SUGARS WITH A NEW FUNCTIONAL GROUP: HYDROXYTHIO(THIOCARBONATE)

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ABSTRACT

The preparation and some properties are described of two sugar derivatives containing a new functional group, namely hydroxythio(thiocarbonate) [ROC(=S)-SOH]. These derivatives were prepared by reaction of hydrogen peroxide with the *O*-(sodium thiolthiocarbonyl) derivative of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7**). These derivatives are acidic enough to be titrated with alkali and, in presence of hydrogen peroxide, are able to initiate graft polymerization of acrylamide. The nature of the linkage between the sugars and polyacrylamide is (in part) a thioester type.

INTRODUCTION

A 1967 patent[1] disclosed a process by which graft polymerization of unsaturated monomers was initiated by using starch or cellulose mono- or dithiocarbonates as substrates. Peroxides, hydroperoxides, peroxyesters, and peroxyacids have been claimed as initiators, and α-methylstyrene, acrylic acid, acrylamide, and acrylonitrile (among others) as monomers. The nature of linkage(s) between the polymerized monomer and the substrate was not described.

Dimov and Pavlov[2] prepared cellulose–acrylonitrile graft polymers by treating cellulose dithiocarbonates with an acrylonitrile–hydrogen peroxide system. They investigated such factors as pH, temperature, and degree of substitution of the dithiocarbonate. The amount of acrylonitrile grafted was almost twice as much at pH 1.5 as at pH 4. An increase in temperature up to 50° increased the amount of the graft. They suggested a mechanism in which the main steps are:

$$\text{Cell-OC(=S)-SH} \rightleftharpoons \text{Cell-OCS:}^- \xrightarrow{\text{HO:OH}} \text{Cell-OCS}\cdot \rightarrow \text{Cell-O}\cdot \xrightarrow{\text{acrylonitrile}} \text{Cell-OCH}_2\text{-CH(CN)}$$

Reactions of hydrogen peroxide, and a hydrogen peroxide–acrylamide system, with 1,2:3,4-di-*O*-isopropylidene-6-*O*-(*S*-sodium thiolthiocarbonyl)-α-D-galactopyranose (**2**) and 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*S*-sodium thiolthiocarbonyl)-α-D-glucofuranose (**8**) are described here.

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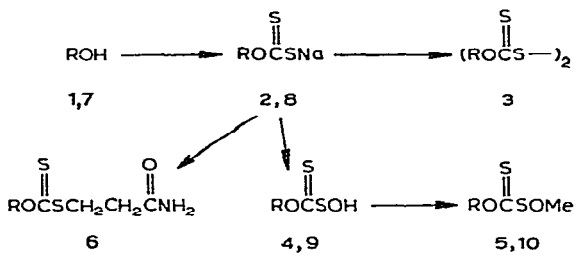
RESULTS AND DISCUSSION

Acidification of an aqueous solution of the dithiocarbonates **2** or **8** immediately decomposes the parent sugar. Consequently, the dithiocarbonic acid [ROC(=S)SH] is not, as had been suggested by Dimov and Pavlov[2], likely to be the intermediate in the grafting reaction. In the presence of hydrogen peroxide at pH about 4–6 and a concentration of about 10% of dithiocarbonate, a crosslinking reaction takes place to give bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-[dithiobis(thioformate)] (**3**) in low yield (see Scheme). When the experiment was repeated, under the



1-6 R = 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl
7-10 R = 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl

Scheme I

same conditions except that the final concentration of dithiocarbonate was decreased to 1%, the crosslinking reaction was much slower and the solution showed an absorption maximum near 300 nm. A maximum in this region is anticipated for the *O*-(*S*-sodium dithiocarbonyl) group, but acidification of the solution did not remove this peak as had been expected. T.l.c. of this solution revealed the presence of a new component (**4**) having an R_F value less than that of the disulfide (**3**) but higher than that of the parent sugar **1**. Compound **4** was isolated crystalline and characterized as 6-*O*-[hydroxythio(thiocarbonyl)]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. To our knowledge, **4** is the only reported compound containing the -OC(=S)SOH group. The structure of **4** was assigned on the basis of elemental analysis and mass-spectral data, which showed a molecular-ion peak at 352. DeJongh and Biemann[3] noted that isopropylidene acetals are most suitable for determining the molecular weight of carbohydrates because the loss of one of the methyl groups from the 2,2-dimethyl-1,3-dioxolane ring gives rise to an abundant fragment of mass M −15. Indeed, the spectrum of **4** reveals a strong peak at *m/e* 337. The i.r. spectrum showed an OH peak at 3300 cm^{-1}, somewhat shifted from the usual absorption range[4] (3700–3500 cm^{-1}) for an unbonded OH group. Reaction of **4** with diazomethane gave the corresponding *O*-methyl derivative (**5**), as shown by elemental analysis and by the 3-proton singlet at τ 6.1 in the n.m.r. spectrum. Compound **4** consumes one equivalent of alkali, and its titration curve (Fig. 1) indicates that it is a weak acid. The u.v. spectrum of the salt, after titration with alkali, showed absorption maxima at 225, 280, and 360 nm

