give 185 mg (64%), melting gradually with decomposition from 110° on (after drying at 30°, 0.1 mm), $[\alpha]^{25}D$ +51° (*c* 1, H_2O) (lit.[10] $[\alpha]^{20}D$ +48.2°).

Anal. Calcd for $C_6H_{13}NO_5 \cdot HCl$: C, 33.41; H, 6.55; N, 6.50; Cl, 16.49. Found: C, 33.20; H, 6.70; N, 6.40; Cl, 16.04.

Registry No.—**2**, 17791-36-5; **3**, 22435-33-2; **4**, 19877-45-3; **5**, 51015-65-7; **6**, 19877-37-3; **7** 2-*O*-benzyl derivative, 51015-66-8; **7** 3-*O*-benzyl derivative, 51015-67-9; **8**, 21395-67-5; **9**, 51015-68-0; **10**, 19877-38-4; **11**, 19887-42-4; **12**, 19877-39-5; **13**, 19877-40-8; **14**, 19877-41-9; **15**, 19877-43-1; **16**, 19877-42-0; **17**, 51015-69-1; **18**, 24558-85-8; **18** hydrochloride, 51015-70-4; **19** α anomer, 51015-71-5; **19** β anomer, 51015-72-6; **20**, 51015-73-7.

References and Notes

(1) (a) Taken in part from the Doctoral Dissertation of P. H., Technische Hochschule Darmstadt, Feb 1969. (b) Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. (c) A preliminary account on part of this work has appeared: F. W. Lichtenthaler and P. Heidel, *Angew. Chem.*, **80**, 441 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 458 (1968).
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Sulfur-Containing Carbohydrates. Synthesis of 1,3,4,6-Tetrathio-D-mannitol[1,2]

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Received September 19, 1973

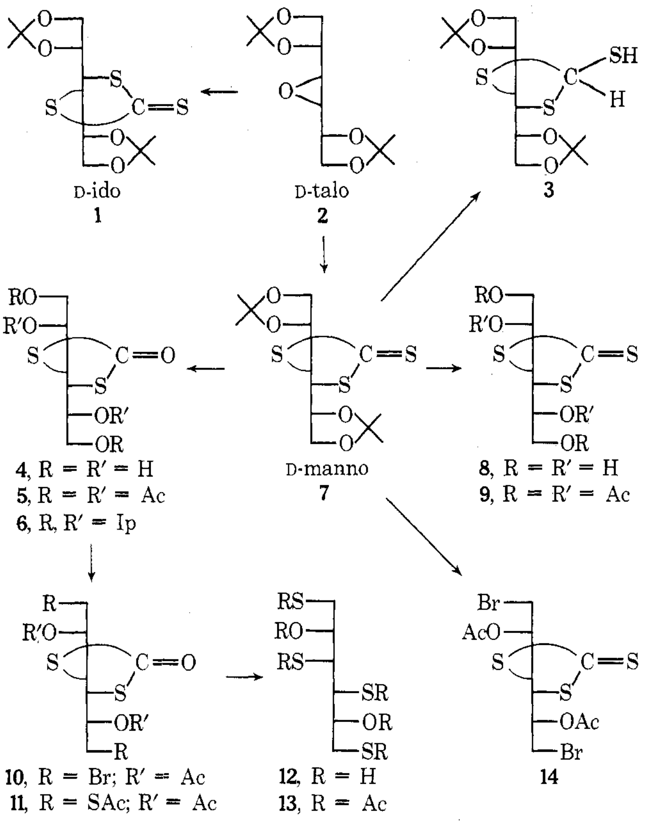
The di-*O*-isopropylidene derivative (**2**) of 3,4-anhydro-D-talitol on reaction with potassium methyl xanthate gave a mixture of two diastereomeric trithiocarbonates. One of these, mp 117°, was assigned the D-manno configuration (**7**), the other, mp 127°, the D-ido configuration (**1**), primarily on the basis of optical rotation studies. The yellow trithiocarbonate **7** was hydrolyzed to the tetrol **8**, which was converted to its tetraacetate **9**. The compound **7** was only partially reduced by lithium aluminum hydride, giving the mercaptodithiolane **3**. When oxidized, the trithiocarbonate **7** gave the corresponding dithiocarbonate **6**. The latter on hydrolysis gave the tetrol **4**, which was converted to its tetraacetate **5**. The dithiocarbonate **6** on reaction with hydrogen bromide in acetic acid gave the 1,6-dibromide dithiocarbonate diacetate **10**. The trithiocarbonate **7** similarly gave the 1,6-dibromide dithiocarbonate diacetate **14**. The compound **10** on reaction with potassium thiolacetate gave the 1,6-dithiol dithiocarbonate tetraacetate **11**. Reduction of the latter finally gave the desired 1,3,4,6-tetrathio-D-mannitol (**12**), mp 124° (hexaacetate mp 165°). Evidence for the constitution, configuration, and conformation of the various products was obtained by a variety of physical methods.

