577. *Cyclitols. Part XII.*[1] *The Formation of Isopropylidene Derivatives by Ketal Interchange.*

By S. J. Angyal and R. M. Hoskinson.

2,2-Diethoxypropane, in the presence of toluene-*p*-sulphonic acid, converts inositols into isopropylidene derivatives. All pairs of 1,2-*cis*-hydroxyl groups react (except for the third pair in cisinositol), and even *trans*-pairs react to a considerable extent, particularly when their reaction is preceded by the formation of a *cis*-ketal. The structures of the resulting ketals have been determined.

In Part I of this Series [2] the preparation of isopropylidene derivatives of cyclitols was described. These derivatives proved very useful in subsequent work but the most important one, 1,2-*O*-isopropylidenemyoinositol, is produced by a laborious method in poor yield. When the compound is synthesised from myoinositol and acetone, the equilibrium is unfavourable for its formation and it is imperative to remove the water formed in the reaction. As azeotropic procedures and the use of various dehydrating agents brought no improvement, we turned to ketal interchange, that is, the reaction with a ketal of acetone in the presence of an acid; in this reaction no water is produced.

Fenton, Salcedo, and Franz have described [3] the preparation of isopropylidene derivatives from *cis*- and *trans*-cyclohexane-1,2-diol by this method but they gave no experimental details. Ketal interchange has been used by other workers [4] recently, particularly since 2,2-dimethoxypropane has become commercially available. We used, 2,2-diethoxypropane (acetone diethyl ketal) at 100° in the presence of toluene-*p*-sulphonic acid. The efficacy of this method is shown by the results obtained with (−)-inositol; whereas the usual method [2] (acetone and zinc chloride) produces a mixture of di- and tri-isopropylidene derivatives in 5 hours, only 2 hours' heating with diethoxypropane was required to afford an excellent yield of the tri-isopropylidene derivative.

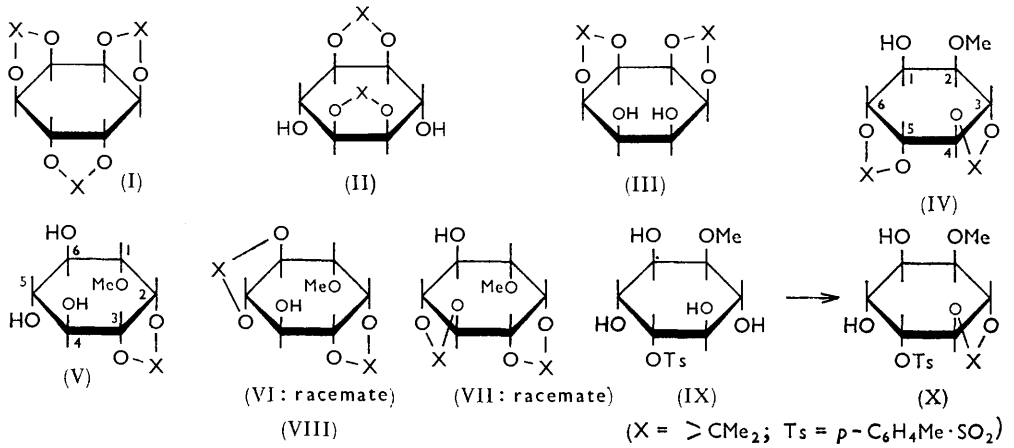
Unfortunately, myoinositol does not react under the same conditions, probably owing to its extreme insolubility in the reagent. Diethoxypropane is decomposed by acids (see below) and the reaction cannot therefore be prolonged beyond 1—2 hours. The new methods, however, produced some interesting derivatives from other cyclitols.

Alloinositol, with three pairs of *cis*-hydroxyl groups, gave a tri-isopropylidene derivative (I), as expected. The structure of this compound was not proved but any other than the 1,2:3,4:5,6-arrangement for the ketal appears unlikely. From mucoinositol a diketal was obtained; the presence of two pairs of *cis*-hydroxyl groups suggests the 1,2:4,5-structure (II) which was confirmed by the observation that the compound was not oxidised by lead tetra-acetate. Lower ketals were not isolated in these cases.

