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Note

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-thio-α-D-glucofuranose 5,6-dithiocarbonate: A versatile intermediate

BARUCH S. SHASHA AND WILLIAM M. DOANE
Northern Regional Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Peoria, Illinois 61604 (U. S. A.)

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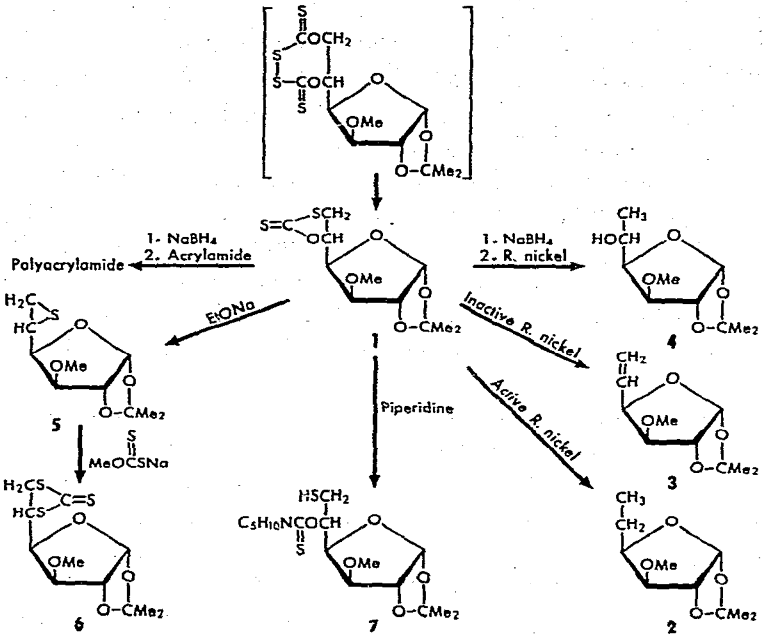
The preparation and decomposition of cyclic dithiobis(thioformates) of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and 1,2:5,6-di-*O*-isopropylidene-D-mannitol were previously reported[1]. The products of decomposition were either cyclic thionocarbonates or cyclic xanthic esters in which inversion of configuration occurred at the site of thiolation. This paper describes extension of the reaction to a terminal diol and a study of the reactions of a terminal cyclic xanthic ester. Xanthation of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose gave the dixanthate, which was coupled to give the dithiobis(thioformate). This derivative was so unstable that dissolution in acetone at ambient temperature caused extensive decomposition to carbonyl sulfide, elemental sulfur, and the cyclic xanthic ester, 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-thio-α-D-glucofuranose 5,6-dithiocarbonate (**1**). When the xanthation, coupling, and decomposition were performed with the 3-position unprotected, a complex mixture was obtained that was not investigated further.

Some reactions of **1** are summarized in the Scheme. Desulfurization of **1** with freshly prepared Raney nickel gave 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose (**2**), but when old Raney nickel (that had lost its activity on storage) was used, the corresponding olefin (5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose, **3**) was obtained. Presumably **3** is an intermediate in the formation of **2**. Desulfurization of tetra-*O*-acetyl-α-D-glucopyranosyl ethylxanthate with Raney nickel has been reported[2] to yield 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-glucitol. The structures of **3** and **2** were consistent with n.m.r. spectra and were verified by comparison with authentic samples. When **1** was reduced with sodium borohydride in methyl sulfoxide (to give thiol) followed by treatment with Raney nickel, 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**4**) was obtained.

In another experiment, the mixture after reduction with borohydride was treated with an aqueous solution of acrylamide in the presence of hydrogen peroxide. Polymerization occurred; precipitation with ethanol gave a white product having a



SCHEME

molecular weight of up to 1 million. As thiolated starch[3] is readily prepared, a similar procedure has potential for preparation of graft copolymers from starch and various monomers such as acrylamide, acrylonitrile, and styrene. Heating **1** in ethanol in the presence of alkali on a steam bath gave a multicomponent mixture (t.l.c.) that gave a negative test for a free -SH group. However, at ambient temperature, the major component was the episulfide (**5**), which gave the 5,6-trithiocarbonate (**6**) by reaction with sodium methylxanthate. Compound **6** was prepared independently by the reaction of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose 6-*p*-toluenesulfonate with sodium methylxanthate. The preparation of trithiocarbonates under similar conditions is known to occur[4] with inversion of configuration at C-5.

