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SUBSTITUTION OF 1,4:3,6-DIANHYDRO-D-MANNITOL DERIVATIVES BY REACTIONS WITH IODIDE

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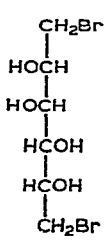
ABSTRACT

Reaction of 1,4:3,6-dianhydro-2,5-di-*O*-mesyl- and -tosyl-D-mannitol with sodium iodide gave a 1:1 mixture of 2,5-dideoxy-2,5-diiodo-D-glucitol (**12**) and -L-iditol (**22**). 1,4:3,6-Dianhydro-2-deoxy-2-iodo-5-*O*-mesyl-D-glucitol (**13**) and the corresponding D-mannitol derivative (**9**) are formed as intermediates. Both **9** and **13**, as well as **12** and **22**, are rapidly isomerized to a mixture of the two in the presence of iodide, proving a fast iodo–iodo substitution reaction. This is restricted to starting materials having the mannitol configuration, as the corresponding 2,5-di-*O*-mesyl-D-glucitol derivative gives only the known 5-deoxy-5-iodo-L-iditol derivative. The possible mechanism of the unusual isomerization reactions is discussed.

INTRODUCTION

The biological pathway, especially including the cytostatically active metabolites, of 1,6-dibromo-1,6-dideoxy-D-mannitol[1] (**1**) is still under discussion. Despite the fact that the corresponding diepoxide **2**, which is formed under mild, basic conditions[2,3] from **1**, has a much stronger biological activity[4], it is still doubtful whether this compound is the real active metabolite[5,6] of **1**. For studying this problem, a biological investigation of 1,6-dibromo-1,2,5,6-tetradeoxy-D-*threo*-hexitol* (**3**) was decided on; owing to lack of hydroxyl groups at C-2 and C-5, this cannot form a



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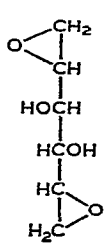

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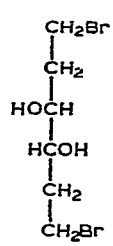

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*"1,6-Dibromo-1,2,5,6-tetradeoxy-D-mannitol".

diepoxide, and, consequently, its biological activity is restricted to the alkylating capacity of the two bromomethylene groups.

DISCUSSION

Compound **3** had been synthesized[7] in 1956, starting from 1,4:3,6-dianhydro-D-mannitol (**4**), which was converted, *via* the 2,5-dichloro-L-iditol derivative **21**, into the corresponding 2,5-dideoxy compound **5**. Opening of the anhydro rings by hydrogen bromide afforded **3**. As the catalytic hydrogenation of **21** had to be conducted in triethylamine at 100°, a more convenient method was desirable for large-scale preparation of **5**. For this reason, the 2,5-diiodo derivative **22** was synthesized, as its iodine atoms should be removable under less drastic conditions.

Compound **22** had been described by several authors[8-10], but, despite the exact analytical data reported, the different samples showed different rotations and melting points. According to the S_N2 type of mechanism, postulated for the substitution reactions of 1,4:3,6-dianhydro-2,5-di-*O*-mesyl- (**6**) and -tosyl-D-mannitol (**7**) with different nucleophiles[9-13], the L-iditol configuration was suggested for **22**.

On treating the dimesyl derivative **6** (according to the literature[8-10]) with sodium iodide in acetone at 120°, a 1:1 mixture of two diiodo isomers was obtained that, after separation by crystallization, proved to possess, respectively, the D-glucitol (**12**) and L-iditol (**22**) configuration*. When *N,N*-dimethylformamide was used as the solvent for the substitution reaction, the diiodo isomers **12** and **22** were again obtained in the same ratio, but t.l.c. investigation showed that a mixture of two monoiodo-monomesyl derivatives is first formed, which is converted only slowly into the mixture of the diiodo derivatives. By interrupting the reaction after the starting material had been used up, the two intermediates, formed in the ratio of 1:4, could be separated by column chromatography; they proved to be 1,4:5,6-dianhydro-2-deoxy-2-iodo-5-*O*-mesyl-D-mannitol (**9**) and -D-glucitol (**13**).