In the course of a project for synthesis of perthio carbohydrates (all oxygen atoms to be replaced by sulfur), we recently prepared a large number of hexitol and cyclitol analogs and their derivatives, in which from two to four of the oxygen atoms were replaced by sulfur.[2a]

Since it has, unfortunately, been necessary to discontinue the perthio carbohydrate project, we are now reporting on some of these partially thiolated products. A literature survey indicates that very few carbohydrates (or other organic compounds) containing three or more mercapto groups are known.[4,5] We are hopeful that some of the compounds now reported will have valuable physical, chemical, and especially biological properties.

The 3-benzoate-4-mesylate derivative[6,7] of 1,2;5,6-di-*O*-isopropylidene-D-mannitol was prepared by an improved method and converted to the di-*O*-isopropylidene derivative, **2** (Chart I), of 3,4-anhydro-D-talitol[7] (equally well named 3,4-anhydro-D-altritol). This epoxide on reac-

Chart I



tion with potassium methyl xanthate gave the expected mixture of diastereomeric trithiocarbonates, 1 and 7, separated by crystallization.[8]

The reduction of a trithiocarbonate with lithium aluminum hydride usually produces a dithiol. However, reduction of 7 proceeded only to the mercaptodithiolane 3, presumably because of steric hindrance.

We have encountered similar behavior with certain cyclitol trithiocarbonates.[9]

The trithiocarbonate diketal 7 was next hydrolyzed to the tetrol 8, which was converted to its tetraacetate 9. Both of these derivatives were also yellow and crystalline. It was hoped that the tetrol 8 could be converted *via* the 1,6-ditosyl derivative into the 1,2,:5,6-diepoxide, from which a hexathio (or at least a tetrathio) alditol should be obtainable. Since this approach was unsuccessful, we next prepared the trithiocarbonate 1,6-dibromide diacetate (14). The tetrol tetraacetate 9 was intended for use in this preparation; however, direct reaction of the trithiocarbonate 7 with hydrogen bromide in acetic acid was found more convenient.

Since the trithiocarbonate dibromide, 14, was obtained only as an impure syrup, attention was shifted to the use of dithiocarbonate derivatives. Permanganate oxidation[10] of the trithiocarbonate 7 gave the expected product, 6, which was converted to the corresponding tetrol and tetraacetate, 4 and 5, both also crystalline. Compounds containing a trithiocarbonate ring have a pronounced yellow color; the dithiocarbonates are colorless.[11]

The dithiocarbonate diketal 6 on reaction with hydrogen bromide in acetic acid gave the dithiocarbonate dibromide diacetate 10. This was a syrup, but on reaction with potassium thiolacetate it gave the crystalline tetraacetate, 11, of the dithiocarbonate 1,6-dithiol-2,5-diol.

The latter intermediate on reduction gave the desired product, 1,3,4,6-tetrathio-D-mannitol (12) in the form of colorless needles, mp 123° (hexaacetate mp 165°). Even the analytically pure product has a slight odor (perhaps owing to traces of impurities). It is quite stable, at least in the crystalline state. The tetrathioldiol and its acetate were characterized by microanalysis, optical rotation, and infrared and nmr spectra.

Table I
Optical Rotations of Some Derivatives of D-Mannitol and D-Iditol

Derivative	Molecular rotation,[a] deg D-Manno	 D-Ido
3,4-*O*-Isopropylidene	+52[b]	−93[c,d]
3,4-*O*-Isopropylidene-1,6-di-*O*-methyl	+65[e]	−33[c,e]
3,4-*O*-Isopropylidene-1,2,5,6-tetra-*O*-tosyl	+58[d]	−84[c,d]
1,2;3,4;5,6-Tri-*O*-isopropylidene	+38[f]	−37[c,d]
1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyl-3,4-dithio	+1082[g]	−1105[h]
1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-carbonyl-3,4-dithio	+226[g]	−628[h]
1,6-Di-*S*-acetyl-2,5-di-*O*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio	+800[g]	−460[h]

[a] (Specific rotation * molecular weight/100); sodium D line; for other conditions, see references. [b] J. C. Irvine and B. M. Paterson, *J. Chem. Soc.*, **105**, 988 (1914). [c] Negative of rotation reported for the L-iditol derivative. [d] E. J. Bourne, G. P. McSweeney, and L. F. Wiggins, *J. Chem. Soc.*, 1408 (1952). [e] L. Vargha and E. Kasztreiner, *Chem. Ber.*, **92**, 2506 (1959). [f] E. Fischer, *Ber.*, **28**, 1168 (1895). [g] This article. [h] G. E. McCasland, A. Zanlungo, and L. J. Durham, to be published.

Efforts to convert the dithiocarbonate dibromide diacetate 10 into a 1,2;5,6-diepoxide, from which hexathio-D-mannitol might be obtainable, have so far been unsuccessful.