Piperidine reacted with **1** to give 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-piperidinothiocarbonyl-6-thio-α-D-glucofuranose (**7**). This reaction is analogous to the reaction previously reported between cyclic thionocarbonate and piperidine[5].

EXPERIMENTAL

General. — Melting points (uncorrected) were determined in a capillary tube. Optical rotations were measured in a 1-dm tube with a Rudolph* polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 137 spectrometer having silver

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*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 mentioned.

chloride optics by using Nujol mulls or films. U.v. spectra were recorded with a Perkin–Elmer Model 202 spectrometer. For t.l.c. Silica Gel G was used as the adsorbent, 9:1 (v/v) carbon disulfide–ethyl acetate as the solvent, and 19:1 (v/v) methanol–sulfuric acid as the spray reagent. Desorption chromatography was carried out by using silicic acid (Mallinckrodt, 100 mesh) or basic alumina (Fisher, 80–200 mesh) as stationary phase and hexane–ethyl acetate as eluant. Raney nickel was activated according to the procedure described by Dominguez *et al.*[6]. 5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose (**2**) and 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose (**3**) were prepared[7] as reference compounds. Determination of carbonyl sulfide was accomplished as described earlier[8]. Newcell Thiol Spray (Newcell Biochemicals) was used for detection of -SH group.

*1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-glucofuranose* (**8**). — 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (6 g) in methyl sulfoxide (6 ml) was treated with pulverized potassium hydroxide (6 g). The mixture was cooled to 5° and treated with methyl iodide (12 ml). The reaction, which was monitored by t.l.c., was stopped after 90 min. Water (100 ml) was added and the mixture was extracted with hexane to yield 4.6 g of a colorless syrup, presumably the 3-*O*-methyl derivative. The 5,6-*O*-isopropylidene group was hydrolyzed by treating the syrup with 30% acetic acid (200 ml) with stirring for 50 min at 44°. Evaporation of the solution at 44° yielded known **8**; $[\alpha]_D^{25}$ $-55°$ (*c* 2, chloroform). Duff and Percival[9] reported $-54°$ in chloroform.

*6-Deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-thio-α-D-glucofuranose 5,6-dithiocarbonate* (**1**). — A solution of **8** (4 g) in a mixture of potassium hydroxide (12 g) in water (8 ml) and methyl sulfoxide (8 ml), was cooled to 5° and treated with carbon disulfide (15 ml). After 15 min, sodium nitrite (5 g) was added, followed by acetic acid in crushed ice to bring the pH to about 4. A stream of air was passed through the mixture to evaporate off the excess carbon disulfide. A brown syrup that precipitated was collected and washed with water. Upon dissolution in acetone, carbonyl sulfide was evolved and elemental sulfur precipitated out. After 15 min, t.l.c. revealed one major component (**1**) which was readily purified (3 g) by desorption chromatography; $[\alpha]_D$ $-43°$ (*c* 2, acetone); λ_{max}^{film} 1060, 1090 cm^{-1} [O(C=S)S]; λ_{max}^{EtOH} 283 nm (ε 17,000). Maxima of 280–282 nm (ε 11,700–12,400) were reported[10] for acylic xanthic esters and maxima of 283–286 nm (ε 12,000–15,150) for cyclic esters. N.m.r. in CCl_4: τ 4.23 (1-proton doublet, $J_{1,2}$ 4.0 Hz, H-1), 4.80 (1-proton apparent quartet, H-5), 5.5 (1-proton doublet, H-2), 5.70 (1-proton doublet of doublets, H-4), 6.18 (1-proton doublet, H-3), 6.32 (2-proton multiplet, H-6 and 6′), 6.52 (3-proton singlet, OCH_3), and 8.5 and 8.7 (3-proton signlets, CMe_2). Assignments were verified by irradiation and decoupling techniques. Compound **1** was stable (t.l.c. and i.r.) for at least 10 min at 180–200°.