On the other hand, cisinositol gave a diketal which consumed one equivalent of lead tetra-acetate and therefore has the 1,2:3,4-di-isopropylidene structure (III); possibly a triketal, which we failed to isolate, was also formed. It is clear that the molecule resists the introduction of a third ketal group, either owing to overcrowding, or because the distortion caused by two adjacent ketal rings increases the puckering of that part of the cyclohexane ring to which the free hydroxyl groups are attached and therefore makes the *cis*-attachment of a further ring more difficult. Evidence is adduced in the following paper that 1,2:3,4-di-*O*-isopropylidenecisinositol exists, in dilute solution in carbon tetrachloride, in the skew conformation. The dihedral angle between the two free hydroxyl groups [5] is then 70·7° (compared with 60° in an undistorted chair) which is unfavourable

[1] Part XI, Angyal and Bender, *J.*, 1961, 4718.
[2] Angyal and Macdonald, *J.*, 1952, 686.
[3] Fenton, Salcedo, and Franz, Abs. 130th Meeting Amer. Chem. Soc., 1956, p. 7-O.
[4] Lorette and Howard, *J. Org. Chem.*, 1960, **25**, 521; Howard and Lorette, *ibid.*, p. 525.
[5] Bottomley and Jefferies, *Austral. J. Chem.*, 1961, **14**, 657.

to *cis*-ketal formation. It is interesting to note the absence of the 1,2:4,5-diketal of cisinositol. The distortion of the six-membered ring on *cis*-fusion with a five-membered ring is such that it favours the introduction of an adjacent five-ring (incipient skew formation) rather than a five-ring on the opposite side (incipient boat formation). Similarly, epi-inositol yields mainly the 1,2:3,4-di-isopropylidene derivative in preference to the 1,2:4,5-compound.[2]



On treatment with acetone and zinc chloride,[2,6] quebrachitol [2-*O*-methyl-(—)-inositol *] forms a monoketal involving the two *cis*-hydroxyl groups, at positions 5 and 6, in no more than 40% yield. Interchange with 2,2-diethoxypropane gave the same derivative in somewhat better yield, and from the mother-liquors a diketal was isolated. Since it was degraded by partial hydrolysis to the 5,6-isopropylidene compound, the diketal must be formulated as 3,4:5,6-di-*O*-isopropylidene-2-*O*-methyl-(—)-inositol (IV). Once in possession of crystals of the diketal, we have shown that the reaction with acetone and zinc chloride also produces small amounts (2%) of the same diketal.

Bien and Ginsburg [7] converted (—)-bornesitol [(1*S*)-1-*O*-methylmyoinositol] into its 2,3-*O*-isopropylidene derivative (V) and also isolated, in small yield, a diketal which may be the 2,3:4,5- or the 2,3:5,6-compound, but its structure was not determined. It appeared that ketal interchange might well produce enough material for a re-investigation; however, since (—)-bornesitol was initially unavailable to us, we used its racemate.[8] Treatment with 2,2-diethoxypropane gave *two* di-isopropylidene derivatives, m. p. 122° and 177°. The former, which was the major product, was methylated, and the isopropylidene groups were removed: 1,4-di-*O*-methylmyoinositol [1] was obtained, identical with the product of methylation of 1,2:4,5-di-*O*-cyclohexylidenemyoinositol.[9] The lower-melting diketal is therefore 2,3:5,6-di-*O*-isopropylidene-1-*O*-methylmyoinositol (VI). It follows that the other diketal is the 2,3:4,5-di-isopropylidene derivative (VII); its methylation, and hydrolysis of the ketal portions, gave the previously unknown 1,6-di-*O*-methylmyoinositol.

