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REACTION OF SOME SULFONIC ESTERS OF D-MANNITOL WITH METHOXIDE, SYNTHESIS OF 2,3 4,5-DIANHYDRO-D-IDITOL*

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ABSTRACT

3,4-Di-*O*-(methylsulfonyl)- and 3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol and their 1,2,5,6-tetraacetates have been synthesized and crystallized By the action of an excess of methanolic barium methoxide during 2 h at 25°, each of these compounds is converted into 2,3 4,5-dianhydro-D-iditol, the structure of which is assigned on the basis of chemical and physical properties, including n m r spectroscopic evidence

INTRODUCTION

In 1947, Wiggins[1] reported the preparation of 1,4 3,6-dianhydro-D-iditol (**6**) by the following series of reactions D-Mannitol (**1**) was condensed with acetone to give 1,2 5,6-di-*O*-isopropylidene-D-mannitol (**2**), and **2** was *p*-toluenesulfonylated to afford the 3,4-di-*p*-toluenesulfonate (**3b**) of **2** Compound **3b** was then treated with 70% acetic acid during 3 h at 70°, giving an unstated yield of an uncharacterized syrup that was formulated as 3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (**4b**) This crude syrup was acetylated with boiling acetic anhydride and sodium acetate to give a 65% yield of a syrup which, it was supposed, was the 1,2,5,6-tetraacetate (**5b**) of **4b** Then, by the action of an excess of sodium methoxide on the crude, syrupy **5b**, Wiggins[1] obtained a syrup, presumed to be 1,4 3,6-dianhydro-D-iditol (**6**) (yield, 54%, calc on **5b**)

However, the syrupy dianhydride had $[\alpha]_D$ −16 7° (water)[1], and, although it crystallized, Wiggins could not recrystallize it In contrast, the enantiomorph (**6-e**) of **6** is readily crystallized and recrystallized, and has[2] m p 64° and $[\alpha]_D$ +20 8° (water), and its hemihydrate has[1] m p 43–45° and $[\alpha]_D$ + 18 4° (water) Moreover, on benzoylation of the syrupy dianhydride (**6**), the yield of the 2,5-dibenzoate of **6** was only 48 5% of the theoretical, instead of the almost 100% to be expected Similarly, methanesulfonylation of the syrup gave the 2,5-dimethanesulfonate of **6**, but in only 40 3% yield Thus, it seems reasonable to conclude that the actual content of compound **6** in Wiggins' syrupy **6** was probably less than 50% (which means that the actual yield of **6** was less than 27%, calc on **5b**)

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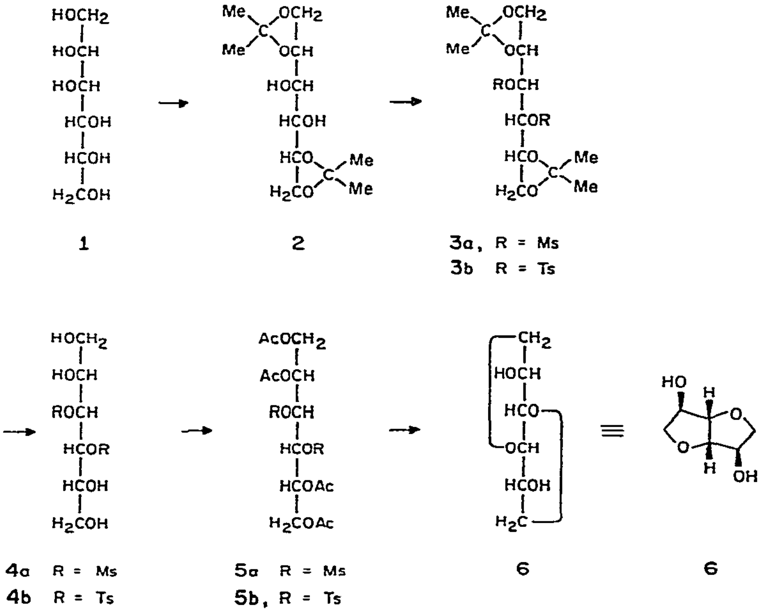
From this evidence alone, it would seem that, not only must Wiggins' "dianhydro-D-iditol" have been grossly impure, but the syrupy tetraacetate (**5b**) and, therefore, the syrupy di-*p*-toluenesulfonate (**4b**) from which it was prepared were probably impure also Consequently, we decided to re-investigate some of these reactions



1

2

3a, R = Ms
3b R = Ts

4a R = Ms
4b R = Ts

5a R = Ms
5b, R = Ts

6

6

RESULTS AND DISCUSSION

In the present study, the preparation of each compound in the sequence **1** to **5b** has been improved, and compound **4b** and its tetraacetate **5b** (obtained as syrups by Wiggins' have been crystallized and characterized In addition, compound **4a** and its tetraacetate (**5a**) have been synthesized from **3a** (already known), and have also been crystallized and characterized

