Reactions of 1,2-*O*-Isopropylidene-α-D-glucofuranose 5,6-Thionocarbonate and Some Related Compounds[1a]

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Methylation of 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate (I) gave only traces of the expected 3-*O*-methyl derivative and mainly 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-(*S*-methyl monothioorthocarbonate) (II). Benzylation of I gave the analogous *S*-benzyl monothioorthocarbonate derivative (III). These etherification reactions are proposed as proceeding *via* an ortho ester type structure (Ia) which is in equilibrium with I. Methylation of 1,2-*O*-isopropylidene-5,6-dithio-β-L-iodofuranose 5,6-trithiocarbonate (X) gave a mixture (XI) of the corresponding 3-*O*-methyl derivative and the *S*-methyl ortho ester derivative, the ratio of which depends on the temperature of the methylation reaction. Methylation of 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate (VII) gave only the expected 3-*O*-methyl derivative (VIII).

The rearrangement–fragmentation of bis(1,2-*O*-isopropylidene-3-*O*-thiocarbonyl-α-D-glucofuranose) disulfide on standing in various organic solvents to give equimolar quantities of 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate (I), 1,2-*O*-isopropylidene-α-D-glucofuranose (IX), carbon disulfide, and free sulfur was reported previously.[2] In the course of elucidation of the structure of I the 3-*O*-acetyl (IV), 3-*O*-(3,5-dinitrobenzoyl) (V), and 3-*O*-(*p*-tolylsulfonyl) (VI) derivatives were obtained in high yields. Attempts to prepare the 3-*O*-methyl derivative gave only traces of the expected product and up to 68% of 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-(*S*-methyl monothioorthocarbonate) (II).[3] Similarly, benzylation of I gave 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-(*S*-benzyl monothioorthocarbonate) (III) in 49% yield (Scheme I). Methylation of the analogous 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate (VII) gave exclusively the 3-*O*-methyl product, whereas methylation of 1,2-*O*-isopropylidene-5,6-dithio-β-L-iodofuranose 5,6-trithiocarbonate (X) gave a mixture (XI) of the 3-*O*-methyl ether and the *S*-methyl ortho ester derivatives.

The structure of II was formulated on the basis of the following experimental evidence. Elemental analysis gave an empirical formula of $C_{11}H_{16}O_6S$, formula weight 276, which indicates the addition of one methylene group to I ($C_{10}H_{14}O_6S$). Molecular weight determination by the Rast method in camphor gave a molecular weight of 280 as the average of three determinations. Absence of the hydroxyl group was shown by infrared analysis and by treatment of an anhydrous ethereal solution of II with metallic sodium from which no hydrogen evolved.

While the ultraviolet spectrum of I showed a strong absorption for the C=S group at 234 mμ (ε 15,000), the spectrum of II had no absorption maximum in this region. The ultraviolet spectra of IV, V, and VI had absorption maxima at 234 mμ with molar extinction coefficients of 14,400, 21,400, and 35,000, respectively. The absence of the C=S group in II was confirmed when its aqueous–acetone solution gave no silver sulfide on treatment with silver nitrate. Similar treatment of I immediately formed silver sulfide and gave VII in nearly quantitative yield. Furthermore, a qualitative test for the C=S group with iodine–sodium azide[4] was negative for II and strongly positive for I.

Possession of the basic 1,2-*O*-isopropylidene-α-D-glucofuranose (IX) structure by both I and II was shown when they were converted to IX in yields of about 90% on treatment with Raney nickel.

While I was rapidly and completely desulfurized on mild treatment with alkali, II was recovered unchanged when treated similarly. Conversely, I was relatively stable to acid treatment, whereas II hydrolyzed rapidly under mild conditions to give methylmercaptan (up to 0.98 mole/mole of II) and VII. The latter was identified by its melting point and mixture melting point with an authentic sample and by its infrared spectrum. The acid lability and alkali stability of II is characteristic of ortho ester type structures.[5] The presence of one alkyl sulfide grouping per mole of II was also shown by titration of II with a standard solution of potassium bromate in acetic acid.[6]

