bicarbonate and 50 ml of water, dried, and evaporated to dryness *in vacuo* to give 740 mg of solid. Recrystallization from ethanol gave 453 mg (48%) of material, mp 143–146°. The analytical sample had mp 151–152°, $[\alpha]^{20}D$ +163° (*c* 0.992, chloroform).

Anal. Calcd for $C_{27}H_{24}O_6S_2$: C, 63.7; H, 4.75; S, 12.6. Found: C, 63.4; H, 4.64; S, 12.6.

D-*erythro*-**2-Methoxytetrahydropyran-3-ol Benzoate (VIb).**—A solution of 500 mg of methyl 3,4-dithio-2,3,4-O,S,S-tribenzoyl-β-L-lyxopyranoside (XIII) in 100 ml of 2-methoxyethanol was treated with 10 g of Davison sponge nickel at reflux under a hydrogen atmosphere for 5 hr. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to dryness *in vacuo* to give 180 mg of a colorless oil. Evaporative distillation at 70° (0.01 mm) gave a colorless distillate: λ_{max}^{film} 5.80 (O-benzoate C=O) and 7.85 (benzoate C–O–C) μ (there was no carbonyl absorption at 6.0 μ which is indicative of S-benzoate); $[\alpha]^{23}D$ +99° (*c* 1.225, chloroform).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.78. Found: C, 66.5; H, 7.30.

The nmr spectrum showed H-1, d (J = 3 cps) at τ 5.20; H-2, m at τ ≃5; H-3 and H-4, m at τ 8.12; and H-5, m at τ 6.40.

Acknowledgment.—The authors are indebted to Mr. O. P. Crews and his group for the preparation of quantities of certain of the intermediates and to Dr. Peter Lim's staff for the optical rotations and nmr spectra. They also wish to thank Professor L. D. Hall for some stimulating discussions on the nmr spectra.

Selective Mesylation of Carbohydrates. II.[1a] Some Mesyl Esters of Methyl α- and β-D-Glucopyranosides, Methyl α- and β-D-Galactopyranosides, and of Methyl α-D-Mannopyranoside[1b]

R. C. CHALK, D. H. BALL, AND L. LONG, JR.

Pioneering Research Division, U. S. Army Natick Laboratories, Natick, Massachusetts

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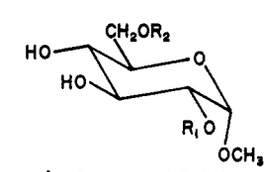
Treatment of methyl α- and β-D-glucopyranosides, methyl α- and β-D-galactopyranosides, and methyl α-D-mannopyranoside with 1, 2, or 3 molar equiv of mesyl chloride at low temperature afforded mixtures of mesyl esters of which the major and some of the minor components were identified. The enhanced reactivity of the C-2 hydroxyl in α-glycosides has not been observed for the β-glycosides of glucose and galactose.

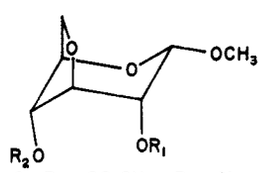
In part I of this series,[1a] we described the preparation in good yield of crystalline methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside (**1**) by a one-step reaction from methyl α-D-glucopyranoside. This compound has proved to be a useful intermediate and in an attempt to obtain other readily available and partially substituted glycosides and to examine the factors controlling the relative reactivities of the ring hydroxyl groups, we have extended the selective mesylation technique to other glycosides. This paper describes the results obtained with the methyl α- and β-glycopyranosides of D-glucose and D-galactose and with methyl α-D-mannopyranoside. These results are summarized in Table I.

The mesylations were carried out by slowly adding mesyl chloride to a solution of the glycoside in anhydrous pyridine at −20 to −40°. In an attempt to increase the selectivity, mesylations were also attempted at about −60° in mixtures of pyridine and triethylamine and of pyridine and dimethylformamide but no significant difference could be observed.

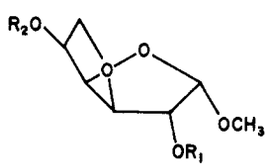
From the reaction of methyl α-D-glucopyranoside with 1 equiv of mesyl chloride, methyl 6-*O*-mesyl-α-D-glucopyranoside (**3**) was obtained as the major product. Its structure was established by acetylation to give methyl 2,3,4-tri-*O*-acetyl-6-*O*-mesyl-α-D-glucopyranoside, previously described by Cramer, *et al.*[2] Several attempts to obtain the yields reported by these workers for the preparation of this compound by a monomolar mesylation of methyl α-D-glucopyranoside followed by acetylation of the reaction mixture were unsuccessful. Although a crystalline product was obtained in good yield, this invariably proved to be a mixture of compounds.[3] Methyl 2,3,4-tri-*O*-acetyl-6-*O*-mesyl-α-D-glucopyranoside could be obtained pure by several recrystallizations but the overall yield, even after fractionation of the mother liquors on silica gel, was no more than 50%.



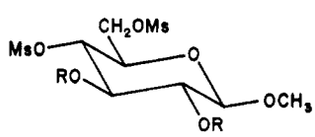
1 $R_1 = R_2 = SO_2CH_3$
2 $R_1 = SO_2CH_3$, $R_2 = H$
3 $R_1 = H$, $R_2 = SO_2CH_3$



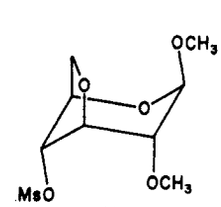
4 $R_1 = SO_2CH_3$, $R_2 = H$
5 $R_1 = R_2 = SO_2CH_3$
6 $R_1 = R_2 = H$



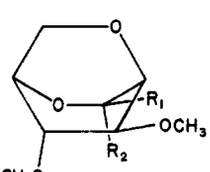
7 $R_1 = SO_2CH_3$, $R_2 = H$
8 $R_1 = R_2 = SO_2CH_3$



9 R = H
10 R = CH_3



11



12 $R_1 = H$, $R_2 = OCH_3$
13 $R_1 = OCH_3$, $R_2 = H$

(1) (a) Part I: A. K. Mitra, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **27**, 160 (1962). (b) Supported in part by the Army Research Office (Durham).

