Anhydro Sugar Formation in Acid and Base Hydrolyses of 3,4-Di-*O*-methylsulfonyl-D-mannitol: a Rapid Route to 1,4:3,6-Dianhydro-D-iditol (D-Isoidide)[1]

DAVID ROY HICKS AND BERT FRASER-REID

Chemistry Department, University of Waterloo, Waterloo, Ontario N2L 3G1

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Brief acid hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-methylsulfonyl-D-mannitol (**1***a*), removes the isopropylidene groups giving the disulfonated hexitol, **2***a*. Upon continued acid hydrolysis of **2***a*, one sulfonate group is lost with formation of a sulfonated monoanhydro hexitol, **5***a*, then the second ester group is lost to give 1,4:3,6-dianhydro-D-iditol (D-isoidide, **3***a*). If the disulfonate, **2***a*, is treated with base, an isomeric dianhydro hexitol, the bisoxirane **4**, is formed. Under similar basic conditions, the monoanhydro hexitol, **5***a*, is stable. On acid hydrolysis, the bisoxirane, **4**, gives hexitols and only 20% of D-isoidide, which indicates that **4** cannot be an intermediate in the conversion of **2***a* to **3***a*. These results indicate that, in **2***a* at least, five-membered anhydro rings are formed preferentially in acid hydrolyses and three-membered rings in saponification.

The stage and course of hydrolysis of **2***a* are readily monitored by observing the τ 4–6 region in the n.m.r. spectra of D_2O samples of the hydrolysate.

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Une hydrolyse acide brève du di-*O*-isopropylidène-1,2:5,6 di-*O*-méthylsulfonyl-3,4 D-mannitol (**1***a*) enlève les groupes isopropylidènes et fournit l'hexitol disulfoné **2***a*. Si l'hydrolyse acide de **2***a* est continuée, un groupe sulfonate est perdu avec formation du monoanhydro hexitol sulfoné **5***a*; un deuxième groupe ester est ensuite perdu pour donner le dianhydro-1,4:3,6 D-iditol (D-isoidide, **3***a*). Si l'on traite le disulfonate **2***a* avec une base, un dianhydro hexitol isomère, le bisoxiranne **4**, se forme. Dans de telles conditions basiques, le monoanhydro hexitol **5***a* est stable. L'hydrolyse acide du bis oxiranne **4** donne des hexitols et seulement 20% de D-isoidide; ce résultat indique que **4** n'est pas un intermédiaire dans la transformation de **2***a* en **3***a*. Ces résultats indiquent que dans **2***a* au moins, les cycles anhydro à cinq membres se forment d'une façon préférentielle par hydrolyse acide et que les cycles à trois membres sont formés par saponification.

L'évolution de l'hydrolyse de **2***a* peut être facilement suivie grâce à la r.m.n.; les observations sont faites dans la région de 4 à 6 τ sur des échantillons de l'hydrolysat en solution dans de l'eau lourde. [Traduit par le journal]

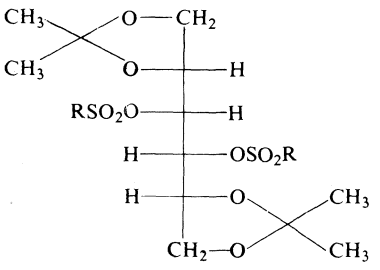
An indication of the importance of anhydro sugars is provided by the fact that a recent review volume contained three articles dealing directly with their chemistry (2–4). As a sub-group of anhydro sugars, the alditol anhydrides are prominent, not only because of what their formation reveals about intramolecular interactions and rearrangements (5, 6) but also because of their increasing industrial biological importance (4, 7). The dianhydrohexitols, for example, have a range of clinical employment that includes coronary care,[2] regulation of glaucoma (8) and cerebro-spinal fluid pressures (9), and emulsifiers for injectable medications (10). In view of these broad interests, we wish to report herein studies that have led to ready syntheses of some anhydro iditols and which clarify some anomalies in the literature relating to the hydrolysis of certain sulfonated hexitols.

Some years ago we required the disulfonated hexitol **2***a* and attempted to obtain this from **1***a* by acid hydrolysis in keeping with a procedure described by Wiggins for the hydrolysis of **1***b* (11). His proof of structure for what he assumed was **2***b*, included treatment of his product with base whereupon a dianhydrohexitol **3***a* was obtained.