The proton magnetic resonance (p.m.r.) spectrum of II had a signal at τ 7.78 for three protons of the *S*-methyl group and no signal at τ 6.5 where *O*-methyl protons of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose 5,6-carbonate (VIII) resonated. The spectrum of II also exhibited the characteristic low-field doublet for H-1 at τ 3.88. Conformational studies by others on numerous 1,2-*O*-isopropylidene-α-D-xylohexofuranose derivatives[7] and ribofuranosides[8] have shown this low-field doublet to be near τ 4 with coupling constants for $J_{1,2}$ in the range of 3.5–3.9 c.p.s. The coupling constant for $J_{1,2}$ in II is 3.6 c.p.s., which corresponds to a dihedral angle of 50° as calculated from a modified[7] Karplus equation. Examination of the Dreiding model of II shows that such a dihedral angle can arise by twisting the model so that C-2 lies below and C-3 lies above the plane containing the other three atoms of the furanose ring. However, a dihedral angle of 50° induces severe ring strain into the model.

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(1) (a) Presented before the Division of Carbohydrate Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article is not copyrighted.

(2) W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, **30**, 162 (1965).

(3) Preliminary communication: B. S. Shasha, W. M. Doane, C. R. Russell, and C. E. Rist, *Nature*, **204**, 186 (1964).

(4) F. Feigel, "Spot Tests," Vol. II, 4th Ed., Elsevier Publishing Co., New York, N. Y., 1954, p. 164.

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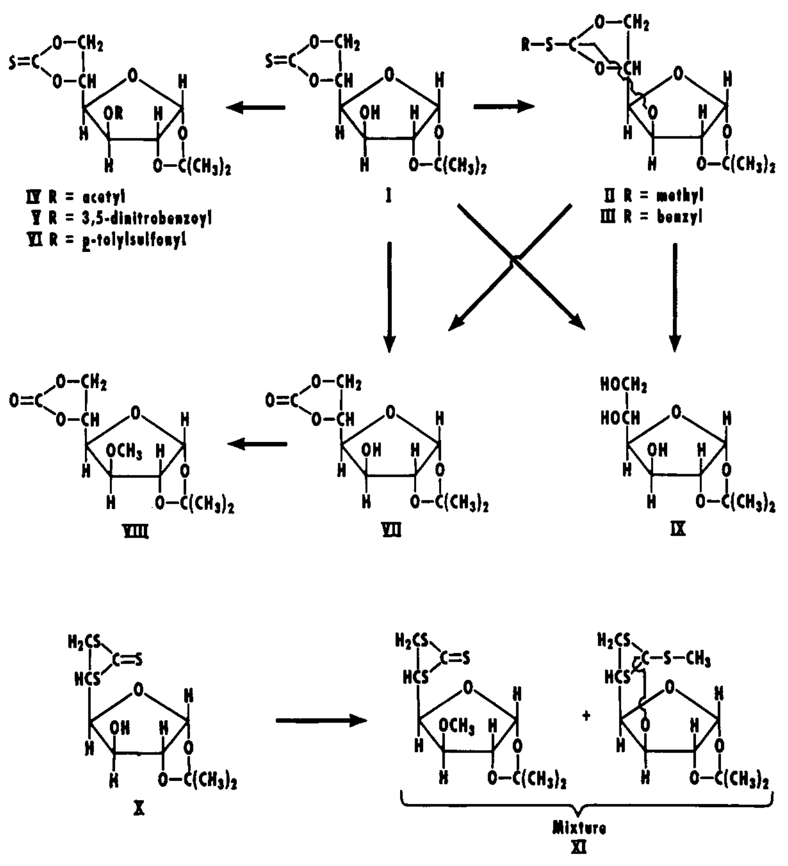
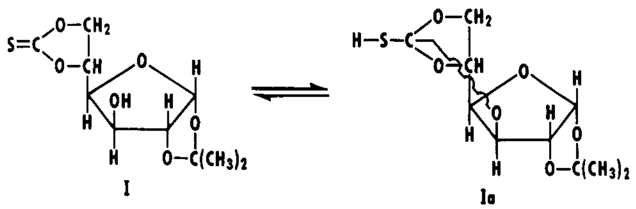
Scheme I



The methylation of I in dioxane or *N*,*N*-dimethylformamide (DMF) with methyl iodide in the presence of either silver oxide or barium oxide proceeded rapidly with the formation mainly of the *S*-methyl ortho ester. Analysis of the sirup remaining after collection of the crystals of II indicated that some of the 3-*O*-methyl product also was formed. The p.m.r. spectrum of the sirup showed a weak signal at τ 6.5 where *O*-methyl protons resonate. The spectrum had a strong signal at τ 7.78, which indicated that more of the *S*-methyl product remained in the sirup.