Previous work has shown that in the transformation of an epoxide to a trithiocarbonate, one but not both of the carbon–oxygen bonds undergoes inversion of configuration. The expected product from a "cis" or erythro epoxide is thus a mixture of two "trans" or threo trithiocarbonates (diastereomers).[12]

The expected product from the 3,4-anhydro-D-talitol derivative, 2, would then be a mixture of the D-manno and D-ido trithiocarbonates, 7 and 1, since positions 2 and 5 would be expected to retain their configurations.[13]

We have assigned the D-manno configuration to the trithiocarbonate of mp 117° (7) and to all of the related series of compounds here reported (3–6 and 8–14), because of striking regularities in their optical rotations. Such derivatives of D-mannitol and their sulfur analogs, and especially those derivatives having a heterocyclic ring attached at positions 3 and 4, have a strong tendency to be dextrorotatory (see Table I).

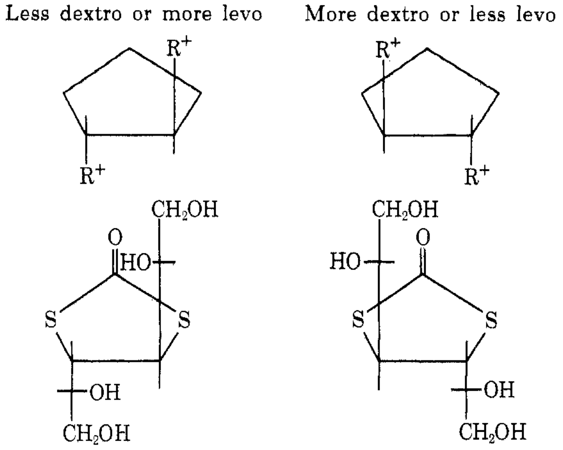
The other trithiocarbonate, 1, mp 127°, and its numerous derivatives (to be described elsewhere)[14] have an equally strong tendency to be levorotatory, and thus we have assigned them the D-ido configuration.

Some theoretical support for these configurational assignments may be found in the optical rotation theories of Whiffen and of Brewster.[15] Derivatives of D-mannitol and D-iditol having a five-membered heterocyclic ring attached to positions 3 and 4 should be roughly comparable to the 1,2-trans disubstituted cyclopentanes shown in Chart II. Each substituent R^+ is assumed to be a *dissymmetric* group, *e.g.*,-$CHOHCH_2OH$. For this reason the two cyclopentane isomers shown in Chart II are *not* mirror images, because the mirror image of R^+ would be R^-. The two isomers in fact would be diastereomers, which should tend to have opposite signs of rotation, but not equal magnitudes of rotation.

According to the Whiffen and Brewster theories,[15] the left-hand cyclopentane diastereomer (Chart II) should be

Chart II

Optical Rotation Predictions[a]



D-ido (diketal −196°) D-manno (diketal 71°)

[a] See ref 15.

levorotatory, because of the (−)-synclinal conformation of its substituents. The right-hand isomer should be dextrorotatory because it is (+)-synclinal. Similar arguments should apply to the two dithiocarbonate diastereomers shown in Chart II.

It would have been very difficult to make the D-manno/D-ido configurational assignments on the basis of pmr spectra alone. However, after making these assignments on the basis of optical rotations, it was noted that our compounds of the D-manno series tend to have distinctly higher values of the coupling constants J_{23} (= J_{45}) than those of the D-ido series.[16]

When we inspected molecular models, each oriented in what appeared to be one of the most favored conformations, a tendency was noted for H-2 and H-3 (or H-4 and H-5) to be antiperiplanar in the D-manno series, but synclinal or gauche in the D-ido series. These findings are qualitatively consistent with the observed pmr data, but do not, of course, permit any precise predictions of the torsional angles or coupling constants. Details of the nmr spectra are given in the Experimental Section.[17]

It might be expected that the (as yet unknown) perthio- or hexathiohexitols will have considerably different properties from ordinary hexitols, because of nonpolar character and inability to form hydrogen bonds.

Our tetrathiohexitols, however, have properties which are not greatly different from ordinary hexitols. The D-manno and D-ido isomers, at least, are crystalline, and have melting points typical of ordinary hexitols. They have very little of the well-known "mercaptan" odor—perhaps none if completely pure. They are less soluble in water and more soluble in organic solvents than ordinary hexitols. For example, they are soluble in boiling (but not cold) isopropyl ether. They are stable in the solid state, but may need to be protected from oxygen in solution. The characteristically weak infrared S-H stretching absorption at about 2550 cm^{-1} is relatively strong in our products having four free -SH groups. Compounds containing the thiocarbonyl (C═S) group gave a characteristic strong stretching absorption at about 1080 cm^{-1}, as previously noted for other thiocarbonyl compounds by Haszeldine and Kidd.[18]

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Nmr spectra were recorded and integrated using Varian A-60D and/or HA-100 spectrometers; chemical shifts are expressed as parts per million (δ) unless otherise noted. Field sweep was used for 60-MHz and frequency sweep for 100-NHz nmr spectra. Infrared spectra using potassium bromide pellets were measured on a Perkin-Elmer Model 337 recording spectrometer.