Similar results were obtained when the 2,5-di-*O*-tosyl derivative **7** was used as the starting material; it gave, besides the two diiodo derivatives **12** and **22**, two iodo-tosyl derivatives having, respectively, the D-mannitol (**11**) and the D-glucitol (**15**) configuration. Formation of all these isomers is contrary to the simple, S_N2 mechanism postulated, according to which 2,5-di-*endo***-arranged leaving-groups are substituted by different nucleophiles, resulting in 2,5-di-*exo* derivatives (D-mannitol→L-iditol).

The separate monoiodo isomers, **9** and **13**, were rapidly isomerized into a mixture of the two on treatment with sodium iodide in *N,N*-dimethylformamide, and the equilibrium mixture so obtained was slowly converted into a mixture of the diiodo

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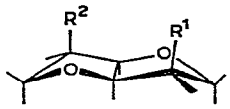
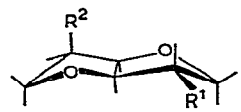
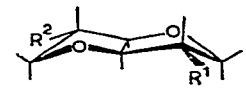
*The configuration of these isomers, as well as that of all the following compounds, was determined by ^{13}C-n.m.r. spectroscopy by use of the field effect. Detailed results are published elsewhere[14]. Compound **22** was identical with that prepared from **4** by reaction with triphenyl phosphite methiodide[16].

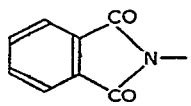
**The descriptors *endo* and *exo* refer to the V-shaped molecule consisting of substituted, *cis*-fused, tetrahydrofuran rings.

4 $R^1 = R^2 = OH$
5 $R^1 = R^2 = H$
6 $R^1 = R^2 = MsO$
7 $R^1 = R^2 = TsO$
8 $R^1 = R^2 = I$
9 $R^1 = I, R^2 = MsO$
10 $R^1 = R^2 = TsO$
11 $R^1 = I, R^2 = TsO$

12 $R^1 = R^2 = I$
13 $R^1 = I, R^2 = MsO$
14 $R^1 = MsO, R^2 = I$
15 $R^1 = I, R^2 = TsO$
16 $R^1 = R^2 = MsO$
17 $R^1 = Br, R^2 = MsO$
18 $R^1 = BzO, R^2 = MsO$
19 $R^1 = BzS, R^2 = MsO$
20 $R^1 = PhtN, R^2 = MsO$

21 $R^1 = R^2 = Cl$
22 $R^1 = R^2 = I$
23 $R^1 = R^2 = MsO$
24 $R^1 = MsO, R^2 = I$
25 $R^1 = R^2 = Br$
26 $R^1 = R^2 = BzO$
27 $R^1 = R^2 = BzS$
28 $R^1 = R^2 = PhtN$
29 $R^1 = BzO, R^2 = OH$

Ms = SO_2Me, Ts = $SO_2C_6H_4Me$-*p*, PhtN = 

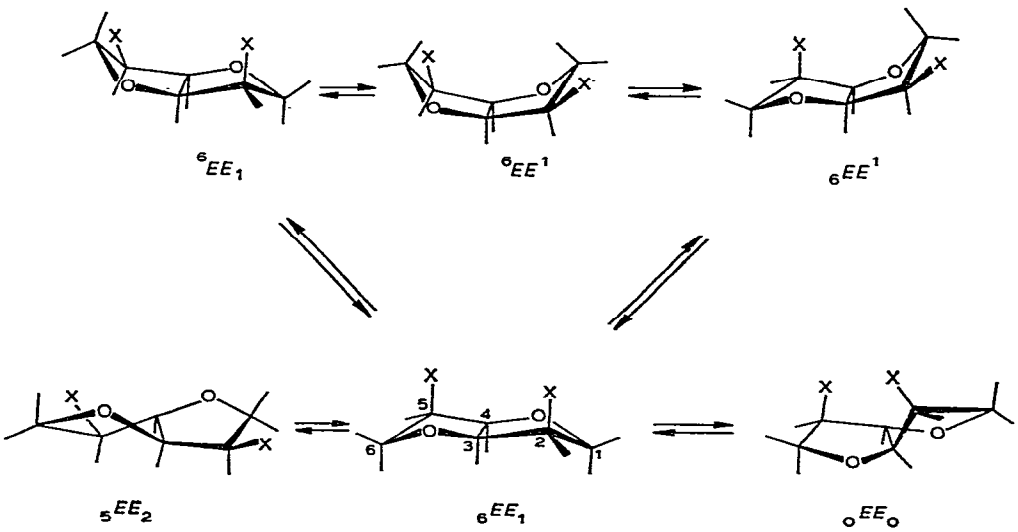
isomers **12** and **22**. Under the same conditions, these two, individual isomers underwent a similarly rapid isomerization, resulting in a 1:1 equilibrium mixture of them.

