The Synthesis of a Glucosaminyl-Muramic Acid Disaccharide: Methyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside[1]

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The syntheses of various derivatives of the methyl α-D-glycoside of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (muramic acid) and of the disaccharide, methyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside are described.

Muramic acid, a 3-*O*-(D-1-carboxyethyl) derivative of 2-amino-2-deoxy-D-glucose, and its parent hexose, 2-amino-2-deoxy-D-glucose, have been shown to be the main components of the peptidoglycan chain, which constitutes the backbone of the cell wall of numerous Gram-positive and Gram-negative bacteria.[3] The action of egg-white lysozyme on isolated cell walls releases various fragments including a tetrasaccharide and a disaccharide containing muramic acid and 2-amino-2-deoxy-D-glucose.[4] The structure of an *O*-2-acetamido-2-deoxy-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid was proposed for the latter compound.[4-6] It was, therefore, of great interest to synthesize this disaccharide, thereby allowing a comparison with the fragment obtained from the cell walls. The present paper described the synthesis of various derivatives of muramic acid including the *O*-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid disaccharide. It should also be noted that this represents the first constitutional synthesis of a 2-amino-2-deoxy-(2-amino-2-deoxyglucosyl)glucose disaccharide.

A stereospecific synthesis of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose, and of several derivatives of it, has been described recently by Matsushima and Park.[7,8] The method used in the present work for the preparation of methyl 2-acetamido-4,6-*O*-benzylidene-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (V) from methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III)[9] follows essentially Matsushima and Park's procedure and requires large quantities of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (II).

Glycosidation of 2-acetamido-2-deoxy-D-glucose (I) with methanol in the presence of an acid catalyst for a few hours gives II, contaminated with about 15 to 20% of the β-anomer.[10] Separation of both anomers can be accomplished by fractional crystallization of the 3,4,6-triacetate derivatives[10] or by chromatography on charcoal.[11] The first method, however, lengthens the synthesis by two additional steps, while the second one cannot be carried out conveniently on large amounts of material. It was found that the purification could be accomplished efficiently by crystallization at the step of the benzylidene derivative III, if the amount of α-anomer were increased in the original mixture. When the glycosidation is carried out for a considerable length of time, the amount of α-anomer reaches 87%, but marked de-*N*-acetylation occurs. The crude mixture, consequently, was re-*N*-acetylated and crystallization gave, in 75–80% yield, a compound II containing about 10% of the β-anomer. This compound II was condensed with benzaldehyde, affording a yield of about 60% of III with m.p. 260–262° and $[\alpha]_D$ +40° (in chloroform), in agreement with the values reported by Wiggins.[12] A similar condensation of the mother liquors from II, containing about 65% of the α-anomer, gave an additional amount of III, raising the total yield to 49% calculated from I. Attempts to prepare III by methylation of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucose in dimethyl sulfoxide solution, as described by Roth and Pigman,[13] resulted in the formation of the 3-*O*-methyl ether of III in addition to the required material.

Since the preparation of L-α-chloropropionic acid (IV) starting from L-alanine[8,14] is expensive, it was replaced by the resolution of the commercial DL-α-chloropropionic acid with cinchonine.[15] The condensation of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III) with IV was carried out as described by Matsushima and Park,[8] giving methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (V).

The crystalline methyl ester VI was obtained by the reaction of diazomethane with V, and removal of the benzylidene group gave crystalline methyl 2-acetamido-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (VII). Alternatively, removal of the benzylidene group from V gave a glassy derivative VIII,[6] which was converted into crystalline VII by treatment with diazomethane. Condensation of VII with triphenylchloromethane resulted in the triphenylmethyl ether IX,