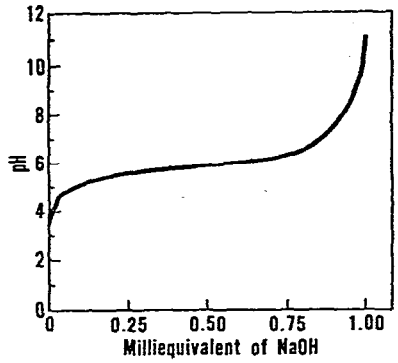


Fig. 1. Titration curve of 6-*O*-[hydroxythio(thiocarbonyl)]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) with alkali.

instead of the maxima at 230 and 340 nm observed for **4**. Acidification of the salt restored the absorption at 230 and 304 nm, although t.l.c. indicated that the acidified solution contained a mixture of several other components besides **4**. Heating **4** with excess alkali gave **1** as the sole sugar derivative (t.l.c.) and, upon acidification of the hydrolyzate, carbon disulfide was liberated.

Treatment of a 1% solution of **8** with hydrogen peroxide gave the corresponding hydroxythio(thiocarbonyl) derivative (**9**), which was isolated as the *O*-methyl derivative (**10**).

When an aqueous solution of **8** was treated with acrylamide in the presence of hydrogen peroxide, polymerization occurred. Precipitation with ethanol gave a white, fibrous product that had an absorption maximum at 280–285 nm, indicative of a compound of the type ROC(=S)SR. Upon treatment with alkali, the absorption maximum disappeared.

To determine the absorption maxima and extinction coefficients of compounds containing the group $ROC(=S)SCH_2CH_2C(=O)NH_2$, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose 6-*O*-(dithiocarbonyl 3-proprionamide) (**6**) was prepared by reaction of the corresponding dithiocarbonic acid with acrylamide. The addition reaction of a dithiocarbonic acid to a double bond has been reported[5].

$$ROCSH + CH_2{=}CHCNH_2 \rightarrow ROCSCH_2CH_2CNH_2$$

Compound **6** had an absorption maximum at 285 nm (ε 9,400).

The next objective was to find out whether the ester linkage is the only type that exists between the D-glucose and the polyacrylamide residues. To answer this question, a solution of the polymer (prepared with **8**) was treated with acid (to hydrolyze the *O*-isopropylidene groups of the D-glucose derivative) and then with periodate. Quantitative determination of formaldehyde in the solution showed that the proportion of D-glucose present in the polymer as determined by this method, is about twice that found after alkali hydrolysis of the polymer and determination

of free D-glucose. No formaldehyde could be detected when the homopolymer was similarly treated. Evidently, more than one type of linkage exists between the D-glucose moiety and polyacrylamide.

When the hydroxythio(thiocarbonyl)derivative **4** was used in the polymerization reaction in place of the *S*-(sodium dithiocarbonate), all of the acrylamide polymerized rapidly. This result may suggest that the $-CS_2OH$ group is an intermediate in the polymerization reaction.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns* apparatus and are uncorrected. Optical rotations were measured in a 1-dm tube with a Rudolph polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 137 or 621 spectrophotometer having silver chloride optics as Nujol mulls or films and the u.v. spectra were recorded with a Perkin–Elmer Model 202 spectrophotometer. N.m.r. spectra were recorded by a Varian HA-100 spectrometer with tetramethylsilane as internal reference standard ($\tau = 10.00$). Mass spectra were obtained with a Nuclide 12-90-G mass spectrometer equipped with a probe inlet. For t.l.c., Silica Gel G served as the adsorbent, 9:1 (v/v) carbon disulfide–ethyl acetate as the solvent (unless stated otherwise), and 9:1 (v/v) methanol–sulfuric acid as the spray reagent. Diazomethane was prepared by reaction of 1-methyl-1-nitrosourea with alkali[6]. Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-[dithiobis(thioformate)] (**3**) was prepared as described previously[7].

*Decomposition of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(S-sodium dithiocarbonyl)-α-D-galactopyranose* (**2**). — To a solution of **1** (100 mg) in methyl sulfoxide (0.1 ml), carbon disulfide (0.1 ml) and 5M sodium hydroxide solution (0.1 ml) were added. The mixture, after being kept for 10 min, was diluted with water to 1 liter. The u.v. spectrum showed a strong absorption maximum at 304 nm that disappeared immediately upon acidification of the solution with diluted hydrochloric acid. When the experiment was repeated and the mixture was diluted to 10 ml (instead of 1 liter) and acidified, t.l.c. revealed one component that corresponded to **1**.