A polarimetric study (see Fig 1) of the formation of **4b** from **3b** revealed why Wiggins' syrupy di-*p*-toluenesulfonate **4b** was impure On treating **3b** with 4 1 (v/v) acetic acid–water at 65°, we found that, at first, the optical rotation rises, reaching a maximum after the elapse of 45 min At this stage, hydrolysis of the isopropylidene acetal groups was essentially complete, because, on arresting the reaction, and removing the solvent, a 93% yield of crystalline **4b** was obtained (Crystalline **4a** was obtained in a yield of 83% by similar treatment of **3a**) However, if the reaction in aqueous acetic acid at 65° is permitted to proceed beyond 45 min, the optical rotation slowly falls, suggesting slow liberation of free *p*-toluenesulfonic acid, possibly with associated dehydrations Consequently, as Wiggins had conducted the hydrolysis with 70% acetic acid for 4 times as long (3 h) at a higher temperature (70°), his syrupy **4b** must have contained artifacts, and these would have led to contamination of his tetraacetate **5b**

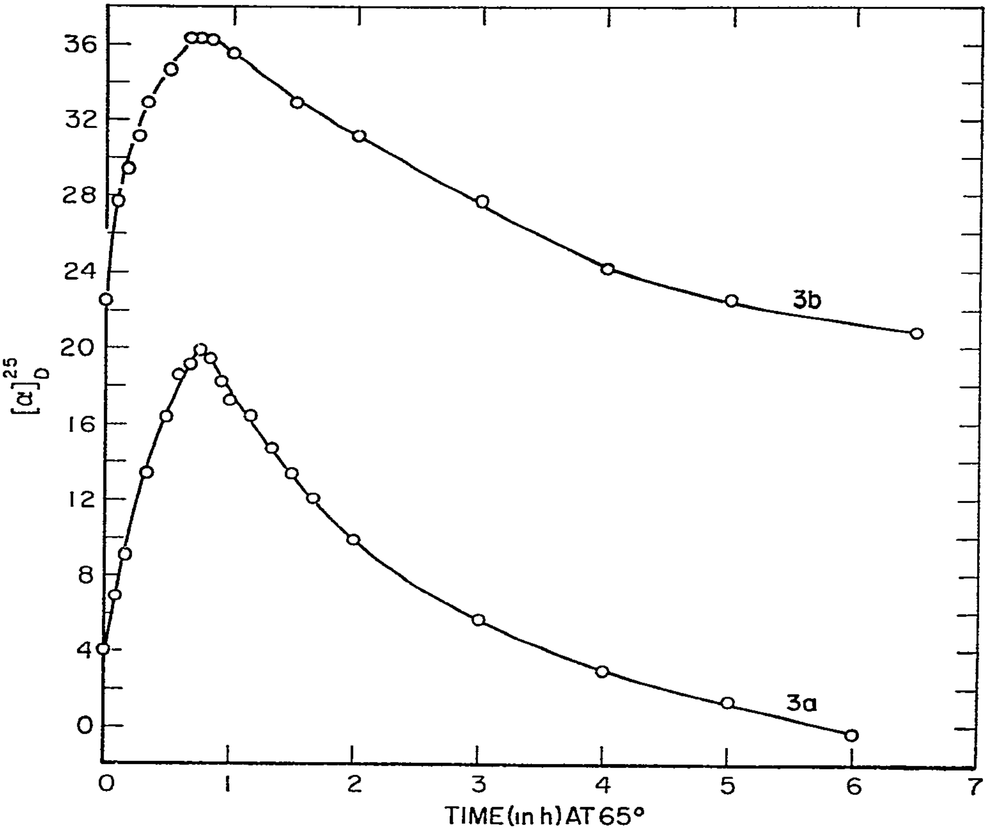


Fig 1 Rate of hydrolysis of 1,2 5,6-di-*O*-isopropylidene-3,4-di-*O*-(methylsulfonyl)-D-mannitol (**3a**) and of 1,2 5,6-di-*O*-isopropylidene-3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (**3b**) in 4 1 (v/v) acetic acid–water at 65°

Acetylation of our crystalline **4a** and **4b** afforded the crystalline tetraacetates **5a** and **5b**, respectively Because the properties of our **4b** and **5b** were quite different from those reported by Wiggins[1] for these two compounds, we decided to saponify the crystalline tetra-*O*-acetyl-di-*O*-*p*-tolylsulfonyl derivative **5b** under his conditions, in the expectation of obtaining a high yield of pure **6**, this product was not, however, obtained Treatment of our pure, crystalline **5b** in chloroform with an excess of sodium methoxide in methanol at 0°, followed by 4 h at 25° (with isolation as described by Wiggins[1], except that carbon dioxide was used instead of 0 5M sulfuric acid to neutralize the base), gave a practically quantitative yield (calculated as dianhydrohexitol) of a product consisting of colorless crystals and a colorless syrup The crystalline product had an elementary analysis corresponding to that calculated for a dianhydrohexitol hemihydrate, but (*1*) its melting point was much higher than that reported[1,2] for 1,4 3,6-dianhydro-L-iditol (**6-e**) or its hemihydrate, (*2*) its specific rotation (in water) was much higher than that expected for **6** on the basis of that of **6-e**, and (*3*) its infrared spectrum differed significantly from that of authentic[*] **6-e** Thin-layer chromatograms of the syrup on Silica Gel G[†][‡], with ethyl acetate as the developer, showed the presence of three compounds, the fastest-moving of which had the same R_F value as authentic **6-e**