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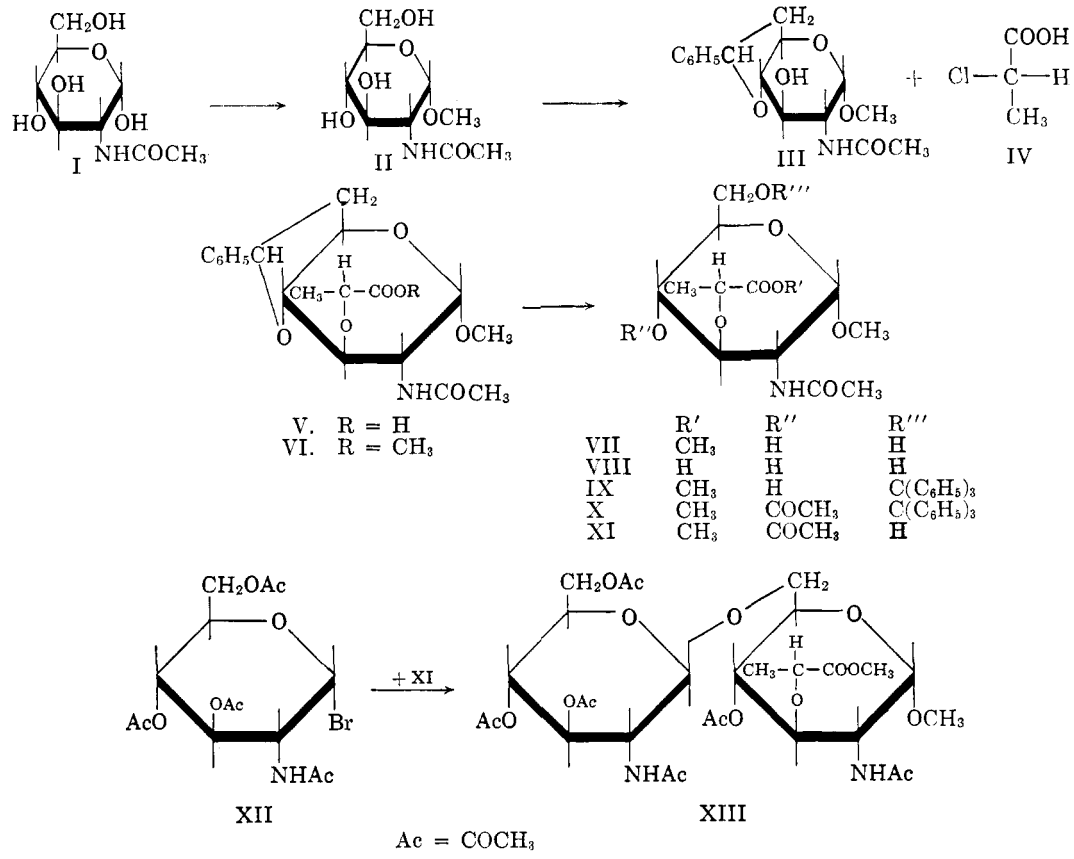

which was further acetylated at position 4 into X. Finally, removal of the triphenylmethyl group gave methyl 2-acetamido-4-*O*-acetyl-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XI). All these derivatives were obtained crystalline and in excellent yields. For the preparation of large amounts of material, steps IX and X were combined and XI was obtained in an over-all yield of 57% from VIII.

Condensation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (XII)[16] with XI in the presence of mercuric cyanide in a mixture of chloroform and nitromethane gave methyl 6-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XIII). Although the yield in this condensation is low (10–15%), a considerable amount of unchanged XI can be recovered from the reaction mixture. Lower yields of a product identical to XIII were obtained when the condensation was carried out in the presence of silver oxide. The β-configuration of the disaccharide linkage formed is established by the low optical rotation ($[\alpha]_D$ +54° in chloroform) of XIII and by its mode of formation.

The synthesis of XIII is a first step in the synthesis of the disaccharide isolated from bacterial cell walls. Removal of the methyl glycoside without scission of the disaccharide bond is being studied at present, and the synthesis of the benzyl glycoside of this disaccharide will be reported later.

Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro or micro (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), which was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or chloroform, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1:50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1:100. The ratio of diameter to length of column was 1:20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (III) from I.—Preliminary experiments with small amounts of material showed that the glycosidation of 2-acetamido-2-deoxy-α-D-glucose (I) with 2% methanolic hydrochloric acid gave products having a positive ninhydrin test after 2 hr. After isolating the product as described below, the optical rotation in water reached a maximum of 120° after 48 hr. at reflux. Reaction for longer periods of time gave appreciable decomposition.

In a 1-l. flask, 50 g. of commercial I was refluxed with 500 ml. of 2% methanolic hydrochloric acid for 48 hr., with exclusion of moisture. The solution was cooled, then stirred overnight with an excess of finely powdered lead carbonate. After filtration, the lead salts were washed with methanol, and the filtrate was evaporated to a sirup, which was dissolved in water and passed through a column of 300 ml. of Amberlite 45-R in the acetate form. The eluate and washings were evaporated to dryness, and the residue was dissolved in 100 ml. of methanol. In order to remove the last traces of hydrochloric acid, a small amount (0.5 to 1 g.) of silver acetate was added, then 15 ml. of acetic anhydride, and the mixture was left at room temperature

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overnight. It then was refluxed for 30 min., filtered, and the filtrate evaporated to dryness. In order to remove the last traces of acetic anhydride, toluene was added twice and evaporated. The crystalline residue was recrystallized from a mixture of ethanol and ether, giving 41.8 g. of a mixture of II and its β-anomer, m.p. *ca.* 195°, $[\alpha]^{24}D$ +109° in water. The mother liquors (12.7 g.) had $[\alpha]D$ +72°.