*Decomposition of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(S-sodium dithiocarbonyl)-α-D-glucofuranose* (**8**). — Compound **8**, prepared by the same procedure as **2**, decomposed immediately upon acidification with dilute hydrochloric acid, to give the parent isopropylidene acetal of the sugar.

*Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-[dithiobis(thioformate)]* (**3**). — To a solution of **1** (1 g) in methyl sulfoxide (1 ml), carbon disulfide (1 ml) and 5M sodium hydroxide (1 ml) were added. After 10 min, the mixture was neutralized (5M acetic acid) and hydrogen peroxide was added dropwise with stirring. A thick syrup that precipitated out of the solution was washed with water. T.l.c. of the syrup showed, besides the starting sugar, one major spot that corresponded to the known **3**.

*Mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

Purification by preparative t.l.c. gave 100 mg (8%) of a crystalline compound, which was recrystallized from alcohol. The m.p. and mixed m.p. with authentic **3** were 131–132°, and the i.r. spectrum was superposable upon that of the authentic sample. (Caution: a strongly exothermic reaction takes place if the peroxide is added all at once.)

Compound **3** was previously prepared in a higher yield by oxidation of **2** with iodine[7].

6-O-[*Hydroxythio(thiocarbonyl)*]-*1,2:3,4-di*-O-*isopropylidene*-α-D-*galactopyranose* (**4**). — To a solution of **1** (1.5 g) in methyl sulfoxide (1.5 ml), carbon disulfide (1.5 ml) and 5M sodium hydroxide (1.5 ml) were added. After 10 min the mixture was neutralized and added to 150 ml of water containing hydrogen peroxide (30%, 5 ml). The mixture, which was clear yellow, turned turbid and white after stiring for a few min. After 30 min, a white precipitate was observed, which was filtered, washed with water, dried, and characterized as **4**. The yields of **4** varied from 600 to 900 mg (30–45%); m.p. 66–68° (carbon disulfide). When **4** was melted (66–68°), allowed to solidify, and then recrystallized (carbon disulfide), the m.p. was raised to 122–124°. Crystallization of a mixture of the low-melting form with the high-melting one gave only the high-melting product. Both samples had the same R_F value (about 0.5) and also had superposable i.r. and u.v. spectra (maxima at 230 and 300 nm); $[\alpha]_D^{25}$ −57° (*c* 1, acetone); *m/e* 352 (M^+), 337 ($M^+-\cdot CH_3$).

Anal. Calc. for $C_{13}H_{20}O_7S_2$: C, 44.3; H, 5.7; S, 18.2. Found: C, 44.5; H, 5.8; S, 17.8.

1,2:3,4-Di-O-*isopropylidene-6*-O-[*methoxythio(thiocarbonyl)*]-α-D-*galactopyranose* (**5**). — A solution of **4** (200 mg) in ether (5 ml) was treated with an excess of a cold, ethereal solution of diazomethane. After about 10 min, t.l.c. showed mainly one spot having R_F ~0.7. Purification by preparative t.l.c. gave 140 mg of the title compound. The i.r. spectrum lacked the absorption at 3300 cm^{-1} that is characteristic of **4**. The u.v. spectrum showed absorption maxima at 228 and 296 nm. The n.m.r. spectrum showed a 3-proton singlet at τ 6.1 (OCH_3).

Anal. Calc. for $C_{14}H_{22}O_7S_2$: C, 46.1, H, 6.1. Found: C, 46.4; H, 6.1.

Alkaline treatment of **4**. — *A.* To a solution of **4** (210 mg) in acetone (10 ml), water (5 ml) was added. The mixture was titrated potentiometrically with sodium hydroxide solution (0.1M). (See Fig. 1 for the titration curve.) The u.v. spectrum of the salt showed absorption maxima at 225, 280, and 360 nm, which changed to 230 and 304 nm upon acidification. T.l.c. of the acidified solution indicated the presence of several components.

B. A solution of **4** (50 mg) in ethanol (2 ml) was treated with sodium hydroxide (1M, 0.1 ml). The mixture was heated for 10 min under reflux. T.l.c. indicated the presence of one component that corresponded to **1**. The i.r. spectrum of an ethereal extract of the hydrolyzate was superposable upon that of the spectrum of authentic **1**.

Upon acidification of the hydrolyzate, carbon disulfide was released and was identified by a procedure described earlier[8].