In an attempt to increase the yield of the new, crystalline dianhydro-D-iditol, the reaction time was increased (16 h at 25°), but t l c of the reaction mixture with 99 1 (v/v) ethyl acetate–methanol showed two main components and three trace components After one development, the fastest-moving component had the same R_F value as that of **6-e**, but a second development with the same solvent mixture showed that they differed Similar treatment of pure, crystalline **5a** in chloroform with methanolic sodium methoxide followed by 2 days in a refrigerator and then 4 days at 25°, caused almost complete disappearance of the component having the same R_F value (1 development) as **6-e** and the appearance of several new components, suggesting the formation of methyl ethers

As the conversion of the tetraacetates **5a** or **5b** into a dianhydrohexitol involves deacetylation, it seemed possible that the acetylation step might be unnecessary This was verified, treatment of pure, crystalline **4a** with an excess of methanolic sodium methoxide only (for 24 h at 25°) gave a mixture similar to that from the tetraacetate **5a** (16 h at 25°)

It was then decided to determine the effect of conducting the reaction for 2 h (instead of 4 h, as described by Wiggins[1]) at 25°, and to employ methanolic barium methoxide (without chloroform) instead of sodium methoxide Under these conditions, only one product was formed (t l c), and compounds **4a** and **4b** (and **5a** and **5b**) each gave an excellent yield of a crystalline compound (*A*) having an elementary analysis agreeing with that calculated for a dianhydrohexitol Its specific rotation was much higher than that expected for compound **6** on the basis of the specific rotation of the enantiomorph[2] (**6-e**), and its melting point and i r spectrum differed from those of **6-e**

Compound *A* was found to have two free hydroxyl groups, because, on acetylation with acetic anhydride–pyridine (160 min at 25°), it afforded a crystalline compound having an elementary composition agreeing with that calculated for a di-*O*-acetyldianhydrohexitol, yield 97% A crystalline dibenzoate was also prepared, its properties differed from those expected for the 2,5-dibenzoate of **6** on the basis of those

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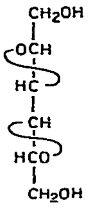
[*] Samples of this compound and its 2,5-dibenzoate were kindly supplied by Dr H G Fletcher, Jr , of the National Institutes of Health, Bethesda, Maryland 20014

[†] From E Merck A-G, Darmstadt, Germany pretreated with water (2 ml per g), air-dried overnight, and activated for 1 h at 110°

[‡] Certain commercial products and instruments are identified in this paper in order to specify adequately the experimental procedure In no case does such identification imply recommendation or endorsement by the National Bureau of Standards, nor does it imply that the product or equipment identified is necessarily the best available for the purpose

of the dibenzoate[2] of 6-e The n m r spectrum of compound *A*, measured in methyl sulfoxide-d_6, showed signals of the hydroxyl protons as a 2-proton, apparent triplet, and hence the two hydroxyl groups are both primary[3] This conclusion was confirmed by the observation that compound *A*, found to be stable in aqueous solution at 25°, is unaffected by sodium metaperiodate in water during 24 h at 25°, showing that the two hydroxyl groups of compound *A* are not vicinal As a further confirmation, the n m r spectra of the diacetate and dibenzoate, measured in chloroform-*d*, showed a downfield shift of the signals of four protons Consequently, the two anhydro rings of compound *A* must involve carbon atoms 2,3,4, and 5 Unless rearrangement occurred after the initial reaction, a 2,5 3,4-dianhydride is ruled out because of the method of preparation, suggesting that compound *A* is the 2,3 4,5- or 2,4 3,5-dianhydride The n m r spectra of compound *A* and its 1,6-diacetate and 1,6-dibenzoate were consistent with either of these structures (and the respective esters thereof) The n m r spectrum of compound *A* showed only four main groups of signals, and, for some compounds, this situation could be attributed to chemical-shift averaging caused by completely free rotation at the C-1–C-2, C-3–C-4, and C-5–C-6 bonds However, inspection of molecular models of the 2,3 4,5- and 2,4 3,5-dianhydrides of D-iditol reveals that, with suitable orientation of the hydroxymethyl groups, each molecule can have a simple, two-fold axis of symmetry vertical to the C-3–C-4 bond As compound *A* and its two diesters are optically active (and therefore lack a plane of symmetry), the optical asymmetry at C-2 differs from that at C-5, and that at C-3 differs from that at C-4 Consequently, it seems reasonable to attribute the observed chemical-shift equivalence of H-1 with H-6 or H-6′, of H-1′ with H-6′ or H-6, of H-2 with H-5, and of H-3 with H-4, to the presence of the two-fold axis of symmetry Such symmetry, which does not make the molecule optically inactive, is nevertheless sufficient to give chemical-shift equivalence of protons located similarly on each half of the chain of carbon atoms Because the 2,4 3,5-dianhydride structure has two oxetan rings, seldom encountered in sugar chemistry, we have assigned the 2,3 4,5-dianhydride structure (7) to compound *A*.



