SYNTHESIS OF NEW SUGAR DERIVATIVES HAVING POTENTIAL ANTITUMOUR ACTIVITY

PART XVII*. SYNTHESIS AND OXIDATION OF 1,4:3,6-BIS(THIOANHYDRO)-D-IDITOL AND ITS 2,5-DIACETATE

J. KUSZMANN AND P. SOHÁR

Research Institute for Pharmaceutical Chemistry, Budapest (Hungary)†

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ABSTRACT

The synthesis of 1,4:3,6-bis(thioanhydro)-D-iditol (**7**) and its 2,5-diacetate (**9**), starting from 3,4-di-*O*-methylsulfonyl-D-mannitol is described. Oxidation of **7** led to the corresponding disulfone **10**; no sulfoxide could be separated. The diacetate **9** gave on oxidation two isomeric (*R,R*)- and (*R,S*)-disulfoxides (**12** and **14**), a sulfone-sulfoxide (**17**), and the disulfone (**11**). Structures were proved by spectroscopic methods.

INTRODUCTION

Dianhydrohexitols containing two tetrahydrofuran[1] or oxirane[2-4] rings are well known in the literature. Of the corresponding dithioanhydro analogues, however, only diepithio isomers have been synthesized[5]; no bis(thioanhydro)hexitols with two tetrahydrothiophene rings have been described.

The oxidation of sugar derivatives having a tretahydrothiophene structure was carried out first by Whistler and coworkers[8], who succeeded in separating two sulfoxide isomers. A similar reaction of a thioanhydroalditol also yielded the expected isomers, but these were not resolved[9]. The present paper describes the synthesis and the oxidation of the first representative of the 1,4:3,6-bis(thioanhydro)hexitols, namely the D-*ido* derivative and its 2,5-diacetate.

DISCUSSION

The present synthesis was accomplished through selective thiolbenzoate displacement of labile, terminal substituents in an appropriately blocked hexitol; thioxide ions at C-1 and C-6, liberated during saponification, displaced sulfonyloxy groups from C-4 and C-3, respectively, forming *cis*-fused tetrahydrothiophene rings. Attempted synthesis of 2,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-3,4-di-*O*-methylsulfonyl-D-mannitol (**1**) was frustrated by an unexpected acetyl migration[6], but selective

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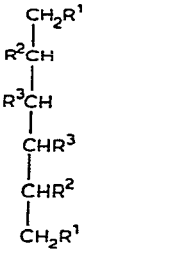
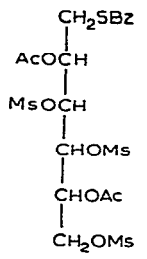
†IV. Ujpest 1. P.O. Box 82.

methanesulfonylation and subsequent acetylation of compound **2** afforded the tetra-*O*-methylsulfonyl derivative **3**; the acetyl groups of this product could be removed by the action of methanolic hydrogen chloride to yield compound **4**. Reaction of the tetrasulfonate **3** with 2 equivalents of potassium thiolbenzoate in acetone gave the crystalline 1,6-di-*S*-benzoate (**5**) as the main product. The mono-*S*-benzoyl intermediate **6**, which was always present in the reaction mixture, could be isolated as a homogenous solid foam by column chromatography of the mother liquor.



1 R^1 = Br; R^2 = AcO; R^3 = MsO
2 R^1 = R^2 = OH; R^3 = MsO
3 R^1 = R^3 = MsO; R^2 = AcO
4 R^1 = R^3 = MsO; R^2 = OH
5 R^1 = BzS; R^2 = AcO; R^3 = MsO



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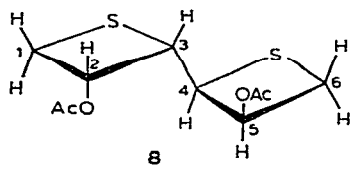

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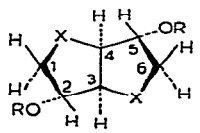


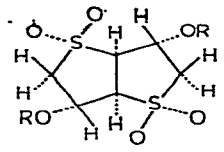
7 R = H; X = S
7a R = H; X = O
9 R = Ac; X = S
9a R = Ac; X = O

On treatment with an excess of sodium methoxide compound **5** gave a crystalline product, whose analytical data were concordant with those calculated for the 1,4:3,6-bis(thioanhydro)hexitol **7**. The n.m.r. spectra of compound **7** and its 2,5-diacetate **9** are very similar to those of the corresponding dianhydro derivative[7] **7a** and its 2,5-diacetate **9a**. In **7** the H-2 and H-5 protons exhibit first-order coupling with the protons of the geminal OH groups, as shown by the doublet splitting of the OH signal. This coupling was removed by addition of D_2O to the sample, as observed by the collapse of the doublet.