To 41.0 g. of the previously described compound was added 32 g. of anhydrous zinc chloride and 125 ml. of benzaldehyde. The mixture was shaken at room temperature for 20 hr., then a mixture of 100 ml. of hexane and 100 ml. of water was added to it, and the shaking was resumed for 30 min. The liquid was decanted, then the addition of water and hexane and decantation were repeated three times. The resulting solid was filtered, washed well on the filter with water and hexane, then dried overnight in a desiccator. It was recrystallized from a mixture of water and methanol, giving 33 g. (55%) of needles (IV), m.p. 260–262°, $[\alpha]^{24}D$ +40° (in chloroform),[17] and 4.5 g. with lower melting point and rotation. The mother liquors with $[\alpha]D$ +72° after similar treatment with benzaldehyde gave an additional crop of 2.5 g., m.p. 258–260°, $[\alpha]D$ +39°, affording a total yield of 35.5 g. (59% from impure II, and 49% from I).

Scission of the benzylidene group of III by heating with 60% acetic acid, or by catalytic hydrogenation, gave methyl 2-acetamido-2-deoxy-α-D-glucopyranoside with melting point and optical rotation identical with those obtained by Kuhn, *et al.*,[10] and by Roth and Pigman.[13]

Acetylation of II with acetic anhydride and pyridine gave the 3-*O*-acetyl derivative, m.p. 209–210°, $[\alpha]^{30}D$ +38° (in chloroform, *c* 0.47).[18]

Methyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (V).—This product was prepared from III and L-α-chloropropionic acid (IV)[15] according to Matsushima and Park,[8] yielding 75–80% of V, m. p. 261–262°, $[\alpha]^{18}D$ +115° (in methanol, *c* 1.28).

Anal. Calcd. for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.64; H, 6.29; N, 3.00.

Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-[D-1-(methylcarboxylate)ethyl]-α-D-glucopyranoside (VI).—A solution of 1.0 g. of V in 50 ml. of warm methanol was cooled to room temperature and a slight excess of diazomethane in ether was added. After 30 min., the solution was evaporated and the residue was recrystallized from methanol to give 0.90 g. (85%) of needles, m. p. 210–211°, $[\alpha]^{24}D$ +106° (in chloroform, *c* 0.87).

Anal. Calcd. for $C_{20}H_{27}NO_8$: C, 58.67; H, 6.65; OCH_3, 15.16. Found: C, 58.57; H, 6.66; OCH_3, 15.34.

Methyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate)-ethyl]-α-D-glucopyranoside (VII).—A solution of 0.90 g. of VI in 8 ml. of 60% acetic acid was heated at 100° for 30 min. The solution was evaporated and the residue co-evaporated successively with water and toluene. The residue was crystallized from a mixture of acetone and ether, giving 0.50 g. (70%), melting after recrystallization from ethyl acetate at 151–152°, $[\alpha]^{27}D$ +129° (in chloroform, *c* 0.65).

Anal. Calcd. for $C_{13}H_{23}NO_8$: C, 48.59; H, 7.22; N, 4.36. Found: C, 48.57; H, 7.21; N, 4.43.

Methyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate)-ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (IX).—To a solution of 0.50 g. of VII in 2 ml. of dry pyridine was added 0.48 g. of triphenylchloromethane. The solution was left for 24 hr. at room temperature and then, after being maintained for 1 hr. at 100°, was poured onto cracked ice and extracted with chloroform. The chloroform solution was washed three times with 10% potassium bisulfate solution and three times with water, dried, and evaporated. The residue was recrystallized from benzene, giving 0.85 g. (95%) of prisms, m.p. 213–215°. Recrystallization from methanol raised the m.p. to 217–218°, $[\alpha]^{25}D$ +70° (in chloroform, *c* 1.10).

Anal. Calcd. for $C_{32}H_{37}NO_8$: C, 68.19; H, 6.62; N, 2.49. Found: C, 68.35; H, 6.69; N, 2.53.

Methyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (X).—A solution of 0.40 g. of IX in 2 ml. of acetic anhydride and 2 ml. of pyridine was left overnight at room temperature. The temperature was then raised to 50° for 1 hr. After evaporation of the solution, the residue was recrystallized from methanol to give 0.40 g. (93%) of prisms, m. p. 213–215°. Further purification by chromatography on silicic acid did not raise the melting point, $[\alpha]^{26}D$ +67° (in chloroform, *c* 1.74).

Anal. Calcd. for $C_{34}H_{39}NO_9$: C, 67.42; H, 6.49. Found: C, 67.48; H, 6.50.

Methyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl-α-D-glucopyranoside (XI). From X.—A solution of 130 mg. of XI in 5 ml. of 60% acetic acid was heated at 100° for 15 min. The residue obtained on evaporation was treated with water. After filtration the aqueous extract was evaporated and the residue crystallized from a mixture of benzene and hexane, giving 73 mg. of needles (92%), m.p. 136–138°. Recrystallization from a mixture of ethyl acetate and hexane raised the m.p. to 140–142°, $[\alpha]^{23}D$ +119° (in chloroform, *c* 0.62).

Anal. Calcd. for $C_{15}H_{25}NO_9$: C, 49.58; H, 6.94; N, 3.86. Found: C, 49.50; H, 7.03; N, 3.86.

From VII.—A solution of 4.0 g. of VII in 16 ml. of pyridine and 3.84 g. of triphenylchloromethane was kept overnight at room temperature. After raising the temperature to 100°, 16 ml. of acetic anhydride was added, the solution was allowed to cool and left at room temperature for 24 hr. The cooled solution then was poured into ice water and the precipitate separated, washed thoroughly with water, and dried.

The solid was heated with 5 ml. of 60% acetic acid at 100° for 15 min., the solution evaporated, and the residue treated with water. Evaporation of the aqueous extract and recrystallization from a mixture of acetone and ether gave 2.6 g. (57%) of needles, m.p. 138–140°, $[\alpha]^{27}D$ +119° (in chloroform, *c* 3.12).

Methyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XIII). A. Using Mercuric Cyanide.—To a stirred solution of 1.06 g. of XI (0.003 mole) in 40 ml. of dry nitromethane was added 0.88 g. (0.0037 mole) of mercuric cyanide and a solution of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (XII) in 15 ml. of chloroform, prepared from 1.5 g. of 2-amino-2-deoxy-D-glucose pentaacetate (0.0037 mole) according to Inouye, *et al.*[16] After 20 hr. at room temperature, the preceding quantities of mercuric cyanide and XII were again added and the reaction allowed to proceed a further 24 hr.

The reaction mixture was diluted with chloroform, washed with a little sodium bicarbonate solution and water, and evaporated. The residue was dissolved in ethyl acetate and chromatographed on silicic acid. Ethyl acetate eluted 0.680 g. of unchanged XI melting at 138–140° after recrystallization from a mixture of acetone and ether. A mixture of ethyl acetate and acetone 1:1 eluted a crystalline product which, after one recrystallization from a mixture of alcohol and acetone, gave 0.23 g. (12%) of white needles, m.p. 288–289°, $[\alpha]^{25}D$ +54° (in chloroform, *c* 2.02).

Anal. Calcd. for $C_{29}H_{44}N_2O_{17}$: C, 50.26; H, 6.40; N, 4.04. Found: C, 49.76; H, 6.57; N, 3.92.

The preceding condensation was repeated twice, using XI recovered from the previous condensation, giving a further 0.17 g., m.p. 288–289°, and 0.20 g. of unchanged XI, m.p. 138–140°.

B. Using Silver Oxide.—To a solution of 0.36 g. (0.001 mole) of XI in 25 ml. of dry chloroform was added 2 g. of silver oxide, 2 g. of Drierite (dehydrated calcium sulfate), and XII, prepared from 0.0025 mole of 2-amino-2-deoxyglucose pentaacetate, added in two equal portions, 24 hr. apart. After 48 hr. at room temperature the solution was treated as in A, giving 0.015 g. (2%) of product, m.p. 287–288°, identical with the disaccharide described previously.

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(17) Neuberger[9] reported m.p. 255°, $[\alpha]D$ +19° (in chloroform, *c* 0.5); Wiggins[12] reported m.p. 255–256°, $[\alpha]D$ +40.0° (in chloroform, *c* 1.5); Roth and Pigman[13] reported m.p. 261–262°, $[\alpha]^{20}D$ +39.5° (in chloroform, *c* 0.5).

