained were found to be identical in color and R_f value with authentic 6-O-ethyl-D-galactose.

S. Deacetylation experiments with anion exchange resin

Dowex I anion exchange resin was air-dried, pulverized and sieved and 25 g. of the 40-80 mesh fraction was placed in a glass tube of 1.8 cm. I.D. closed at one end with a constriction and glass wool plug. The length of the resin column was 23.5 cm. after wetting and the liquid capacity was 25 ml. The column was treated with 10% aqueous sodium hydroxide, washed free of base with water and then washed with successive 50 ml. portions of 20, 40, 60, 80 and 90% aqueous methanol and was then ready for use. The same column was used throughout and was regenerated after each experiment by washing out with the aqueous solutions applied in the reverse order followed by their reapplication in the original order. Direct application of 90% aqueous methanol to the water-wet column caused the formation of air bubbles in the column.

In a typical deacetylation experiment 5 ml. of a 90% aqueous methanol solution containing 0.5000 g. of sucrose octaacetate (m.p. 88.5-89.0°C, $[\alpha]_D^{21} = +59.5^\circ$ (c = 0.79 in chloroform))

(32) was run into the prepared column and washed in with 10 ml. of the solvent. The loaded column was allowed to stand for 24 hours and was then eluted with 90% aqueous methanol; successive 200 ml. fractions of the eluate was separately collected and evaporated to dryness. The yield of colorless, sirupy residue recovered from each fraction is shown in TABLE VIII. The dried residues were dissolved in water and combined and the aqueous solution was filtered and evaporated to a colorless sirup and seeded with sucrose. After 2 days the completely crystalline product (254 mg.) was pulverized, washed with 5 ml. of methanol and dried in vacuo. The dried sugar (232 mg., 92% yield) melted at $184-6^{\circ}$, $[\alpha]_D^{19} = +65.5^{\circ}$ ($c = 1.664$ in water) and had the crystal form and taste of pure sucrose. A paper chromatogram of the sirup developed with butanol-ethanol-water (4:1.1:1.9) showed a well-defined spot, $R_f 0.15$, which corresponded to sucrose (99); the Raybin test (89) was positive.

The acetates of the monosaccharide derivatives (TABLE VIII) were treated by the above procedure and the corresponding deacetylated compounds were quantitatively recovered in the first two or three 200 ml. fractions of eluate, whereas eight fractions were required for complete recovery of sucrose (TABLE VIII).

In a preliminary experiment a solution of 1.000 g. of sucrose octaacetate in 50 ml. of 90% aqueous methanol was passed through the column at a flow rate of one ml. per minute and the column was then washed out with a further 50 ml. of the

solvent at the same rate. Evaporation of the eluate yielded 0.93 g. of a colorless sirup, which did not crystallize on seeding with sucrose octaacetate and sucrose and showed no spot for sucrose when chromatographed on paper. When this sirupy product was again run through the column, the eluate yielded crystalline sucrose.

TABLE VII

Deacetylation of Sugar Acetates on a Column of AnionExchange Resin

<u>Sugar Acetate</u>	<u>Deacetylated Product</u>			
	Yield %	m.p.°C.	Mixed* m.p.°C.	Reported m.p.°C.
Sucrose octaacetate	92	184-186	**	185-188 (100) 187 (14)
D-Mannitol hexaacetate	95	164-166	164-166	166 (101)
Cyclohexyl- β -D-glucopyranoside tetraacetate	97	134-135	134-135	133-135 (102)
Methyl-4-O-methyl β -D-glucopyranoside triacetate	99	100-101	100-101	101-102 (73) 102-103 (103)

* With authentic specimens of the non-acetylated sugar derivatives.

** The melting point of even very pure sucrose is reported to vary with the medium used for purification; a mixed melting point was therefore not definitive (101).

TABLE VIIIElution of Deacetylated Compounds from the Resin Column

<u>Fraction Number*</u>	<u>Weight of Saccharide Recovered (mg.)</u>			
	<u>Sucrose</u>	<u>D-Mannitol</u>	<u>C.G.**</u>	<u>M.M.G.***</u>
1	4	29	124	157
2	22	68	0	0
3	57	10	-	0
4	73	0	-	-
5	58	-	-	-
6	34	-	-	-
7	18	-	-	-
8	8	-	-	-
Total yield:	<u>274</u>	<u>107</u>	<u>124</u>	<u>157</u>
Weight of washed and dried crys- talline residue:	232	102	118	155
Theoretical yield:	253	105	122	156

* Successive 200 ml. portions of the eluate.

** Cyclohexyl- β -D-glucopyranoside.

*** Methyl-4-O-methyl- β -D-glucopyranoside.

CLAIMS TO ORIGINAL RESEARCH

1. Four new derivatives of sucrose have been prepared and their structures established. These compounds are:

1',4,6'-tri-O-methyl sucrose, 1', 6,6'-tri-O-trityl sucrose, 2,3,3',4,4'-penta-O-acetyl sucrose and 2,3,3',4,4'-penta-O-methyl sucrose.

2. A new di-O-methyl-D-fructose derivative has been prepared and characterized as 1, 6-di-O-methyl-D-fructose.

3. The direct tritylation of sucrose was reexamined and shown to lead to a mixture of tritylated sucrose derivatives and reducing sugars.

4. The selective detritylation of sucrose derivatives was accomplished by catalytic hydrogenation and by graded hydrolysis.

5. The course of the Purdie methylation of sucrose derivatives was studied by means of chromatography. Acetyl migration from C₄ to C₆ in the glucose moiety of sucrose has been shown to occur under the methylation conditions.

6. The Adelman vinylation procedure was applied to selectively substituted sucrose and D-galactose derivatives and the usefulness of this reaction in the carbohydrate field was assessed.

7. A new compound, 6-O-ethyl-D-galactose has been synthesised for the first time by two different routes which establish the structure.

8. The deacetylation of the acetate derivatives of several carbohydrates by passage through columns of basic ion exchange resin was developed as a rapid and convenient laboratory method particularly applicable to acid-sensitive compounds.

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