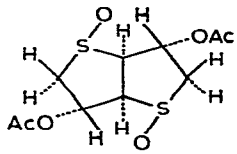
Mass-spectral investigation of the diester **9** also proved the presence of the two five-membered, fused rings, since although the *m/e* 262 (M, 100%), 202 (M-AcOH), and 142 (M-2AcOH, 71%) peaks appeared in the spectrum, no *m/e* 131 (M/2) peak could be detected. The latter should be characteristic for a diacetate of structure **8**.

Oxidation of compound **7** with two equivalents of hydrogen peroxide in acetic acid failed to produce sulfoxides; aside from unchanged starting material, only the disulfone **10** was formed. Since this product appeared to result from low solubility of compound **7** in the reaction mixture, the more soluble di-*O*-acetyl derivative **9** was

employed in further studies. Oxidation of compound **9** with an excess of hydrogen peroxide afforded the disulfone **11**, which could also be obtained by acetylation of compound **10**. Oxidation of **9** with two equivalents of hydrogen peroxide in acetic acid[9], or with sodium periodate in methanol–water[8], led to two isomeric sulfoxides



10 R = H
11 R = Ac



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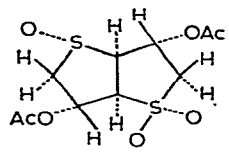

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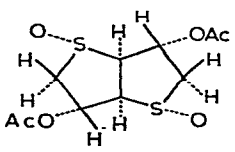

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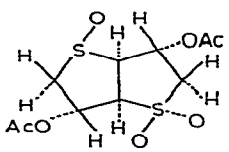

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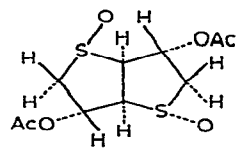

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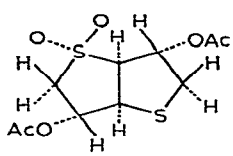

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(**12**, m.p. 238–240° and **14**, m.p. 171–172°) the structures of which were proved by spectroscopic methods. Both compounds gave qualitatively identical mass spectra, differing only in the relative intensities of peaks (Table I). This observation excludes the possibility of a monosulfone structure **15** that would give the same analytical data, but a mass spectrum different from those of the three sulfoxide isomers **12**, **13**, and **14** theoretically possible.

The asymmetric (*R*,*S*)-disulfoxide structure of isomer **14** was unambigously proved by its i.r. spectrum, which indicated the presence of two nonequivalent SO groups (Table II), and by its n.m.r. spectrum, in which the *O*-acetyl groups gave two, separate singlets, due to their nonequivalence. For the symmetric disulfoxide, structure **12** was chosen on the basis of its n.m.r. data, taking into consideration the

TABLE I

MASS-SPECTRAL DATA (RELATIVE %) OF 2,5-DI-*O*-ACETYL-1,4:3,6-BIS(THIOANHYDRO)-D-IDITOL (*R*,*R*)- AND (*R*,*S*)-DISULFOXIDE

Compound	*m/e* 294 (M)	*m/e* 252 (M-42)	*m/e* 235 (M-AcO)	*m/e* 126 (M-SO-2AcOH)	*m/e* 43 $(CH_3CO)^+$
12	51.8	21.0	51.8	35.0	100
14	64.0	27.0	47.5	58.6	100

