SELECTIVE SUBSTITUTION IN SUCROSE

II. THE SYNTHESIS OF 2,3,3′,4,4′-PENTA-*O*-METHYL SUCROSE AND C_4 TO C_6 ACETYL MIGRATION IN SUCROSE[1]

G. G. McKeown[2] and L. D. Hayward

ABSTRACT

Deacetylation of crystalline tri-*O*-trityl-penta-*O*-acetyl sucrose gave an amorphous tri-*O*-trityl sucrose derivative and methylation of this product followed by graded hydrolysis with acetic acid yielded a sirupy penta-*O*-methyl sucrose. Hydrolytic cleavage of the penta-*O*-methyl sucrose to nearly equal amounts of 2,3,4-tri-*O*-methyl-D-glucose and 3,4-di-*O*-methyl-D-fructose established the original positions of the *O*-trityl groups at the primary carbons in the sucrose molecule. It was therefore evident that acetyl migration from C_4 to C_6 in the glucose moiety had occurred during an earlier synthesis of 1′,4,6′-tri-*O*-methyl sucrose from the tri-*O*-trityl-penta-*O*-acetyl sucrose. The probable conformation of the transition state in the acyl migration is discussed.

INTRODUCTION

The synthesis of 1′,4,6′-tri-*O*-methyl sucrose from tri-*O*-trityl-penta-*O*-acetyl sucrose was described in Part I (14). The occurrence of an *O*-methyl group at C_4 of the glucose unit in the tri-*O*-methyl sucrose end product indicated either that C_4 of the glucose unit had been originally substituted by an *O*-trityl group in preference to C_6, or that the *O*-trityl substitution had been at C_6 and the *O*-acetyl group on C_4 had migrated to C_6 during the subsequent detritylation or methylation steps. The objective of the work described here was to establish the structure of the tri-*O*-trityl-penta-*O*-acetyl sucrose and thus provide a decision between the two possibilities. The structural proof is outlined in Fig. 1.

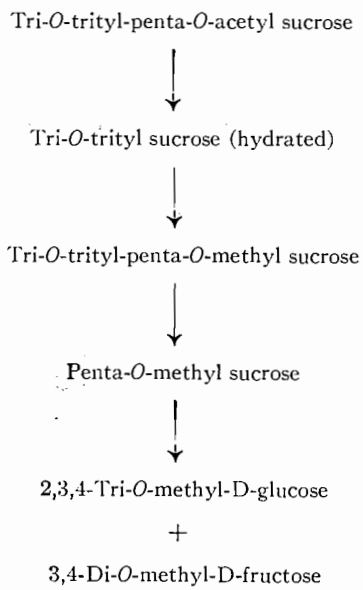


FIG. 1. Proof of the structure of the tri-*O*-trityl-penta-*O*-acetyl sucrose.

[1]*Manuscript received April 18, 1957.*
Contribution from the Department of Chemistry, University of British Columbia, Vancouver, B.C.
[2]*Present address: Department of National Health and Welfare, Ottawa, Ontario.*

Our attempts to prepare tri-*O*-trityl sucrose by direct tritylation of sucrose yielded an intractable mixture (14); however, the pure compound was readily obtained by deacetylation of the crystalline tri-*O*-trityl-penta-*O*-acetyl sucrose. The product was a colorless glass, $[\alpha]_D^{22}$ +14.7° (c = 3.3 in chloroform), with a trityl content corresponding to that calculated for a tetrahydrate of tri-*O*-trityl sucrose. The powdered material reduced Fehling's solution only after acid hydrolysis, and acetylation gave back the original tri-*O*-trityl-penta-*O*-acetyl sucrose in 83% yield. Catalytic hydrogenation of the tri-*O*-trityl sucrose yielded only a trace of sucrose; catalyst poisoning as encountered in the attempted hydrogenolysis of the tri-*O*-trityl-penta-*O*-acetyl sucrose (14) appeared to halt the reaction at an intermediate stage.