(2) (a) B. Helferich and A. Gnuchtel, *Ber.*, **71B**, 712 (1938); (b) F. Cramer, H. Otterbach, and H. Springmann, *ibid.*, **92**, 384 (1959).

(3) Among those identified were the diacetate of **1**, methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside, and methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-glucoside.

TABLE I
PRODUCTS FROM SELECTIVE MESYLATIONS

Methyl D-glycoside	Moles of mesyl chloride	Crystalline product	Isolated yield, %	Crystalline derivative
α-Glucopyranoside	2	2,6-Di-*O*-mesyl[a]	51	2,6-Di-*O*-mesyl-3,4-di-*O*-methyl[a]
	1	2,6-Di-*O*-mesyl	10	3,4-Di-*O*-acetyl-2,6-di-*O*-mesyl
		2-*O*-Mesyl[b]	2.5	
		6-*O*-Mesyl	20	2,3,4-Tri-*O*-acetyl-6-*O*-mesyl[c]
β-Glucopyranoside	2	Tri-*O*-mesyl	3	
		4,6-Di-*O*-mesyl	13	4,6-Di-*O*-mesyl-2,3-di-*O*-methyl
		2,6-Di-*O*-mesyl	4	2,6-Di-*O*-mesyl-3,4-di-*O*-methyl
		Di-*O*-mesyl	4	
		6-*O*-Mesyl	4	
α-Mannopyranoside	3	2,3,6-Tri-*O*-mesyl	41	2,3,6-Tri-*O*-mesyl-4-*O*-methyl
α-Galactopyranoside	3	2,3,6-Tri-*O*-mesyl	30	
	2	2,3,6-Tri-*O*-mesyl	10	
		2,6-Di-*O*-mesyl[d]	20	3,4-*O*-Isopropylidene-2,6-di-*O*-mesyl
				2,6-Di-*O*-mesyl-3,4-di-*O*-methyl
		3,6-Di-*O*-mesyl	4	3,6-Di-*O*-mesyl-2,4-di-*O*-methyl
β-Galactopyranoside	2	3,6-Di-*O*-mesyl	26	3,6-Di-*O*-mesyl-2,4-di-*O*-methyl

[a] See ref 1. [b] See ref 13. [c] See ref 2. [d] See ref 9.

Treatment of **1** with alkali gave crystalline methyl 3,6-anhydro-2-*O*-mesyl-α-D-glucopyranoside (**4**) in 60% yield. Its structure was established by mesylation which gave methyl 3,6-anhydro-2,4-di-*O*-mesyl-α-D-glucopyranoside (**5**). This was also obtained by mesylation of methyl 3,6-anhydro-α-D-glucopyranoside (**6**) which was prepared by alkaline saponification of **3**.

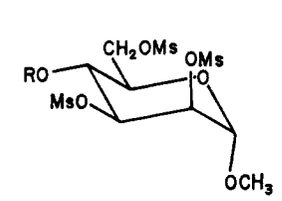
The physical constants of **4** were found to have changed after the compound had been stored at room temperature for several months and the nmr spectrum indicated that a pyranoside to furanoside rearrangement had occurred to give methyl 3,6-anhydro-2-*O*-mesyl-α-D-glucofuranoside (**7**). Mesylation of **7** gave, in 73% yield, a crystalline methyl 3,6-anhydro-di-*O*-mesyl-α-D-glucoside which was different from **5** and which probably had the furanose structure **8**.

Dimolar mesylation of methyl β-D-glucopyranoside proved to be much less selective than for the α anomer. The major product was shown to be methyl 4,6-di-*O*-mesyl-β-D-glucopyranoside (**9**) since methylation gave a crystalline dimethyl ether which was identical with methyl 4,6-di-*O*-mesyl-2,3-di-*O*-methyl-β-D-glucopyranoside (**10**), prepared by an unambiguous route. From the methylation of **9** at room temperature with methyl iodide and silver oxide in dimethylformamide, a second crystalline product was obtained and was tentatively identified as methyl 3,6-anhydro-4-*O*-mesyl-2-*O*-methyl-β-D-glucopyranoside (**11**).[4]

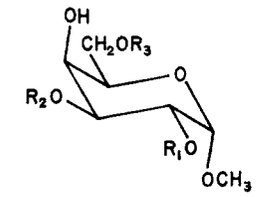
A second methyl di-*O*-mesyl-β-D-glucopyranoside was probably the 2,6 isomer. It afforded a crystalline dimethyl ether which gave two products when treated with alkali. These were separated by chromatography on silica gel and the faster moving, which contained no hydroxyl or sulfonyl groups, gave a mass spectrum with a molecular ion peak at *m/e* 204 and showed a similar fragmentation pattern to that of methyl 2,6-anhydro-3,4-di-*O*-methyl-α-D-mannoside (**12**)[5] and is therefore probably the β anomer **13**.

The mono-*O*-mesyl derivative was shown to be methyl 6-*O*-mesyl-β-D-glucopyranoside since it was readily converted to the known methyl 6-deoxy-6-iodo-β-D-glucopyranoside by treatment with sodium iodide in dimethylformamide. The third di-*O*-mesyl derivative[6] and tri-*O*-mesyl derivative were not identified.

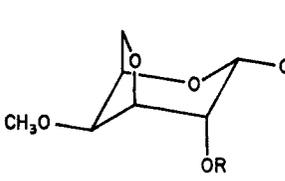
Methylation of the methyl tri-*O*-mesyl-α-D-mannopyranoside, the major product from di- and trimolar mesylations of methyl α-D-mannopyranoside, gave a crystalline methyl ether but attempts to saponify this resulted, not unexpectedly, in decomposition and the formation of complex mixtures. The methyl ether



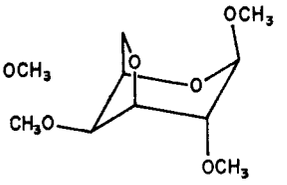
14 R = CH_3
15 R = H



16 $R_1 = R_3 = SO_2CH_3$, $R_2 = H$
17 $R_1 = R_2 = R_3 = SO_2CH_3$
18 $R_1 = R_2 = SO_2CH_3$, $R_3 = H$
19 $R_1 = H$, $R_2 = R_3 = SO_2CH_3$



20 R = SO_2CH_3
21 R = H



22

was found to be identical with methyl 2,3,6-tri-*O*-mesyl-4-*O*-methyl-α-D-mannopyranoside (**14**) which was

(4) During this work, it was observed that when methylations were carried out in dimethylformamide at room temperature, two side reactions were possible if the appropriate structures were present: (a) 3,6-anhydro ring formation, and (b) conversion of a primary mesyloxy group to a methoxy group. Although of some diagnostic value, these side reactions lower yields and could be greatly reduced by carrying out the methylation at 0° and by working up the reaction as soon as it was shown to be complete by tlc.