1,2:5,6-Di-O-*isopropylidene-3*-O-[*methoxythio(thiocarbonyl)*]-α-D-*glucofuranose*

(**10**). — To a solution of **7** (1 g) in methyl sulfoxide (1 ml), carbon disulfide (1 ml) and sodium hydroxide (5M, 1 ml) were added. After a few minutes, the mixture was poured into 100 g of ice–water containing hydrogen peroxide (30%, 3 ml). This mixture was stirred for 10 min and then acidified with dilute hydrochloric acid, and extracted with cold ether saturated with diazomethane. Evaporation of the ether extract gave a yellowish syrup that, according to t.l.c. ,contained the starting isopropylidene acetal together with another component, which was isolated by preparative t.l.c. to yield 187 mg of the title compound; $[\alpha]_D^{25}$ −12.5° (*c* 2, $CHCl_3$); λ_{max}^{EtOH} 234 (ε 10,500) and 300 nm (5,150).

Anal. Calc. for $C_{14}H_{22}O_7S_2$: C, 46.1; H, 6.1. Found: C, 45.8; H, 6.3.

When the experiment was performed without acidification, an additional component was detected by t.l.c. This component was isolated and identified (t.l.c., u.v., and i.r.) as the known 1,2:5,6-di-*O*-isopropylidene-3-*O*-[(methylthio)thiocarbonyl]-α-D-glucofuranose. Others had previously prepared this compound by treatment of the corresponding xanthate with iodomethane[9].

Polymerization of acrylamide. — *A.* A solution of **8** (100 mg) in water (1 ml) was added to a preheated (50°) mixture containing acrylamide (10 g) and hydrogen peroxide (30%, 1 ml) in 50 ml of water. The solution turned cloudy immediately and, after 10 min, the polymer was precipitated into ethanol in a Waring Blendor. The solid was collected, retreated in a Waring Blendor with ethanol, filtered, and dried to yield 5 g of product; $\lambda_{max}^{H_2O}$ 280–285 nm (ε 9,000). The product had an intrinsic viscosity $[\eta]$ of 0.882 in M sodium nitrate at 30°, corresponding to $\bar{M}_w$ of 102,000 based on the following equation[10].

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

A sample of the polymer (200 mg) in 10 ml of water was treated with sodium hydroxide (0.5M, 0.5 ml) and heated on a steam bath until there was no absorption maximum in the region 280–300 nm. The sample was acidified (conc. hydrochloric acid, 1 ml) and heated for 2 min on a steam bath. The solution was neutralized and the content of D-glucose as, determined by D-glucose oxidase, was determined to be 0.12%. When the alkaline treatment was omitted, a negligible proportion of D-glucose was found.

In another experiment, a sample of the polymer (200 mg) in water (5 ml) was treated with concentrated hydrochloric acid (0.5 ml) and heated for 2 min on a steam bath. The solution was neutralized and diluted with water to 10 ml. A sample of this solution (2 ml) was treated with periodate (5mM, 0.5 ml) and the formaldehyde released was determined with 2,4-pentanedione reagent. A standard solution of D-glucose (50.5 mg/l) was run simultaneously. The amount of D-glucose found by this procedure was 0.25%.

B. To a preheated (50°) solution of acrylamide (10 g) in water (50 ml) containing hydrogen peroxide (30%, 1 ml), **4** (50 mg) in acetone (1 ml) was added in one portion. The mixture was kept for 10 min, before it was processed as in part *A* to yield 10 g of product, $\lambda_{max}^{H_2O}$ 280–285 nm.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose 6-O-(dithiocarbonyl-3-propionamide (**6**). — A solution of **1** (1.2 g) in methyl sulfoxide (1 ml) was treated with carbon disulfide (0.5 ml) and sodium hydroxide (0.5M, 1.2 ml). After 10 min, the mixture was neutralized with acetic acid, and acrylamide (1.2 g) in water (2 ml) was added. After a further 10 min, sulfuric acid (2.5M, 0.9 ml) was added dropwise with constant mixing of the reaction mixture, followed by water (about 30 ml). A thin syrup separated from the solution, which was collected and washed with water and dried to yield 500 mg of residue. According to t.l.c. (ethyl acetate as solvent), the residue contained one major component. The product was dissolved in ether (5 ml) and precipitated with *n*-hexane (2 ml). The precipitate was collected, dried, and analyzed; $[\alpha]_D^{25}$ −58° (*c* 1, acetone); λ_{max}^{EtOH} 285 nm (ε 9,400).

Anal. Calc. for $C_{16}H_{25}NS_2 \cdot 1/2\ H_2O$: C, 46.2; H, 6.25; S, 15.3. Found: C, 46.0; H, 6.3; S, 14.7.

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