TABLE II

I.R. DATA (CM^{-1}) FOR 2,5-DI-*O*-ACETYL-1,4:3,6-BIS(THIOANHYDRO)-D-IDITOL AND ITS OXIDATION PRODUCTS

Compound	*Oxidation state of sulfur*	*νC=O (ester)*	*νS=O*	$\nu_{as}SO_2$	$\nu_{s}SO_2$	*νC=O (ester)*
9	S; S	1745				1240; 1035
12	(*R*)SO; (*R*)SO	1735	1020			1235; 1050
14	(*R*)SO; (*S*)SO	1730	1020 1050			1245; 1035
16	(*S*)SO; SO_2	1745	1020	1320	1140	1230; 1050
11	SO_2; SO_2	1740		1320	1135	1245; 1025

following. The absolute configurations of sugar sulfoxides were determined by the analysis of their n.m.r. spectra first by Foster *et al.*[10], who showed, that the deshielding effect of the SO group causes a downfield shift in the signals of protons that are in "*syn*-axial" relation to it. Accordingly H-2 and H-5 should be deshielded in structure **12**, whereas in structure **13** the signals of the H-3 and H-4 protons should be shifted towards lower field. As the H-2 and H-5 signals of the symmetric disulfoxide appear at lower field (by 0.27 p.p.m.). whereas the signal of the H-3 and H-4 protons remained practically unchanged when compared with those in compound **9**, both sulfoxide groups must occupy *endo* positions, a condition met only in the (*R*,*R*)-disulfoxide **12**.

It is noteworthy that, of the two disulfoxides the (*R*,*S*)-isomer **14** was invariably formed to a greater extent (~90%) during the oxidation; the relative proportions were nearly independent of the oxidant used. According to the n.m.r. spectrum of compound **14**, no conformational changes took place in Me_2SO-d_6 solution upon heating to 150°. Similar investigation of the (*R*,*R*)-isomer **12** could not be performed because it decomposed at elevated temperatures in Me_2SO-d_6 solution.

On oxidation with an excess of hydrogen peroxide, both isomers gave the same disulfone **11** described above. When the oxidation of **12** or **14** was conducted with one equivalent of hydrogen peroxide, a new compound could be separated in addition to unchanged starting material and the disulfone **11**. According to analytical and spectroscopic data, this compound was one of the theoretically possible sulfone-sulfoxides

16 or **17**. By consideration of its n.m.r. parameters it is thought to have structure **17** rather than **16**. Benzene-induced, solvent shifts[11] could not be employed in this case for determining the structure because of the insolubility of the sulfone-sulfoxide in benzene.

In biological tests, compounds **2**, **3**, **4**, **7**, **10**, **11**, **12**, and **14** showed LD_{50} values above 1000 mg/kg (intraperitoneally, mouse). They displayed no cytostatic effect on Ehrlich ascites carcinoma, and S-180 sarcoma in 100 mg/kg/day × 5 doses. On Yoshida s.c. sarcoma most of them showed a very slight activity (**2**, 25%; **3**, 22%; **4**, 7%; **7**, 15%; **10**, 17%; and **11**, 12%). The sulfoxides **12** and **14** showed no inhibitory effect on Yoshida s.c. sarcoma, but produced an increase in survival time of 12% and 14%, respectively, on Ehrlich ascites carcinoma. The low activity of the 1,3,4,6-tetra-*O*-methylsulfonyl-D-mannitol (**4**) is remarkable, as the corresponding 1,2,5,6-tetra-*O*-methylsulfonyl isomer has been introduced for clinical evaluation recently (Zytostop®) because of its strong cytostatic effect.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on microscope slides coated with Kieselgel G, with carbon tetrachloride–ethyl acetate 1:1 (*A*), 5:1 (*B*), acetic acid–water 50:1 (*C*), and water saturated *n*-butanol (*D*) as solvent. Detection reagents used were 0.1M potassium permanganate–M sulfuric acid (1:1), and 4-(*p*-nitrobenzyl)pyridine followed by 2M sodium hydroxide and heating at 105°. N.m.r. spectra were recorded at 60 MHz with a Varian A-60D spectrometer. by using trifluoroacetic acid solutions and Me_4Si as internal standard. Mass spectra were recorded on a Varian MAT-SM-1 instrument with a direct-inlet system and an evaporation temperature of 23°. All evaporations were carried out in a rotary evaporator under diminished pressure, after drying the organic solutions over sodium sulfate. Light petroleum used had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1) if not otherwise stated.