3-*O*-Benzoyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol. The following procedure was found much better than one previously reported.[6] A solution of 44.9 g of the mannitol diketal[19] (mp 120°) in 90 ml of dry pyridine was cooled to 0–5°, and 24.9 g of benzoyl chloride was added dropwise with stirring during 1 hr.

After 24 hr at 25°, the mixture was slowly poured into 900 ml of saturated sodium bicarbonate solution, with vigorous stirring. The syrup which separated was washed repeatedly with water by decantation, causing it to crystallize, dry weight 50.1 g.

By using isopropyl ether for recrystallization, we were able to omit the previously reported[6] column chromatography. The product was obtained as colorless crystals, 35.6 g (57%), mp 104–105° (reported[6] mp 104–107°, yield 46%).

3-*O*-Benzoyl-4-*O*-methanesulfonyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol. This compound was prepared from the above 3-*O*-benzoate diketal (mp 105.5°) in the manner reported by Baker and Haines,[7] giving 47.3 g (96%) of a syrup, which was used directly in the next step (reported[7] yield 96%).

3,4-Anhydro-1,2;5,6-di-*O*-isopropylidene-D-talitol (2). The following procedure gave a much higher yield than one previously reported.[7] To a solution of 42.6 g of the 3-*O*-benzoyl-4-*O*-methanesulfonyl diketal of D-mannitol[7] in 100 ml of dry chloroform, a solution of 2.34 g of sodium in 140 ml of absolute methanol was added dropwise with stirring during 1 hr.

After stirring for 38 hr at 25°, the mixture was boiled under reflux for 2 hr. The cooled, filtered mixture was evaporated, and the residue was dissolved in 70 ml of chloroform. The solution was washed with water, dried, and evaporated, giving a syrup, from which methyl benzoate was removed by distillation (0.2 Torr, 90° bath).

The cooled residual syrup crystallized on seeding, giving 21.6 g (92%) of colorless crystalline product, mp 53–55° (reported[7] mp 53–55°), yield 59%. A sample was further purified by high-vacuum distillation: mp 56–57°; nmr ($CDCl_3$) δ 1.34, 1.39, 1.45, and 1.48 (each s, 3, isopropylidene methyl), 3.05 (m, 2, H-3 and H-4), 3.8–4.3 (m, 6, H-1, H-1′, H-2, H-5, H-6, H-6′); nmr (C_6F_6) δ 1.30 (s, 3), 1.36 (s, 6), 1.42 (s, 3), 3.87 (m, 2), 3.6–4.3 (m, 6).

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-iditol (1). To a solution of 25.0 g of the above 3,4-anhydro-D-talitol diketal (mp 55°) in 50 ml of methanol was added a solution of 25.0 g of potassium hydroxide and 63.0 g of carbon disulfide in 300 ml of methanol, and the mixture was boiled under reflux for 18 hr.

The solution was evaporated, and the residual brown solid was crystallized from aqueous methanol, giving 11.1 g of a yellow solid. This material was extracted with 20 ml of boiling chloroform. The filtered extract was evaporated, and the crystalline residue was recrystallized from *n*-hexane, giving 4.50 g of crystals, mp 122–124°. A second crop, 1.0 g, mp 120–124°, was obtained.

The combined crops (5.50 g) were recrystallized again, giving 4.60 g (17%) of the pure D-ido stereoisomer, yellow plates, mp 126–127°. The further characterization and reactions of this stereoisomer will be described elsewhere.[14]

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-mannitol (7). The combined mother liquors from the D-ido stereoisomer (see above) were evaporated to about half volume and cooled, causing separation of crystals, which were recrystallized from petroleum ether, giving 1.15 g of product, mp 113–115°.

This product was recrystallized, giving 650 mg (2.3%) of the D-manno stereoisomer, yellow plates, mp 116–117°. A portion was again recrystallized for analysis, giving yellow plates: mp 116–116.5°; $[\alpha]^{23}D$ 322° (*c* 2, $CHCl_3$); ir (KBr) 1080 (C═S), 1060, 1125, and 1145 cm^{-1} (dioxolane C–O); nmr ($CDCl_3$) δ 1.37, 1.48 (each s, 6, isopropylidene methyl), 3.80 (q, 2, $J_{12} = J_{56} = 3.4$, $J_{11'} = J_{66'} = 9$ Hz, H-1 and H-6), 4.22 (q, 2, $J_{1'2} = J_{56'} = 5.5$, $J_{11'} = J_{66'} = 9$ Hz, H-1′ and H-6′).

Anal. Calcd for $C_{13}H_{20}O_4S_3$: C, 46.40; H, 5.99; S, 28.59. Found: C, 46.30; H, 5.99; S, 28.40.

3,4-Thiocarbonyldithio-D-mannitol (8). A stirred mixture of 1.2 g of the above diisopropylidene derivative (mp 117°) with 160 ml of 95% ethanol and 5.2 ml of 6 *N* hydrochloric acid was boiled under reflux until complete dissolution (15 min), then for 3 hr more.