The treatment of I with benzyl bromide and silver oxide also produced an ortho ester structure (III) as the major reaction product. Elemental analysis gave the formula, $C_{17}H_{20}O_6S$, which indicates the addition of 1 mole of benzyl group to 1 mole of I. The infrared spectrum showed no hydroxyl absorption, whereas the ultraviolet spectrum showed no absorption maximum at 234 mμ for the C=S group. The absence of the C=S group was confirmed when no silver sulfide was formed on treatment of an acetone solution of III with aqueous silver nitrate. Acid hydrolysis of III gave benzyl mercaptan and VII. The same products were formed from III upon standing for a few days at room temperature.

The formation of the ortho ester structures (II and III) as the main reaction products suggests that I exists in solution in the following equilibrium. However, since the ultraviolet spectrum of I had a molar extinction coefficient at 234 mμ of 15,000 (whereas the molar extinction coefficient of IV in which no such equilibrium is possible was 14,400) and since the infrared spectrum of I showed no absorption for a sulfhydryl group, the equilibrium must be shifted greatly to the left. Diphenylpicrylhydrazyl (DPPH) was employed to detect the presence of the sulfhydryl group in Ia. This stable organic radical is sensitive for a sulfhydryl group.[9]



I

Ia

Since the C=S group also might react with DPPH,[10] but at a much slower rate, the reaction rates of I and IV with DPPH were compared. Although both compounds reacted with DPPH, I did so approximately eleven times faster. Attempts were unsuccessful to detect the sulfhydryl group by oxidation with iodine. Some iodine was consumed but presumably to form VII (on the basis of infrared analysis) and not the disulfide. It is known that tertiary sulfhydryl groups are only oxidized slowly and nonstoichiometrically by iodine.[11]

The esterification of I with acetic anhydride, *p*-toluenesulfonyl chloride, or 3,5-dinitrobenzoyl chloride gave the 3-ester derivatives in high yields, but none of the corresponding ortho ester derivatives could be isolated. Similarly, the 3-acetate was obtained in high yields when I was treated with acetic anhydride in the presence of sulfuric acid as a catalyst or without any catalyst, which indicates that pH has little effect on the pathway of esterification. However, since the rate of

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[9] M. S. Blois, *Nature*, **181**, 1199 (1958).

[10] H. M. Klouwen, *Arch. Biochem. Biophys.*, **99**, 116 (1962).

[11] M. S. Kharasch, W. Nudenberg, and G. J. Mantell, *J. Org. Chem.*, **16**, 524 (1951).

esterification for a hydroxyl group is faster than for a sulfhydryl group, the equilibrium mixture (I $\rightleftharpoons$ Ia) might be expected to yield mainly the 3-ester.

A similar equilibrium seems to exist in a solution of X since methylation of X in DMF with methyl iodide and barium oxide gave a sirup (XI) that contained both the corresponding *O*-methyl derivative and an *S*-methyl orthoester derivative in a ratio dependent on the temperature of the reaction. Because the infrared spectrum of the sirup showed no hydroxyl absorption, complete methylation must have occurred. The ultraviolet spectrum of the sirup showed an absorption maximum at 315 mμ with ϵ 6000–9000 (dependent on temperature of the reaction) compared with the value of 15,000 for unreacted X. Since no sulfur was lost during methylation, the reduction in absorption at 315 mμ is thought due to the formation of the *S*-methyl ortho ester. Signals at τ 7.62 and 6.53 corresponding to the protons of the *S*-methyl and *O*-methyl groups were revealed in the p.m.r. spectrum of the sirup. Approximate amounts of the components were estimated from p.m.r. analyses to be 75% for the *O*-methyl derivative and 25% for the *S*-methyl derivative when the methylation reaction was done at 25°. When the methylation reaction was carried out at 0°, the respective amounts were 88 and 12%. Similar values for the *O*-methyl isomer were obtained by desulfurization of the reaction mixtures with Raney nickel and then determination of the methoxyl content of the desulfurized products.