Methylation of the hydrated tri-*O*-trityl sucrose by the Purdie method proceeded very slowly and 11 treatments were required to achieve a satisfactory degree of substitution. The course of the reaction was followed by detritylating and hydrolyzing a sample after each methylation and chromatographing the hydrolyzate on paper. The final product was a colorless glass, $[\alpha]_D^{17}$ +32.4° (c = 6.14 in chloroform), with trityl and methoxyl contents corresponding to a tri-*O*-trityl-penta-*O*-methyl sucrose.

The fully methylated tri-*O*-trityl sucrose was detritylated by graded hydrolysis in 98% acetic acid solution on the steam bath (14) and the course of the reaction was followed with a polarimeter. The specific rotation of the methylated tri-*O*-trityl sucrose in glacial acetic acid was approximately +50° and the assumption was made that the specific rotation of the corresponding penta-*O*-methyl sucrose would be in the range of +50° to +65° since sucrose, tri-*O*-methyl sucrose, and octa-*O*-methyl sucrose showed similar values (14). Taking into account the large change in molecular weight it was calculated that the apparent specific rotation of the acetic acid solution during the hydrolysis would decrease from about +50° to about +20° if detritylation were the predominant reaction. If hydrolysis of the glycosidic bond and mutarotation of the monosaccharides occurred concurrently and at a comparable rate, the optical rotation would decrease to zero, since the equilibrium specific rotations of the partially methylated D-glucose and D-fructose fragments were opposite in sign and nearly equal in magnitude (7, 9, 12, 13). Actually the observed apparent specific rotation decreased according to a second-order reaction rate curve from the initial value of +48.8° to +19.8° in 50 minutes; at this point, where the optimum yield of penta-*O*-methyl sucrose was expected, the reaction was interrupted by evaporation of the solvent under reduced pressure and below 50° C.

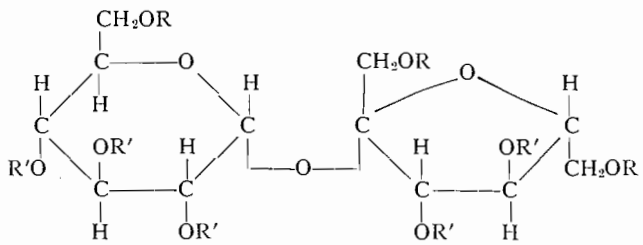
The sirupy detritylated product was separated from the triphenyl carbinol by extraction with water and was purified by chromatography on a cellulose column. The appropriate fractions from the column yielded 18.5% of the theoretical amount of pure penta-*O*-methyl sucrose as a colorless, viscous sirup, $[\alpha]_D^{23}$ +64.3° (c = 1.46 in water), which had the correct methoxyl content and reduced Fehling's solution only after acid hydrolysis. A sample of the sirup was hydrolyzed with 0.05 N sulphuric acid and the hydrolyzate was separated on a cellulose column into two chromatographically pure fractions which analyzed correctly for a tri-*O*-methyl hexose and a di-*O*-methyl hexose. The yields of the hexose derivatives isolated were 89% and 75% of the theoretical values respectively.

The sirupy tri-*O*-methyl hexose was identified as 2,3,4-tri-*O*-methyl-D-glucose on the following evidence: (*a*) the equilibrium specific rotation, $[\alpha]_D^{24}$ +70.6° (c = 3.26 in water), was in good agreement with previously reported values (7, 12); (*b*) paper chromatograms of the compound developed with two different solvents showed a single spot

identical in color and R_f value to that produced by an authentic sample of 2,3,4-tri-*O*-methyl-D-glucose; (*c*) treatment of the sugar derivative with aniline gave in good yield a crystalline product melting at 127–128° C. which showed no depression in melting point on admixture with an authentic sample of 2,3,4-tri-*O*-methyl-D-glucose anilide.*

The sirupy di-*O*-methyl hexose was identified as 3,4-di-*O*-methyl-D-fructose on the following evidence: (*a*) the specific rotation of our compound, $[\alpha]_D^{24}$ −58.5° (c = 2.0, equilibrium value in water), was in good agreement with previously reported values (9, 13); (*b*) a paper chromatogram of the compound showed a single spot of the color characteristic of a ketose and with R_{TG} value in agreement with the recorded value (8); (*c*) periodate oxidation of the sugar derivative consumed 1.8 moles of periodate and produced 1.53 moles of formaldehyde. Although the theoretical behavior of 3,4-di-*O*-methyl-D-fructose toward periodate required values of 2.0 and 2.0 moles respectively, this sugar derivative has been reported to give low yields of formaldehyde of the order of 1.5 moles (4) under the same conditions.