(5) E. D. M. Eades, D. H. Ball, and L. Long, Jr., *J. Org. Chem.*, **30**, 3949 (1965).

(6) Methyl 2,3-di-*O*-mesyl-β-D-glucopyranoside, prepared by mesylation of methyl 4,6-*O*-ethylidene-β-D-glucopyranoside, followed by hydrolysis with Dowex 50W (H^+) resin, was found not to be identical with this compound.

prepared by mesylation of the known methyl 4-*O*-methyl-α-D-mannopyranoside.[7] The methyl tri-*O*-mesyl-α-D-mannopyranoside was therefore the 2,3,6 isomer **15** which is analogous to the tribenzoate recently reported.[8]

The tri-*O*-mesyl derivative obtained from the mesylation of methyl α-D-galactopyranoside was shown to be the 2,3,6 isomer **17** since monomolar mesylations of methyl 2,6-di-*O*-mesyl-α-D-galactopyranoside (**16**)[9] and of methyl 2,3-di-*O*-mesyl-α-D-galactopyranoside (**18**), prepared by an unambiguous route, both gave **17**. This isomer is that expected by analogy with selective benzoylation results.[8]

In addition to **16**, a second methyl di-*O*-mesyl-α-D-galactopyranoside was obtained in about 4% yield from the dimolar mesylation. It was shown to be the 3,6 isomer **19** since it was different from **16** and **18** and since monomolar mesylation again gave **17**. A third crystalline di-*O*-mesyl derivative was not characterized.

Methylation of **19** gave a crystalline dimethyl ether in good yield but room temperature methylation of **16** afforded a crystalline anhydro compound in addition to the expected dimethyl ether. The anhydro compound was shown to be methyl 3,6-anhydro-2-*O*-mesyl-4-*O*-methyl-α-D-galactopyranoside (**20**) since reduction with lithium aluminum hydride gave the known methyl 3,6-anhydro-4-*O*-methyl-α-D-galactopyranoside (**21**).[10]

From the dimolar mesylation of methyl β-D-galactopyranoside, a crystalline di-*O*-mesyl ester was obtained in 26% yield. This gave a crystalline dimethyl ether which, when treated with alkali, gave the known methyl 3,6-anhydro-2,4-di-*O*-methyl-β-D-galactopyranoside (**22**)[11] in 39% yield. The methyl di-*O*-mesyl-β-D-galactopyranoside was therefore the 3,6 isomer and the saponification results indicate that the mesyl group at C-3 is hydrolyzed at least as rapidly as that at C-6.

In contrast to the good yields of the useful 2,6-dimesylate (**1**), readily obtained from methyl α-D-glucopyranoside, the above results are somewhat disappointing from a preparative viewpoint. Methyl 3,6-di-*O*-mesyl-β-D-galactopyranoside may be the most useful intermediate arising from this work. For the α-glycosides examined, the C-2 hydroxyl is the most reactive of the ring hydroxyls, as would be expected from previous work. However, this was not found to hold for the two β-glycosides examined which have equatorial methoxyl groups at C-1 in the preferred conformations. Clearly, more than one factor controls the relative reactivities of the ring hydroxyls but more examples must be investigated before generalizations are possible.

Selective mesylation results with some methyl pentosides will be reported in part III of this series.

Experimental Section[12]

Procedure for Selective Mesylations.—The methyl glycoside was dissolved in anhydrous pyridine (7–8 ml/g of glycoside) and the solution was externally cooled to −40° with Dry Ice–acetone. Mesyl chloride was added dropwise during 1–2 hr and the temperature was maintained below −20°. The reaction mixture was stored at −20° for 24 hr and any pyridine hydrochloride that formed was then removed by filtration. The solution was allowed to stand at room temperature for 24 hr and then concentrated to remove most of the pyridine. Where advantageous (*e.g.*, with tri-*O*-mesyl derivatives which are readily soluble in chloroform), the reaction mixture was partitioned between chloroform and water at this stage and in other cases, the mixture was fractionated by column chromatography on silica gel using the solvent indicated by tlc.

Monomolar Mesylation of Methyl α-D-Glucopyranoside.—Treatment of methyl α-D-glucopyranoside (40 g) with 1 equiv of mesyl chloride afforded a thick syrup which was fractionated on a column of silica gel (800 g) with methyl ethyl ketone as solvent. Fractions were collected and combined according to the results of tlc (methyl ethyl ketone) and three main fractions were obtained.

Fraction 1 (4.6 g) crystallized and recrystallization from water gave component A which was shown by melting point and mixture melting point to be identical with methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside (**1**).[1]

Fraction 2 (10.1 g) was a mixture of three main components (A, B, and C).

Fraction 3 (11.9 g) crystallized and recrystallization from 1-propanol gave component C (9.1 g) with mp 99–101°, $[\alpha]^{20}D$ +115° (*c* 1.1, water).

Anal. Calcd for $C_8H_{16}O_8S$: C, 35.29; H, 5.88; S, 11.76. Found: C, 35.46; H, 5.83; S, 11.43.

