CYCLITOLS

PART XXXIII[1]. A PRACTICAL SYNTHESIS OF *cis*-INOSITOL*

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ABSTRACT

cis-Inositol was synthesized from *epi*-inositol in seven steps in an overall yield of 25%. The required inversion at C-6 was achieved by oxidation with methyl sulphoxide–acetic anhydride followed by stereospecific reduction.

INTRODUCTION

cis-Inositol (**8**) is a remarkable compound. Its six hydroxyl groups are all in *cis* arrangement to each other, and each of its two equivalent chair conformers has three *syn*-axial hydroxyl groups. Owing to its unique configurational features, *cis*-inositol forms strong complexes with borate ion[2] and with several cations[3]. Its reactions are of potential interest, but their study has, so far, been hampered by the difficulty of synthesizing *cis*-inositol. It was first obtained by a tedious separation from the many other products formed[4] in the hydrogenation of hexahydroxybenzene.

A more promising approach appeared to be that involving inversion at C-6 of *epi*-inositol (**1**). A derivative of 6-*O*-*p*-tolylsulphonyl-*epi*-inositol, not readily prepared, has been solvolysed[5], but the reaction resulted in only partial inversion, the products being *epi*- and *cis*-inositol in poor yield.

The methods[6] more recently developed for oxidizing secondary hydroxyl groups have now been examined for removal of the asymmetry at C-6 by oxidation, followed by inversion at C-6 by reduction of the resulting ketone to the diastereoisomer of the original compound. These efforts were successful.

New methods have also been devised for synthesizing a derivative of *epi*-inositol in which every hydroxyl group, except that on C-6, is protected. These reactions resulted in a method by which *cis*-inositol can be produced from *epi*-inositol in seven steps with an overall yield of about 25%.

RESULTS AND DISCUSSION

Two di-isopropylidene acetals of *epi*-inositol have been prepared by heating *epi*-inositol with acetone containing zinc chloride[7]. The major product is the 1,2:3,4-

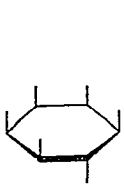
*Dedicated to Dr. Nelson K. Richtmyer in honour of his 70th birthday.

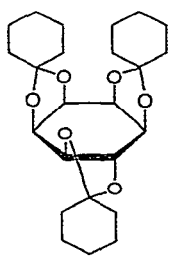
diacetal, but it is not formed in high yield, and is difficult to separate from the 1,2:4,5-diacetal and other products. In this laboratory, cyclohexylidene acetals have, for some time, been preferred to the isopropylidene acetals, because the former are produced in better yield and are easier to purify[8]. Accordingly, *epi*-inositol was condensed with cyclohexanone under mild conditions, but, surprisingly, the two diacetals were produced in almost equal proportions, and the compound that crystallized readily from the reaction mixture was the 1,2:4,5-diacetal, not the desired 1,2:3,4-diacetal[9].

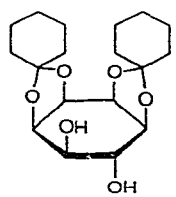
A less direct route to the 1,2:3,4-diacetal was therefore studied. Condensation of *epi*-inositol with cyclohexanone in the presence of benzene and *p*-toluenesulphonic acid, with azeotropic removal of water, gave 1,2:3,4:5,6-tri-*O*-cyclohexylidene-*epi*-inositol (**2**) in 50–60% yield. Recondensation of *epi*-inositol recovered from the mother liquors by hydrolysis resulted in a total yield of 70–75% of the triacetal. The 1,2:4,5-diacetal was isolated from the final mother liquors; the structure of this compound follows from its resistance to oxidation by periodate[9].

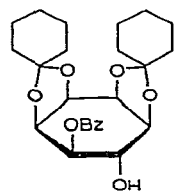
As with the analogous derivative of *chiro*-inositol[8], mild hydrolysis of 1,2:3,4:-5,6-tri-*O*-cyclohexylidene-*epi*-inositol with acid removes the *trans*-acetal grouping (from O-5 and O-6) first. The product is, however, susceptible to further hydrolysis, and, in order to obtain the 1,2:3,4-diacetal in good yield, a solvent mixture (benzene–light petroleum) in which it has very low solubility has to be used. Coupled with nucleation, this procedure results in crystallization of the diacetal from the reaction mixture in about 70% yield.