While our work was underway. Tipson and Cohen reported a detailed study (12) in which they followed the course of the hydrolysis by polarimetry which allowed them to isolate **2***a* and *b* in quantitative yields. They showed that

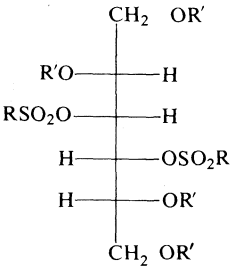
[1]For a preliminary account of this work, see ref. 1.

[2]For an impressive bibliography, see ref. 113 in our ref. 4.



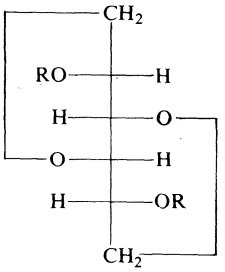
1

a R = CH_3
b R = $C_6H_4CH_3$



2

a R′ = H; R = CH_3
b R′ = H; R = $C_6H_4CH_3$
c R′ = Ac; R = CH_3
d R′ = Ac; R = $C_6H_4CH_3$



3

a R = H
b R = Ac
c R = $PhCO_2$
d R = Ms
e R = Ts

under Wiggins' conditions a considerable amount of sulfonic acid was liberated and, more seriously, that treatment of the disulfonate **2***a* or *b* with base produced not **3***a* but the isomeric dianhydride **4**.

We report herein our own observations which remove the apparent conflict in the results from both laboratories.

In an attempt to generate **2***a*, we treated the dimesylate **1***a* with ion exchange resin (H^+) and boiling water for 3 h and acetylated the product directly. However, the crystalline acetate contained no methanesulfonyl groups, judging from the absence of appropriate n.m.r. resonances $\tau \sim 6.8$. The possibility that the sulfonate groups had been lost during the acetylation step was excluded by showing (t.l.c.) that the hydrolysis product was regenerated upon saponification of the acetylated product. Direct comparison of derivatives of the hydrolysis product with those of the authentic L-enantiomer (see Experimental) established that 1,4:3,6 dianhydro-D-iditol (D-isoidide, **3***a*) had been produced.

Upon more cautious hydrolysis, it was found that if the suspension of **1***a* and resin in water was heated until dissolution just occurred, the desired dimesylate **2***a* could be obtained contaminated with ~10% of the monoanhydro product **5***a*. If the hydrolysis was permitted to go for 10 min beyond dissolution, compound **5***a* was the principal product. Continuation of the hydrolysis for 30 min gave D-isoidide, **3***a*, which underwent no further changes even after 4 h exposure to the reaction medium.

The structure of **2***a* was at first authenticated by treating the crude hydrolysis product with acetone and zinc chloride, whereupon the starting material (**1***a*) was regenerated in 79% yield. Subsequently, an authentic sample of the tetraacetate **2***c*[3] prepared by the method of Tipson and Cohen (12) was found to be identical to the corresponding material obtained from our preparation.

The gross structure of compound **5***a* was indicated by conversion to a crystalline triacetate **5***b* which gave correct elemental analysis. The 100 MHz spectrum of the latter (**5***b*) ($CDCl_3$; TMS) showed a multiplet for H-2 and H-5 at τ 4.4–4.8. The signal for H-3 was a prominent triplet at τ 4.98, $J_{23} = J_{34} = 6.0$ Hz. The triol **5***a* could be regenerated quantitatively from the triacetate (**5***b*) by hydrolysis with methanol–water–triethylamine. The location of the methylsulfonyl group at carbon-3 is based on the assumption that acid-catalyzed migration of the sulfonyl group is highly unlikely. The latter also suggests the D-talitol configuration for **5** and this conclusion is supported by the fact that acid hydrolysis of **5***a* affords 1,4:3,6-dianhydro-D-iditol (**3***a*), the displacement being assumed to occur with the usual inversion.

[3]We are grateful to Dr. Tipson for a specimen of **2***c* (12).