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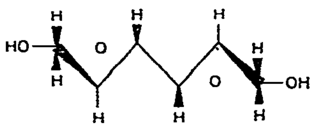

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Incidentally, occasion was taken to prepare the hexakis(methanesulfonate) and hexakis-(*p*-toluenesulfonate) of **1**

EXPERIMENTAL

General methods — All melting points are corrected I r spectra were recorded with a Perkin–Elmer Model 137 "Infracord" or (for spectra of higher resolution) with a Model 257 grating i.r. spectrophotometer. N.m.r. spectra were recorded with a Varian A-60 n.m.r. spectrometer, with tetramethylsilane (τ 10.00) as internal standard.

*1,2:5,6-Di-O-isopropylidene-*D*-mannitol* (**2**). — The method of Baer[4] was simplified. Anhydrous zinc chloride (70.4 g) was placed in a 500-ml Erlenmeyer flask, 352 ml of acetone (reagent grade) was added, the flask was quickly stoppered, and the suspension was swirled until the salt had dissolved. The suspension was filtered (fluted, soft paper) into a 500-ml, round-bottomed flask containing 36.4 g (0.2 mole) of **1** and an egg-shaped stirring-bar, and the suspension was magnetically stirred (under a reflux condenser) in a bath of cool water until the alditol had just dissolved (2 h). The solution was poured immediately, with stirring, into a beaker containing a solution of 88 g of potassium carbonate in 88 ml of water. (If necessary, the resulting mixture could then safely be kept at room temperature for several days, with no deleterious effects.) The suspension was now filtered with suction. The precipitate was stirred three times with chloroform, and the suspension was filtered each time, the combined extracts were dried (anhydrous sodium sulfate), and evaporated to dryness, giving 25.4 g of colorless crystals. The aqueous layer was extracted three times with chloroform, and the combined extracts were similarly treated, to give 16.8 g of colorless crystals.

For recrystallization, the total product was dissolved in chloroform (1 ml per g), heptane (10 ml per g) was added, the mixture was boiled under reflux, the hot solution was filtered (fluted, soft paper), and the filtrate was diluted with heptane (10 ml per g) and kept overnight in a refrigerator, to give 27.7 g (53%) of colorless crystals of **2** (pure enough for the next step), m.p. 120–121°, $\nu_{\max}^{\mathrm{KCl}}$ 1387 (CMe$_2$), 1376 (CMe$_2$), 1160, 1126, and[5] 1044 cm^{-1} (1,3-dioxolane ring).

*1,2:5,6-Di-O-isopropylidene-3,4-di-O-(methylsulfonyl)-*D*-mannitol* (**3a**). — The method of Bladon and Owen[6] was improved. In a 250-ml, three-necked, round-bottomed flask (equipped with a stirrer, pentane thermometer, and pressure-equalizing dropping funnel) was placed 13.2 g (0.05 mole) of **2**, 30 ml of dry pyridine was added, and the solution was cooled in ice–salt to −10°. A solution of 9.5 ml of methanesulfonyl chloride in 20 ml of dry pyridine was now added dropwise, with stirring, at such a rate that the temperature remained below −5° (12 min). The mixture was then stirred for 1 h at −10°, the bath was removed, and stirring was continued for a further 5 h. The mixture was recooled to −10°, and water was added in portions (1+1+1+2+5+10 ml) at 5-min intervals, with stirring, so that the temperature remained below −5°. Water (100 ml) was added, the suspension was filtered, and the colorless crystals were washed thoroughly with water, and dried at 0.1 torr over phosphorus pentaoxide, wt., 19.8 g, m.p. 138–141°. The filtrate and washings were combined and extracted with chloroform, the extracts were combined and washed successively with excess potassium hydrogen sulfate solution, water, sodium hydrogen carbonate solution, and water, dried (anhydrous sodium sulfate), and evaporated to dryness, to give 1.0 g of crystalline product, total yield 20.8 g (99%). The compound (**3a**) was recrystallized from boiling absolute methanol (6 ml per g), m.p. 143–144°

(lit[6] m p 143–144°), $[\alpha]_D^{25}$ +4 1° (*c* 4 2, 4 1 acetic acid– water), ν_{max}^{Nujol} no OH bands, 1359 (S = O), 1175 (S = O, 1,3-dioxolane), 1145, and 1040 cm^{-1} (1,3-dioxolane) The compound should be stored in a refrigerator