Refractionation of fraction 2 on a column of silica gel (450 g) with methyl ethyl ketone as solvent afforded additional amounts of component A (2.7 g) and component C (2.3 g). Component B (1.4 g) was also obtained crystalline and after recrystallizations from ethanol and 1-propanol had mp 113–116°, not depressed by admixture with authentic methyl 2-*O*-mesyl-α-D-glucopyranoside (**2**), $[\alpha]^{25}D$ +118° (*c* 0.8, chloroform), in good agreement with values previously reported.[13]

Methyl 3,4-Di-*O*-acetyl-2,6-di-*O*-mesyl-α-D-glucoside.—Acetylation of **1** (10 g) with pyridine and acetic anhydride at room temperature gave a sirupy product which was purified by chromatography on a column of silica gel using chloroform–ethyl acetate (3:7) as eluent. The chromatographically pure product crystallized after several months and recrystallization from ethanol afforded 9.3 g (75%) with mp 143.5–144.5°, $[\alpha]^{21}D$ +122° (*c* 1.7, chloroform).

Anal. Calcd for $C_{13}H_{22}O_{12}S_2$: C, 35.94; H, 5.07; S, 14.74. Found: C, 35.78; H, 5.11; S, 14.99.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-mesyl-α-D-glucoside.—Acetylation of component C (from the above monomesylation) (2.0 g) with acetic anhydride and pyridine at room temperature gave a syrupy product which was purified by chromatography on a column of silica gel with benzene–ethanol (97:3) as solvent. The purified acetate crystallized and after recrystallizations from benzene and from ethanol, the product (2.1 g, 72%) had mp 115–116°, $[\alpha]^{20}D$ +143° (*c* 1.0, pyridine).

Anal. Calcd for $C_{14}H_{22}O_{11}S$: C, 42.21; H, 5.53; S, 8.05. Found: C, 42.39; H, 5.67; S, 7.97.

A sample of methyl 2,3,4-tri-*O*-acetyl-6-*O*-mesyl-α-D-glucoside, prepared according to the procedure of Cramer, *et al.*,[2b] was shown to be identical with the above product by mixture melting point and by comparison of their infrared and nmr spectra.

(7) W. N. Haworth, L. N. Owen, and F. Smith, *J. Chem. Soc.*, 88 (1941).

(8) A. C. Richardson and J. M. Williams, *Chem. Commun.* (London), 104 (1965).

(9) A. B. Foster, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2542 (1949).

(10) P. A. Rao and F. Smith, *ibid.*, 229 (1944).

(11) W. N. Haworth, J. Jackson, and F. Smith, *ibid.*, 620 (1940).

(12) Solutions were concentrated under reduced pressure. Melting points were determined with a Thomas–Hoover capillary melting point apparatus and optical rotations were measured using an ETL-NPL automatic polarimeter. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer and nmr spectra were recorded on a Varian Model A-60 spectrometer. Ascending thin layer chromatography (tlc) was performed on 0.25-mm layers of silica gel G (distributed by Brinkmann Instruments, Inc., Great Neck, L. I., N. Y.). For the detection of spots, the plates were sprayed successively with a 1% solution of α-naphthol in ethanol and with 10% sulfuric acid and were then heated. Silica gel column chromatography was performed on a silica gel, grade 950, 60–200 mesh from the Davison Company, Baltimore 3, Md., or on silica gel, Woelm activity grade I, for absorption chromatography (distributed by Alupharm Chemicals, New Orleans, La.). The microanalyses were done by Mr. C. DiPietro, the nmr spectra by Mr. F. H. Bissett, and the mass spectra by Mr. M. L. Bazinet, all of these laboratories.

(13) R. W. Jeanloz and D. A. Jeanloz, *J. Am. Chem. Soc.*, **80**, 5692 (1958).

Methyl 3,6-Anhydro-2,4-di-*O*-mesyl-α-D-glucopyranoside (5).—To a solution of **3** (3.1 g) in ethanol (25 ml) was added 1 *N* sodium hydroxide (12 ml), and the solution was heated at 80° for 1 hr. The solution was then cooled, neutralized (solid carbon dioxide), and concentrated, and the residue was extracted with hot acetone. Concentration of the extracts afforded a syrup which crystallized and recrystallization from ethyl acetate gave pure methyl 3,6-anhydro-α-D-glucopyranoside (**6**) (1.1 g, 55%) with mp 108°, $[\alpha]^{25}D$ +52° (*c* 1.0, water).

Treatment of this compound with mesyl chloride in anhydrous pyridine at 0° afforded a crystalline di-*O*-mesyl derivative in 73% yield. Recrystallization from ethanol afforded pure methyl 3,6-anhydro-2,4-di-*O*-mesyl-α-D-glucopyranoside (**5**) with mp 158–159.5°, $[\alpha]^{25}D$ +64° (*c* 0.8, chloroform).

Anal. Calcd. for $C_9H_{16}O_9S_2$: C, 32.53; H, 4.82; S, 19.28. Found: C, 32.37; H, 4.83; S, 19.09.

Methyl 3,6-Anhydro-2-*O*-mesyl-α-D-glucopyranoside (4).—A solution of **1** (8.4 g) in ethanol (100 ml) and 1 *N* sodium hydroxide (30 ml) was heated at 65–70° for 2 hr. The solution was then cooled, neutralized (solid carbon dioxide), and concentrated, and the residue was extracted with hot acetone. Concentration of the extracts afforded a syrup which crystallized, and recrystallization from ethanol afforded a methyl anhydro-*O*-mesyl-α-D-glucoside (3.6 g, 60%) with mp 116–118°, $[\alpha]^{20}D$ +77° (*c* 1.3, water).

Anal. Calcd for $C_8H_{14}O_7S$: C, 37.79; H, 5.51; S, 12.60. Found: C, 37.74; H, 5.57; S, 12.69.

Treatment of this compound with mesyl chloride in anhydrous pyridine at 0° afforded in 90% yield, a crystalline methyl anhydrodi-*O*-mesyl-α-D-glucoside with mp 158–159.5°, $[\alpha]^{25}D$ +63° (*c* 1.1, chloroform). This compound was shown to be identical with **5** (see above) by mixture melting point and by comparison of their infrared and nmr spectra.