The isolation and identification of the partially substituted hexose units established the structure of the penta-*O*-methyl sucrose as the 2,3,3′,4,4′-penta-*O*-methyl derivative (I*a*). The structures of the tri-*O*-trityl sucrose and the tri-*O*-trityl-penta-*O*-acetyl sucrose could then be designated as I*b* and I*c* respectively. The trityl groups therefore occupied the three primary hydroxyl groups of the sucrose molecule and it followed that the *O*-acetyl group at C_4 of the glucose moiety had actually migrated to C_6 during the synthesis of 1′,4,6′-tri-*O*-methyl sucrose (14).



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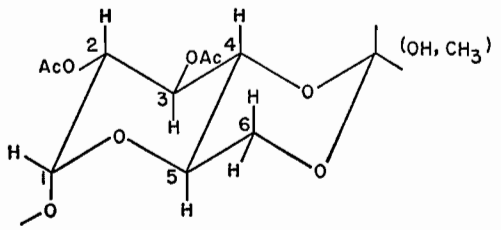
(*a*) R = H, R′ = CH_3
(*b*) R = $C(C_6H_5)_3$, R′ = H
(*c*) R = $C(C_6H_5)_3$, R′ = $COCH_3$
(*d*) R = H, R′ = $COCH_3$

The formation of cyclic ortho-acid ester has long been accepted as the intermediate step involved in acyl migration in polyols and aminoalcohols (5, 6). On this basis the migration of acetyl from C_4 to C_6 in the glucopyranose unit of the penta-*O*-acetyl sucrose (I*d*) involved a transition state in which a *m*-dioxane ring was fused to the pyranose ring at C_4 and C_5 (10). The well-established (15) preference for the *trans*-two chair conformation in such fused-ring systems suggested that the transition state had conformation II. This conformation of the glucose moiety was identical with that in crystalline sucrose as established by Beevers and co-workers (2, 3) from X-ray diffraction studies. The preference for the same conformation in weakly alkaline solutions of other poly-*O*-acyl-D-glucopyranose derivatives would be consistent with the facile C_4 to C_6 acyl migrations which have been reported (16). The assignment of the equatorial and axial positions on the *m*-dioxane ring to the methyl and hydroxyl groups of the orthoester could not be

The authors wish to thank Dr. G. G. S. Dutton for a sample of 2,3,4-tri-O-methyl-D-glucose anilide.



II

made from examination of the molecular models. The relative non-bonded interactions of axial methyl and hydroxyl substituents on cyclohexane rings have not been assessed (1).

EXPERIMENTAL

Paper chromatograms were prepared with the following solvent systems: (A) butanol: ethanol: water, 5:1:4; (B) methyl ethyl ketone: water azeotrope and *p*-anisidine spray reagent. Fructose derivatives, including sucrose, were distinguished from glucose derivatives by heating the developed and sprayed chromatograms for 1.5 minutes, which caused the preferential development of the yellow, U.V.-fluorescent ketose spots; heating for the usual 10 minutes caused the appearance of spots for both glucose and fructose derivatives (11). All melting points were corrected.

Tri-O-trityl Sucrose Tetrahydrate

To a solution of 10.0 g. of tri-*O*-trityl-penta-*O*-acetyl sucrose (14) in 25 ml. of anhydrous tetrahydrofuran were added 100 ml. of anhydrous methanol and 5 ml. of 0.1 *N* sodium methoxide solution. The solution was heated to reflux for 10 minutes, kept at room temperature overnight, and then evaporated to dryness under reduced pressure. The residue was taken up in ethyl acetate and washed with water; evaporation of the organic layer yielded a colorless glass (8.6 g., 103% yield calculated as anhydrous tri-*O*-trityl sucrose) which was ground to a fine white powder. The product softened at 125–130° C. and had $[\alpha]_D^{22}$ +14.7° (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. 1068. Found: trityl, 63.6, 63.5%; mol. wt. 950 (Rast). The compound was soluble in methanol and ethanol, insoluble in water and petroleum ether, and reduced Fehling's solution only after acid hydrolysis. When left standing for more than a year samples in various solvents failed to crystallize.

