Note

O→S Migration of an alkylidene group in a dithiohexitol derivative[1]

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The known 3,4-anhydro-1,2:5,6-di-*O*-isopropylidene-D-talitol was treated[2] with potassium methylxanthate to give a mixture of two diastereomeric trithiocarbonates, m.p. 127° and 117°. The trithiocarbonate having m.p. 127° was reduced with lithium aluminum hydride to give the corresponding dithiol, m.p. 138–139°. This dithiol has tentatively been assigned the D-*ido* configuration (**1**) (see below).

It was expected that acidic hydrolysis of **1** would readily yield the 3,4-dithiohexitol **2**. The actual hydrolytic product (m.p. 103.5–105°) retained, surprisingly, one isopropylidene group, as shown by n.m.r. spectroscopy and microanalysis. The residual isopropylidene group had become attached to sulfur, not oxygen, as demonstrated by n.m.r. spectral comparison of the product with the *O,O,S*-triisopropylidene[2] derivative and other *O*-isopropylidene derivatives. The *S*-isopropylidene methyl protons produced a sharp singlet (area 6 H) at δ 1.92. The *O*-isopropylidene protons in similar compounds produce a sharp singlet at about δ 1.35. The overall result was migration of one isopropylidene group from oxygen to sulfur; the other group presumably was liberated as acetone, and the product is formulated as the *S*-isopropylidene tetrol **3**.

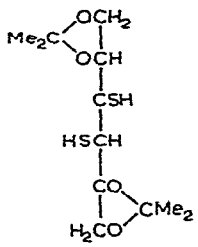
For this migration, three possible mechanisms were considered: (*1*) *intramolecular* transfer of an alkylidene group, as by a 1→3, O→S shift of the first alkylidene linkage, followed by a 2→4, O→S shift of the second alkylidene linkage; (*2*) *intermolecular* transfer of an alkylidene group from oxygen in one molecule to sulfur in another molecule; or (*3*) *external return* of hydrolytically liberated acetone from the solution, by reaction with SH groups in a molecule of the starting material (or its hydrolytic product).

To gain information on the actual mechanism, the hydrolysis of **1** was repeated in the presence of added acetone-d_6. The deuterium content of the isopropylidene methyl groups in the isolated pure product (**3**), was measured by integration of the p.m.r. spectrum. The results were as follows: (*1*) By using 10 moles of acetone-d_6 per mole of starting material, the product methyl groups contained 80 $\pm$5% of deuterium (predicted for exclusive intramolecular or intermolecular transfer, 0%; predicted for complete equilibration, 83.3%). (*2*) With one mole of acetone-d_6 per mole of starting material, the deuterium content was 43 $\pm$5% (predicted for complete equilibration, 33.3%).

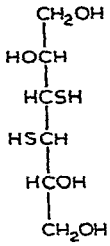
A deuterium content found that was higher than the value for "complete

equilibration" may be attributed to reaction of some of the SH groups in the starting material with acetone-d_6 *before* complete hydrolysis of the *O*-isopropylidene groups. It should be noted that each molecule of starting material contains twelve methyl protons, whereas each acetone-d_6 molecule contains only six deuterons. The word *migration* appears best to describe the overall experimental result. In any particular case, the actual group-transfer may or may not be intramolecular.

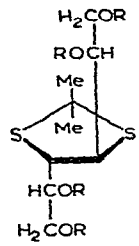
We conclude that this particular O→S alkylidene migration is due primarily to external return (mechanism *3*).



1



2



3 R = H
4 R = Ac

The two diastereomeric trithiocarbonates, m.p. 127° and 117°, derived from 3,4-anhydro-1,2:5,6-di-*O*-isopropylidene-D-talitol (see above) in all probability have the D-*ido* and D-*manno* configurations, assuming *trans*-opening of the epoxide ring. Extensive comparisons of the optical rotations of various heterocyclic derivatives of D-mannitol and D-iditol, and their respective dithio analogs, lead us to believe that the trithiocarbonate having m.p. 127° (and thus all of its derivatives here described) have the D-*ido* configuration[2]. N.m.r. evidence is less useful, but appears to be consistent with the D-*ido* assignment[2].

In 1960 S. M. Iqbal and L. N. Owen, by a similar reaction of 3,4-anhydro-1,2:5,6-di-*O*-isopropylidene-D-talitol, obtained a trithiocarbonate [reported[3c] m.p. 108–110°), and reduced it to a dithiol [reported[3c] m.p. 133–135°, $[\alpha]_D^{22}$ −10° (*c* 3.6)]. We now believe that each of these products was a mixture of the D-*ido* and D-*manno* diastereoisomers

The tetrol **3** was converted into the tetraacetate **4**, m.p. 63°, which had an appropriate n.m.r. spectrum and microanalysis.

These findings are of interest, since relatively little is known[3] about O→S or S→O migrations, especially of alkylidene groups.