Rearrangement of 4.—After **4** had been stored at room temperature for 6 months, it was observed that its physical constants had changed to mp 92–93°, $[\alpha]^{25}D$ +162.5° (*c* 1.2, water), although no decomposition appeared to have occurred, and the nmr spectrum was consistent with a pyranoside → furanoside rearrangement. Treatment of the rearranged product with mesyl chloride in anhydrous pyridine at 0° afforded a crystalline product in 73% yield which, after recrystallization from ethanol, had mp 88–90°, $[\alpha]^{25}D$ +172° (*c* 1.2, chloroform), and which is probably methyl 3,6-anhydro-2,5-di-*O*-mesyl-α-D-glucofuranoside (**8**).

Anal. Calcd for $C_9H_{16}O_9S_2$: C, 32.53; H, 4.82; S, 19.28. Found: C, 32.75; H, 5.01; S, 19.13.

Dimolar Mesylation of Methyl β-D-Glucopyranoside.—Examination by tlc (ethyl acetate) of the product from a dimolar mesylation of methyl β-D-glucopyranoside (14 g) indicated that at least six components were present and the mixture was fractionated on a column of silica gel (700 g) with ethyl acetate as eluent.

Fraction 1 (2.4 g) was a mixture of two components A and B.

Fraction 2 (0.4 g) contained mainly component B which crystallized. After recrystallization from ethanol, component B (0.3 g) had mp 168–170°, $[\alpha]^{21}D$ +4.8° (*c* 1.0, acetone).

Anal. Calcd for $C_{10}H_{20}O_{12}S_3$: C, 28.04; H, 4.68; S, 22.43. Found: C, 28.21; H, 4.91; S, 22.15.

Fraction 3 (5.0 g) contained four components (B, C, D, and E), two of which crystallized. After fractional crystallizations from ethanol, components D and E were each obtained in pure form and both showed correct analyses for methyl di-*O*-mesylhexosides.

Component D (0.8 g) had mp 163.5–164°, $[\alpha]^{21}D$ −23° (*c* 1.0, water).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 31.08; H, 5.12; S, 18.49.

Component E (2.8 g) had mp 140–142°, $[\alpha]^{21}D$ −8.0° (*c* 1.0, water).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.98; H, 5.22; S, 18.39.

Fraction 4 (4.0 g) was a mixture of two components E and F.

Fraction 5 (0.9 g) contained component F which crystallized and was recrystallized from 1-propanol: yield 0.8 g, mp 138°, $[\alpha]^{21}D$ −28° (*c* 2.0, water).

Anal. Calcd for $C_8H_{16}O_8S$: C, 35.29; H, 5.88; S, 11.76. Found: C, 35.22; H, 5.84; S, 11.73.

Fractions 1 and 4 were combined and refractionated on a column of silica gel (400 g) and component C was obtained crystalline in a yield of 1.1 g. After recrystallization from ethanol, component C had mp 124–125°, $[\alpha]^{21}D$ −6.7° (*c* 1.0, water), and gave an analysis indicating a methyl di-*O*-mesylhexoside.

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.86; H, 5.16; S, 18.43.

Methylation of Component D.—Component D (0.45 g) was dissolved in anhydrous dimethylformamide (5 ml) and to the solution was added methyl iodide (1 ml) and silver oxide (1 g), and the mixture was stirred magnetically at room temperature for 24 hr in the absence of light. Solids were removed by filtration and washed with dimethylformamide. The combined filtrate and washings were concentrated to a yellow residue which was extracted with chloroform. Concentration of the extracts afforded a syrup which crystallized and recrystallization from ethanol afforded 0.29 g (63%) with mp 109–110° and $[\alpha]^{28}D$ −18° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.04; H, 5.96; S, 16.96.

Treatment of a portion (100 mg) of this product with 1 *N* sodium hydroxide at 95° for 17 hr gave two products (tlc in ether). The hydrolysate was deionized (Amberlite MB 3 resin), concentrated, and fractionated on a column of silica gel with ether as eluent. The faster moving component was isolated in low yield as a syrup (8 mg) which had $[\alpha]^{21}D$ −105° (*c* 1.0, chloroform) and gave an orange-red spot on thin layer plates with the α-naphthol–sulfuric acid reagents. The infrared spectrum indicated the absence of sulfonyl and hydroxyl groups. The mass spectrum gave a molecular ion peak at *m/e* 204 and was very similar to the spectrum of methyl 2,6-anhydro-3,4-di-*O*-methyl-α-D-mannopyranoside (**12**).[5] These results indicate that component D is probably methyl 2,6-di-*O*-mesyl-β-D-glucopyranoside.

Methylation of Component E.—Component E (1.6 g) was methylated as described above. Examination of the resultant syrup (1.5 g) by tlc (ethyl acetate) indicated two main products and the syrup was fractionated on a column of Woelm silica gel (130 g) with ethyl acetate as solvent.

The faster moving component crystallized and was recrystallized from ethanol: yield 0.54 g, mp 88–89.5°, $[\alpha]^{21}D$ −28° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.13; H, 5.84; S, 16.84.

This product was shown to be identical with methyl 4,6-di-*O*-mesyl-2,3-di-*O*-methyl-β-D-glucoside (**10**) (see below) by melting point and mixture melting point and by comparison of their infrared and nmr spectra.

The slower moving component crystallized and was recrystallized from ether–hexane: yield 0.23 g, mp 60–61.5°, $[\alpha]^{21}D$ −112° (*c* 0.7, chloroform).

Anal. Calcd for $C_9H_{16}O_7S$: C, 40.30; H, 5.97; S, 11.94. Found: C, 40.65; H, 6.10; S, 11.86.

The analysis, infrared, and nmr spectra tentatively identified this compound as methyl 3,6-anhydro-4-*O*-mesyl-2-*O*-methyl-β-D-glucopyranoside (**11**).