2,5-Di-O-acetyl-1,3,4,6-tetra-O-methylsulfonyl-D-mannitol (**3**). — To a solution of 3,4-di-*O*-methylsulfonyl-D-mannitol[3,4] (**2**, 33.8 g) in pyridine (200 ml) was added a solution of methanesulfonyl chloride (17 ml) in pyridine (100 ml) during 30 min at −10°. The reaction mixture was kept for 1 h at room temperature, then cooled to 0° and treated with acetic anhydride (100 ml). The solution was kept overnight at room temperature and then poured on ice. The slurry was extracted with chloroform, and the organic solution was washed, dried, and evaporated. The residue was suspended in methanol, filtered, and washed with methanol to give, after recrystallization from methanol (700 ml), compound **3** (50 g, 86.5%), m.p. 108–110°, $[\alpha]_D^{20}$ +11.4° (Found: C, 29.25; H, 4.47; S, 22.04. $C_{14}H_{26}O_{16}S_4$ calc.: C, 29.06; H, 4.53; S, 22.17%).

1,3,4,6-Tetra-O-methylsulfonyl-D-mannitol (**4**). — A slurry of compound **3** (5.8 g) in methanol (200 ml) was saturated with hydrogen chloride at 10°. The mixture was stirred until complete dissolution had occurred, and was kept for 4 days at room temperature. The slurry was evaporated to 50 ml, chilled, and filtered to yield com-

pound **4** (3,3 g, 66.5%) m.p. 131–132° (not raised by recrystallization from ethyl acetate), $[\alpha]_D^{20}$ +31.9° (c 1, *p*-dioxane) (Found: C, 24.44; H, 4.31; S, 25.83. $C_{10}H_{22}O_{14}S_4$ calc.: C, 24.28; H, 4.48; S, 25.94%).

The same compound was obtained by treating the dimethylsulfonyl derivative **2** (3.4 g) in pyridine (20 ml) with a solution of methanesulfonyl chloride (1.9 ml) in pyridine (10 ml) for 15 min, with cooling to keep the reaction mixture below −10°. The reaction mixture was kept overnight at room temperature and poured onto ice. The precipitated oil became crystalline only after inoculation. The filtered and washed crude material (3.5 g. 70.6%) m.p. 120–122° gave on recrystallization from ethyl acetate pure compound **4** (2.4 g, 48.5%) m.p. 131–132° alone, and in admixture with the compound just described.

*2,5-Di-*O*-acetyl-1,6-di-*S*-benzoyl-3,4-di-*O*-methylsulfonyl-1,6-dithio-*D*-mannitol* (**5**) *and 2,5-di-*O*-acetyl-1-*S*-benzoyl-3,4,6-tri-*O*-methylsulfonyl-1-thio-*D*-mannitol* (**6**). — A solution of compound **3** (18 g) and potassium thiolbenzoate (12 g) in acetone (600 ml) was heated for 5 h on a steam bath with strong stirring. The cooled slurry was filtered and washed with acetone. The solid residue, obtained after evaporation of the solvent was treated with chloroform and water. The organic layer was washed with 5% aqueous sodium hydrogen carbonate and water, dried, and evaporated. The residue was recrystallized from methanol (30 ml) to give a crude product (12.4 g, 60.3%), which on recrystallization from ethyl acetate–ether yielded compound **5** (10.3 g, 50.6%), m.p. 107–109°, $[\alpha]_D^{20}$ +31.6°, R_F 0.80 (solvent *A*) (Found: C, 46.97; H, 4.75; S, 19.52. $C_{26}H_{30}O_{12}S_4$ calc.: C, 47.11; H, 4.56; S, 19.53%).

The combined mother liquors showed by t.l.c. two main components (R_F 0.80 and 0.55, solvent *A*). The residue after evaporation was chromatographed on silicic acid (carbon tetrachloride) with solvent *A* as eluant. Evaporations of the fractions yielded an additional 1.5 g (7.3%) of compound **5** and 5.6 g (29%) of compound **6** as a solid foam, m.p. 60–70°, $[\alpha]_D^{20}$ +34.1°, R_F 0.55 (solvent *A*) (Found: C, 38.52; H, 4.57; S, 20.48. $C_{20}H_{28}O_{14}S_4$ calc.: C, 38.70; H, 4.55; S, 20.66%).

