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.

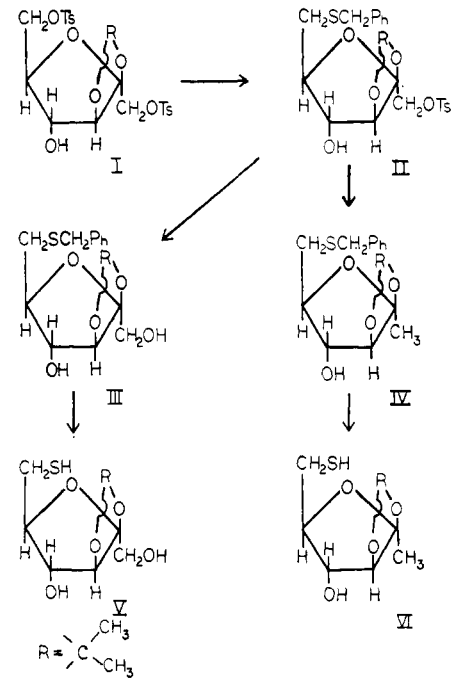
The starting material was 2,3-*O*-isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-fructofuranose (I).[7,8] The 1-*O*-*p*-tolylsulfonoxy group of this compound, as in other analogous sulfonated ketoses,[9,10] does not undergo nucleophilic displacement easily. Thus, reaction of the compound with sodium benzyl 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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produces multicomponent sirups. Paper chromatographic analyses indicate that, in some instances, the same compounds are produced by both methanolysis and hydrolysis. Compound VI is easily dehydrated in acid solution. Treatment of it with an acidic aqueous solution of 2,4-dinitrophenylhydrazine produces the crystalline 2,4-dinitrophenylhydrazone of methyl 2-thienyl ketone.

Hydrolysis of V likewise produces a complex mixture but with the reducing sugar as the major component. 6-Deoxy-6-mercapto-D-fructose is obtained from the mixture by Celite column chromatography.

Infrared spectra of this amorphous sugar shows no SH stretching or carbonyl absorption. Thus, it appears that a major portion of the sugar exists in the pyranose ring form. As with D-xylothiapyranose,[3] only 80% of the total sulfur can be titrated iodometrically over a two-hour period.

Experimental

2,3-*O*-Isopropylidene-1,6-di-*O*-*p*-tolylsulfonyl-D-fructofuranose (I).—This compound was prepared as described by Morgan and Reichstein,[7] starting with 100-g. portions of D-fructose. On recrystallization from ethyl acetate–hexane, the product had m.p. 131°, $[\alpha]^{25}D$ + 22.1° (*c* 2.4, chloroform).

6-Deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-1-*O*-*p*-tolylsulfonyl-D-fructofuranose (II).—A solution of sodium benzyl mercaptide was prepared by reaction of 15.3 g. of elemental sodium with 78.0 ml. of benzyl mercaptan in 900 ml. of anhydrous methanol. During the reaction, the mixture was maintained under flowing oxygen-free, anhydrous nitrogen and was cooled by an ice bath. Following reaction of the sodium, 90.0 g. of compound I was added and the solution was refluxed for 4 hr. It was then concentrated under reduced pressure to a slurry, and after the addition of 1 l. of chloroform the mixture was extracted twice with water, three times with saturated aqueous sodium hydrogen carbonate solution, and then with water until the washings were neutral. After drying the chloroform solution over sodium sulfate, it was concentrated to a sirup which retained a slight odor of benzyl mercaptan. On standing several hours at 25°, crystallization occurred; yield 60 g. (74%). Several recrystallizations from ethyl acetate–hexane produced a pure compound; m.p. 120–121°, $[\alpha]^{25}D$ −6.7° (*c* 2.0, chloroform).

Anal. Calcd. for $C_{23}H_{28}O_7S_2$: C, 57.47; H, 5.87; S, 13.34. Found: C, 57.55; H, 5.68; S, 13.20.