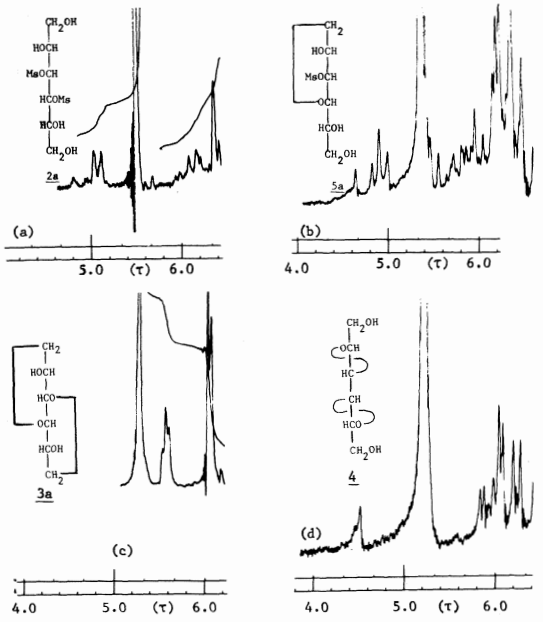


FIG. 1. Nuclear magnetic resonance spectra in D_2O (Me_2CO or TSP as internal standard): *a*, 3,4-di-*O*-methylsulfonyl-D-mannitol (**2***a*); *b*, 1,4-anhydro-3-*O*-methylsulfonyl-D-talitol (**5***a*); *c*, 1,4:3,6-dianhydro-D-iditol (D-isoidide) (**3***a*); *d*, 2,3:4,5-dianhydro-D-iditol (**4**).

The successive stages of hydrolysis of **1***a*, are conveniently determined by observing the low-field region of 60 MHz spectra of the hydrolysate in deuterium oxide (Fig. 1). Thus H-3 (≡H-4) of **2***a* appears as a doublet[4] with a spacing of 6.0 Hz at τ 5.03 (Fig. 1*a*). In compound **5***a* (Fig. 1*b*), H-3 is a triplet at τ 4.87, with a spacing of 6.0 Hz. In D-isoidide (**3***a*; Fig. 1*c*), there are no signals to low field of DOH and a triplet for H-2 (≡H-5) with a spacing of ~2 Hz is seen at τ 5.85. The singlet for H-3 (≡H4) is masked by the DOH peak.[4]

In addition to the data outlined in the preceding paragraph, the relative amounts of **2***a*, **3***a*, and **5***a* present at any stage can be readily determined by acetylating the crude mixture and studying its n.m.r. spectrum. This is particularly advantageous since the H-3 signals for **2***a* and **5***a* overlap (see Fig. 1*a* and *b*). In **2***c*, the methylsulfonyl groups are isochronous, occurring at τ 6.80, whereas in **5***b* the corresponding signal occurs at τ 6.83. With **3***b* the signal for H-3 (≡H-4) is a sharp spike at τ 5.54 (13*a*) in which region the other two compounds **2***b* and **5***b* give no signals.

We established that hydrolysis of the ditosylate **1***b* followed a course similar to that of the dimesylate **1***a* giving D-isoidide (**3***a*) when ion exchange resin was used as the acid catalyst. However, when the hydrolyses were done using aqueous acetic acid as described by Wiggins (11), the product, analyzed by t.l.c., showed only a small amount of D-isoidide (**3***a*) and no evidence of **2***b*. However it seemed clear that any D-isoidide he did obtain had been formed during the acid hydrolysis step and not during the saponification step as he had assumed.

The formation of the bisoxirane **4** from **2***a* as reported by Tipson and Cohen (12) was verified. Indeed the conversion of **2***a* to **4** could be accomplished more conveniently by allowing a solution of **2***a* in methanol–water–triethylamine to stand at room temperature for 30 min. The low-field portion of the n.m.r. spectrum of **4** in D_2O is shown in Fig. 1*d*. This portion of the spectra in Fig. 1, taken in conjunction with the absence of methylsulfonyl signals, allows **3***a* to be readily differentiated from **4**.