The solution was evaporated, giving a syrup. Portions of ethyl acetate were repeatedly added and evaporated. The final residue, still a syrup, was dissolved in boiling ethyl acetate. The solution on cooling gave 400 mg of crystals, mp 112–115°. This product was recrystallized, giving 250 mg (27%) of crystals as yellow plates: mp 116–117.5°; $[\alpha]^{24}_{\mathrm{D}}$ 284° (*c* 0.7, $CHCl_3$); ir (KBr) 1065 (C=S) and 3400 cm^{-1} (broad, OH); nmr (100 MHz, D_2O with DSS) δ 4.48 (d, 2, $J = 8.5$ Hz, H-3 and H-4).

Anal. Calcd for $C_7H_{12}O_4S_3$: C, 32.80; H, 4.72; S, 37.52. Found: C, 32.90; H, 4.93; S, 37.16.

1,2,5,6-Tetra-*O*-acetyl-3,4-thiocarbonyldithio-D-mannitol (9). A solution of 70 mg of the tetrol in 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride was kept at 25° for 24 hr. The solution was then evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide. The residual solid (110 mg) was crystallized from isopropyl ether, giving 65 mg (56%) of crystals, mp 67.5–69°.

A portion recrystallized for analysis gave yellow plates: mp 67.5–68.5°; $[\alpha]^{24}_{\mathrm{D}}$ 271° (*c* 0.5, $CHCl_3$); ir (KBr) 1060 (C=S) and 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.18 (s, 6, acetate methyl at 1 and 6, or 2 and 5), 2.24 (s, 6, acetate methyl at 2 and 5, or 1 and 6), 4.43 (q, 2 $J_{11'} + J_{66'} = 13$, $J_{12} = J_{56} = 5$ Hz, H-1 and H-6), 4.54 (d, 2, $J_{23} = J_{45} = 9$ Hz, H-3 and H-4), 4.80 (q, 2, $J_{1'2} = J_{56'} = 3$, $J_{11'} = J_{66'}$, H-1′ and H-6′), 5.67 (m, 2, H-2 and H-5).

Anal. Calcd for $C_{15}H_{20}O_8S_3$: C, 42.44; H, 4.75; S, 22.66. Found: C, 42.90; H, 4.77; S, 21.89.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-thiocarbonyldithio-D-mannitol (14). A 200-mg portion of the above trithiocarbonate diketal (mp 117°) was dissolved in 2.0 ml of a 30% solution of hydrogen bromide in anhydrous acetic acid. The solution was kept at 25° for 6 hr, then poured with stirring into 20 ml of saturated sodium bicarbonate solution. The resulting mixture was extracted with chloroform (two 50-ml portions) and the combined chloroform extracts were washed, dried, and evaporated.

The resulting syrup was purified by column chromatography on Woelm silica gel (20 × 1 cm), using benzene as solvent and eluent. The product was obtained as 150 mg (55%) of a yellow syrup, which could not be crystallized, but showed only one spot on thin layer chromatography, nmr ($CDCl_3$) δ 2.18 (s, 6, acetate methyl).

1,2;5,6-Di-*O*-isopropylidene-3,4-dithio-D-mannitol 3,4-Trithioorthoformate (Mercaptodithiolane Diketal) (3). A solution of 150 mg of the above trithiocarbonate diketal (mp 117°) in 25 ml of dry tetrahydrofuran was added dropwise to a slurry of 45 mg of lithium aluminum hydride in 2.5 ml of dry ether. After disappearance of yellow color, the mixture was stirred for 1 hr more.

Excess hydride was destroyed by careful addition of water at 0°, and the mixture was adjusted to pH 4 and immediately extracted with ether. The ether extract was immediately washed with sodium bicarbonate solution, and further processed in the usual manner.

The solid residue obtained by evaporation was crystallized from *n*-hexane, giving 50 mg of crystals, mp 86–92°. This product was recrystallized, giving 30 mg (20%) of material, mp 96–97°. A portion recrystallized for analysis gave colorless needles: mp 97–98°; $[\alpha]^{24}_{\mathrm{D}}$ 105° (*c* 0.6, $CHCl_3$); ir (KBr) 1040, 1060, and 1150 (dioxolane C–O), 2520 cm^{-1} (SH); nmr ($CDCl_3$) δ 1.33 (s, 3), 1.37 (s, 3), and 1.44 (s, 6), isopropylidene methyl groups, 2.93 (d, 1, -SH), 5.67 (d, 1, $J = 7$ Hz, -CHSH).

Anal. Calcd for $C_{13}H_{22}O_4S_3$: C, 46.13; H, 6.55; S, 28.42. Found: C, 46.16; H, 6.46; S, 28.30.

1,2;5,6-Di-*O*-isopropylidene-3,4-carbonyldithio-D-mannitol (6). To a cooled solution of 1.50 g of the above trithiocarbonate (mp 117°) in 50 ml of reagent-grade acetone, 3.7 g of powdered potassium permanganate was added in portions with stirring at 25° during 2 hr. After 1 hr more, the precipitate was collected and washed with acetone (three 10-ml portions).