These experiments were then repeated with (—)-bornesitol, kindly given to us by Professor Ginsburg. Again, two diketals were obtained; the major product, m. p. 134—136°, apparently identical with the compound described by Bien and Ginsburg,[7] had an infrared spectrum, in chloroform solution, superimposable on that of the racemic compound, m. p. 122°. It is therefore the 2,3:5,6-diketal (VIII). By methylation and

* The (+)- and (—)-symbols, placed *immediately* before " inositol," denote the configurational series and not necessarily the sign of rotation of the complete compound (see *J.*, 1958, 375, footnote).

[6] Posternak, *Helv. Chim. Acta*, 1952, **35**, 50.
[7] Bien and Ginsburg, *J.*, 1958, 3189.
[8] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[9] Angyal, Tate, and Gero, *J.*, 1961, 4116.

hydrolysis it gave [1] natural liriodendritol. The other diketal, m. p. 210°, was obtained in an amount insufficient for further investigation.

In Part I of this Series [2] it was concluded that, on treatment of a cyclitol with zinc chloride and acetone, normally only *cis*-hydroyl groups react; ketal formation across *trans*-hydroxyl groups occurs only with cyclitol derivatives which already contain two *cis*-ketal groups. The derivatives of quebrachitol and bornesitol described above contain a *trans*-ketal and only one *cis*-ketal: ketal interchange promotes a more favourable equilibrium in the direction of cyclic ketals than does the reaction with acetone. A similar conclusion was reached [9] in regard to the formation of cyclohexylidene ketals, a reaction in which water is removed azeotropically.

It was of interest to find out whether a cyclitol without adjacent *cis*-hydroxyl groups could be forced to give a ketal. A suitable derivative, soluble in diethoxypropane, was available in 5-*O*-tosylquebrachitol [2-*O*-methyl-5-*O*-tosyl-(−)-inositol] (IX), which had been prepared [10] by Miss M. Pitman in this laboratory from 5,6-*O*-isopropylidenequebrachitol by the following steps: acetylation, hydrolysis to 1,3,4-tri-*O*-acetylquebrachitol, toluenesulphonylation, and deacetylation. In the toluenesulphonylation, the equatorial 5-hydroxyl group reacts in preference to the 6-axial one, as shown by solvolysis [10] of the tosyl compound which gave 1-*O*-methylmucoinositol.

5-*O*-Tosylquebrachitol (IX) reacted with 2,2-diethoxypropane and gave a monoketal in small yield. There are two pairs of contiguous hydroxyl groups in 5-tosylquebrachitol, both *trans*; the 1- and the 6-hydroxyl group are both axial, and those at positions 3 and 4 both equatorial. Only the latter would be expected to form a ketal, leaving the axial hydroxyl groups free. Oxidation by lead tetra-acetate was used to prove this structure. Diaxial glycols are oxidised very slowly by this reagent in acetic acid,[11] but Goldschmid and Perlin have recently shown [12] that in pyridine they react at a reasonable rate whereas glycols with more favourable steric arrangements react very rapidly. The isopropylidene derivative of 5-*O*-tosylquebrachitol reacts slowly with the reagent, indicating the axial nature of the hydroxyl groups, and it is therefore assigned the 3,4-*O*-isopropylidene-2-*O*-methyl-5-*O*-tosyl-(−)-inositol (X) structure.

2,2-Diethoxypropane, like other similar ketals, readily dissociates [13] into ethyl isopropenyl ether and ethanol when heated with acids. This is the reason why the ketal interchange mixture boils on the steam-bath, although 2,2-diethoxypropane has b. p. 115°. It was found, however, that at the end of the reaction the volatile products consist mostly of ethanol and some 2,2-diethoxypropane. The unsaturated ether is rapidly polymerised and remains in the reaction mixture. This is a disadvantage of the ketal interchange method. Inositol diketals are readily separated by virtue of their solubility in water but triketals have solubilities similar to those of the polymer; triketals also distil *in vacuo*, and, chromatographed on alumina, move with polymer fractions of lower molecular weight; and their crystallisation is often impeded by the polymer. Hence the poor yield, on isolation, of some triketals which are believed to be formed in good yield.