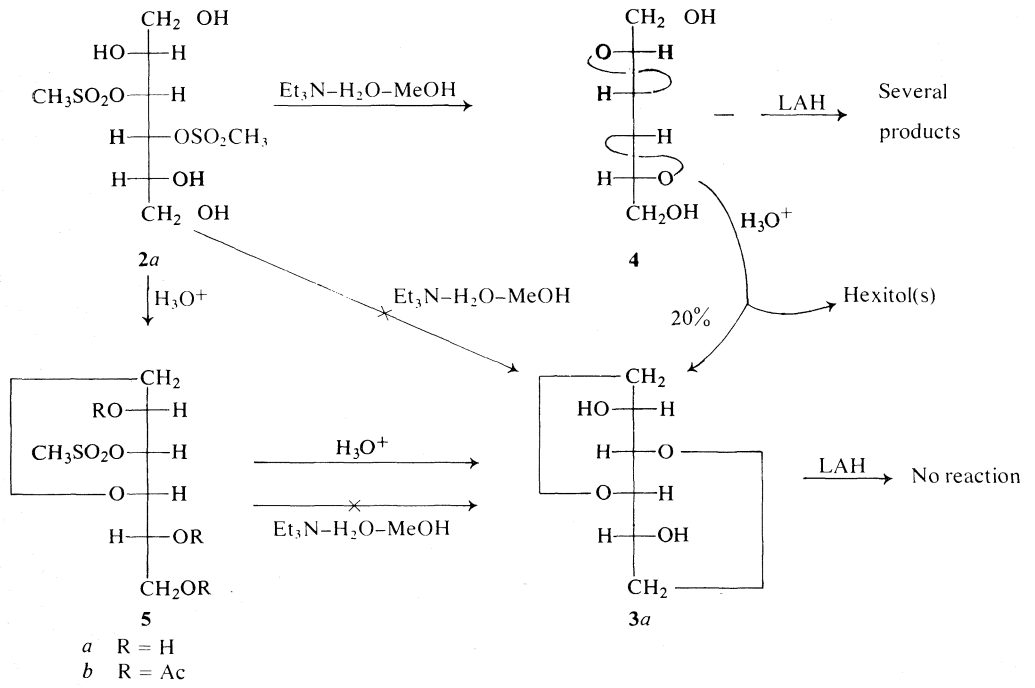
As a first step in clarifying the discrepancy in the results of Wiggins (11) and Tipson and Cohen (12), we established that the bisoxirane **4** was not an intermediate in the acid-catalyzed transformation of **2***a* to **3***a*. Thus treatment of **4** with the ion exchange resin (H^+) gave only ~20% of D-isoidide (**3***a*) as determined by n.m.r. spectroscopy. Furthermore, paper chromatography of the product revealed material with the same R_f as D-mannitol,[5] as well as other substances.

Scheme 1 summarizes some other observations on these materials. As was expected, D-isoidide, (**3***a*), was stable to lithium aluminum hydride but the bisoxirane **4** was cleaved giving several products. The monoanhydro compound **5***a*, which furnishes D-isoidide (**3***a*) on heating with acid, is stable to the methanol–water–triethylamine medium used for the conversion of **2***a* to **4** (*vide infra*).

The size of the anhydro rings formed during hydrolyses of sulfonate esters is influenced by a number of factors such as steric interactions, conformational changes, etc. However, in alkaline media three- and five-membered rings appear

[4]For detailed discussion of the p.m.r. spectra of dianhydro hexitols, see ref. 13*a*.

[5]Hydrolysis of **4** could conceivably give hexitols other than D-mannitol but this possibility was not examined.



SCHEME 1

to be favored, the smaller ring being formed more readily (2–4, 6). This conclusion is upheld in the present study (Scheme 1) since base hydrolysis of **2***a* gave **4** but no **3***a*. Again, the stability of the monoanhydro compound **5***a* to base is revealing. Thus, while formation of a 2,3-oxirane from **5***a* is impossible since the 2-hydroxy and sulfonyloxy groups are in *cis* relationship, there are no steric barriers to the formation of **3***a*.

In contrast to the foregoing, anhydro rings formed in acidic media are invariably five-membered even when six- and/or three-membered rings are plausible alternatives (14). This situation is quite contrary to the preferences normally displayed in carbocyclic systems where three-membered rings are most readily formed (15). In this connection it is worthwhile to repeat that the possibility of **4** having been formed first in the acid hydrolysis of **2***a* and subsequently being converted to **3***a* has been excluded (*vide supra*).