1,6-Dideoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (IV).—A solution of 25 g. of II in 250 ml. of tetrahydrofuran was cooled to 0°, and 3 g. of lithium aluminum hydride was added. After 0.5 hr. the solution was warmed to 25° for 2 hr., and then refluxed for 48 hr. Sufficient water was added to destroy excess reagent and 100 ml. of saturated aqueous sodium sulfate solution was added. The mixture was made slightly acidic with dilute hydrochloric acid, and the tetrahydrofuran phase was drawn off. The aqueous phase was extracted three successive times with 100-ml. portions of chloroform. The chloroform extracts and the removed tetrahydrofuran were combined and extracted once with water. On drying the organic phase with sodium sulfate and evaporation to a sirup, crystals appeared; yield, 12.5 g. (77.5%). Two recrystallizations produced pure compound IV; m.p. 93°, $[\alpha]^{25}D$ −34.8° (*c* 2.0, chloroform). A 1-g. portion of compound IV was dissolved in 30 ml. of ethanol containing 5 g. of freshly prepared Raney nickel. This suspension was stirred at reflux for 40 hr. and filtered. Concentration of the filtrate produced crystals which were sublimed at 60° (0.2 mm.). The resulting 1,6-deoxy-2,3-*O*-isopropylidene-D-fructofuranose[7] was recrystallized from ethyl acetate–hexane; m.p. 59–62°, $[\alpha]^{25}D$ +8.2° (*c* 3.6, methanol).

6-Deoxy-2,3-*O*-isopropylidene-6-thiobenzyl-D-fructofuranose (III).—A 23-g. sample of II was slurried with 300 ml. of methanol and 150 g. of 5% sodium amalgam was added with vigorous stirring. After 2 hr., 50 ml. of water was added and stirring was continued for 24 hr. The decanted methanol solution was cooled to 0°, acidified with 5 *N* hydrochloric acid solution, and extracted with four successive 100-ml. portions of chloroform. The combined chloroform extracts were washed once with saturated sodium hydrogen carbonate solution, then with water, and dried over sodium sulfate. Concentration produced compound III, which crystallized; yield, 14.3 g. (97%). The compound was recrystallized from ethyl acetate–hexane; m.p. 95–96°, $[\alpha]^{25}D$ −13.9° (*c* 2.4, methanol). A 1-g. sample of compound III was desulfurized with Raney nickel as described previously to produce 6-deoxy-2,3-*O*-isopropylidene-D-fructofuranose[7]; m.p. 114°, $[\alpha]^{25}D$ +6.5° (*c* 3.2, methanol), after sublimation at 115–130° and 0.2-mm. pressure.

1,6-Dideoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (VI).—A 10-g. sample of compound IV was dissolved in 100 ml. of liquid ammonia held in an acetone–Dry Ice bath. The atmosphere above the solution was continuously swept with oxygen-free, anhydrous nitrogen and small pieces of sodium were added while the solution was stirred. The addition of sodium was continued until the characteristic blue color was maintained for 15 min. An excess of ammonium chloride (10 g.) was then added, and the ammonia was allowed to evaporate in a stream of nitrogen. The dry solids were extracted three times with boiling chloroform in 50-ml. portions, and the combined extracts were washed with water and dried over sodium sulfate. Concentration of the chloroform produced a sirup which gave crystals of compound VI. This was recrystallized from ethyl acetate–hexane; yield, 5.8 g. (82%), m.p. 70–72°, $[\alpha]^{25}D$ −2.8° (*c* 2.7, chloroform).

Anal. Calcd. for $C_9H_{16}O_4S$: C, 49.07; H, 7.32; S, 14.56. Found: C, 49.32; H, 7.54; S, 14.68.