Experimental

2,2-Diethoxypropane was prepared according to Hurd and Pollack's direction.[14] Paper chromatography was carried out as previously described,[15] with acetone–water (4 : 1) as solvent. Oxidations with lead tetra-acetate in dry pyridine, performed according to Goldschmid and Perlin's direction,[12] were always accompanied by blank experiments, since it was found that the reagent deteriorated rapidly. Light petroleum had b. p. 60—80°.

Ketal Interchange of (−)-Inositol with 2,2-Diethoxypropane.—Dry, powdered (−)-inositol

[10] Angyal and Anderson, *Adv. Carbohydrate Chem.*, 1959, **14**, 155.
[11] Angyal and Young, *J. Amer. Chem. Soc.*, 1959, **81**, 5251, 5467.
[12] Goldschmid and Perlin, *Canad. J. Chem.*, 1960, **38**, 2280.
[13] Killian, Herion, and Nieuwland, *J. Amer. Chem. Soc.*, 1935, **57**, 544.
[14] Hurd and Pollack, *J. Amer. Chem. Soc.*, 1938, **60**, 1905.
[15] Angyal, McHugh, and Gilham, *J.*, 1957, 1432.

(195 g.) was added to a solution of toluene-*p*-sulphonic acid (5 g.) in 2,2-diethoxypropane (1 l.). The mixture was heated on a steam-bath, whereupon it became red, then purple as gentle refluxing commenced after 10 min., and finally dark green. Similar colour changes were observed in all ketal interchange reactions. Complete dissolution of the inositol had occurred after 2 hours' heating. Volatile products (300 ml.), b. p. 74—80°, were then removed by distillation. The remaining viscous solution was diluted with light petroleum (400 ml.) and cooled to about 5°. Crystallisation was induced by scratching, and after 1 hr. the product (250 g.) was filtered off and washed with light petroleum (2 × 200 ml.). 1,2:3,4:5,6-Tri-*O*-isopropylidene-(−)-inositol [2] (220 g., 67·8%), m. p. 213—214°, was obtained by recrystallisation of the crude product from ethanol.

The volatile products were water-souble and showed the presence of an unsaturated compound in small proportion (bromine in CCl_4); they yielded acetone 2,4-dinitrophenylhydrazone, m. p. 125—126°, and ethyl *N*-α-naphthylurethane, m. p. 78—79°. The infrared spectrum showed peaks characteristic of ethanol and, with lower intensity, of 2,2-diethoxypropane, but not of unsaturated ethers.

1,2:3,4:5,6-*Tri*-O-*isopropylidenealloinositol* (I).—When alloinositol (100 mg.), 2,2-diethoxypropane (3 ml.), and toluene-*p*-sulphonic acid (10 mg.) were heated at 100°, the inositol readily dissolved. After 30 min. the solution was diluted with dry benzene (30 ml.) and poured into a solution of sodium hydrogen carbonate (5 ml., 10%); the organic layer was washed with water (3 × 10 ml.). Samples of both layers were hydrolysed with dilute acid and, on paper chromatography, both showed the presence of alloinositol, suggesting that at least two ketal derivatives had been formed.

The organic layer, which contained most of the inositol, was dried ($MgSO_4$) and evaporated at reduced pressure, and the residual viscous gum was distilled, yielding a pale yellow semi-crystalline material (0·3 g.), b. p. 80°/1 mm., a mixture of the triketal and polymer arising from the acid-catalysed decomposition of 2,2-diethoxypropane. Attempts to separate these by chromatography on alumina were unsuccessful. A partial separation was achieved by vacuum-sublimation (80—90°/1 mm.) which yielded *tri*-O-*isopropylidenealloinositol* (30 mg., 18%), m. p. 107° (Found: C, 60·0; H, 8·0. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·05%).

The aqueous layers from three such experiments were combined, evaporated to dryness, and extracted with boiling chloroform (50 ml.). Evaporation of the solvent yielded a viscous gum (60 mg.) which, after solution in benzene (2 ml.) and storage overnight at 5°, had deposited crystals (3 mg.), m. p. 181—183°, in an amount insufficient for further characterisation.