The combined filtrates were evaporated, and the solid residue was extracted with boiling benzene (three 10-ml portions). The combined benzene extracts on evaporation gave 1.25 g (87%) of crystalline product, mp 73–74.5°.

A portion was recrystallized for analysis from methanol–water, giving colorless plates: mp 73–73.5°; $[\alpha]^{24}_{\mathrm{D}}$ 71° (*c* 0.6, $CHCl_3$); ir (KBr) 1025, 1070, and 1150 (dioxolane C–O), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.38 (s, 6) and 1.48 (s, 6), isopropylidene methyl groups, 3.34 (m, 2, H-3 and H-4).

Anal. Calcd for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.83; H, 6.20; S, 20.91.

3,4-Carbonyldithio-D-mannitol (4). A stirred solution of 400 mg of the above diisopropylidene derivative (mp 74°) in 8.0 ml of 40% aqueous acetic acid was heated at 100° for 11 hr. The solution was evaporated, and the residual syrup was vacuum dried (0.5 Torr, 70°). The dried syrup was crystallized from ethyl acetate, giving 110 mg of product, mp 121–124°. This material was recrystallized, giving 70 mg, mp 122–123.5°. A second crop of 100 mg, mp 122–124°, was obtained from the first crystallization filtrate, total yield 210 mg (70%).

A portion of the recrystallized first crop was again recrystallized for analyses, giving colorless needles: mp 122–123°; $[\alpha]^{23}_{\mathrm{D}}$ 62° (*c* 2.4, methanol); ir (KBr) 1650 (C=O) and 3400 cm^{-1} (broad, OH); nmr (D_2O with DSS) δ 4.38 (d, 2, $J_{23} = J_{45} = 8.5$ Hz, H-3 and H-4).

Anal. Calcd for $C_7H_{12}O_5S_2$: C, 34.99; H, 5.03; S, 26.69. Found: C, 35.02; H, 4.95; S, 25.79.

1,2,5,6-Tetra-*O*-acetyl-3,4-carbonyldithio-D-mannitol (5). A solution of 150 mg of the above tetrol (mp 123°) in 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride was kept at 25° for 24 hr. The solution was evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide. The residual syrup was crystallized from a mixture of benzene and *n*-hexane, giving 220 mg (88%) of colorless needles: mp 84–85°; $[\alpha]^{23}_{\mathrm{D}}$ 132° (*c* 1.6, $CHCl_3$); ir (KBr) 1655 (carbonyldithio C=O) and 1750 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.08 (s, 6) and 2.15 (s, 6), acetate methyl at 1,6 and 2,5, respectively.

Anal. Calcd for $C_{15}H_{20}O_9S_2$: C, 44.11; H, 4.94; S, 15.70. Found: C, 44.01; H, 4.90; S, 15.19.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-carbonyldithio-D-mannitol (10). An 800-mg portion of the above dithiocarbonate diketal (mp 74°) was dissolved in 7.0 ml of an anhydrous 32% solution of hydrogen bromide in acetic acid. After 4 hr at 25° the solution was poured with stirring into saturated sodium bicarbonate solution. The syrup which separated was washed repeatedly with water by decantation, then dissolved in chloroform. The dried solution on evaporation gave the product as a syrup which could not be crystallized, but had an appropriate spectrum: nmr ($CDCl_3$) δ 2.23 (s, 6, acetate methyl), 4.32 (d, 2, $J_{23} = J_{45} = 9$ Hz, H-3 and H-4), 3.85 (m, 4) and 5.32 (m, 2), second-order pattern attributed to H-1, H-1′, and H-2, and to H-6, H-6′, and H-5.

1,6-Di-*S*-acetyl-2,5-di-*O*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio-D-mannitol (11). A stirred mixture of 500 mg of the above dibromide diacetate (syrup), 600 mg of potassium thiolacetate, and 20 ml of reagent-grade acetone was boiled under reflux for 24 hr. The cooled, filtered mixture was evaporated, and the residual syrup was partitioned between chloroform and water. The suitably processed chloroform phase on evaporation gave a deep-brown syrup.

Since charcoal decolorization using ethyl acetate as solvent was ineffective, the decolorization was repeated using isopropyl ether. The latter solution on cooling gave 200 mg (42%) of colorless, crystalline product, mp 100–102.5°.

A portion was recrystallized for analysis, giving colorless needles: mp 102–103°; $[\alpha]^{23}_{\mathrm{D}}$ 182° (*c* 1.9, $CHCl_3$); ir (KBr) 1655 (dithiocarbonyl C=O), 1702 (thioacetate C=O), and 1745 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.10 (s, 6) and 2.37 (s, 6), *O*- and *S*-acetate methyl, respectively.

Anal. Calcd for $C_{15}H_{20}O_7S_4$: C, 40.89; H, 4.58; S, 29.11. Found: C, 40.86; H, 4.61; S, 29.47.