1,2 5,6-Di-O-isopropylidene-3,4-di-O-p-tolylsulfonyl-D-mannitol (**3b**) — To minimize concomitant formation of the mono-*p*-toluenesulfonate[7], the procedure of Brigl and Gruner[8] was modified[9] To 52 5 g (0 2 mole) of **2** in a 1-liter Erlenmeyer flask was added 336 ml of dry pyridine, then 84 g of *p*-toluenesulfonyl chloride was added in one portion, the flask was stoppered, and the mixture was swirled at room temperature until the crystals had dissolved Crystallization of pyridinium chloride began after about 4 h The mixture was kept for 7 days at 25°, and then cooled in ice–salt to below −1° It was processed as for **3a**, but with double the proportions of water, followed by an equal volume of water, and the resulting, colorless crystals were removed by filtration, washed with water, pressed, and dissolved in chloroform The chloroform solution was washed as for **3a**, dried, and evaporated to dryness, affording a practically quantitative yield of colorless crystals Recrystallization from boiling absolute methanol (5 ml per g) gave 91 6 g (80%) of **3b**, m p 119–120°, $[\alpha]_D^{26}$ +8 6° (*c* 4 0, chloroform), $[\alpha]_D^{27}$ +22 5° (*c* 1 0, 4 1 acetic acid–water) [lit[8] m p 120–121°, $[\alpha]_D$ +9 3° (chloroform)]; ν_{max}^{Nujol} no OH bands, 1605 (phenyl C = C), 1355 and 1183 (S = O), 820 cm^{-1} (*p*-substituted phenyl)

After shorter reaction times, the yield and m p of once-recrystallized product were 3 days, 60%, 113–115°, 5 days, 70%, 119–120°

Rate of hydrolysis of **3a** *by aqueous acetic acid* — Finely powdered **3a** (20 000 g) was weighed into a 50-ml volumetric flask, 4 1 (v/v) acetic acid–water was added to the mark, the suspension was shaken at room temperature until all of the crystals had dissolved (15 min), and the solution was cooled in ice Portions (6 ml) of this solution were placed in Pyrex test tubes, which were then cooled in Dry Ice–chloroform, sealed, and stored in the refrigerator until used For a determination, a tube was warmed to room temperature and was then heated, in a bath maintained at 65°, for a chosen period of time The tube was removed from the bath, rapidly cooled in Dry Ice–chloroform, opened, warmed to room temperature, and the specific rotation of the solution determined (2-dm tube) The results are given in Fig 1, from which it may be seen that, after the elapse of 45 min at 65°, hydrolysis of the isopropylidene groups was complete, thereafter, slow hydrolysis of the sulfonic ester groups continued After 45 min, the solution had $[\alpha]_D^{27}$ +19 9° (calc on the original wt of **3a**); $[\alpha]_D^{27}$ +24 6° (calc as **4a**)

Rate of hydrolysis of **3b** *by aqueous acetic acid* — Finely powdered **3b** (10 000 g) was weighed into a 100-ml volumetric flask, and 4 1 (v/v) acetic acid–water was added to the mark The determinations were then performed as described for the hydrolysis of **3a** The results are given in Fig 1, from which it may be seen that the hydrolysis is similar to that of **3a** After 45 min, the solution had $[\alpha]_D^{27}$ +36 3° (calc on the original wt of **3b**), $[\alpha]_D^{27}$ +42 2° (calc as **4b**)

3,4-Di-O-(methylsulfonyl)-D-mannitol (**4a**). — In a 500-ml, round-bottomed flask were placed 200 ml of acetic acid, 50 ml of water, and an egg-shaped, magnetic stirring-bar, the flask was closed with a loose-fitting stopper bearing a thermometer, and the solution was heated (in a bath at 67°), with stirring, until its temperature reached 65° (30 min) Compound **3a** (10 5 g, 0 025 mole) was now added, the flask was closed, and the suspension was stirred at 65° until all of the crystals had dissolved (2 min) The resulting solution was heated for 45 min at 65°, cooled in ice, and evaporated under diminished pressure (bath temp 35°) to a colorless syrup which was (3 times) dissolved in 50 ml of water and the solution was re-evaporated to a syrup The syrup was dissolved in 50 ml of absolute ethanol, and the solution was evaporated to a syrup which crystallized, the mass was stirred with absolute ethanol (5 ml per g) and filtered, to give colorless crystals, wt 6 1 g (72%), m p 111–114° The mother liquor afforded a second crop, 0 9 g, m p 104–108° The total yield was 7 0 g (83%) It was recrystallized from absolute ethanol (5 ml per g), m p 113–115°, $[\alpha]_D^{26}$ +30 6° (*c* 1 0, water), ν_{max}^{Nujol} 3546 (OH), 1359 (S = O), 1170 cm^{-1} (S = O)

Anal Calc for $C_8H_{18}O_{10}S_2$ C, 28 4, H, 5 4, S, 19 0. Found C, 28 5, H, 5 2, S, 18 9

On recrystallization from cold absolute methanol (30 ml per g) by the addition of dry ether (50 ml per g), it crystallized with 1 molecular proportion of methanol; m p 102–103° (softens at 77°), $[\alpha]_D^{27}$ +28 4° (*c* 1 0, water)

Anal Calc for $C_8H_{18}O_{10}S_2$ CH_3OH. C, 29 2, H, 6 0, S, 17 3 Found C, 29 0, H, 5 8, S, 17 5