1,2:4,5-*Di*-O-*isopropylidenemucoinositol* (II).—Mucoinositol (100 mg.), 2,2-diethoxypropane (3 ml.), and toluene-*p*-sulphonic acid (10 mg.) were heated on a steam-bath. Dissolution was rapid, and after 1 hr. the mixture was diluted with dry benzene (20 ml.) and worked up as above. Only traces of inositol derivatives were found in the benzene layer. There was no unchanged mucoinositol.

The aqueous layer was evaporated to dryness *in vacuo* and the residue extracted with boiling chloroform (30 ml.) for 20 min. The extracts were dried ($MgSO_4$) and evaporated. The resulting semi-crystalline solid was dissolved in benzene from which 1,2:4,5-*di*-O-*isopropylidenemucoinositol* (100 mg., 69·5%) was deposited. The compound melts at 184° after changing from rectangular plates to needles at about 170° (Found: C, 55·2; H, 7·7. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·75%).

The diketal did not react with lead tetra-acetate in pyridine solution.

1,2:3,4-*Di*-O-*isopropylidenecisinositol* (III).—Cisinositol (100 mg.), 2,2-diethoxypropane (2 ml.), and toluene-*p*-sulphonic acid (5 mg.) were submitted to the ketal interchange reaction. Rapid dissolution occurred, and being heated for 30 min. the solution was diluted with benzene (10 ml.) and worked up as described above. Most of the inositol derivatives were found in the aqueous layer. This was therefore evaporated *in vacuo*, the residue was extracted with boiling chloroform (30 ml.) for 20 min., and the extract evaporated. A solution of the resulting solid (50 mg.) in benzene–light petroleum (1 : 1, 5 ml.) deposited 1,2:3,4-*di*-O-*isopropylidenecisinositol* (30 mg., 21%) as rectangular plates, m. p. 210° (Found: C, 55·4; H, 7·5. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·75%).

To a 0·037M-solution of lead tetra-acetate in pyridine sufficient diketal was added to make a 0·01M-solution. Rapid glycol scission occurred, as indicated by the consumption of lead tetra-acetate (0·21, 0·72, 0·90, 0·95, 1·02, 1·08, and 1·11 mol. after 1, 8, 15, 24, 41, 61, and 91 min., respectively).

Some of the diketal was treated with 2,2-diethoxypropane under the usual conditions. Most of it remained unchanged but chromatographic evidence was obtained for the presence of another inositol derivative, presumably a triketal, in the organic layer.

Ketal Interchange Reaction of Quebrachitol with 2,2-Diethoxypropane. Dry, powdered quebrachitol (50 g.), toluene-*p*-sulphonic acid (2·0 g.), and 2,2-diethoxypropane (200 ml.) were heated on a steam-bath. After 30 min., when complete dissolution of the quebrachitol had occurred, the mixture was poured into a solution of sodium hydrogen carbonate (5 g.) in water (300 ml.), and the organic layer extracted with water (2 × 50 ml.). The combined aqueous layers were evaporated, and the residue was extracted with boiling ethyl acetate (200 ml.) which deposited 5,6-*O*-isopropylidene-2-*O*-methyl-(−)-inositol (30·0 g., 49·8%), m. p. 134—135° (lit.,[6] 135—137°). (Alternatively, the monoketal was isolated in separate experiments by dilution of the reaction mixture with light petroleum from which solution it crystallised in 1 hr. at 5°.)

The remaining organic layer was diluted with benzene (100 ml.), dried (K_2CO_3), and evaporated at reduced pressure to a gum. A solution of the latter in light petroleum deposited 1,2:3,4:5,6-tri-*O*-isopropylidene-(−)-inositol (2·0 g.), m. p. 212—213°, arising from (−)-inositol present in the crude quebrachitol.