A 250-mg. portion of compound VI was dissolved in 10 ml. of methanol and 10 ml. of 2 *N* hydrochloric acid solution was slowly added. The progress of the hydrolysis, at 25°, was followed by periodically chromatographing aliquots on paper. Chromatograms were irrigated with 1-butanol–ethanol–water (40:11:19 v./v.) and sprayed with silver nitrate solution.[16] After 4 hr. of hydrolysis, there were four chromatographic components of approximately equal intensity having $R_{glucose}$ values of 1.9, 2.8, 4.4, and 4.9. Methanolysis of compound VI for 24 hr. at 25° with 0.5% methanolic hydrogen chloride solution produced components with $R_{glucose}$ values of 2.3, 2.8, 3.3, 4.4, and 4.9.

A 0.5-g. portion of compound VI was dissolved in 5 ml. of 30% perchloric acid solution containing 0.4 g. of 2,4-dinitrophenylhydrazine. After warming the solution at 60° for 5 min. a crystalline precipitate appeared. Recrystallization from dimethylformamide produced material which had m.p. 244–245°.

Methyl 2-thienyl ketone was prepared as described elsewhere.[17] Its 2,4-dinitrophenylhydrazone was prepared as described for compound VI and was recrystallized from dimethylformamide; m.p. 244–245°,[18] m.m.p. with the hydrazone of compound VI, 244–245°. The X-ray diffraction patterns of the two hydrazones were identical.

6-Deoxy-2,3-*O*-isopropylidene-6-mercapto-D-fructofuranose (V).—This compound was produced by reduction of compound III with sodium in liquid ammonia as described before. Since precipitation occurred as the reaction progressed, it was necessary, for easy stirring, to employ 200 ml. of ammonia for each 10 g. of compound III. After the blue color persisted for 0.5 hr., compound V was isolated in the usual fashion, and recrystallized from hexane; yield, 5.8 g. (81%), m.p. 76–77°, $[\alpha]^{25}D$ +4.9° (*c* 2.1, methanol).

Anal. Calcd. for $C_9H_{16}O_5S$: C, 45.75; H, 6.80; S, 13.57. Found: C, 45.79; H, 6.99; S, 13.75.

Compound V could be easily hydrolyzed to the free 6-deoxy-6-mercapto-D-fructose. A 5-g. portion of V was dissolved in 50 ml. in 1 *N* hydrochloric acid in 50% aqueous methanol. The hydrolysis was allowed to proceed for 24 hr. at 25°. The solution was neutralized with Amberlite IR-4B (OH) and concen-

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trated to a sirup. Paper chromatograms, irrigated and sprayed, with the reagents indicated previously, showed one major component having $R_{glucose}$ 1.3.

The sugar was purified by elution from a Celite column[19] using 1-butanol saturated with water as the mobile phase; $[\alpha]^{25}D$ −179° (*c* 0.9, water).

Anal. Calcd. for $C_6H_{12}O_5S$: S, 16.3. Found: S, 16.4.

A 26-mg. sample of this sugar was dissolved in 2% acetic acid solution and titrated with standard iodine solution. After 2 hr. at 25°, 2.0 ml. of 0.0530 *N* iodine solution was consumed.

A portion of the purified sugar was dissolved in water to an initial concentration of 3.8 mg./ml. and used in a series of measurements in a vapor pressure osmometer. Calcd.: mol. wt., 196. Found: mol. wt., 198.

Thioglycosides of 3-Amino-3-deoxy-D-mannose[1]

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The reaction of some D-mannose derivatives with ethanethiol and concentrated hydrochloric acid was investigated. Mercaptolysis of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (II) gives a mixture of the crystalline ethyl 3-amino-3-deoxy-1-thio-α- and β-D-mannopyranoside hydrochlorides (40% I and 60% III) in high yield, readily separable as the crystalline tetraacetates (IV and VII). The structures of I and III were established by periodate oxidation data on the corresponding *N*-acetyl derivatives (V and VIII). The behavior of a number of simple sugars in the mercaptalation reaction was examined.