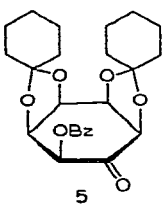
Partial benzoylation of the diacetal **3** at 70° gave a mixture of the 5,6-dibenzoate with two monobenzoates. The main product, readily isolated by recrystallization, is the 5-benzoate (**4**). Angyal and Gilham[10] obtained the 5-*p*-toluenesulphonate from 1,2:3,4-di-*O*-isopropylidene-*epi*-inositol by partial *p*-toluenesulponylation, and similar instances are known in which a hydroxyl group having a neighbouring *cis*-oxygen

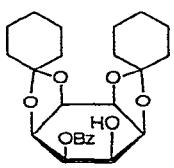


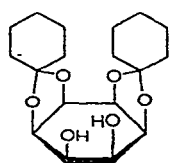












atom is acylated in preference to the one lacking this feature. There is some evidence[11] that hydroxyl groups that are hydrogen-bonded intramolecularly undergo esterification more rapidly than those which are not. Like its di-isopropylidene analogue[12], 1,2:3,4-di-*O*-cyclohexylidene-*epi*-inositol probably adopts that skew form in which the hydroxyl group on C-5 is strongly, and that on C-6 only weakly, hydrogen-bonded.

When the benzoylation of the diacetal is conducted at 100°, the proportion of the 6-benzoate in the products is considerably increased, and it is readily isolated.

The structures of the two monobenzoates were not directly proved, but were deduced from the subsequent reactions of the 5-benzoate (**4**). In the n.m.r. spectrum of **4**, the signals for all the ring protons overlap, but, in that of the 6-benzoate, the H-5 and H-6 resonances are clearly distinguishable and show that this compound, also, is present in a skew form[12], because the value of $J_{1,6}$ (5.8 Hz) is too low for axial–axial coupling in a chair form, but is compatible with a skew form.

Many instances have been described lately of the oxidation of isolated hydroxyl groups in acetals of sugars, and these often proceed in good yield[6]. However, the oxidation of the 5-monobenzoate (**4**) to the corresponding ketone (**5**) proved rather difficult. The compound was unaffected by most of the common oxidizing agents used for this purpose, including chromium trioxide in pyridine[13], methyl sulphoxide–*N*,*N*′-dicyclohexylcarbodiimide[14], methyl sulphoxide–sulphur trioxide–pyridine[15], ruthenium tetraoxide[16], and lead tetraacetate in pyridine[17]. Oxidation was successfully achieved with the methyl sulphoxide–acetic anhydride reagent[18], an oxidant that has proved particularly useful for the oxidation of hindered alcohols[18,19].

Initially, the oxidation was performed by adding the 5-benzoate (**4**) to 7:1 methyl sulphoxide–acetic anhydride at about 80°; the yield of the ketone (**5**) was approximately 45%. It was assumed that the rest of the alcohol was converted into the corresponding (methylthio)methyl ether; formation of such an ether has been observed in many oxidations with methyl sulphoxide[18,20], and it sometimes is the major product[21,22]. The yield of the ketone was increased to 62% by increasing the ratio of methyl sulphoxide to acetic anhydride to 10:1 and diluting the reaction mixture with benzene. Under these conditions, the 6-(methylthio)methyl ether was isolated as a by-product in 20% yield.

Reduction of the ketone **5** by sodium borohydride is stereoselective, and the main product (**6**) of the reaction is that resulting from approach from the less-hindered, equatorial side. Stereospecificity, or a high degree of stereoselectivity, has been observed in the sodium borohydride reductions of several similar ketones[22,23]; the unsubstituted 2,3,4,6/5-pentahydroxycyclohexanone ("*epi*-inosose") is also reduced exclusively to *epi*-inositol under these conditions[24]. 5-*O*-Benzoyl-1,2:3,4-di-*O*-cyclohexylidene-*cis*-inositol (**6**) was obtained in almost quantitative yield; it was debenzoylated to the dicyclohexylidene acetal (**7**), again in almost quantitative yield. Hydrolysis with acid then gave *cis*-inositol (**8**), shown by gas chromatography[25] to be free from *epi*-inositol.