Synthesis of Methyl 4,6-Di-*O*-mesyl-2,3-di-*O*-methyl-β-D-glucopyranoside.—Methyl 2,3-di-*O*-methyl-β-D-glucopyranoside,[14] mp 54–57° and $[\alpha]^{24}D$ −36° (*c* 0.6, chloroform), was prepared from the 4,6-*O*-ethylidene derivative[15] by treatment with Dowex 50W (H^+) resin in methanol at 50° for 5 hr. A solution of the glycoside (1.1 g) in anhydrous pyridine (15 ml) was treated with mesyl chloride (2 ml) at 0°. After purification by chromatography on a column of silica gel (100 g) with ether as eluent, the product crystallized and, after recrystallization from ethanol, had mp 88–89.5°, $[\alpha]^{25}D$ −28° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.15; H, 5.92; S, 16.78.

Identification of Component F.—Treatment of the methyl *O*-mesyl-β-D-glucopyranoside (component F) (0.30 g) in dimethylformamide (5 ml) with sodium iodide (0.18 g) afforded methyl 6-deoxy-6-iodo-β-D-glucopyranoside in 53% yield, mp 157–158°, $[\alpha]^{22}D$ −16.2° (*c* 1.0, water). Raymond and Schroeder[16] report mp 157–158° and $[\alpha]^{26}D$ −17° (*c* 5.0, water) for methyl 6-deoxy-6-iodo-β-D-glucopyranoside. Component F is therefore methyl 6-*O*-mesyl-β-D-glucopyranoside.

Selective Mesylation of Methyl α-D-Mannopyranoside.—Treatment of methyl α-D-mannopyranoside (25 g) with 2 equiv of mesyl chloride afforded a syrup which contained three main

(14) J. W. H. Oldham, *J. Am. Chem. Soc.*, **56**, 1360 (1934).

(15) R. L. Mellies, C. L. Mehltretter, and C. E. Rist, *ibid.*, **73**, 294 (1951).

(16) A. L. Raymond and E. F. Schroeder, *ibid.*, **70**, 2785 (1948).

components (tlc in methyl ethyl ketone). Fractionation on a column of silica gel (800 g) with chloroform–methyl ethyl ketone (11:9) as solvent afforded the fastest moving compound in crystalline form. After recrystallization from ethanol the yield was 7.9 g, mp 158–160°, $[\alpha]^{25}D$ +32° (*c* 1.7, pyridine).

Anal. Calcd for $C_{10}H_{20}O_{12}S_3$: C, 28.04; H, 4.68; S, 22.43. Found: C, 28.23; H, 4.72; S, 22.57.

The other components of the mixture, probably di-*O*-mesyl esters, could not be obtained pure and were not further examined.

Since a tri-*O*-mesylmannoside was formed in moderate yield from the dimolar mesylation, methyl α-D-mannopyranoside was treated with 3 equiv of mesyl chloride under the above conditions and the crystalline ester was obtained in 41% yield.

Methylation of the Methyl Tri-*O*-mesyl-α-D-mannopyranoside.—To a solution of the above methyl tri-*O*-mesyl-α-D-mannopyranoside (6.5 g) in dimethylformamide (100 ml) was added methyl iodide (12 ml) and silver oxide (12 g) and the mixture was stirred magnetically in the dark at 0°.[4] After 5 hr, tlc (ether–methyl acetate, 4:1) indicated complete methylation, and the mixture was filtered, the residue was washed with dimethylformamide, and the filtrate and washings were concentrated to a syrup which was extracted with chloroform. Concentration of the extracts afforded a syrup which crystallized: yield 4.2 g, 63%. After two recrystallizations from chloroform–hexane, the product had mp 105–108°, $[\alpha]^{20}D$ +43° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{12}S_3$: C, 29.86; H, 4.98; S, 21.72. Found: C, 30.14; H, 4.98; S, 22.05.

An attempt to remove the mesyl groups by alkaline saponification resulted in extensive decomposition.

Synthesis of Methyl 2,3,6-Tri-*O*-mesyl-4-*O*-methyl-α-D-mannoside.—Methyl 4-*O*-methyl-α-D-mannopyranoside[7] was treated with excess mesyl chloride, affording the tri-*O*-mesyl derivative in 77% yield, after recrystallization from chloroform–hexane: mp 105–107°, $[\alpha]^{21}D$ +38° (*c* 2.0, chloroform). This compound was shown by mixture melting point and by comparison of their infrared and nmr spectra to be identical with the product obtained by methylation of the methyl tri-*O*-mesyl-α-D-mannopyranoside.

Dimolar Mesylation of Methyl α-D-Galactopyranoside.—Treatment of anhydrous methyl α-D-galactopyranoside (10 g) with 2 equiv of mesyl chloride afforded a syrup which was fractionated on a column of silica gel (800 g.) with chloroform–methyl ethyl ketone (1:3) as solvent.

Fraction 1 (2.5 g) contained one component which crystallized. Recrystallization from ethanol afforded a tri-*O*-mesylgalactoside (2.3 g, 10%) with mp 168.5–169.5°, $[\alpha]^{25}D$ +108° (*c* 1.0, pyridine).

Anal. Calcd for $C_{10}H_{20}O_{12}S_3$: C, 28.04; H, 4.68; S, 22.43. Found: C, 28.13; H, 4.70; S, 22.37.

Fractions 2, 3, and 4 (9.3 g) were crystalline but not homogeneous and tlc (ethyl acetate or chloroform–methyl ethyl ketone, 1:3) indicated at least four components. The major component, a di-*O*-mesylgalactoside (A), was obtained pure by several recrystallizations from ethanol: yield 3.6 g, 20%, mp 145–146.5°, $[\alpha]^{25}D$ +105° (*c* 2.4, pyridine).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.99; H, 5.26; S, 18.26.

Foster, *et al.*,[9] report mp 145–146°, $[\alpha]^{20}D$ +110° (pyridine), for methyl 2,6-di-*O*-mesyl-α-D-galactopyranoside (**16**).

Treatment of the di-*O*-mesyl galactoside with acetone–concentrated sulfuric acid afforded, in 50% yield, crystalline methyl 3,4-*O*-isopropylidene-2,6-di-*O*-mesyl-α-D-galactoside with mp 124–126°, $[\alpha]^{25}D$ +134° (*c* 0.6, pyridine), in good agreement with reported values.[9]

After removal of most of the 2,6 isomer, a second di-*O*-mesyl derivative (B) crystallized. Recrystallization from ethanol afforded 0.8 g, 4%, mp 149–150°, $[\alpha]^{25}D$ +122° (*c* 1.5, pyridine).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 31.29; H, 5.33; S, 18.22.