The objective of this investigation was to study apparent anomalies in the reactions of D-mannose derivatives with ethanethiol in concentrated hydrochloric acid solution and to devise a suitable preparative route to 1-thioglycosides of 3-amino-3-deoxy-D-mannose.

The reaction between aldoses and alkanethiols in concentrated aqueous acid, at about 0°, leads to the formation of the acyclic dithioacetals in high yield when these products are removed from the reaction sphere by crystallization[2] or by rapid neutralization of the acid.[3] If this, apparently initial, product is not so removed or if the dithioacetal is put back into the system,[4] 1-thioglycosides are formed and hydrolysis to the aldose occurs. The 1-thioglycosides found, in the cases investigated, have been pyranosides. The reaction can be influenced by steric factors, such as sugar configuration, and by polar factors, such as those introduced by the presence of an amino group.

Prolonged treatment of D-mannose with ethanethiol and concentrated (12 *N*) hydrochloric acid at room temperature, under conditions wherein any dithioacetal formed would not separate, gave a 31% yield of the ethyl 1-thio-α- and β-D-mannopyranosides, isolated as the tetraacetates.[5] In our hands, a paper chromatographic study of this reaction (Table I) showed that after five minutes all of the D-mannose had reacted, and that the diethyl dithioacetal was the principal product, although small proportions of two thioglycosides were present. Levene and Meyer[6] reported isolation of D-mannose diethyl dithioacetal in 63% yield after five minutes under similar conditions. At longer reaction times, the intensities of the thioglycoside zones increased at the expense of the dithioacetal, and a weaker zone corresponding to D-mannose appeared. The distribution of the four products, by visual comparison, was essentially constant after four hours.

TABLE I

PAPER CHROMATOGRAPHIC DATA[a] ON MERCAPTOLYSIS OF ALDOSE DERIVATIVES AT 25°

Compound (*c* 10, 12 *N* HCl)	Time of reaction, min.	Observed products[b]			
		Aldose	Dithioacetal	Anomeric thiopyranosides[c]	
		R_{man} 1.00	R_{man} 2.66	R_{man} 2.11	R_{man} 2.39
D-Mannose[d]	5	...	++++	+	(+)
	60	+	++++	+++	++
	240	+	++++	+++	+++
	1440	++	+++	+++	+++
		R_g 1.00	R_g 2.75	R_g 2.23	R_g 2.52
D-Glucose[d]	5	(+)	++++	(+)	...
	60	(+)	++++	+	...
	240	++	++	++	+
	1440	+++	...	++	+
		R_{gal} 1.00	R_{gal} 2.85	R_{gal} 2.17	
D-Galactose[d]	5	+	++++	+	
	60	...	+++	+	
	240	...	+++	+	
	1440	++	(+)	++	

[a] Details given in Experimental. [b] Relative intensity, estimated visually. These values do not necessarily represent relative absolute intensities since the components vary in their reactivity with the spray reagent. [c] Probable identities, not compared with known samples. The zone R_{gal} 2.17 was elongated and possibly a mixture of two incompletely resolved zones. [d] The *R* values refer to the respective parent aldose; mannose, glucose, or galactose, denoted as a subscript, with a 4:1:5 1-butanol–ethanol–water system.

Under similar conditions, D-glucose gives ethyl 1-thio-α-D-glucopyranoside in 15% yield, together with unchanged D-glucose and, probably, some β-D anomer; no diethyl dithioacetal was detected.[4] D-Glucose diethyl dithioacetal and ethyl 1-thio-α-D-glucofuranoside are converted into the acid-resistant[7] ethyl 1-thio-α-D-glucopyranoside by 22% hydrochloric acid under the same conditions, whether or not ethanethiol is present, and some D-glucose is formed.[4] Our paper chromatographic studies confirm these results and show that the behavior of D-galactose is closely similar (Table I); in each case the initial reaction of the sugar with ethanethiol and concentrated hydrochloric acid at room temperature is rapid, with almost complete

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