*3,4-Di-O-p-tolylsulfonyl-*D*-mannitol* (**4b**). — The conditions of Brigl and Gruner[8] were modified as follows the concentration of **3b** in the initial solution was almost halved, a temperature of 65° (instead of 60°) was used, and the reaction time was diminished from 4 h to 45 min Compound **3b** (11 4 g, 0 02 mole) was treated as described for the preparation of **4a** from **3a**, after removal of the aqueous acetic acid at the conclusion of the hydrolysis, the resulting colorless syrup was dissolved in chloroform, and the solution was washed successively with aqueous sodium hydrogen carbonate solution (until free from acid) and water, dried (anhydrous sodium sulfate), and evaporated to dryness under diminished pressure, giving a colorless, flaky glass which was dried at 0 2 torr, wt 9 7 g (99%) This was dissolved in chloroform (10 ml per g) and the solution was refrigerated, to give (in two crops) 9 1 g (93%) of colorless crystals, m p 128–129° Alternatively, the flaky glass was dissolved in absolute methanol (1 ml per g), water was added dropwise to faint opalescence, and the solution was refrigerated, to give colorless crystals, wt 8 7 g (89%), m p 130–131° It was recrystallized from cold absolute methanol (12 ml per g) by gradual addition of pentane (24 ml per g), m p 133–134°, $[\alpha]_D^{25}$ +50 4° (*c* 1 0, absolute methanol), +40 1° (*c* 1.0, 4 1 acetic acid–water), +47 1° (*c* 1 0, dry pyridine), ν_{max}^{Nujol} 3448 (OH), 1600 (phenyl C = C), 1351, 1190, and 1176 (S = O), 820 cm^{-1} (*p*-substituted phenyl)

Anal Calc for $C_{20}H_{26}O_{10}S_2$· C, 49 0, H, 5 3; S, 13 1 Found C, 49 1; H, 5 5; S, 12 9

*1,2,5,6-Tetra-O-acetyl-3,4-di-O-(methylsulfonyl)-*D*-mannitol* (**5a**) — To a solution of 10 ml of acetic anhydride in 10 ml of dry pyridine at 0° was added 3 4 g (0 01 mole) of **4a**, and the suspension was swirled at 0° until the crystals had dissolved

The solution was kept overnight at 25°, and poured, with stirring, onto 100 ml of chopped ice, to give 3 5 g of colorless crystals The aqueous solution was extracted with chloroform and the extract was processed as usual, to give a further 1 5 g of product, total yield, quantitative The compound was recrystallized from absolute methanol (8 ml per g) by adding pentane (5 ml per g), m p 81–83°, $[\alpha]_D^{29}$ +30 2° (*c* 1 0, absolute methanol), ν_{max}^{Nujol} no OH bands, 1745 (ester C = O), 1351, 1176 cm^{-1} (S = O)

Anal Calc for $C_{16}H_{26}O_{14}S_2$: C, 37 9, H, 5 2, S, 12 7 Found C, 38 1; H, 5 1, S, 12 6

*1,2,5,6-Tetra-O-acetyl-3,4-di-O-p-tolylsulfonyl-*D*-mannitol* (**5b**) — The following procedure gave a crystalline product To 9 8 g (0 02 mole) of **4b** was added 30 ml of dry pyridine, the flask was quickly stoppered, and the suspension was swirled until the crystals had dissolved The colorless solution was cooled for 5 min in ice–salt, 30 ml of acetic anhydride was added, and the solution was swirled and then kept in the bath for 5 min The solution was now kept for 3 h at 25°, and poured onto chopped ice, with stirring The mixture was extracted with chloroform, and the extract was washed successively with potassium hydrogen sulfate solution, water, and sodium hydrogen carbonate solution, dried (anhydrous sodium sulfate), and evaporated to dryness under diminished pressure, giving a pale-yellow syrup (12 9 g) which was dissolved in 66 ml of absolute ethanol at room temperature After being kept overnight at room temperature, an almost solid mass of colorless crystals was obtained, this was refrigerated overnight, and filtered, to give 11 3 g (86%) of crystals These were recrystallized from absolute ethanol (5 ml per g), m p 83–84°, $[\alpha]_D^{27}$ +28 5° (*c* 1 0, chloroform), ν_{max}^{Nujol} no OH bands, 1754 (ester C = O), 1600 (phenyl C = C), 1176 (S = O), 813 cm^{-1} (*p*-substituted phenyl)

Anal Calc for $C_{28}H_{34}O_{14}S_2$ C, 51 1, H, 5 2, S, 9 7 Found C, 50 8, H, 5 2, S, 9 6