Experimental

Melting points were determined on a Fischer-Johns heating stage and are uncorrected. Nuclear magnetic resonance spectra were determined using a Varian T-60 or Varian HA-100 spectrometer, solvents being D_2O (with acetone or sodium trimethylsilyl-2,2,3,3-tetradeuteriopropionate (TSP) as internal standards) or $CDCl_3$ (TMS).

*3,4-Di-O-methylsulfonyl-*D*-mannitol (**2***a*) and its Tetraacetate (**2***c*)*

(*a*) Compounds **2***a* and *c* were prepared in excellent yield, following the conditions of Tipson and Cohen (12).

(*b*) Distilled water (13 ml) was added to a mixture of 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-methylsulfonyl-D-mannitol (**1***a*) (16) (1.0 g; 0.024 mol) and Dowex 50W-X2 (H^+ form) resin (2 g), contained in a 100-ml conical flask equipped with a reflux condenser and standing on an efficient magnetic stirrer hot plate. Vigorous stirring was begun and the heat was turned up to a maximum. When compound **1***a* had just dissolved, the flask was removed, cooled in an ice-water bath, and then filtered, the resin being washed with water. The filtrate was neutralized with barium carbonate and the mixture filtered once more. The filtrate was evaporated under reduced pressure and the residue, which invariably contained barium salts, was extracted with hot ethanol. The hot ethanol was filtered and evaporation of the filtrate gave syrupy material (0.78 g) whose 60 MHz n.m.r. spectrum in D_2O (acetone as internal standard) showed a doublet at τ 5.03 for H-3 ($\equiv$ H-4), J_{23} ($\equiv J_{45}$) = 6.0 Hz (see Fig. 1*a*), and a singlet at τ 6.83 for CH_3SO_3—.

The material was authenticated as being **2***a* by treating the syrupy product with anhydrous zinc chloride (0.7 g) and reagent grade acetone (5 ml), which had been dried over and distilled from anhydrous potassium carbonate, for 2 h at room temperature. The solution was poured into water (10 ml) containing dissolved potassium carbonate (1 g) and the organic substance recovered by extraction into methylene chloride. The extract was dried with sodium sulfate and evaporated to dryness dissolved in ethanol, whereupon a crystalline substance identical to the starting material (**1***a*) was obtained (0.79 g, 79% yield).

In another experiment, the syrupy preparation of **2***a* remaining after evaporation of the ethanol was acetylated for 7 h with acetic anhydride (5 ml) and pyridine (5 ml). Conventional work-up afforded a residue whose n.m.r. spectrum in $CDCl_3$ (TMS) showed two spikes for CH_3SO_3— at τ 6.80 and 6.83. By comparison with the pertinent signal in authentic **2***c* prepared by the method of Tipson and Cohen (12), the τ 6.80 signal was ascribed to **2***c*. The τ 6.83 signal arose from the monoanhydro compound **5***b*. The latter was present in 5–10% in all our preparations of compound **2** and undoubtedly inhibited crystallization of **2***a*. Chromatographic separation could not be achieved; however, fractional crystallization could be induced if the acetylated mixture containing **2***c* and **5***b* was seeded with crystalline **2***c* (12). In this way crystalline **2***c* (0.88 g; 70% from **1***a*), m.p. 80–83° (lit. (12) 81–83°) was obtained.

Nuclear magnetic resonance (100 MHz) of **2***c* ($CDCl_3$; TMS): τ 4.78 (s, 4, H-2,3,4,5); τ 5.40–584 (m, 4, H-1,1′, 6,6′), τ 6.80 (s, 6, CH_3SO_3); τ 7.88 (s, 6, CH_3CO_2), τ 7.94 (s, 6, CH_3CO_2).

*1,4-Anhydro-3-O-methylsulfonyl-*D*-talitol (5a) and its Triacetate (5b).*

The suspension of the diisopropylidene dimesylate (**1***a*) in water, was treated as described above for preparation of **2***a*. However, heating under reflux was continued for 10 min beyond dissolution before removing the flask and subjecting the contents to work-up as described for **2***a*. The n.m.r. spectrum of the product in D_2O (acetone as internal standard), Fig. 1*b*, showed a prominent triplet with a spacing of 5.0 Hz at τ 4.87, which was ascribed to H-3. In some preparations, small amounts (~5%) of D-isoidide (**3***a*), could be detected in the n.m.r. spectrum of the crude material by the presence of a characteristic triplet at τ 5.85.