(18) Wiggins[12] reported m.p. 203–205°, $[\alpha]D$ +33 (in chloroform); Meyer zu Reckendorf and Bonner[19] reported m.p. 210–211°, $[\alpha]D$ +37.8° (in chloroform, *c* 0.06).

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mido - 4,6 - *O* - benzylidene - 2 - deoxy - α - D - glucopyranoside and Dr. J. T. Park for making available before publication the manuscript describing the procedure used in the present study for the preparation of methyl 2-acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside.

Derivatives of 6-Deoxy-6-mercapto-D-fructose[1]

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6-Deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose and 1,6-dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose are prepared. Acid hydrolysis of the former compound produces 6-deoxy-6-mercapto-D-fructose which seems to exist with sulfur in a pyranose ring. 1,6-Dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose is unstable in acid solution and readily dehydrates to methyl 2-thienyl ketone.

Previous workers[2-6] have prepared a number of aldoses wherein the normal pyranose ring oxygen is replaced with a sulfur atom. Such sugars represent a new class of compounds which are not only of chemical interest but, where they are analogs of metabolic sugars, are also of biological interest. This work reports the preparation of 6-deoxy-6-mercapto-D-fructose, the first ketose which could cyclize with a sulfur atom in a pyranose ring.

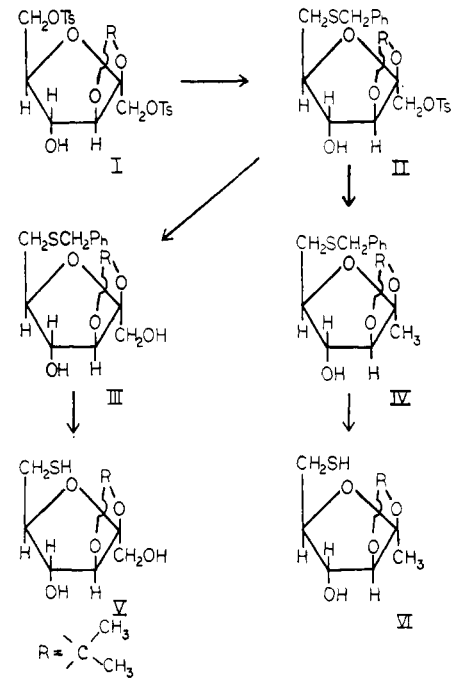
The starting material was 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-fructofuranose (I).[7,8] The 1-*O*-*p*-tolylsulfonoxy group of this compound, as in other analogous sulfonated ketoses,[9,10] does not undergo nucleophilic displacement easily. Thus, reaction of the compound with sodium benzyl mercaptide in boiling methanol leads only to the displacement of the 6-*O*-*p*-tolylsulfonoxy group with the production of 6-deoxy-2,3 - *O* - isopropylidene - 6 - thiobenzyl - 1 - *O* - *p* - tolylsulfonyl-D-fructofuranose (II).

The remaining ester group is hydrolyzed only with difficulty but is removed by lithium aluminum hydride, a reagent successfully employed[11-13] for removal of *p*-tolylsulfonyl substituents. In most instances lithium aluminum hydride removes a primary *p*-tolylsulfonoxy group by alkyl–oxygen fission, but Schmidt and Karrer report that this reagent, on reaction with 2,3:4,5-di-*O*-isopropylidene - 1 - *O* - *p* - tolylsulfonyl - D - fructopyranose, produces the sugar alcohol. They believe this type of cleavage is a consequence of the sterically hindered position of the ester. Reaction of compound II with lithium aluminum hydride, however, involves desulfonoxylation since the major sugar derivative is 1,6 - dideoxy - 2,3 - *O* - isopropylidene - 6 - thiobenzyl-D-fructofuranose (IV). Evidence for this structure is given by desulfurization with Raney nickel to produce the known 1,6-dideoxy derivative.

Examination of models indicates that the *p*-tolylsulfonyl ester is in a more sterically hindered position in the 2,3:4,5-di-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-fructopyranose of Schmidt and Karrer than is the ester of compound II, thus supporting the view[14] that the course of desulfonylation with lithium aluminum hydride is dependent on the steric make-up of the attacked molecule.

Desulfonylation of compound II with sodium amalgam produces 6-deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (III) in good yield. Desulfurization of this compound with Raney nickel produces the expected 6-deoxy derivative.

Reaction of compounds III and IV with sodium in liquid ammonia[15] gives 6-deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (V) and 1,6-dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (VI), respectively.



Both mercapto compounds V and VI are unstable in acid solution. Either methanolysis or hydrolysis of VI

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