Anal. Calc. for $C_{11}H_{16}O_5S_2$: C, 45.3; H, 5.5; S, 21.8. Found: C, 45.3; H, 5.8; S, 21.7.

*Reactions of **1** with Raney nickel.* — Compound **1** (400 mg) was heated in ethanol (10 ml) under reflux with freshly prepared Raney nickel to yield a major component that was purified by desorption chromatography (230 mg) and characterized by comparison (t.l.c., i.r., and n.m.r.) with an authentic sample as 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hexofuranose (**2**). When the experiment was repeated with inactive Raney nickel (which had lost its activity on storage), 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-hex-5-enofuranose (**3**), 220 mg was obtained and identified by comparison with an authentic sample.

6-Deoxy-1,2-O-isopropylidene-3-O-methyl-α-D-glucofuranose (**4**). — To a solution of **1** (250 mg) in methyl sulfoxide (1 ml), sodium borohydride (60 mg) was added. After 10 min, excess borohydride was decomposed with acetic acid and the mixture was extracted with ether. The extract showed a major spot on t.l.c. that gave a positive test for -SH. After evaporation of the ether, the resulting syrup was dissolved in ethanol (5 ml) and refluxed with activated, freshly prepared Raney nickel for 30 min. After filtration and concentration, compound **4** was purified by desorption chromatography to yield 120 mg of product, $\lambda_{\max}^{\text{film}}$ 3650, 3020, 1450, 1380, 1260, 1225, 1175, 1135, 1080, 1025, 900, and 865 cm^{-1}; n.m.r. ($CDCl_3$): τ 4.15 (1-proton doublet, H-1), 5.45 (1-proton doublet, H-2), 6.08 (multiplet, H-3, H-4, H-5), 6.55 (singlet, 3 protons OMe), 6.9 (broad singlet, 1 proton OH, disappeared on exchange with D_2O), and 8.65 (multiplet, 9 protons C-Me). Previously[11], compound **4** was prepared by catalytic reduction of 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose.

Anal. Calc. for $C_{10}H_{18}O_5$: C, 55.0; H, 8.2. Found: C, 54.6; H, 8.4.

5,6-Dideoxy-5,6-epithio-1,2-O-isopropylidene-3-O-methyl-β-L-idofuranose (**5**). — A solution of **1** (275 mg) in ethyl alcohol (5 ml) was treated with sodium hydroxide solution (12.5M, 1 ml) for 5 min, neutralized with acetic acid, and extracted with chloroform (10 ml). T.l.c. showed mainly one component having an R_F value slightly lower than that of **1**. Evaporation of the solvent yielded 210 mg of syrupy **5**, which was purified by desorption chromatography. On storage at 5° in hexane, compound **5** crystallized, m.p. 75–85° and, after recrystallization from heptane, m.p. 86–87°, $[\alpha]_D^{25}$ −52° (*c* 1, acetone); n.m.r. ($CDCl_3$): τ 4.10 (1-proton doublet, $J_{1,2}$ 4.0 Hz, H-1), 5.42 (1-proton doublet, H-2), 6.4 (2-proton multiplet H-3 and H-4), 6.6 (3-proton singlet, OMe), 6.88 (1-proton multiplet H-5), 7.58 and 7.83 (2 protons, 2 sets of multiplets H-6 and H-6′), 8.55, 8.7 (3-proton singlets, CMe_2). Assignments were verified by irradiation and decoupling techniques. The mass spectrum showed a high-mass peak at *m/e* 232. Major fragments were at *m/e* 217 (M−15), 175, 174, 147, 144, 143, 141, 118, 115, 97, 90, 87, 85, 71, 59, 58, 57, and 57. The base peak was at *m/e* 85.

Anal. Calc. for $C_{10}H_{16}O_4S$: C, 51.7; H, 6.9; S, 13.8. Found: C, 51.7; H, 6.9; S, 14.0.