1,3,4,6-Tetrathio-D-mannitol (12). A 250-mg portion of the above tetrathiomannitol dithiocarbonate tetraacetate (mp 103°) dissolved in 2.0 ml of anhydrous tetrahydrofuran was added dropwise to a slurry of 800 mg of lithium aluminum hydride in 10 ml of anhydrous ether. The reaction was conducted under dry nitrogen.

After 4 hr at 25°, excess hydride was destroyed with water in the usual manner, and the slightly acidified (pH 4) aqueous phase was extracted repeatedly with ether. The combined ethereal extract was washed with 5% sodium bicarbonate solution, dried, and evaporated.

The residual solid was crystallized from isopropyl ether, giving 32 mg (23%) of crystalline product, mp 118–120°. A portion was recrystallized for analysis, giving 9 mg of colorless needles: mp 122.5–123.5°; ir (KBr) 2520 (SH) and 3300 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 2.17 (s, 6) and 2.43 (s, 6), *O*- and *S*-acetate methyl, respectively, 3.28 (q, 2, $J_{12} = J_{56} = 6.5$, $J_{11'} = J_{66'} = 15$ Hz, H-1 and H-6), 3.65 (q, 2, $J_{1'2} = J_{56'} = 3.5$, $J_{11'} = J_{66'} = 15$ Hz, H-1′ and H-6′), 4.28 (d, 2, $J_{23} = J_{45} = 8$ Hz, H-3 and H-4), 5.39 (m, 2, H-2 and H-5).

1,3,4,6-Tetra-*S*-acetyl-2,5-di-*O*-acetyl-1,3,4,6-tetrathio-D-mannitol (13). Attempted preparation of a second crop of tetrathiomannitol from the combined mother liquors (see above) gave only a syrup. This material (62 mg) was dissolved in a mixture of 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride. After 24 hr at 25°, the mixture was evaporated in a vacuum desiccator over sulfuric acid and sodium hydroxide.

The yellow, solid residue was purified by column chromatography using Woelm silica gel (250 × 10 mm) and ethyl acetate as solvent. The column was eluted with 100 ml of *n*-hexane–isopropyl ether (2:1) and then with 50 ml of pure isopropyl ether. The latter eluate on evaporation give 40 mg (32%) of slightly yellow product, mp 162–164°. The chromatographic purification was repeated in the same manner, giving 30 mg of colorless crystals, mp 163–164°.

A portion was recrystallized for analysis from *n*-hexane, giving colorless needles: mp 163.5–164.5°; $[\alpha]^{23}\mathrm{D}$ 94° (*c* 1.2, $CHCl_3$); ir (KBr) 1690 and 1705 (*S*-acetate C═O), 1750 cm^{-1} (*O*-acetate C═O); nmr ($CDCl_3$) δ 2.07 (s, 6) and 2.32 (s, 6), *O*-acetate methyl and *S*-acetate methyl, respectively.

Anal. Calcd for $C_{18}H_{26}O_8S_4$: C, 43.36; H, 5.26; S, 25.72. Found: C, 43.42; H, 5.20; S, 25.50.

Acknowledgment. This research was made possible by a grant (AM-11433) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. We are grateful to the National Science Foundation for a Chemistry Research Instruments Program Grant to the Department of Chemistry, University of San Francisco, for purchase of a Varian A-60D nuclear magnetic resonance spectrometer. We would like to thank Dr. Leroy F. Johnson, formerly of Varian Associates, Palo Alto, Calif., for carbon-13 nmr spectra.

Registry No.—**1**, 51051-69-5; **2**, 24808-13-7; **3**, 51051-70-8; **4**, 51051-71-9; **5**, 51051-72-0; **6**, 51051-73-1; **7**, 51051-74-2; **8**, 51051-75-3; **9**, 51051-76-4; **10**, 51051-77-5; **11**, 51051-78-6; **12**, 51051-79-7; **13**, 51051-80-0; **14**, 51051-81-1; 3-*O*-benzoyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol, 51051-82-2; 3-*O*-benzoyl-4-*O*-methanesulfonyl-1,2;5,6-di-*O*-isopropylidene-D-mannitol, 51051-83-3.

References and Notes

(1) Presented in part to the Division of Organic Chemistry at the 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, and to the Division of Carbohydrate Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(2) (a) For preceding publication on thio carbohydrates, see G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, **37**, 1201 (1972). (b) For preceding publication on alicyclic carbohydrates, see J. Shapira, T. Putkey, A. Furst, and G. E. McCasland, *Carbohyd. Res.*, **25**, 535 (1972); see also Y. Sanemitsu, N. Kurihara, M. Nakajima, G. E. McCasland, L. F. Johnson, and L. C. Carey, *Agr. Biol. Chem.*, **36**, 845 (1972).

(3) (a) To whom any communications should be addressed, at the University of San Francisco; (b) Stanford University.

(4) Reported preparations of compounds containing more than three mercapto groups include (a) 1,2,3,4-butanetetrathiol, see C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964); (b) tetra(mercaptomethyl)methane, M. W. Farlow and F. K. Signaigo, *Chem. Abstr.*, **40**, 5763 (1946).