Treatment of this ester with silver oxide and methyl iodide in dimethylformamide at 0° afforded, in 74% yield, a crystalline methyl di-*O*-mesyl-di-*O*-methyl-α-D-galactopyranoside with mp 138–139°, $[\alpha]^{25}D$ +118° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.04; H, 5.90; S, 17.22.

Fraction 5 (50 mg) contained a third di-*O*-mesyl galactoside (C) which crystallized and recrystallization from ethanol afforded 40 mg, mp 163.5–164.5° dec, $[\alpha]^{25}D$ +120° (*c* 1.0, pyridine).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.40; H, 5.41; S, 17.80.

Trimolar Mesylation of Methyl α-D-Galactopyranoside.—Treatment of anhydrous methyl α-D-galactopyranoside (2.5 g) with 3 equiv of mesyl chloride afforded a syrup which was taken up in water. The aqueous solution was extracted with chloroform, and the extracts were dried (magnesium sulfate) and concentrated to a crystalline solid. Recrystallization from ethanol afforded the above methyl tri-*O*-mesyl-α-D-galactoside (1.6 g, 30%).

Methylation of 16.—Treatment of **16** (0.45 g) in dimethylformamide (5 ml) with methyl iodide (1 ml) and silver oxide (1 g) at room temperature for 18 hr afforded a syrup (two components as shown by tlc in ether) which was fractionated on a column of silica gel (50 g) with ether as eluent.

Fraction 1 (0.15 g) contained the faster moving component which crystallized and was recrystallized from ether: yield 0.13 g, 38%, mp 83–85°, $[\alpha]^{25}D$ +61° (*c* 1.0, chloroform).

Anal. Calcd for $C_9H_{16}O_7S$: C, 40.30; H, 5.97; S, 11.94. Found: C, 40.47; H, 6.13; S, 12.04.

Reduction of this compound (a methyl anhydro-*O*-mesyl-*O* methyl-α-D-galactoside) with lithium aluminum hydride in refluxing tetrahydrofuran was complete in 12 hr and the product was isolated crystalline in 69% yield. Recrystallization from ethanol afforded methyl 3,6-anhydro-4-*O*-methyl-α-D-galactopyranoside (**21**), mp 45–50°, $[\alpha]^{25}D$ +74° (*c* 1.0, water). Rao and Smith[10] reported mp 55°, $[\alpha]^{16}D$ +75° (*c* 0.6, water).

Fraction 2 (0.03 g) was a mixture of the two components.

Fraction 3 (0.14 g) contained the slower moving component which crystallined. Recrystallization from ethanol afforded pure methyl 2,6-di-*O*-mesyl-3,4-di-*O*-methyl-α-D-galactoside (0.13 g, 29%), mp 146.5–147.5°, $[\alpha]^{25}D$ +95° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 35.08; H, 5.99; S, 17.00.

Methyl 2,3-Di-*O*-mesyl-α-D-galactopyranoside (**18**).—Treatment of methyl 4,6-*O*-ethylidene-α-D-galactopyranoside[17] with 2 equiv of mesyl chloride afforded the 2,3-di-*O*-mesyl derivative in 84% yield after recrystallization from ethanol: mp 161–162.5°, $[\alpha]^{25}D$ +142° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{20}O_{10}S_2$: C, 35.10; H, 5.32; S, 17 02. Found: C, 35.12; H, 5.20; S, 16.70.

A solution of this compound (2.0 g) in methanol (120 ml) was stirred with Dowex 50W (H^+) ion-exchange resin at 50° for 24 hr. The resin was removed by filtration and the filtrate was concentrated to a syrup which crystallized. Recrystallization from 1-propanol afforded pure methyl 2,3-di-*O*-mesyl-α-D-galactopyranoside (**18**) (1.1 g, 60%) with mp 113–114°, $[\alpha]^{25}D$ +111° (*c* 1.0, pyridine).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 31.13; H, 5.23; S, 18.25.

Monomolar Mesylation of 18.—Treatment of **18** (1.0 g) with 1 equiv of mesyl chloride by the selective mesylation procedure described above gave a syrup which was taken up in water. The aqueous solution was extracted with four 8-ml portions of chloroform, and the extracts were dried ($MgSO_4$) and concentrated. The extracts contained a small amount of fully mesylated methyl α-D-galactopyranoside which appeared to hinder crystallization of the main product but after fractionation on a column of silica gel (130 g), with ethyl acetate as eluent, a portion of the major product was obtained crystalline. After recrystallization from ethanol the yield was 0.4 g, 31%, mp 168.5–169°, not depressed by admixture with the crystalline methyl tri-*O*-mesylgalactoside obtained above. The two compounds had identical infrared spectra. The trimesylate obtained by partial mesylation of methyl α-D-galactopyranoside therefore has mesyloxy groups at C-2 and C-3.

Monomolar Mesylation of 16.—A portion of **16** (0.3 g) was treated with 1 equiv of mesyl chloride as described above. Once again, the presence of a small amount of the tetra-*O*-mesyl derivative appeared to hinder crystallization but the product was induced to crystallize without chromatographic fractionation. Recrystallization from ethanol afforded 0.09 g, 25%, mp 165–167°, not depressed by admixture with the above methyl tri-*O*-mesyl-α-D-galactopyranoside. The infrared spectra of the two compounds were identical and the trimesylate is therefore methyl 2,3,6-tri-*O*-mesyl-α-D-galactopyranoside (**17**).

Identification of Component B.—The second crystalline methyl di-*O*-mesyl-α-D-galactopyranoside isolated from the dimolar mesylation (0.24 g) was treated with 1 equiv of mesyl chloride as described above. Some of the main product crystallized without chromatographic fractionation and recrystalliza-

(17) D. H. Ball, *J. Org. Chem.*, **31**, 220 (1966).

tion from ethanol gave 0.07 g, 24%, with mp 165–167°, not depressed by admixture with **17**. The infrared spectrum of this compound was identical with that of **17**. Since component B is different from **16** and **18**, it must be methyl 3,6-di-*O*-mesyl-α-D-galactopyranoside (**19**).