5,6-Dithio-1,2-O-isopropylidene-3-O-methyl-β-L-idofuranose 5,6-trithiocarbonate (**6**). — (*a*) From **5**. A solution of **5** (25 mg) in methanol (0.5 ml) was refluxed for 30 min with carbon disulfide (0.5 ml) and pulverized sodium hydroxide (100 mg). Water (5 ml) was added and a stream of air was passed through the mixture to evaporate excess carbon disulfide. The water was decanted from the yellow syrup and the latter was washed with water. On standing, the syrup crystallized to yield 20 mg of **6**.

(*b*) *From* **8**. A solution of **8** (700 mg) in pyridine (10 ml) was cooled to 0°. *p*-Toluenesulfonyl chloride (400 mg) in 3 ml of chloroform was added in small portions with stirring. The yellow solution, which was kept for 16 h at 25°, was poured into water (100 ml) and extracted with chloroform (10 ml). After evaporation of the chloroform, methanol (5 ml), carbon disulfide (3 ml), and pulverized sodium hydroxide (300 mg) were added. After the mixture had been heated for 2 h under reflux, compound **6** was separated as in part (*a*), to yield 180 mg; m.p. 86–87°, $[\alpha]_D^{25}$ $-18°$ (*c* 1, acetone); λ_{max}^{EtOH} 316 nm (ε 16,000). An absorption maximum at 315 nm (ε 15,000) was reported[12] for 5,6-dideoxy-1,2-*O*-isopropylidene-5,6-dithio-*β*-L-idofuranose 5,6-trithiocarbonate.

Anal. Calc. for $C_{11}H_{16}O_4S_3$: C, 42.8; H, 5.2; S, 31.2. Found: C, 42.6; H, 5.4; S, 31.4.

Polymerization of acrylamide. — A solution of **1** (35 mg) in methyl sulfoxide (0.2 ml) was treated with sodium borohydride (6 mg). After 10 min, excess borohydride was decomposed by acetic acid. The mixture, after dilution with acetone (0.5 ml), was added to a preheated (65°) solution of acrylamide (5 g) in water (50 ml) containing hydrogen peroxide (2 ml, 20%). After 10 min at 65°, the solution was diluted with 50 ml of water and the polymer formed was precipitated by ethanol in a Waring Blendor. The solid was collected, retreated in a Waring Blendor with ethanol, filtered off, and dried to yield 4.8 g of product. The product had an intrinsic viscosity $[\eta]$ of 1.90 in M sodium nitrate at 30°, corresponding to $\bar{M}_w$ of 416,000 based on the following equation[13]:

$$[\eta] = 3.73 \times 10^{-4} \bar{M}_w \, 0.66$$

A product was obtained having an intrinsic viscosity of 3.46, corresponding to $\bar{M}_w$ of 1,020,000 when the experiment was repeated but with a solution containing 10 mg of **1**. No polymer was formed when the experiment was repeated without **1**.

*1,2-O-Isopropylidene-3-O-methyl-5-O-piperidinothiocarbonyl-6-thiol-α-*D*-glucofuranose* (**7**). — A solution of **1** (150 mg) in diethyl ether (3 ml) was treated with piperidine (0.3 ml) and kept for 5 min. Acetic acid (10%, 7 ml) was added and the mixture was extracted with ether. T.l.c. showed a major component (R_F 0.50), which was isolated by desorption chromatography to yield 101 mg of the piperidine derivative **7** as a syrup, $[\alpha]_D^{24}$ $-6°$ (*c* 4, acetone); λ_{max}^{EtOH} 253 nm (ε 16,600). The i.r. spectrum showed absorption for the presence of thiocarbonyl (1250 cm^{-1}) but no absorption for hydroxyl; n.m.r. ($CDCl_3$): τ 4.15 (1-proton doublet, H-1), 4.3 (1-proton multiplet, H-5), 6.65 (singlet, 3-protons OMe), 8.6 (singlet, 1 proton SH, disappeared on exchange with D_2O), and 8.55 and 8.75 (2 singlets, 6 protons C-Me).

Anal. Calc. for $C_{16}H_{27}NO_5S_2$: S, 17.0. Found: S, 16.7.

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