The mother-liquors were evaporated and the residue distilled *in vacuo*. The diketal was recovered as a pale yellow viscous oil (16·0 g., 22·7%), b. p. 150°/4 mm. After 6 weeks the oil had solidified. Recrystallisation of the solid from light petroleum at −30° yielded 3,4:5,6-*di*-O-*isopropylidene*-2-O-*methyl*-(−)-*inositol* (IV) (10·0 g., 14·2%), m. p. 69—70°, $[\alpha]_D^{25}$ −2·7° (*c* 3·4 in $CHCl_3$) (Found: C, 57·0; H, 8·0. $C_{13}H_{22}O_6$ requires C, 57·0; H, 8·1%).

Acetylation of this diketal with acetic anhydride and sodium acetate gave the monoacetyl derivative as an oil; it was crystallised and recrystallised from light petroleum at −30°, to yield 1-O-*acetyl*-3,4:5,6-*di*-O-*isopropylidene*-2-O-*methyl*-(−)-*inositol*, m. p. 112—113° (Found: C, 56·9; H, 7·4. $C_{15}H_{24}O_7$ requires C, 56·95; H, 7·65%).

Partial Hydrolysis of 3,4:5,6-*Di*-O-*isopropylidene*-2-O-*methyl*-(−)-*inositol.*—The diketal (0·2 g.), dissolved in 80% acetic acid (1 ml.), was set aside for 15 min. After evaporation to dryness *in vacuo* the crystalline residue was extracted with light petroleum (3 ml.) to remove unchanged starting material. The insoluble residue crystallised from ethyl acetate (3 ml.) and yielded 5,6-*O*-isopropylidene-2-*O*-methyl-(−)-inositol (81 mg., 48%), m. p. and mixed m. p. 134—135°.

Di-isopropylidene Derivatives of (±)-*Bornesitol.*—(±)-Bornesitol [8] (1·0 g.), toluene-*p*-sulphonic acid (100 mg.), and 2,2-diethoxypropane (20 ml.) were heated under reflux on a steam-bath for 1 hr. Complete dissolution occurred. After the volatile products (8 ml.), b. p. 74—80°, had been removed by distillation, hot benzene (30 ml.) was added, and the solution was poured into 10% sodium hydrogen carbonate solution (30 ml.) and extracted with water (3 × 30 ml.). The combined aqueous extracts were evaporated *in vacuo* and the residue was extracted with boiling chloroform (50 ml.). Evaporation of the solvent left a gum (1·0 g.) which on dissolution in ethyl acetate–light petroleum (15 ml., 1 : 9) deposited a mass of needles and rosettes. Extraction with boiling light petroleum (40 ml.) for 30 min. left the rosettes, which recrystallised from ethyl acetate–light petroleum (15 ml., 1 : 9) to yield long needles of (±)-2,3:4,5-*di*-O-*isopropylidene*-1-O-*methylmyoinositol* (VII) (50 mg., 3·6%), m. p. 177° (Found: C, 56·75; H, 8·0. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1%. For a chloroform solution, infrared absorption bands were found at 865, 895, 965, 1020, 1040, 1070, 1105, and 1165 $cm.^{-1}$.

The light petroleum solution, on cooling, deposited long needles of (±)-2,3:5,6-*di*-O-*isopropylidene*-1-O-*methylmyoinositol* (VI) (0·42 g., 31%), m. p. 122° (Found: C, 56·8; H, 8·0%), $\lambda_{max.}$ 865, 900, 980, 1005, 1045, 1070, 1105, and 1155 $cm.^{-1}$.

Methylation of the Di-isopropylidene-(±)-*bornesitol, m. p.* 122°.—To a solution of the diketal (60 mg.) in freshly distilled dimethylformamide (1 ml.) freshly prepared silver oxide [16] (0·45 g.) and methyl iodide (0·45 ml.) were added.[17] The mixture was shaken for 12 hr. and the silver salts were then removed and washed with dimethylformamide (1 ml.) and chloroform (1 ml.). The filtrate was mixed with a solution of potassium cyanide (100 mg.) in water (10 ml.) and was extracted with chloroform (3 × 5 ml.).

The chloroform extracts were washed with water (2 × 5 ml.), dried ($MgSO_4$), and evaporated *in vacuo* to an oil which did not crystallise. Hydrolysis with 2N-hydrochloric acid (2 ml.) at

[16] Bates *et al.*, "Polarimetry, Saccharimetry, and the Sugars," Nat. Bur. Stand., Circular C440, Washington, 1942, p. 507.