Dimolar Mesylation of Methyl β-D-Galactopyranoside.—The syrupy product obtained by treatment of methyl β-D-galactopyranoside (25 g) with 2 equiv of mesyl chloride was fractionated on a column of silica gel (700 g) with ethyl acetate as solvent. The main component of the mixture, a methyl di-*O*-mesyl-β-D-galactoside, was obtained crystalline in 26% yield. After recrystallization from ethanol, it had mp 144–145°, $[\alpha]^{25}D$ +22° (*c* 1.3, acetone).

Anal. Calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.14; S, 18.28. Found: C, 30.77; H, 5.18; S, 18.19.

To a solution of this compound (0.7 g) in dimethylformamide (10 ml) at 0° was added methyl iodide (2 ml) and silver oxide (2 g), and the mixture was stirred in the dark. After 20 hr, tlc (ether–methyl acetate, 1:2) indicated complete methylation and the formation of a single product. The mixture was filtered and the filtrate was concentrated to a residue which was extracted with chloroform. Concentration of the extracts afforded a crystalline methyl di-*O*-mesyldi-*O*-methyl-β-D-galactoside (0.6 g, 78%). After recrystallization from ethanol, the crystals had mp 95–97°, $[\alpha]^{21}D$ −11.2° (*c* 1.0, chloroform).

Anal. Calcd for $C_{11}H_{22}O_{10}S_2$: C, 34.91; H, 5.86; S, 16.94. Found: C, 34.99; H, 5.88; S, 17.21.

A solution of the methyl di-*O*-mesyldi-*O*-methyl-β-D-galactopyranoside (0.3 g) in 1 *N* sodium hydroxide (30 ml) was boiled under reflux. The reaction was followed by tlc (ethyl acetate) and, after 2 hr, no starting material remained. The solution was cooled, deionized (Amberlite MB 3 resin), and concentrated to a syrup which partially crystallized. The crystalline product was purified by sublimation: yield 0.07 g, 39%, mp 83°, $[\alpha]^{25}D$ −74° (*c* 0.7, water).

Anal. Calcd for $C_9H_{16}O_6$: C, 52.94; H, 7.84. Found: C, 53.16; H, 8.00.

Haworth, *et al.*,[11] report mp 83° and $[\alpha]D$ −77° (water) for methyl 3,6-anhydro-2,4-di-*O*-methyl-β-D-galactopyranoside (**22**). The infrared spectrum recorded for this compound[18] was identical with that obtained for the above product.

(18) R. Stephens and D. H. Whiffen, from a collection of the University of Birmingham, also available in DMS Index No. 4533, Butterworth and Co. (Publisher), Ltd., London.

Derivatives of α-D-Glucothiopyranose[1]

R. M. ROWELL AND ROY L. WHISTLER

Department of Biochemistry, Purdue University, Lafayette, Indiana

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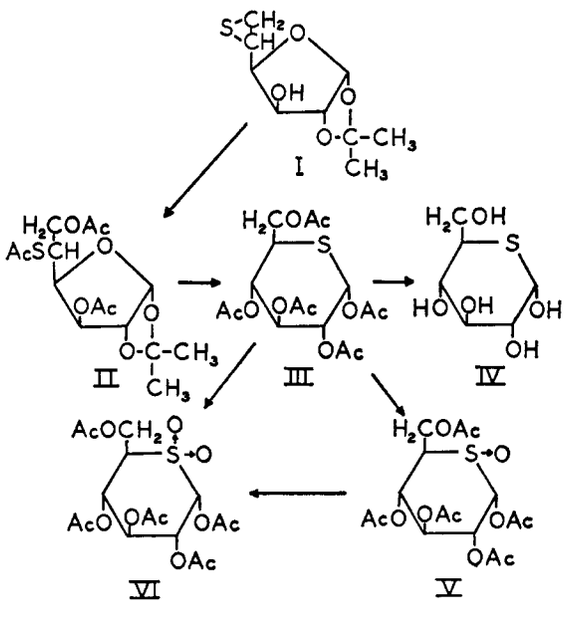
Treatment of 5-deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thioacetyl-α-D-glucofuranose with 50% aqueous acetic acid followed by acetylation gives the penta-*O*-acetate of α-D-glucothiopyranose. Deacetylation of this pentaacetate produces the crystalline α-D-glucothiopyranose. Oxidation of the sugar pentaacetate with sodium metaperiodate in methanol and water gives a sulfoxide. Oxidation of this sulfoxide or direct oxidation of the pentaacetate with peracetic acid gives the sulfone.

Two reports have appeared on the formation of 5-deoxy-5-thiohexoses and their derivatives. One of these[2] dealt with the preparation of penta-*O*-acetyl-L-idothiopyranose and a second[3] with the preparation of methyl D-glucothiopyranoside. The present report describes the preparation of crystalline α-D-glucothiopyranose and the sulfoxide and sulfone oxidation products of its pentaacetate.

The starting material, 5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose[4] (I), is acetolyzed with a solution of acetic anhydride, acetic acid, and potassium acetate to open the 5,6-epithio ring and give 5-deoxy-3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-5-thioacetyl-α-D-glucofuranose[3] (II) (Scheme I). It is assumed that the acetate ion attacks the 5,6-epithio ring in a manner similar to its attack on the 5,6-anhydro derivative with retention of the D-gluco configuration[5] and attachment of the thioacetate at carbon C-5. This material shows a characteristic absorption for a thiol acetate in the ultraviolet[6] spectrum at 230–240 mμ and in the infrared[7] spectrum at 1675 cm.$^{-1}$.

SCHEME I



Acetolysis[8] of II with sulfuric acid, acetic acid, and acetic anhydride produces a syrupy pentaacetate.[3] Usually acetone sugar derivatives, when subjected to sulfuric acid, give rise to condensation products which hinder the crystallization and hence the purification of the reaction product. To overcome this difficulty in the present preparation, the triacetate II is first treated with aqueous acetic acid to initially hydrolyze

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(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

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