Acetylation of 71 mg. of the powdered glass with pyridine (2 ml.) and acetic anhydride (1 ml.) for 24 hours at room temperature and crystallization of the product from chloroform–methanol yielded 66 mg. (83%) of tri-*O*-trityl-penta-*O*-acetyl sucrose, m.p. 233–234° C., not depressed on admixture with an authentic specimen.

Methylation of Tri-O-trityl Sucrose

Tri-*O*-trityl sucrose tetrahydrate, 8.6 g., was dissolved in 50 ml. of methyl iodide and treated with 10 g. of silver oxide and 15 g. of Drierite at reflux temperature for 24 hours. The mixture was then filtered, the solids were washed with chloroform, and the combined filtrate and washings were evaporated to yield a colorless glass. The glass was methylated a second time and a sample of the colorless product was then hydrolyzed and detritylated by heating for 3 hours on the steam bath in aqueous acetic acid. A paper chromatogram of the hydrolyzate indicated it 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 spots (Solvent A) were respectively faint, yellow, R_f 0.13; distinct, yellow, R_f 0.28; distinct, yellow, R_f 0.51 (probably di-*O*-methyl-D-fructose and di-*O*-methyl-D-glucose); distinct, red-brown, R_f 0.74.

The glassy product was remethylated a further nine times by essentially the same procedure and a sample of the methylated material was hydrolyzed and examined on a paper chromatogram after each treatment. D-Fructose and di-*O*-methyl-D-glucose were absent after five methylations but a faint spot for mono-*O*-methyl-D-fructose persisted to the 10th methylation. The methoxyl content increased as follows: after seven methylations, 11.7%; after eight methylations, 12.6%; after nine methylations, 13.0%. The final product (11 methylations) was a colorless glass which was pulverized and dried *in vacuo*, $[\alpha]_D^{17}$ +32.4° (c = 6.14 in chloroform). Analysis: Calc. for $C_{74}H_{74}O_{11}$: trityl, 64.1%; OCH_3, 13.6%. Found: trityl, 63.9, 64.4%; OCH_3, 13.3, 13.4%.

Penta-O-methyl Sucrose

In a preliminary experiment 1 g. of methylated tri-*O*-trityl sucrose was dissolved in 25 ml. of glacial acetic acid, 1 ml. of water was added, and the solution was refluxed for 30 minutes, then evaporated under reduced pressure. The dried, partially crystalline residue was extracted with cold water and the filtered extract was evaporated to give a colorless sirup, 368 mg. (102% yield calculated as penta-*O*-methyl sucrose), $[\alpha]_D^{25}$ +28.3° (c = 7.36 in ethanol). Paper chromatography indicated that the sirup was a mixture of mono-*O*-methyl-D-fructose, 3,4,-di-*O*-methyl-D-fructose, 2,3,4-tri-*O*-methyl-D-glucose, tetra-*O*-methyl sucrose, and penta-*O*-methyl sucrose. The spots (Solvent A) were respectively faint, yellow, R_f 0.29 (R_{TG} 0.35); distinct, yellow, R_f 0.51 (R_{TG} 0.61); distinct, red-brown, R_f 0.71 (R_{TG} 0.85); faint, yellow, R_f 0.61 (R_{TG} 0.73); very distinct, yellow, R_f 0.77 (R_{TG} 0.93). The previously reported R_{TG} values for 2,3,4-tri-*O*-methyl-D-glucose and 3,4-di-*O*-methyl-D-fructose were 0.85 and 0.61 respectively in this solvent system (8). Heating a developed and sprayed chromatogram for 1.5 minutes produced only one ketose spot of R_f 0.75 (R_{TG} 0.91) which probably represented the penta-*O*-methyl sucrose and indicated its presence in high concentration.