*2,3.4,5-Dianhydro-*D*-iditol* (7) — Methanolic barium methoxide was prepared by the method of Weltzien and Singer[10], as this gives a more concentrated solution than the method of Isbell[11] To a solution of 3,4-di-*O*-*p*-tolylsulfonyl-D-mannitol (**4b**, 19 7 g, 0 04 mole) in 525 ml of absolute methanol was added 146 ml (0 08 mole) of 0 56M barium methoxide in methanol, causing immediate formation of a colorless precipitate The suspension (protected from carbon dioxide) was stirred magnetically for 2 h at 25°, and then carbon dioxide was passed in for 10 min Water (200 ml) was added, giving a colorless solution, and carbon dioxide was passed in until the solution was neutral (Alkacid test paper) The resulting suspension was gently heated until boiling and then cooled somewhat, decolorizing carbon (1 g) was added, and the suspension was boiled briefly, cooled, and filtered with suction The insoluble matter was washed with three 10-ml portions of water, and the filtrate and washings were combined, and evaporated to dryness under diminished pressure The resulting, colorless, crystalline mass was dried at 30°/0 05 torr, and extracted with three 250-ml portions of boiling 2-butanone under reflux The extracts were combined, and evaporated to dryness under diminished pressure, giving colorless crystals which were dried at 30°/0 05 torr over phosphorus pentaoxide, wt 5 8 g (99%) On recrystallization from ethanol–pentane (yield 5 3 g, 91%) or ethyl acetate (15 ml/g), it had m p 100–101°, $[\alpha]_D^{25}$ +82 1° (*c* 1 0, water), unchanged after 48 h at 25°, $[\alpha]_D^{25}$ +84 5° (*c* 1 0, abs methanol), ν_{max}^{Nujol} 3290 (OH), 3010, 1242, 886, 763 cm^{-1} (epoxide), n m r data (methyl sulfoxide-d_6, 60 MHz) τ 5 16 (2-proton triplet, $J_{OH,1} = J_{OH,1'} = J_{OH,6} = J_{OH\ 6}$ 5 4 Hz, two OH groups), τ 6 17–6 56 (4-proton complex multiplet, H-1, H-1′, H-6, H-6′), τ 6 95 (2-proton, complex multiplet, H-2 and H-5), τ 7 24 (2-proton, apparent singlet, H-3 and H-4) On addition of a trace of trifluoroacetic acid, the triplet at τ 5 16 and a water peak at τ 6 64 disappeared and were replaced by a sharp singlet at τ 5 77 (exchangeable OH), and the complex multiplet at τ 6 17–6 56 became a pair of quartets forming the AB part of an ABX subsystem composed of H-1, H-1′, and H-2, or H-6, H-6′, and H-5 The signal at τ 7 24 now appeared as a narrow, apparent triplet On addition of a further quantity of trifluoroacetic acid, the singlet at τ 5 77 moved downfield to τ 4 80, thus confirming its assignment as an OH resonance The AB quartets showed $J_{1,2} = J_{5\ 6}$ ~3 5 Hz, $J_{1\ 2} = J_{5\ 6}$ ~4 5 Hz, and $J_{1\ 1'} = J_{6\ 6'}$ 12 3 Hz

Anal Calc for $C_6H_{10}O_4$ C, 49 3, H, 6 9 Found C, 49 1, H, 7 1

*1 6-Di-O-acetyl-2,3 4,5-dianhydro-*D*-iditol* —To a solution of 0 292 g (2 mmoles) of **7** in 14 ml of dry pyridine at 0° was added 10 ml of acetic anhydride, with stirring and exclusion of moisture The mixture was stirred for 5 min, the ice bath was removed, and the solution was kept for 160 min and then poured, with stirring, onto chopped ice The mixture was extracted with chloroform, and the extract was processed in the usual way, dried (anhydrous sodium sulfate), and evaporated to dryness The resulting syrup crystallized from ethanol–pentane, yield of crystals, 0 440 g (96 6%) It was recrystallized from hot isopropyl alcohol, colorless crystals, m p 48–49 5°, $[\alpha]_D^{22}$ +87 0° (*c* 2 1, chloroform), ν_{max}^{Nujol} no OH bands, 1739 (ester C = O), 1258 (ester C–O), 1227 (ester C–O), 889 (epoxide), 763 cm^{-1} (epoxide), n m r data (CDCl$_3$, 60 MHz) τ 5 58 (2-proton quartet, $J_{1,2} = J_{5,6}$ ~3 3 Hz, $J_{1\ 1'} = J_{6\ 6}$ 12 5 Hz, H-1 and H-6), τ 6 02 (2-proton quartet, $J_{1'\ 2} = J_{5\ 6'}$ ~5 5 Hz, $J_{1\ 1'} = J_{6\ 6'}$ 12 5 Hz, H-1′ and H-6′), τ 6 79 (2-proton, complex multiplet, H-2 and H-5), τ 7 02 (2-proton, narrow triplet, H-3 and H-4), τ 7 92 (6-proton singlet, two acetyl methyls)

Anal Calc for $C_{10}H_{14}O_6$ C, 52 2; H, 6 1 Found C, 52 1, H, 6 2.