The most serious limitation on this synthesis is the availability of the starting material, namely, *epi*-inositol. This compound is prepared by oxidation of the

commercially available *myo*-inositol with nitric acid to 2,3,4,6/5-pentahydroxycyclohexanone, which is then catalytically hydrogenated to *epi*-inositol[26]. The oxidation is difficult to perform on a large scale, and the yield is only 10–15%. The preparation of *epi*-inositol was more tedious and time-consuming than any of the subsequent steps involved in the synthesis therefrom of *cis*-inositol.

EXPERIMENTAL

General. — Melting points, which are uncorrected, were determined for a compound between soda-glass microscope cover-slides on a Kofler micro melting-point apparatus. Thin-layer chromatography was conducted on glass slides (8 × 2″) covered with Silica Gel HF_{254} (E. Merck), with chloroform as the developer. Spots were detected under an ultraviolet lamp or by absorption of iodine vapour. Gas–liquid chromatography was performed with a custom-built instrument equipped with a glass column (4 ft × 0.25 in.) of 1.5% LAC-1R-296 on Chromosorb W, and a flame-ionization detector. The carrier gas was nitrogen at a flow rate of 30 ml.min^{-1}. Solutions in organic solvents were dried with anhydrous magnesium sulphate, and evaporated under diminished pressure. Light petroleum was the fraction having b.p. 60–80°. Microanalyses were made by Dr. E. Challen of this School, and by the Australian Microanalytical Service, Melbourne. N.m.r. spectra were recorded on a Varian A-60 spectrometer for solutions in chloroform-*d*, with tetramethylsilane as the internal standard. I.r. spectra were recorded with a Perkin–Elmer Infracord spectrophotometer, for Nujol mulls. Benzene, cyclohexanone, methyl sulphoxide, and acetic anhydride were freshly distilled before use. Pyridine was freshly distilled from potassium hydroxide before use.

epi-*Inositol* (**1**). — 2,3,4,6/5-Pentahydroxycyclohexanone was prepared by the method of Posternak[26]. *myo*-Inositol (240 g) was oxidized in 20-g batches, and the resulting ketone was purified through its phenylhydrazone. Pure 2,3,4,6/5-pentahydroxycyclohexanone was isolated in a yield of 23.3 g (9.7%); it was hydrogenated in the presence of Adams' platinum catalyst (0.21 g), and, on filtration and evaporation, *epi*-inositol (22.3 g, 96%) was obtained as an off-white powder.

1,2:3,4:5,6-Tri-O-*cyclohexylidene*-epi-*inositol* (**2**). — A mixture of *epi*-inositol (20 g), cyclohexanone (400 ml), and benzene (200 ml) was boiled under a reflux condenser (Dean–Stark separator), with stirring, until no more water collected (15 min). After the mixture had been cooled, *p*-toluenesulphonic acid (0.22 g) was added, and refluxing was continued for 3 h, by which time, 7.2 ml of water had collected and dissolution of the inositol was almost complete. The mixture was cooled, and shaken thoroughly with a solution of sodium hydrogen carbonate (2.2 g) in water (100 ml). The organic layer was separated, and steam-distilled (to remove cyclohexanone and benzene). The water was removed by decantation, and the amorphous solid remaining was dissolved in hot 95% ethanol (200 ml). On being kept overnight in a refrigerator, the solution deposited crystals (36.7 g). T.l.c. of this material showed that it was a mixture of the triacetal and 1,2:4,5-di-*O*-cyclohexylidene-*epi*-inositol.

After one recrystallization from 95% ethanol (180 ml), the triacetal **2** (26.5 g, 59%) was obtained pure, m.p. 157–160° (lit.[9] m.p. 157–158°). For analysis, it was recrystallized from light petroleum.

Anal. Calc. for $C_{24}H_{36}O_6$: C, 68.55; H, 8.7. Found: C, 68.53; H, 8.6.