Methylated tri-*O*-trityl sucrose, 2.28 g., was dissolved in 50 ml. of glacial acetic acid, 1 ml. of water was added, and the solution was heated on the steam bath under a reflux condenser. The apparent specific rotation of the solution, measured at room temperature, was +48.8°, +38°, +35°, +28.2°, +24.2°, +22.0°, and +19.8° after 0, 5, 10, 20, 30, 40, and 50 minutes respectively. The solution was then evaporated as rapidly as possible under reduced pressure and at a bath temperature below 50° C. and the partly crystalline residue was dried *in vacuo* over sodium hydroxide pellets. Extraction of the residue with cold water and evaporation of the solvent yielded a colorless sirup (700 mg., 85% calculated as penta-*O*-methyl sucrose), which was dissolved in 2 ml. of Solvent B and run onto a 50×2.6 cm. diam. column of cellulose. The chromatogram was developed with the same solvent and fractions of approximately 10 ml. were collected over 5-minute intervals and examined in the polarimeter and by paper chromatography. The bulk of the penta-*O*-methyl sucrose was found in four fractions which were combined, concentrated, and rechromatographed by the same procedure. Pure penta-*O*-methyl sucrose, 153 mg. (18.5% yield), was recovered from three fractions of the final eluate as a colorless viscous sirup, $[\alpha]_D^{23}$ +64.3° (c = 1.46 in water). Analysis: Calc. for $C_{17}H_{32}O_{11}$: OCH_3, 37.6%. Found: OCH_3, 37.7, 37.2%. The product reduced Fehling's solution only after acid hydrolysis.

Acid Hydrolysis of the Penta-O-methyl Sucrose

Penta-*O*-methyl sucrose, 146 mg., was dissolved in 10 ml. of 0.05 *N* sulphuric acid and the solution was heated on the steam bath for 2 hours. The hydrolyzate was neutralized with solid barium carbonate, filtered, and evaporated to dryness and the residue was extracted with acetone. The sirup recovered by evaporation of the acetone extract was chromatographed on a cellulose column with Solvent B 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.

The tri-*O*-methyl hexose was a colorless, viscous sirup, $[\alpha]_D^{24}$ +70.6° (c = 3.26 in water, equilibrium value). Analysis: Calc. for $C_9H_{18}O_6$: OCH_3, 41.8%. Found: OCH_3, 41.1, 41.6%. Paper chromatograms of the compound revealed a single spot identical in color and R_f value to that obtained with authentic 2,3,4-tri-*O*-methyl-D-glucose using both Solvents A and B; red-brown spots were obtained with R_f values of 0.71 and 0.52 respectively. A sample of the tri-*O*-methyl hexose, 36 mg., was refluxed with 70 mg. of aniline and 2 ml. of absolute ethanol for 6 hours. The yellow sirup, 48 mg., was recovered by evaporation of the volatile components under reduced pressure, and crystallized in fine colorless needles upon seeding with 2,3,4-tri-*O*-methyl-D-glucose anilide. After three recrystallizations from ether – petroleum ether the derivative melted at 127–128° C. and the melting point was not depressed by admixture with an authentic specimen of 2,3,4-tri-*O*-methyl-D-glucose anilide.

The di-*O*-methyl hexose was a colorless, viscous liquid, $[\alpha]_D^{24}$ −58.5° (c = 2.0 in water, equilibrium value). Analysis: Calc. for $C_8H_{16}O_6$: OCH_3, 29.8%. Found: OCH_3, 29.5, 29.6%. A paper chromatogram of the compound prepared with Solvent A showed a single, bright yellow, U.V.-fluorescent spot of R_f 0.51 (R_{TG} 0.61). A 20.8 mg. sample of the compound was oxidized with 20 ml. of 0.02 *M* sodium metaperiodate at room temperature. The consumption of periodate after 6 hours was 1.5 moles; after 24 hours, 1.7 moles; after 48 hours, 1.8 moles. In 48 hours, 1.53 moles of formaldehyde was produced as determined by the formation of the dimedone complex which melted at 186–188° C.

ACKNOWLEDGMENT

One of us (G. G. M.) wishes to thank Canadian Industries Limited for the Fellowship he received during the research.

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