The crude syrup was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) for 7 h, and the acetylated material was recovered following customary work-up.

The residue crystallized from methanol, 0.72 g (82% from **1***a*), m.p. 103–104°; $[\alpha]_D^{23}$ +9.52° (*c*, 3.19 in $CHCl_3$).

Anal. Calcd. for $C_{13}H_{20}O_{10}S$: C, 42.38; H, 5.47; S, 8.70. Found: C, 42.58; H, 5.48; S, 8.74.

*1,4:3,6-Dianhydro-*D*-iditol (*D*-Isoidide, 3a)*

(*a*) The acid-catalyzed hydrolysis of compound **1***a* as described above, was allowed to continue for *at least* 30 min beyond dissolution, this being the minimum time for complete reaction. However, prolonged reflux for periods up to 4 h could be safely maintained, without affecting the yield or quality of product. The resin was removed by filtration and the organic material **3***a* was recovered as described above for **2***a*.

(*b*) The dimesylate, **1***a*, (5.0 g; 0.012 mol) or the ditosylate, **1***b*, (7.0 g; 0.012 mol) was dissolved in dioxan (40 ml), water (20 ml), and sulfuric acid (2.5 ml). The solution was refluxed for 3 h, cooled, neutralized with solid sodium bicarbonate, and evaporated. The organic material recovered, as in part *a*, was a syrup, (~2.3 g).

The syrups from either parts *a* or *b* failed to crystallize even though they were chromatographically pure (t.l.c. in ethyl acetate) with R_f 0.2 and gave almost quantitative yields of crystalline diacetate, dibenzoate, and dimesylate which were characterized as described below.

*2,5-Di-O-acetyl-1,4:3,6-dianhydro-*D*-iditol (3b)*

A sample of the syrupy 1,4:3,6-dianhydro-D-iditol (**3***a*) prepared as described in part *a* above from 6.0 g of dimesylate **1***a* was acetylated at room temperature with acetic anhydride (15 ml) and pyridine (15 ml) for 7 h. The mixture was cooled in ice and the excess acetic anhydride destroyed by adding 25 ml of methanol. Evaporation gave a syrup which was freed from pyridine by azeotropic distillation with toluene and was then set to crystallize from chloroform – petroleum ether (35–60°). The first (2.70 g; m.p. 49–52°) and second (0.32 g) crops of crystals amounted to 92% yield.

The material after two recrystallizations from methanol had the physical constants m.p. 55–56°; $[\alpha]_D^{23}$ −89.0° (*c*, 4.2 in $CHCl_3$). The corresponding values for an authentic sample of the enantiomer, 2,5-di-*O*-acetyl-1,4:3,6 dianhydro-L-iditol,[6] were 55–56°, mixture m.p. 59–66°, and +89.6°.

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.03; H, 6.15.

*2,6-Di-O-benzoyl-1,4:3,6-dianhydro-*D*-iditol (3c)*

The syrupy dianhydro derivative (**3***a*) prepared from the dimesylate, **1***a* (7.0 g; 0.017 mol) as described above in *a* was dissolved in pyridine (30 ml). To the ice-cold solution was added benzoyl chloride (9.0 ml; 0.076 mol) and the solution was allowed to warm up to, and stand at room temperature overnight. The mixture was poured into ice and water and the resulting oil was extracted with methylene chloride. After washing with 4 *N* sulfuric acid and saturated sodium bicarbonate the methylene chloride layer was dried and then evaporated. The syrup crystallized from ether – petroleum ether (5.2 g; 89%), m.p. 97–103°. The material after recrystallization from chloroform – petroleum ether, gave the following data: m.p. 110–111.5° $[\alpha]_D^{23}$ −132.0° (*c*, 2.17 in $CHCl_3$). The corresponding literature (13*c*) values for the L-enantiomer are 110–111° and +134.3°. Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.78; H, 5.12. Found: C, 67.09; H, 5.16.

*1,4:3,6-Dianhydro-2,5-di-O-methylsulfonyl and -di-O-p-tolylsulfonyl-*D*-iditol 3d and 3e, Respectively*

Samples of the syrupy dianhydro iditol, **3***a*, prepared as in *a* above, were mesylated and tosylated in a manner similar to that described for benzoylation above. The crystalline products had the following physical constants.