*1,4:3,6-Bis(thioanhydro)-*D*-iditol* (**7**). — A solution of compound **5** (66.2 g in dry chloroform (1 liter) and dry methanol (1 liter) was cooled to 10° and treated with 4M methanolic sodium methoxide (55 ml). After 1 h at room temperature, the reaction mixture, which had formed a precipitate, was neutralized with a stream of gaseous CO_2. The filtrate was evaporated, and the residue was extracted with hot ethyl acetate (3 × 200 ml). The residue that remained after evaporation of the filtered extracts was treated with ether (200 ml) and kept in a refrigerator for 4 h. The filtered, crude dithioanhydro derivative was washed with ether (14.4 g, 81%) and recrystallized from water (50 ml) to give pure compound **7** (9.7 g, 54%), m.p. 147–149°, $[\alpha]_D^{20}$ −195.4° (*c* 1, *N,N*-dimethylformamide), −176.4° (*c* 1, *p*-dioxane), R_F 0.75 (ethyl acetate), 0.25 (solvent *A*), n.m.r. data: δ 5.35 (2-proton doublet, OH-2 and OH-5), 4.38 (2-proton multiplet, H-2 and H-5), 3.95 (2-proton singlet, H-3 and H-4), 3.35 and 2.73 (4-proton AMX multiplet, H-1, H-1′, H-6, and H-6′). (Found: C, 40.59; H, 5.75; S, 36.18. $C_6H_{10}O_2S_2$ calc.: C, 40.42; H, 5.65; S, 35.97%).

The same compound **7** (0.2 g, 42%) was obtained by treating the diacetate **9**

(0.7 g) in methanol with a catalytic amount of sodium methoxide, concentrating the solution, and recrystallizing the residue from water.

2,5-Di-O-acetyl-1,4:3,6-bis(thioanhydro)-D-iditol (**9**). — A solution of compound **7** (8.5 g) in pyridine (20 ml) was treated with acetic anhydride (15 ml) and kept overnight at room temperature. The reaction mixture was poured onto ice, and the resultant precipitate was filtered and washed with water. A solution of the crude ester (11.0 g, 88%) in ether (20 ml) was filtered through charcoal, treated with light petroleum (20 ml), and concentrated to a volume of 20 ml. The crystalline compound **9** was filtered off and washed with light petroleum (10.5 g, 83.8%), m.p. 52–53°, $[\alpha]_D^{20}$ −153.6°, R_F 0.55 (solvent *B*), ν_{max}^{KBr} 1745, 1240, 1035 cm^{-1} (ester groups), n.m.r. data: δ 5.48 (2-proton multiplet, H-2 and H-5), 4.20 (2-proton singlet, H-3 and H-4), 3.68 and 2.96 (4-proton AM(X)-multiplet, H-1, H-1′, H-6 and H-6′), 2.08 (6-proton singlet, acetyl CH_3) (Found: C, 45.93; H, 5.63; S, 24.45. $C_{10}H_{14}O_4S_2$ calc.: C, 45.78; H, 5.38; S, 24.45%).

1,4:3,6-Bis(thioanhydro)-D-iditol disulfone (**10**). — The bis(thioanhydride) **7** (1.8 g) was dissolved with heating in acetic acid (20 ml), whereupon the solution was quickly chilled and 33% hydrogen peroxide (10 ml) was added with cooling to maintain the temperature of the reaction mixture below 20°. Crystals began to separate from the solution in 20 h. After four days these were filtered and washed with ethanol to give pure compound **10** (2.1 g, 86.5%), m.p. 299–300° (unaltered after recrystallization from 17 volumes of water), R_F 0.60 (solvent *C*), $[\alpha]_D^{20}$ −87.2° (*c* 1, Me_2SO), ν_{max}^{KBr} 3470 (OH), 1300 (ν_{as} SO_2), 1140 (ν_s SO_2), 1105 cm^{-1} (C–OH) (Found: C, 29.77; H, 4.34; S, 26.51. $C_6H_{10}O_6S_2$ calc.: C, 29.74; H, 4.16; S, 26.47%).