(5) (a) The preparation of a tetrathiohexitol was reported by S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960). It had the L-ido configuration, and the sulfur groups were at positions 1, 2, 5, and 6 (isolated as hexaacetate, mp 133–135°). It should be noted that the tetrathiohexitols now reported by us have the D (ido or manno) configuration, and the sulfur groups are at positions 1, 3, 4, and 6.[5b] (b) This article describes a new series of stereoisomers (hexitol sulfur analogs). It is almost certain that the compounds in this series all have the *same* configuration (D-manno or D-ido), because the reactions employed would not invert position 2 or 5, and would retain or produce a threo configuration at positions 3 and 4.

Optical rotation studies further indicate, in the author's opinion, that the series configuration is D-manno (not D-ido), with a *very high probability*.

The reader is cautioned, however, that this rotation-based configurational assignment (like many similar assignments in the field of carbohydrates) *cannot be regarded as absolutely certain*. Accordingly (as suggested by a referee) we recommend that the D-manno assignments in this article be considered tentative until more rigorous evidence, *e.g.*, X-ray or neutron diffraction studies, is available. (Nmr spectra were recorded for these compounds, but could not be interpreted in terms of configuration.)

(6) J. M. Sugihara and G. U. Yuen, *J. Amer. Chem. Soc.*, **79**, 5780 (1957).

(7) (a) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963); (b) *ibid.*, **28**, 438 (1963).

(8) In 1960 L. N. Owen and S. M. Iqbal by a similar reaction of 3,4-anhydro-1,2;5,6-di-*O*-isopropylidene-D-talitol obtained a trithiocarbonate (reported mp 108–110°) and reduced it to a dithiol. We now believe that each of these products was a mixture of the D-ido and D-manno diastereomers. See *J. Chem. Soc.*, 1030 (1960).

(9) For an example of the formation of a mercaptodithiolane diketal in the cyclitol series, see G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 459, 462 (1963).

(10) F. Runge, Z. El-Hewehi, H. J. Renner, and E. Taeger, *J. Prakt. Chem.*, **11**, 284 (1960).

(11) For discussion of the chemistry of trithiocarbonates and dithiocarbonates, see D. S. Breslow and H. Skolnik, "Multi-Sulfur and Sulfur and Oxygen Five and Six-Membered Heterocycles," Part I, A. Weissberger, Ed., Interscience, New York, N. Y., 1966, Chapter 5, Part II.

(12) A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960). See also C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.*, 1050 (1946).

(13) J. Kuszman and L. Vargha have recently reported the preparation of a 1,2;5,6-diepithio derivative of L-iditol, and many related intermediates, which may be of interest in connection with the work now reported by us. See *Carbohyd. Res.*, **11**, 165 (1969).

(14) G. E. McCasland, A. B. Zanlungo, and L. J. Durham, to be published.

(15) (a) D. H. Whiffen, *Chem. Ind. (London)*, 964 (1956); (b) J. J. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475, 5483 (1959).

(16) Although D-mannitol and its thio analogs and derivatives are dissymmetric and optically active, the molecules of such compounds here discussed nearly all contain a twofold simple symmetry axis (point group C_2). This causes nmr chemical-shift equivalence of the protons connected directly or indirectly to carbon atoms 1 and 6, 2 and 5, and 3 and 4 in the hexitol chain.

(17) In March 1970, Leroy F. Johnson at Varian Associates, Palo Alto, Calif., recorded the carbon-13 nmr spectrum of a sample of the D-manno trithiocarbonate diketal, mp 117°, provided by us. The spectrum was recorded with a Varian HA-100 spectrometer at 25.15 MHz, using benzene as solvent (400 mg/ml, 8-mm tube), 25 scans, noise decoupled. The spectrum was consistent with the proton spectrum, but as yet has not yielded additional structural information. Details of this work will be reported elsewhere.

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Scission of the Sulfur–Sulfur Bond in Dipurinyl and Dipyrimidinyl Disulfides by Cyanide[1,2]

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Received August 13, 1973

Bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide, its methyl analog, and bis(9-methyl-6-thiopurine) disulfide are decomposed quantitatively into the corresponding thiocyanato and thio derivatives by CN^- buffered at pH 7. 4-Thiocyanatouridine and its methyl analog decompose quantitatively in alkali to the corresponding thio and oxo compounds in 2:7 and 1:1 ratio, respectively. 9-Methyl-6-thiocyanatopurine decomposes in alkali to 9-methyl-6-thiopurine. The reaction of the three above-mentioned disulfides in unbuffered CN^- apparently proceeds through the intermediate formation of the thio and thiocyanato derivatives, the latter decomposing *in situ* under alkaline conditions in the same manner. Synthesis and properties of 4-thiocyanatouridine, its methyl analog, 9-methyl-6-thiocyanatopurine, and bis(1-methyl-4-thiouracil) disulfide are described.

The extreme susceptibility of the disulfide bond in bis(1-β-D-ribofuranosyl-4-thiouracil) disulfide and its methyl analog to nucleophilic attack by OH^- reported earlier from this laboratory[3] led us to extend this study to the