The presence of an acid labile *S*-methyl group, and presumably of the ortho ester type, in XI was shown by treatment of XI with 0.2 *N* hydrochloric acid solution at 25° for 2.5 hr. As expected by analogy to the acid hydrolysis of II, the infrared spectrum of the hydrolyzate showed absorption bands corresponding to hydroxyl and carbonyl groups. The p.m.r. spectrum of the hydrolysate had no signal for an *S*-methyl group.

In contrast to the related sulfur derivatives, methylation of VII in DMF with methyl iodide and silver oxide gave only the 3-*O*-methyl derivative. The infrared spectrum of the methylated derivative showed no hydroxyl absorption but a strong absorption for the cyclic carbonate group. The p.m.r. spectrum gave a signal at τ 6.57 for the *O*-methyl group corresponding to 3.04 protons.

Experimental

Melting points were determined in capillary tubes in a Büchi[12] melting point apparatus and were corrected. Optical rotations were measured at 5893 Å. with a Rudolph polarimeter. Ultraviolet spectra were determined with a Beckman DU spectrophotometer in which ethanol was used as the solvent. Infrared spectra were recorded by a Perkin-Elmer Infracord spectrophotometer with silver chloride optics as Nujol mulls. The p.m.r. spectra were recorded by a Varian A-60 n.m.r. spectrometer, with tetramethylsilane as the external standard.

3-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-Thionocarbonate (IV).—The preparation of IV by treatment of a pyridine solution of I with acetic anhydride was described earlier.[2] IV was also prepared by using sulfuric acid as the catalyst. To a suspension of 500 mg. of I in 5 ml. of acetic anhydride was added 0.5 ml. of concentrated sulfuric acid. Dissolution occurred rapidly, and the solution was allowed to stand at 25° for 2 hr. The product was isolated by precipitation into cold water, washed thoroughly with water, and crystallized from an ethanol-water mixture to afford 500 mg. (86%). A high yield of IV was also obtained by treating I with acetic anhydride and no catalyst at 25° for 2 days.

1,2-*O*-Isopropylidene-3-*O*-(3,5-dinitrobenzoyl)-α-D-glucofuranose 5,6-Thionocarbonate (V).—To a solution of 600 mg. of I in 8 ml. of dry pyridine was added 1.0 g. of 3,5-dinitrobenzoyl chloride. The yellow solution was allowed to stand at 25° for 2 days. The crystals that formed were filtered and washed with ethanol; yield 1.0 g. (96%), m.p. 230–232°. Recrystallization from a dioxane–water mixture gave m.p. 237–239°, $[\alpha]^{20}\text{D}$ −78° (*c* 2, dioxane).

Anal. Calcd. for $C_{17}H_{16}N_2O_{11}S$: C, 44.7; H, 3.5; N, 6.1; S, 7.0. Found: C, 44.6; H, 3.5; N, 6.0; S, 7.0.

1,2-*O*-Isopropylidene-α-D-glucofuranose 3,5,6-(*S*-Methyl Monothioorthocarbonate (II). A.—To a solution of 500 mg. of I in 1.5 ml. of DMF were added 15 ml. of methyl iodide and 1.5 g. of silver oxide. The mixture was stirred at 25° for 16 hr., then diluted with 20 ml. of chloroform, and filtered. The precipitate was washed with additional chloroform, and the combined solutions were evaporated under reduced pressure at 65° to a sirup that crystallized partly from acetone. The crystals were removed by filtration, and a few drops of water were added to the remaining acetone solution. After standing at room temperature for 2 hr. the acetone–water mixture yielded additional crystals of II. The filtrate was concentrated to a sirup, washed with water, and dried to afford about 50 mg. of sample, the p.m.r. spectrum of which showed the presence of an *S*-methyl group and *O*-methyl group in a ratio of 2:1. The combined crystalline compound II weighed 360 mg. (68%), m.p. 162–175°, and after recrystallization from acetone gave large transparent needles, m.p. 178–180°, $[\alpha]^{20}\text{D}$ −3.3° (*c* 3, chloroform).

Anal. Calcd. for $C_{11}H_{16}O_6S$: C, 47.8; H, 5.8; S, 11.6; mol. wt., 276. Found: C, 47.8; H, 5.7; S, 11.6; mol. wt., 280 (Rast in camphor).

B.—A solution of 1.0 g. of I in 50 ml. of freshly dried redistilled dioxane was treated with 30 ml. of methyl iodide and 3 g. of silver oxide. The mixture was stirred at 25° for 16 hr., then filtered, and evaporated under reduced pressure to a sirup. Crystallization from acetone afforded 540 mg. (51%) of II.