In further experiments, the substitution reactions of the corresponding 2,5-di-*O*-mesyl-D-glucitol (**16**) and -L-iditol (**23**) derivative were investigated, but, in accordance with the literature[9–13], only the 2-*endo* mesyloxy group of **16** was replaced by iodide, to afford the L-iditol isomer **24**, whereas **23** remained unchanged under similar conditions.

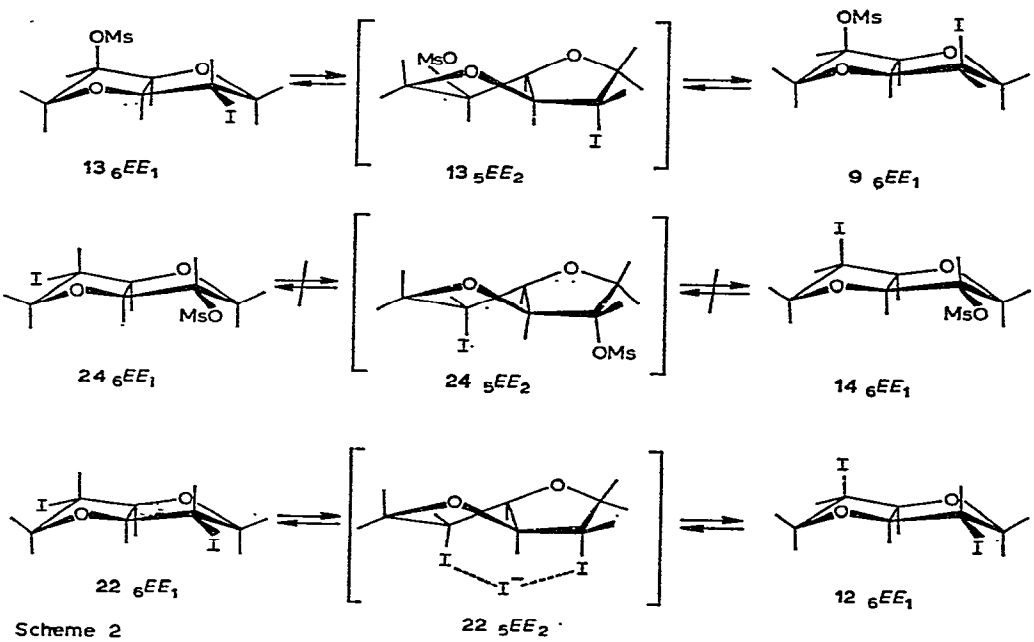
On the other hand, the 2,5-di-*O*-mesyl-D-mannitol derivative **6** reacted with other nucleophiles, such as bromide, benzoate, thiobenzoate, or phthalimide, according to the simple, S_N2 type of mechanism, giving, besides the mono-substituted D-glucitol derivatives (**17–20**), only the disubstituted L-iditol derivatives (**25–28**), respectively*. No isomerization reaction of either isomer could be observed. Consequently, partially the mannitol configuration, and partially the ambivalent character of the iodide (not only a nucleophile, but also a leaving group) must play a special role in the exceptional reactions of compounds **6** and **7** with sodium iodide.

The mechanism of these unusual reactions can be explained by taking into consideration the conformations of the *cis*-fused tetrahydrofuran rings (see Scheme 1). Owing to the ring-fusion, the free rotation of the individual, five-membered rings is restricted[15], and only C-2 and C-5 can move independently of each other. These two atoms can be situated "beneath" or "above" the plane of the four other atoms, affording the ${}_6EE_1$, ${}^6EE_1$, ${}_6EE^1$, and ${}^6EE^1$ conformations. In the latter, the substituents at C-2 and C-5 are diequatorially arranged in the D-mannitol configuration, but this conformation is disfavored, because of the strong interaction of H-1 and H-6.

*In the case of sodium benzoate, besides the MsO → BzO replacement, some MsO → HO replacement also occurred (**29**), because of the aqueous medium.



Scheme 1



Scheme 2

The diequatorial arrangement of the substituents on C-2 and C-5 can, however, also be achieved by the twisted conformation $_5EE_2$ in which C-2 and C-5 are turned out of the plane of the molecule. The other twisted conformation, $_oEE_o$, is disfavored, because of the strong interactions of the substituents on C-2 and C-5.