3*d*: m.p. 159–160°; $[\alpha]_D^{23}$ −31.60° (*c*, 1.77 in $(CH_3)_2CO$); corresponding values for authentic L-enantiomer,[6] m.p. 160–161° mixture m.p. 144–145°; $[\alpha]_D^{23}$ +31.65°.

3*e*: m.p. 105–106°; $[\alpha]_D^{23}$ −31.1° (*c*, 2.66 in $CHCl_3$); corresponding literature values for L-enantiomer 105.5–106°; +33.2° (13*b*).

*2,3:4,5-Dianhydro-*D*-iditol, 4*

(*a*) The diisopropylidene-dimesylate **1***a* (1.0 g), was deacetonated as described above to give syrupy **2***a* which was dissolved in 30 cc dry methanol. Barium methoxide (0.0048 mol) in 10 cc methanolic solution was added, and after 2 h the reaction mixture was processed as described by Tipson and Cohen (12) with the exception that the product was freed from inorganic salts by extraction into isopropyl alcohol and filtration. The

[6]We are grateful to Dr. G. H. S. Thomas for the authentic sample (13*a*).

filtrate was concentrated whereupon crystals of the desired material (**4**) formed spontaneously, 0.27 g (78%), m.p. 100–101°; $[\alpha]_D^{23}$ +78.1° (*c*, 1.04 in water) (lit. (12) m.p. 100–101°; $[\alpha]_D^{25}$ +82.1°).

(*b*) Syrupy **2***a* (0.5 g) was dissolved in 20 ml of methanol–water–triethylamine (5:4:1) mixture and allowed to stand for 30 min after which the solution was evaporated to dryness. It was redissolved in water (30 ml), and stirred with barium carbonate to remove the sulfonic acid. The solids were removed by filtration, the filtrate evaporated to dryness and extracted with isopropyl alcohol. Crystalline material (0.153 g) identical to that in part *a*, was obtained.

The low field n.m.r. spectrum of **4** is shown in Fig. 1*d* for comparison with the other materials in this series.

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1. B. Fraser-Reid and D. R. Hicks. J. Chem. Soc. Chem. Commun. 19 (1972).
2. N. R. Williams. Adv. Carbohydr. Chem. Biochem. **25**, 109 (1970).
3. J. Defaye. Adv. Carbohydr. Chem. Biochem. **25**, 181 (1970).
4. S. Soltzberg. Adv. Carbohydr. Chem. Biochem. **25**, 229 (1970).
5. F. H. Newth. Quart. Rev. (London), **13**, 30 (1959); A. C. Cope and T. Y. Shen. J. Am. Chem. Soc. **78**, 5912 (1956); J. A. Mills. Adv. Carbohydr. Chem. **10**, 1 (1955).
6. D. H. Ball and F. W. Parrish. Adv. Carbohydr. Chem. **23**, 233 (1968); **24**, 139 (1969).
7. L. F. Wiggins. Adv. Carbohydr. Chem. **5**, 191 (1950).
8. B. Becker, A. E. Kolker, and T. Krupin. Arch. Opthalmol. **78**, 147 (1967).
9. B. L. Wise, J. L. Mathis, and J. H. Wright. J. Neurosurg. **25**, 183 (1966).
10. A. F. Woodhour and T. B. Stim. Chem. Abs. **61**, 13136 (1964).
11. L. F. Wiggins. J. Chem. Soc. 1403 (1947).
12. R. S. Tipson and A. Cohen. Carbohydr. Res. **7**, 232 (1968).
13. (*a*) F. J. Hopton and G. H. S. Thomas. Can. J. Chem. **47**, 2395 (1969). (*b*) A. C. Cope and T. Y. Shen. J. Am. Chem. Soc. **78**, 3177 (1956); H. G. Fletcher, Jr. and R. M. Geopp, Jr. J. Am. Chem. Soc. **68**, 939 (1946).
14. J. Defaye and J. Hildesheim. Tetrahedron Lett. 313 (1968).
15. H. O. House. Modern synthetic reactions. 2nd ed. W. A. Benjamin Inc., Menlo Park. 1972. p. 542.
16. P. Bladon and L. Owen. J. Chem. Soc. 598 (1950).