EXPERIMENTAL

*3,4-S-Isopropylidene-3,4-dithio-*D*-iditol* (**3**). — 1,2:5,6-di-*O*-isopropylidene-3,4-dithio-D-iditol (**1**, 440 mg, m.p. 138°) was dissolved in 4.4 ml of a 9:1 (v/v) mixture of trifluoroacetic acid and water, and the solution was stirred for 10 min at room temperature. The solution was then evaporated *in vacuo* and the residual syrup was treated with anhydrous ether (10 ml). The solid product that separated was filtered off, giving 130 mg (35%) of **3** as colorless crystals, m.p. 104–105°; recrystallized from

ethyl acetate it had m.p. 103.5–104.5°, $[\alpha]_D^{23}$ −44.0° (*c* 3, pyridine); ν_{max}^{KBr} 3300 (O–H stretch), 1390 (C–H bend, *gem*-dimethyl), 1030 and 1105 cm^{-1} (C–O stretch); n.m.r. data (60 MHz, pyridine) δ 1.92 (6-proton singlet, *S*-isopropylidene methyl), 4.05 and 4.15 (4-proton pair of doublets, H-1, H-1′, H-6, and H-6′), 4.70 (2-proton triplet, H-2 and H-5), 4.92 (2-proton wide singlet, H-3 and H-4).

Anal. Calc. for $C_9H_{18}O_4S_2$: C, 42.497; H, 7.133; S, 25.211. Found: C, 42.39; H, 6.99; S, 25.16.

Reaction in the presence of acetone-d_6. — *A.* Compound **1** (440 mg, m.p. 139°, 1.5 mmole) was dissolved in a solution of acetone-d_6 (0.87 g, 1.1 ml, 15 mmole) in 8.0 ml of 9:1 (v/v) trifluoracetic acid–water. The solution was stirred for 15 min at room temperature and then evaporated *in vacuo*. The residual syrup was treated as previously described, affording 120 mg of colorless crystals, m.p. 103–104.5°. The deuterium content (20%) of the isopropylidene group in the product was determined by integration of the p.m.r. spectrum (see Introductory Section).

B. Compound **1** (147 mg) was treated as in *A*, but by using 29 mg of acetone-d_6 and 30 ml of aqueous trifluoroacetic acid. The product (14 mg) had m.p. 100–103°, and the isopropylidene group had a deuterium content of 43% as determined by p.m.r.

*1,2,5,6-Tetra-*O*-acetyl-3,4-*S*-isopropylidene-3,4-dithio-*D*-iditol* (**4**). — To a solution of 3,4-*S*-isopropylidene-3,4-dithio-D-iditol (**3**, 140 mg, m.p. 105°) in anhydrous pyridine, acetic anhydride (1.08 g, 1.0 ml) was added. The solution was kept for 24 h at room temperature and then it was evaporated in a vacuum over sulfuric acid and sodium hydroxide. The residual syrup crystallized when mixed with *n*-hexane, giving 200 mg (100%) of **4** as colorless needles, m.p. 60–62°. The product was recrystallized from the same solvent, giving 140 mg, m.p. 62–63°. A sample was recrystallized for microanalysis, m.p. 63–63.5°, $[\alpha]_D^{23}$ −39.4° (*c* 0.73, chloroform); ν_{max}^{KBr} 2950 (C–H stretch), 1750 (acetate C=O), 1390 (C–H bend, *gem*-dimethyl)., 1210 (C–O stretch), 1035 cm^{-1} (C–O stretch); n.m.r. data (60 MHz, chloroform-*d*): δ 1.81 (6-proton singlet, *S*-isopropylidene methyl), 2.08 and 2.12 (12 protons, singlets, acetate methyl), 3.92 (2-proton multiplet, H-3 and H-4), 4.25 (4-proton multiplet, H-1, H-1′ H-6 and H-6′), 5.50 (2-proton multiplet, H-2 and H-5).

Anal. Calc. for $C_{17}H_{26}O_8S_2$: C, 48.327; H, 6.203; S, 15.179. Found: C, 48.32; H, 6.23; S, 15,17.

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REFERENCES

1 For preceding publications, see G. E. McCasland, S. Furuta, and A. Furst, (a) *J. Amer. Chem. Soc.*, 85 (1963) 2866; (b) *J. Org. Chem.*, 29 (1964) 724.
2 G. E. McCasland and A. B. Zanlungo, unpublished work.
3 (a) L. N. Owen and L. W. C. Miles, *J. Chem. Soc.*, (1952) 817; (b) L. N. Owen and J. S. Harding, *ibid.*, (1954) 1528; (c) L. N. Owen and S. M. Iqbal, *ibid.*, (1960) 1030; (d) L. N. Owen and J. S. Harding, *ibid.*, (1954) 1536. See also R. B. Martin and R. I. Hendrick, *J. Amer. Chem. Soc.*, 84 (1962) 106.