On applying this conformational scheme to the iodo-mesyl-D-glucitol derivative **13**, it may be seen (Scheme 2), that the $_6EE_1$ is, energetically, as much favored as the

$_5EE_2$ conformation, both having one axial and one equatorial substituent. In **13**-$_5EE_2$, there is no steric hindrance to prevent an iodo–iodo substitution; consequently, the **13**⇄**9** equilibration takes place. As the diaxial arrangement of the substituents on C-2 and C-5 in **9**-$_6EE_1$ is energetically less favored than the equatorial–axial arrangement in the **13**-$_6EE_1$ isomer, the equilibrium is shifted towards the latter.

In the iodo-mesyl-L-iditol isomer **24**, obtained from the D-glucitol derivative **16**, the iodo group could be substituted only in the $_5EE_2$ conformation, which, according to the diaxial arrangement of the substituents on C-2 and C-5, is sterically disfavored. Consequently, no iodo-isomerization to the D-glucitol isomer **14** takes place.

Isomerization of the diiodo-L-iditol derivative **22**, leading to an equilibrium of **12** and **22**, should also proceed *via* the $_5EE_2$ conformation, but, in this case, the axial arrangement of the two iodo substituents might be stabilized by formation of a complex with iodide, present in the reaction mixture. The further isomerization of the D-glucitol derivative **12** to the corresponding D-mannitol isomer **8** is very unlikely, because of the strong, steric interaction of the two iodo atoms in the latter isomer.

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was effected on Kieselgel G with carbon tetrachloride–ethyl acetate, 3:1 (*A*), and 9:1 (*B*). For detection, 1:1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). All evaporations were conducted in a rotary evaporator under diminished pressure, after the organic solutions had been dried with sodium sulfate. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1), if not stated otherwise.

Treatment of compound **6** *with sodium iodide.* — A solution of compound **6** (15.0 g) and sodium iodide (45.0 g) in *N*,*N*-dimethylformamide (300 mL) was boiled for 30 min. The cooled slurry was filtered, the filtrate was evaporated, and the residue was partitioned between chloroform and water. The brown, organic solution was successively washed with a 5% aqueous solution of sodium thiosulfate and water, dried, and evaporated. The syrupy residue was a mixture of four components, which were separated by column chromatography (solvent *A*). The first fraction (R_F 0.9) gave, after evaporation, and crystallization from ethanol, a 1:1 mixture of the diiodo isomers **12** and **22** (3.6 g, 19.8%), m.p. 68–70°, $[\alpha]_D^{20}$ +90°; lit.[8] m.p. 69–70°, $[\alpha]_D^{20}$ +101.4°; lit.[9] m.p. 61–62°, lit.[10] m.p. 61–63°, $[\alpha]_D^{21}$ +107.9°.

This material was recrystallized three times from methanol (20 mL) to give 1,4:3,6-dianhydro-2,5-dideoxy-2,5-diiodo-D-glucitol (**12**) (0.8 g), m.p. 116–118°, $[\alpha]_D^{20}$ +30°.

The methanolic mother-liquors were combined, and evaporated, and the residue was twice recrystallized from light petroleum, to give 1,4:3,6-dianhydro-2,5-dideoxy-2,5-diiodo-L-iditol (**22**) (0.2 g), m.p. 86–87°, $[\alpha]_D^{20}$ +138°; lit.[16] m.p. 84–85°, $[\alpha]_D^{26}$ +136.5° (*c* 3.1, $CHCl_3$).

Anal. Calc. for $C_6H_8I_2O_2$: C, 19.80; H, 2.19; I, 69.30. Found for **12**: C, 19.85; H, 2.34; I, 68.91. Found for **22**: C, 19.88; H, 2.32; I, 68.97.

The second fraction (R_F 0.5) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-5-*O*-(methylsulfonyl)-D-glucitol (**13**) (3.2 g, 19.2%), m.p. 86–87°, $[\alpha]_D^{20}$ +78°.

The third fraction (R_F 0.3) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-5-*O*-(methylsulfonyl)-D-mannitol (**9**) (0.8 g, 4.8%), m.p. 120–121°, $[\alpha]_D^{20}$ +126°.

Anal. Calc. for $C_7H_{11}IO_5S$: C, 25.30; H, 3.32; I, 38.0; S, 9.65. Found for **13**: C, 25.74; H, 3.06; I, 37.18; S, 9.97. Found for **9**: C, 25.74; H, 3.39; I, 37.07; S, 9.82.