C.—To a solution of 500 mg. of I in 5 ml. of DMF were added 2 ml. of methyl iodide and 1.84 g. of anhydrous barium oxide. After the mixture was stirred at 25° for 4 hr. II (65% yield) was isolated as in part A.

Desulfurization of II with Raney Nickel.—To a solution of 200 mg. of II in 10 ml. of dioxane was added an excess of active Raney nickel.[13] The mixture was refluxed on a steam bath for 2 hr., cooled to room temperature, and filtered. The Raney nickel was washed with dioxane, and the combined solutions were evaporated to a sirup, which crystallized to afford 141 mg. (88%) of 1,2-*O*-isopropylidene-α-D-glucofuranose (IX), m.p. 163–164°. The identification of IX was made by comparison of its melting point and its infrared spectrum with those of an authentic sample. Desulfurization of I by the same procedure also gave IX in a high yield.

1,2-*O*-Isopropylidene-α-D-glucofuranose 3,5,6-(*S*-Benzyl Monothioorthocarbonate) (III).—A solution of 1.0 g. of I in 2 ml. of DMF was treated with 4 ml. of benzyl bromide and 3.0 g. of silver oxide. After shaking for 16 hr. the reaction mixture was diluted with 50 ml. of chloroform and filtered. The filtrate was evaporated to a sirup and washed with water. After decanting most of the water, the residue was extracted with ethyl ether. The extract was dried over anhydrous magnesium sulfate and evaporated to a thick sirup which was crystallized by addition of a small volume of hexane. The crystals were filtered and washed with a few milliliters of ethanol; yield 660 mg. (49%), m.p. 169–170°, $[\alpha]^{20}\text{D}$ +25.4° (*c* 0.6, acetone) and +10.4° (*c* 0.6, dioxane).

Anal. Calcd. for $C_{17}H_{20}O_6S$: C, 58.0; H, 5.7; S, 9.1. Found: C, 57.7; H, 5.9; S, 8.6.

Although III decomposed on standing at 25° to give benzyl mercaptan and VII, no odor of benzyl mercaptan could be detected after storing III at −5° in the absence of moisture for several weeks.

Acid Hydrolysis of II and III.—A solution of 150 mg. of II in 5 ml. of acetone was treated with 1 ml. of 1 *N* hydrochloric acid, and the solution was allowed to stand at 25° for 3 hr. Acetone

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[12] Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not named.

[13] X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

(20 ml.) was then added, and the solution was neutralized with silver carbonate and filtered. After the residue was washed with acetone, the wash was combined with the filtrate. Following evaporation, the crystals that formed were washed with benzene (3 ml.) and dried to afford 126 mg. (90%) of VII, m.p. 229–230°. The infrared spectrum was identical with one from authentic VII. A similar hydrolysis of 200 mg. of III gave 110 mg. (79%) of VII.

In preliminary trial runs the amount of methyl mercaptan formed from 1 mole of II, when subjected to different concentrations of nitric acid at 25° for 1 hr., was determined by slight modification of the method of Malisoff and Anding.[14] The results were as follows.

HNO_3 added, *N*	8	6	1	0.1	0.01
CH_3SH, mole	0.94	0.97	0.83	0.19	0.09

The rate of formation of methylmercaptan from 1 mole of II on addition of 6 *N* nitric acid was as follows.

Min.	5	10	25	60	120
CH_3SH, mole	0.41	0.64	0.89	0.98	0.96

A typical example of the hydrolysis of II and of subsequent determination of the methyl mercaptan formed is as follows. To a solution of 41.0 mg. of II in 5 ml. of chloroform were added 10 ml. of 0.05 *N* silver nitrate solution and 2 ml. of 6 *N* nitric acid. After the flask was shaken for 1 hr., 5 ml. of ferric alum indicator was added, and the reaction mixture was titrated with a standard solution of ammonium thiocyanate (0.050 *N*).

Qualitative Test for Sulfhydryl Group with Diphenylpicrylhydrazyl (DPPH).—To a solution of 11.8 mg. (0.45 mmole) of I in 10 ml. of absolute ethanol was added 0.4 ml. of DPPH reagent (10.0 mg. of DPPH in 1 ml. of acetone diluted to 200 ml. with ethanol). The reddish solution turned colorless after 4 min. Similarly, 13.7 mg. (0.45 mmole) of IV turned colorless after 45 min.