[17] Kuhn, Trischmann, and Löw, *Angew. Chem.*, 1955, **67**, 32.

100° for 30 min., followed by evaporation *in vacuo*, yielded crystals, which on recrystallisation from anhydrous ethanol gave (±)-1,4-di-*O*-methylmyoinositol (20 mg., 47·0%), m. p. 200—202° (Found: C, 45·9; H, 7·8. Calc. for $C_8H_{16}O_6$: C, 46·15; H, 7·8%). The m. p. was not depressed on admixture with (±)-liriodendritol [1] (m. p. 203°); the infrared spectra were identical.

Methylation of the Di-O-isopropylidene-(±)-bornesitol, m. p. 177°.—The diketal (80 mg.) was methylated by the procedure last described. The product was again a non-crystallisable oil which, after hydrolysis by dilute hydrochloric acid and recrystallisation from anhydrous ethanol, yielded (±)-1,6-*di*-O-*methylmyoinositol* (30 mg., 53·1%), m. p. 196—197° (Found: C, 46·1; H, 7·8. $C_8H_{16}O_6$ requires C, 46·15; H, 7·75%).

Di-isopropylidene Derivatives of (−)-*Bornesitol.*—The procedure described above was repeated with (−)-bornesitol (1·0 g.). Unchanged bornesitol (0·2 g.) was recovered by filtration after 1 hr. The derivative insoluble in light petroleum was (1*S*)-2,3:4,5-*di*-O-*isopropylidene*-1-O-*methylmyoinositol* (45 mg., 4·0%), m. p. 210° (Found: C, 57·1; H, 8·0. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1%). The soluble compound was (1*S*)-2,3:5,6-di-*O*-isopropylidene-1-*O*-methylmyoinositol (VIII) (150 mg., 13·9%), m. p. 134—136° (Found: C, 57·2; H, 8·2%).

The latter derivative had an infrared spectrum (10% solution in chloroform) superimposable on that of (±)-2,3:5,6-di-*O*-isopropylidene-1-*O*-methylmyoinositol, m. p. 122°, and is apparently identical with the diketal, m. p. 138—139°, prepared by Bien and Ginsburg.[7]

2-O-*Methyl*-5-O-*tosyl*-(−)-*inositol* (IX) (with Miss M. Pitman).—5,6-*O*-Isopropylidene-2-*O*-methyl-(−)-inositol (53 g.), acetic anhydride (250 ml.), and anhydrous sodium acetate (20 g.) were heated at 100° for 3 hr. The mixture was then poured into water (300 ml.) and was extracted with chloroform (3 × 300 ml.); the extracts were washed with water (2 × 500 ml.), dried ($MgSO_4$), and evaporated. The resulting triacetate did not crystallise; its solution in 80% acetic acid (200 ml.) was heated at 100° for 1 hr. and then evaporated *in vacuo*. A solution of the residue in ethyl acetate–light petroleum (2 : 1) deposited 1,3,4-*tri*-O-*acetyl*-2-O-*methyl*-(−)-*inositol* (45·0 g., 66%), m. p. 123—126°. Two recrystallisations raised the m. p. to 129—130°; $[\alpha]_D^{19}$ was −75·5° (*c* 1 in $CHCl_3$) (Found: C, 48·65; H, 6·35. $C_{13}H_{20}O_9$ requires C, 48·75; H, 6·3%).