2,5-Di-O-acetyl-1,4:3,6-bis(thioanhydro)-D-iditol disulfone (**11**). — *A*. A solution of the diacetate **9** (0.26 g) in acetic acid (2.5 ml) and 33% hydrogen peroxide (1 ml) was kept for 15 h at room temperature. After removal of solvents the residue was treated with water, filtered, and washed with water to yield crude **11** (0.20 g, 62.4%, m.p. 192–195°) which was recrystallized from ethyl acetate–light petroleum or from water (0.14 g, 42.9%), m.p. 197–199°, R_F 0.55 (solvent *C*), 0.75 (solvent *D*), $[\alpha]_D^{20}$ −44.7° (*c* 1, acetone), −65° (*c* 1, *p*-dioxane), mass spectrum: *m/e* 310 (M-16), 266 (M-AcOH), 262 (M-SO_2), 202 (M-SO_2-AcOH); n.m.r. data: δ 5.98 (2-proton multiplet, H-2 and H-5), 4.60 (2-proton singlet, H-3 and H-4), 3.90 and 3.70 (4-proton AB(X)-multiplet, H-1, H-1′, H-6 and H-6′), 2.25 (6-proton singlet, acetyl CH_3) (Found: C, 36.85; H, 4.46; S, 19.77. $C_{10}H_{14}O_8S_2$ calc.: C, 36.80; H, 4.33; S, 19.65%).

B. A solution of **12** or **14** (0.20 g) in acetic acid (2 ml) and 33% hydrogen peroxide (0.6 ml) was kept for 3 days at room temperature. The crystals that separated were filtered off and washed with water to give the disulfone (0.17 g, 76.5%), identical with compound **11** already described.

C. The diol-sulfone **10** (0.5 g) was heated in pyridine (1 ml) and acetic anhydride (1 ml) until complete dissolution occurred. The reaction mixture was kept overnight and the poured into water. The crystals were filtered, and recrystallized from ethyl acetate–light petroleum to give pure disulfone (0.6 g, 89.5%), identical with compound **11** already described.

2,5-Di-O-acetyl-1,4:3,6-bis(thioanhydro)-D-iditol (R,R)- *and* (R,S)-*disulfoxide* (**12** *and* **14**). — *A*. A solution of the diacetate **9** (13.1 g) in acetic acid (130 ml) was stirred with sodium periodate (23.5 g) for 3 days at room temperature. T.l.c. indicated that the starting material (R_F 0.95, solvent *D*) and the intermediate (R_F 0.60) had disappeared, and only the spots of the disulfoxides (R_F 0.20 and 0.30) could be detected. The slurry was filtered, the salts were washed with acetic acid, and the filtrate was evaporated below 40°. The solid residue was boiled in chloroform (100 ml), filtered with charcoal, and evaporated to 40 ml. The separated material was dissolved by heating and the solution was slowly cooled to room temperature. The fine needles of compound **12** that separated were filtered off and washed with chloroform (0.7 g, 4.75%), m.p. 238–240° (decomp.) after recrystallization from 10 parts of water, R_F 0.20 (solvent *D*), $[\alpha]_D^{20}$ −170.5° (*c* 0.5, water); n.m.r. data: δ 5.86 (2-proton multiplet, H-2 and H-5), 4.33 (2-proton multiplet, H-3 and H-4), 3.67 and 3.25 (4-proton AB(X) multiplet, H-1, H-1′, H-6 and H-6′), 1.88 (6-proton singlet, acetyl CH_3).

The chloroform solution was evaporated to 30 ml and diluted with ether (30 ml). The solid material that separated was filtered and washed with ether (10.8 g, 73.4%). Recrystallization from water (10 ml) gave rough prisms of compound **14** (6.2 g, 42.1%), m.p. 171–172°. R_F 0.30 (solvent *D*), $[\alpha]_D^{20}$ −137° (*c* 0.5, water), −187° (chloroform); n.m.r. data: δ 6.07 (1-proton multiplet, H-5), 5.85 (1-proton multiplet, H-2), 4.64 (1-proton multiplet, H-3), 4.60 (1-proton multiplet, H-4), 3.58 (1-proton multiplet, H-1), 3.42 (2-proton singlet, H-6 and H-6′), 2.91 (1-proton multiplet, H-1′), 1.93 and 1.88 (three-3-proton singlet, acetyl CH_3).