1,2-*O*-Isopropylidene-5,6-dithio-β-L-idofuranose 5,6-Trithiocarbonate (X).—For the preparation of X the method of Creighton and Owen[15] was modified. A solution of IX (22.5 g.) in 250 ml. of dry pyridine was cooled to 0°. *p*-Toluenesulfonyl chloride (17.5 g.) in 150 ml. of chloroform was added in small portions with stirring. The yellow solution was kept at 25° for 16 hr. After evaporating most of the pyridine at 40° under reduced pressure, the sirup was dissolved in chloroform and washed successively with an aqueous solution of sodium hydrogen phosphate and water. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated to dryness. The colorless sirup was dissolved in 600 ml. of methanol and treated with 32 g. of pulverized potassium hydroxide and 140 ml. of carbon disulfide. The solution was refluxed for 2.5 hr. and then cooled to room temperature. The yellow reaction mixture was added slowly with stirring to 2 l. of cold water. After standing for 1 hr. the yellow crystalline product was filtered and washed with water to afford 16 g. (53%) of X, m.p. 176–176.5°. Creighton and Owen reported m.p. 179–180°.[15] The ultraviolet spectrum showed an absorption maxima at 315 mμ (ϵ 15,000). McSweeney and Wiggins[16] reported ϵ 13,500–15,000.

Anal. Calcd. for $C_{10}H_{14}O_4S_3$: C, 40.8; H, 4.8; S, 32.7. Found: C, 40.8; H, 4.9; S, 32.6.

Methylation of X.—A solution of 1 g. of X in 1.2 ml. of dry DMF was treated with 20 ml. of methyl iodide and 3 g. of anhydrous barium oxide. The mixture was stirred at 25° for 3 hr. and then was diluted with 30 ml. of chloroform, filtered, and concentrated under reduced pressure at 25°. The sirup was washed with water, dissolved in ether, and dried over anhydrous magnesium sulfate. Evaporation of the ether gave a yellow sirup, the infrared spectrum of which showed no absorption of a hydroxyl group. The ultraviolet spectrum had an absorption maximum at 315 mμ (ϵ 6000).

Anal. Calcd. for $C_{11}H_{16}O_4S_3$: C, 42.9; H, 5.2; S, 31.2. Found: C, 43.8; H, 5.6; S, 29.5.

When methylation was done at a higher temperature, or for a longer period of time, or with silver oxide in place of barium oxide, a strong absorption for a carbonyl was observed. When methylation was done at 0°, the infrared spectrum of the resulting sirup showed no hydroxyl or carbonyl absorption. The ultraviolet spectrum had an absorption maximum at 315 mμ with a molar extinction coefficient of 9000.

The p.m.r. spectra of the products methylated at 25 and 0° showed the presence of both *O*-methyl and *S*-methyl groups. To determine the ratio of these groups, the products were desulfurized with Raney nickel and the methoxyl contents of the resulting sirups were determined. The results indicated that the ratios of the *O*-methyl product to the *S*-methyl product were 9:1 and 7:3 at 0 and 25°, respectively.

1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-glucofuranose 5,6-Carbonate (VIII).—A solution of 1 g. of VII in 5 ml. of DMF was treated with 20 ml. of methyl iodide and 3 g. of silver oxide at 25° for 18 hr. After dilution with 30 ml. of chloroform, the mixture was filtered and evaporated at 70° to a sirup, which was dissolved in chloroform and washed successively with an aqueous sodium cyanide solution and water. The chloroform solution was dried over anhydrous magnesium sulfate, then filtered, and evaporated to a sirup, which partially crystallized on long standing at room temperature; $[\alpha]^{20}_D$ −49.4° (*c* 6.4, chloroform). The infrared spectrum showed no absorption for a hydroxyl group and a strong absorption for a cyclic carbonate.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.8; H, 6.2. Found: C, 50.8; H, 6.4.

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(14) W. M. Malisoff and C. E. Anding, Jr., *Ind. Eng. Chem., Anal. Ed.*, **7**, 86 (1935).

(15) A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960).

(16) G. P. McSweeney and L. F. Wiggins, *Nature*, **168**, 874 (1951).