After having been kept for 7 days, a mixture of the triacetate (26·0 g.), toluene-*p*-sulphonyl chloride (16·5 g.), and dry pyridine (60 ml.) was decomposed by the addition of water (400 ml.) and extracted with chloroform (3 × 200 ml.). The extract was evaporated, and the residue heated on the steam-bath with 2N-hydrochloric acid (150 ml.) for 2 hr. Evaporation of the solution yielded a mixture (35 g.) of quebrachitol and tosylquebrachitol which was dissolved in acetone (50 ml.) and chromatographed on a column of cellulose powder with 90% acetone. The fractions which contained the tosyl compound (as determined by paper chromatography) were combined and evaporated, and the residue crystallised from anhydrous ethanol to give 2-O-*methyl*-5-O-*tosyl*-(−)-*inositol* (15·1 g., 53·5%), m. p. 178—180° (decomp.), $[\alpha]_D^{22}$ −50·0° (*c* 1 in anhyd. EtOH) (Found: C, 48·5; H, 5·8. $C_{14}H_{20}O_8S$ requires C, 48·25; H, 5·8%). The *tetra-acetate* crystallised from ethyl acetate–light petroleum in needles, m. p. 140—141°, $[\alpha]_D^{19}$ −43·2° (*c* 1 in $CHCl_3$) (Found: C, 50·95; H, 5·45. $C_{22}H_{28}O_{12}S$ requires C, 51·15; H, 5·45%).

Under more vigorous conditions of toluenesulphonylation some ditosyl compound is also produced. 1,3,4-Tri-*O*-acetyl-2-*O*-methyl-(−)-inositol (40 g.), toluene-*p*-sulphonyl chloride (38 g.), and dry pyridine (29 ml.) were heated at 100° for 3 hr. Water (200 ml.) and chloroform (100 ml.) were added and the product was extracted in chloroform (2 × 200 ml.) which was then evaporated. The residue was heated with 2N-hydrochloric acid at 100° for 2 hr., the solution was decanted from insoluble gum, and evaporated, and the residue was crystallised from anhydrous ethanol to give 2-*O*-methyl-5-*O*-tosyl-(−)-inositol (9 g., 21%), m. p. 173—174° (decomp.). The insoluble gum was dried at 100° *in vacuo*, and solidified after being stirred with ethyl acetate–light petroleum (9 : 1); crystallisation from the same solvent gave 5,6-*di*-O-*tosyl*-2-O-*methyl*-(−)-*inositol* (7 g., 9%), m. p. 166—167°, $[\alpha]_D^{25}$ −55° (*c* 2 in EtOH) (Found: C, 50·2; H, 5·0. $C_{21}H_{26}O_{10}S_2$ requires C, 50·2; H, 5·2%).

3,4-O-*Isopropylidene*-2-O-*methyl*-5-O-*tosyl*-(−)-*inositol* (X).—2-*O*-Methyl-5-*O*-tosyl-(−)-inositol (2·0 g.), 2,2-diethoxypropane (20 ml.), and toluene-*p*-sulphonic acid (100 mg.) were heated at 100°. Rapid dissolution occurred, and after 1 hr. dry benzene (30 ml.) was added and the mixture worked up as previously described. Paper chromatography showed the presence of unchanged starting material in the aqueous phase. The benzene layer was dried (K_2CO_3) and evaporated *in vacuo*, and the derivative precipitated as a gum (0·64 g.) by addition of light

petroleum (30 ml.) to the residue. The monoketal was crystallised and recrystallised from benzene to yield needles of 3,4-O-*isopropylidene*-2-O-*methyl*-5-O-*tosyl*-(−)-*inositol* (100 mg., 4·5%), m. p. 153° (Found: C, 52·2; H, 6·3. $C_{17}H_{24}O_8S$ requires C, 52·55; H, 6·2%).

To a 0·037M-solution of lead tetra-acetate in pyridine sufficient monoketal was added to make a 0·01M-solution. Consumption of the reagent was slow: 0·07, 0·12, 0·21, 0·33, 0·44, and 0·54 mole after 1, 5, 12, 22, 55, 85, and 120 min., respectively, compared with the reaction of 1,2:3,4-di-*O*-isopropylidenecisinositol (see above) or that of 1,2:3,4-di-*O*-isopropylidene-(−)-inositol (which, under the same conditions, consumed 0·32, 0·80, 0·83, 0·88, 0·94, and 1·00 mol. after 1, 9, 20, 44, 100, and 120 min. respectively).

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School of Chemistry, University of New South Wales,
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