Isomerization of **9**:**13** *and of* **12**:**22**. — A solution of the corresponding isomer (0.15 g) and sodium iodide (0.4 g) in *N*,*N*-dimethylformamide (5 mL) was kept at the boiling temperature. According to t.l.c., the equilibrium **9**⇄**13** was achieved within 20 min, and that of **12**⇄**22**, within 15 min.

Treatment of compound **7** *with sodium iodide.* — *Method a.* A solution of compound **7** (9.1 g) and sodium iodide (18.0 g) in *N*,*N*-dimethylformamide (120 mL) was boiled for 15 min. The mixture was processed as described for compound **6**. The syrupy residue obtained was a mixture of four components, which were separated by column chromatography (solvent *B*). The first fraction (R_F 0.8) gave, after evaporation, and crystallization from ethanol, a mixture of **12** and **22** (2.1 g, 28.8%), m.p. 68–70°, $[\alpha]_D^{20}$ +90°.

The second fraction (R_F 0.5) gave, after evaporation and crystallization from ethanol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-5-*O*-*p*-tolylsulfonyl-D-glucitol (**15**) (2.0 g, 24.4%), m.p. 109–110°, $[\alpha]_D^{20}$ +71°.

The third fraction (R_F 0.2) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2-deoxy-2-iodo-5-*O*-*p*-tolylsulfonyl-D-mannitol (**11**) (0.45 g, 5.5%), m.p. 137–137.5°, $[\alpha]_D^{20}$ +107°.

Anal. Calc. for $C_{13}H_{15}IO_5S$: C, 38.06; H, 3.69; I, 30.94; S, 7.82. Found for **15**: C, 38.27; H, 3.79; I, 30.14; S, 7.94. Found for **11**: C, 38.23; H, 3.77; I, 30.17; S, 7.97.

Method b. A solution of compound **7** (30 g) and sodium iodide (3.0 g) in acetone (30 mL) was stirred in a sealed tube for 6 h at 120°. The mixture was cooled, the salts were filtered off, and the pale-brown solution was evaporated. The residue was partitioned between ether and water. The organic solution was successively washed with a 5% aqueous solution of sodium thiosulfate and water, dried, and evaporated. The syrupy residue was a mixture of four components, which were separated by column chromatography (solvent *B*). The first fraction (R_F 0.8) gave, after evaporation, and crystallization from ethanol, a mixture of **12** and **22** (0.5 g, 20.8%), m.p. 68–70°, $[\alpha]_D^{20}$ +90°.

The second fraction (R_F 0.5) gave, after evaporation, and crystallization from ethanol, **15** (0.75 g, 27.7%) identical with that obtained *via* method *a*.

The third fraction (R_F 0.2) gave, after evaporation, and crystallization from ethanol, **11** (0.1 g, 3.7%) identical with that obtained *via* method *a*.

Treatment of compound **6** *with sodium bromide.* — A solution of compound **6**

(18.0 g) and sodium bromide (37.2 g) in *N,N*-dimethylformamide (360 mL) was boiled for 1 h. The slurry was cooled, and filtered, the filtrate was evaporated, and the residue was partitioned between chloroform and water. The organic solution was washed with water, dried, and evaporated. The syrupy residue was a mixture of two components, which were separated by column chromatography (solvent *A*). The first fraction (R_F 0.85) gave, after evaporation, and crystallization from light petroleum, 1,4:3,6-dianhydro-2,5-dibromo-2,5-dideoxy-L-iditol (**25**) (4.8 g, 30%), m.p. 69–70°, $[\alpha]_D^{20}$ +107°.

Anal. Calc. for $C_6H_8Br_2O_2$: C, 26.47; H, 2.97; Br, 58.77. Found: C, 26.91; H, 3.13; Br, 58.41.

The second fraction (R_F 0.45) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2-bromo-2-deoxy-5-*O*-(methylsulfonyl)-D-glucitol (**17**) (4.2 g, 24.5%), m.p. 98–100°, $[\alpha]_D^{20}$ +89°.

Anal. Calc. for $C_7H_{11}BrO_5S$: C, 29.28; H, 3.85; Br, 27.83; S, 11.17. Found: C, 29.64; H, 4.03; Br, 27.47; S, 11.24.