Evaporation of the mother liquor gave a mixture of compounds **12** and **14** that was separated by repeated recrystallization from chloroform and water as above. The total yield of the (*R,R*)-disulfoxide **12** was 0.97 g (6.6%) and that of the (*R,S*)-isomer **14** was 9.85 g (67%) (Found for compound **12**: C, 40.62; H, 5.04; O, 32.50; S, 21.47; for compound **14**: C, 40.56; H, 4.62; O, 32.43; S, 21.83. $C_{10}H_{14}O_6S_2$ calc.: C, 40.80; H, 4.79; O, 32.62; S, 21.79%).

B. A solution of the diacetate **9** (7.35 g) in methanol (140 ml) was treated with a warm solution (30°) of sodium periodate (13.5 g) in water (140 ml). The sodium iodate, which started to separate immediately, was filtered off after 2 h and was washed with methanol and hot chloroform (4 × 50 ml). The combined filtrate was evaporated and the dry residue was dissolved in hot chloroform (200 ml) filtered through charcoal, and reevaporated, to yield a mixture of compounds **12** and **14** (7.9 g, 96.4%). This mixture was boiled in chloroform (40 ml) and refrigerated. Fine needles of compound **12** were filtered off and washed with chloroform (0.5 g, 6.1%). The filtrate was evaporated and the residue recrystallized from water (7 ml) to yield compound **14** (0.4 g 48.5%). The residue, obtained after evaporation of the mother liquor was recrystallized from chloroform and water, respectively, as already described, to give 0.66 g (8.0% overall yield) of compound **12** and 5.8 g (70.3% overall yield) of compound **14**. Both compounds were identical with the disulfoxide isomers obtained via route *A*.

2,5-Di-O-acetyl-1,4:3,6-bis(thioanhydro)-D-iditol sulfone-sulfoxide (**16** *or* **17**). —

A solution of the disulfoxide mixture **12**+**14** (1.5 g) (obtained according to route *B*) in acetic acid (15 ml) and 33% hydrogen peroxide (0.55 ml) was kept at 60° and monitored by t.l.c. (solvent *D*). In addition to the spots of the starting materials (R_F 0.20 and 0.30) two new spots having R_F 0.40 (sulfone-sulfoxide) and 0.75 (disulfone) appeared during the reaction. After 8 h the spot of the sulfone-sulfoxide was very intense and that of R_F 0.20 could no longer be detected. The solution was concentrated, and the residue was purified by azeotropic distillation, first with water and then with ethanol. The residue was boiled with chloroform (5 ml), chilled, filtered, and washed with chloroform (2 × 5 ml) to give crude disulfone **11** (0.32 g, 19.6%). The filtrate was evaporated and recrystallized from water (5 ml) to give a mixture (0.65 g) of compound **11** and the sulfone-sulfoxide. Recrystallization from water gave, on slow cooling, fine needles of compound **11** (0.20 g, 12.2%), that were filtered off before the bushy crystals of the sulfone-sulfoxide started to separate. Concentration of the filtrate to 5 ml gave the pure sulfone-sulfoxide (**16** or **17**) (0.34 g, 21.9%), m.p. 205–208°, $[\alpha]_D^{20}$ −102.4° (*c* 0.5, water), −136° (*c* 1, acetone), R_F 0.40 (solvent *D*); n.m.r. data: δ 6.3 (1-proton multiplet, H-2), 6.0 (1-proton multiplet, H-5), 4.7 (1-proton multiplet, H-4), 4.5 (1-proton multiplet, H-3), 4.0 (1-proton multiplet, H-1'), 3.9 (1-proton multiplet, H-6'), 3.7 (1-proton multiplet, H-6), 3.4 (1-proton multiplet, H-1) 2.25 (6-proton singlet, acetyl CH_3), mass spectrum: *m/e* 310 (M), 250 (M-AcOH), 64 $(SO_2)^+$, 43 $(CH_3CO)^+$ (Found: C, 38.58; H, 4.53; O, 35.96; S, 20.61, $C_{10}H_{14}O_7S_2$ calc.: C, 38.80; H, 4.55; O, 35.92; S, 20.72%).

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