*2,3 4,5-Dianhydro-1,6-di-O-benzoyl-*D*-iditol* —To a solution of 0 73 g (5 mmoles) of 7 in 4 ml of dry pyridine, cooled in ice–salt, was added 1 5 ml of benzoyl chloride with stirring The crystalline mass was kept for 1 h at 10°, and then recooled in ice–salt, moist pyridine (5 ml containing 1 drop of water) was added, the suspension was stirred, and cooling was continued for 30 min Saturated, aqueous sodium hydrogen carbonate solution (2 ml) was added, with stirring, slight effervescence occurred, the crystals dissolved, and then new crystals formed The mixture was kept for 30 min at 0°, a further 2 ml of the hydrogen carbonate solution was added (giving more crystals), and the suspension was stirred and filtered The crystals were washed successively with water, sodium hydrogen carbonate solution, and water, and dissolved in chloroform The solution was washed successively with sodium hydrogen carbonate and water, dried (anhydrous sodium sulfate), and evaporated to dryness to give a mass of colorless crystals that was dried at 25°/0 3 torr, wt 1 77 g (100%) It was recrystallized from absolute ethanol (20 ml per g), m p 95–96°, $[\alpha]_D^{21}$ +63 8° (*c* 1 0, chloroform), ν_{max}^{Nujol} no OH bands, 1721 (benzoic ester), 1595 (C = C), 1311, 1282 (benzoic ester), 1245 (epoxide), 1176 (ester C–O), 1120 (benzoic ester C–O), 895, 886 (epoxide), 768 (epoxide), 707 cm^{-1} (phenyl), n m r data ($CDCl_3$, 60 MHz) τ 1 86–2 05 (4-proton, complex multiplet, aromatic *ortho*-protons), τ 2 40–2 74 (6-proton, complex multiplet, aromatic *meta*- and *para*-protons), τ 5 29 (2-proton quartet, $J_{1,2} = J_{5\ 6}$ ~3 3 Hz, $J_{1\ 1'} = J_{6\ 6'}$ 12 4 Hz, H-1 and H-6), τ 5 73 (2-proton quartet, $J_{1',2} = J_{5\ 6'}$ ~5 3 Hz, $J_{1,1} = J_{6,6}$ 12 3 Hz, H-1′ and H-6′), τ 6 62 (2-proton, complex multiplet, H-2 and H-5), τ 6 88 (2-proton, narrow triplet, H-3 and H-4)

Anal Calc for $C_{20}H_{18}O_6$ C, 67 79; H, 5 12 Found C, 67 73, H, 5 15

*1,2,3,4,5,6-Hexa-*O-*(methylsulfonyl)-*D-*mannitol* — A suspension of **1** (9.1 g, 0 05 mole) in 90 ml of dry pyridine was stirred for 5 min, and then cooled to −10° With stirring and cooling, 28 5 ml of methanesulfonyl chloride was rapidly added, and, after 30 min, the cooling bath was removed The mixture was stirred for 5 h at room temperature, recooled to −5°, and processed as for the preparation of **3a**, giving faintly pink crystals, wt 32 1 g (99%) It was recrystallized from *N,N*-dimethylformamide (5 ml per g) by treatment with decolorizing carbon, filtration, and addition of absolute methanol (20 ml per g), colorless crystals, m p 183–184° (softening at 178°, bath preheated to 168° and heated at 4°/min), $[\alpha]_D^{26}$ +32 9° (*c* 2 08, *N,N*-dimethylformamide), ν_{max}^{Nujol} no OH bands, 1361, 1351, 1337, 1182, 1167 (S = O), 901, 862 cm^{-1} (C–O–S)

Anal Calc for $C_{12}H_{26}O_{18}S_6$ C, 22 2, H, 4 0, S, 29 6 Found C, 22 0, H, 3 8, S, 29 3

*1,2,3,4,5,6-Hexa-*O-p-*tolylsulfonyl-*D-*mannitol* — A suspension of **1** (1 82 g, 0 01 mole) in 18 ml of dry pyridine was stirred, and cooled to −5° *p*-Toluenesulfonyl chloride (14 3 g) was added, and the mixture was stirred for 30 min The cooling bath was then removed, and the mixture was kept for 2 days at room temperature, recooled to −5°, and treated with water as for the preparation of **3b** The resulting mixture was extracted with chloroform, and the extract was washed successively with aqueous potassium hydrogen sulfate solution, water, aqueous sodium hydrogen carbonate solution, and water, it was then dried (anhydrous sodium sulfate) and evaporated under diminished pressure to a syrup The syrup was dissolved in acetone, the solution was treated with decolorizing carbon, the mixture was filtered, and the filtrate was evaporated to dryness The product was crystallized from acetone (1 ml per g) by addition of absolute ethanol (5 ml per g) to give crop 1, 7 23 g, m p 124–126°; crop 2, 0 1 g, m p 120–126°, total yield 7 33 g (66%) Recrystallized from acetone–absolute ethanol, the product had m p 127–128°, $[\alpha]_D^{27}$ +29 3° (*c* 2 0, acetone), ν_{max}^{Nujol} no OH bands, 1592 and 1488 (phenyl C = C), 1348 (S = O), 1206 and 1119 (*p*-substituted phenyl), 1190 and 1172 (S = O), 870 (C–O–S), and 815 cm^{-1} (*p*-substituted phenyl)

Anal Calc for $C_{48}H_{50}O_{18}S_6$ C, 52 06; H, 4 6, S, 17 4 Found C, 52 02, H, 4 5, S, 17 4

After other reaction times, the yields of crude, crystalline product were 1 day, 39%, 5 days, 68%

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