Treatment of compound **6** *with sodium benzoate.* — A solution of compound **6** (10.5 g) and sodium benzoate (15.1 g) in *N,N*-dimethylformamide (200 mL) and water (20 mL) was boiled for 24 h. The slurry was cooled, and evaporated, and the residue was partitioned between chloroform and water. The organic solution was washed with water, dried, and evaporated. The syrupy residue was a mixture of three components, which were separated by column chromatography (solvent *A*). The first fraction (R_F 0.85) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2,5-di-*O*-benzoyl-L-iditol (**26**) (4.2 g, 34.1%), m.p. 109–110°, $[\alpha]_D^{20}$ +135°; lit.[12] m.p. 110.6–111.4°, $[\alpha]_D^{20}$ +134.2° (*c* 3.0, $CHCl_3$).

The second fraction (R_F 0.4) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2-*O*-benzoyl-5-*O*-(methylsulfonyl)-D-glucitol (**18**) (0.8 g, 7.0%), m.p. 136–137°, $[\alpha]_D^{20}$ +78°.

Anal. Calc. for $C_{14}H_{16}O_7S$: C, 51.21; H, 4.91; S, 9.76. Found: C, 51.54; H, 4.98; S, 9.59.

The third fraction (R_F 0.3) gave, after evaporation, and crystallization from water, 1,4:3,6-dianhydro-2-*O*-benzoyl-L-iditol (**29**) (2.4 g, 27.6%), m.p. 90–92°, $[\alpha]_D^{20}$ +70°.

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.38; H, 5.74.

Treatment of compound **6** *with potassium thiolbenzoate.* — A solution of compound **6** (6.0 g) and potassium thiolbenzoate (6.0 g) in pyridine (60 mL) was boiled for 1 h. The cooled mixture was poured onto ice (600 g), and the precipitate was filtered off. This crude product was a mixture of two components, which were separated by column chromatography (solvent *A*). The first fraction (R_F 0.85) gave, after evaporation, and crystallization from ethanol, 1,4:3,6-dianhydro-2,5-di-*S*-benzoyl-2,5-dithio-L-iditol (**27**) (2.0 g, 26.0%), m.p. 125–126°, $[\alpha]_D^{20}$ +41°.

Anal. Calc. for $C_{20}H_{18}O_4S_2$: C, 62.15; H, 4.69; S, 16.59. Found: C, 62.08; H, 4.57; S, 16.55.

The second fraction (R_F 0.3) gave, after evaporation, and crystallization from

ethanol, 1,4:3,6-dianhydro-2-*S*-benzoyl-5-*O*-(methylsulfonyl)-2-thio-D-glucitol (**19**) (1.7 g, 25%), m.p. 164–165°, $[\alpha]_D^{20}$ +138°.

Anal. Calc. for $C_{14}H_{16}O_6S_2$: C, 48.80; H, 4.68; S, 18.60. Found: C, 49.20; H, 4.79; S, 18.89.

The L-iditol derivative **27** is obtained as the sole product (6.9 g, 90%) when the reaction mixture is boiled for 3 h.

Treatment of compound **6** *with potassium phthalimide.* — A solution of compound **6** (6.0 g) and potassium phthalimide (8.0 g) in *N*,*N*-dimethylformamide (120 mL) was boiled for 6 h. The mixture was cooled, and poured into water (800 mL), and the precipitate was filtered off. The dried, crude product was extracted with ethanol (100 mL), and the insoluble material was recrystallized from ethyl acetate, to yield 1,4:3,6-dianhydro-2,5-dideoxy-2,5-di(phthalimido)-L-iditol (**28**) (5.2 g, 64%), m.p. 239.5–241.5°, $[\alpha]_D^{20}$ +165°; lit.[12] m.p. 243.4–243.6°, $[\alpha]_D^{20}$ +168° (*c* 1.0 $CHCl_3$).

The ethanolic extract was filtered with the aid of charcoal, the filtrate evaporated, and the residue crystallized from ethanol, to give 1,4:3,6-dianhydro-2-deoxy-5-*O*-(methylsulfonyl)-(2-phthalimido)-D-glucitol (**20**) (0.4 g, 5.7%), m.p. 166–168°, $[\alpha]_D^{20}$ +126°.

Anal. Calc. for $C_{15}H_{15}NO_7S$: C, 50.98; H, 4.28; N, 3.96; S, 9.08. Found: C, 51.23; H, 4.39; N, 4.17; S, 8.83.

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