1,2:4,5-Di-O-cyclohexylidene-epi-inositol. — The mother liquors from the two recrystallizations of the triacetal **2** were combined and evaporated to dryness. The residual oil was dissolved in hot light petroleum (150 ml) and the solution cooled, whereupon a crystalline solid separated. One recrystallization from methanol gave 1,2:4,5-di-*O*-cyclohexylidene-*epi*-inositol (3.5 g, 9%), m.p. 212° (lit.[9] m.p. 211–212°).

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.5; H, 8.3. Found: C, 63.25; H, 8.25.

Recovery of epi-*inositol.* — All mother liquors from the preparation of the diacetal were evaporated to dryness. The residual oil was dissolved in hot 95% ethanol (70 ml), and the solution was boiled under reflux. To this boiling solution was added concentrated hydrochloric acid (6 ml), and refluxing was continued for 2 h. After the mixture had been cooled, the insoluble *epi*-inositol deposited (~5 g, 25%) was filtered off.

1,2:3,4-Di-O-cyclohexylidene-epi-inositol (**3**). — A suspension of 1,2:3,4:5,6-tri-*O*-cyclohexylidene-*epi*-inositol (37.1 g) in light petroleum (371 ml), benzene (74 ml), and 95% ethanol (22 ml) was boiled under reflux until a clear solution was obtained, and cooled to room temperature. A solution of *p*-toluenesulphonic acid (0.82 g) in 95% ethanol (10 ml) was added to the stirred solution, and the mixture was nucleated with 1,2:3,4-di-*O*-cyclohexylidene-*epi*-inositol, and stirred for 20 h. The insoluble material was filtered off, and washed successively with petroleum ether, 5% sodium hydrogen carbonate solution, and water. The solid was then dissolved in chloroform (500 ml), and the solution was washed with 5% sodium hydrogen carbonate solution (250 ml) and water (2 × 250 ml), briefly dried, and evaporated, to give compound **3** (21.2 g, 71%) as a colorless solid, m.p. 182–183° (lit.[9] m.p. 181–182°).

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.5; H, 8.3. Found: C, 63.75; H, 8.45.

5-O-Benzoyl-1,2:3,4-di-O-cyclohexylidene-epi-inositol (**4**). — A solution of compound **3** (18.8 g) in dry pyridine (96 ml) was heated in an oil bath at ~70°, and benzoyl chloride (9.35 g) was added dropwise to the stirred solution. Heating was continued for 5 h at 70–75°, and the mixture then cooled, kept for 40 h at room temperature, and poured into 2% sodium hydrogen carbonate solution (600 ml), whereupon a white solid was precipitated. Chloroform (200 ml) was added, the mixture was shaken, and the organic layer was separated. The aqueous layer was extracted with four 100-ml portions of chloroform, and the extracts were combined, washed successively with water (250 ml), 3% hydrochloric acid (6 × 250 ml), and water (2 × 250 ml), and evaporated. Examination of the crude product (27.7 g) by t.l.c. revealed that the major product was the desired 5-benzoate; this was contaminated with **3** and the 6-benzoate and 5,6-di-benzoate. A solution of the mixture in chloroform (318 ml) was boiled under reflux, and light petroleum (535 ml) was added. On

cooling to room temperature and keeping for 20 h at 0°, compound **4** (12.6 g, 51%), m.p. 225–228°, was deposited. For analysis, a sample was recrystallized repeatedly from methanol, whereby the m.p. was raised to 228–231°.

Anal. Calc. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.25. Found: C, 67.85; H, 7.0.

The mother liquors from the recrystallization of compound **4** were combined and evaporated to dryness. The residue was dissolved in dry methanol (150 ml), a small piece of sodium was added, and the solution was boiled for 2 h under reflux, cooled, and kept overnight at room temperature. The solvent was evaporated off, and water (100 ml) and then chloroform (200 ml) were added. After thorough shaking in a separating funnel, the chloroform layer was separated; it was washed with water until the washings were no longer alkaline, dried, and evaporated, and the residual solid was dried *in vacuo* to remove methyl benzoate. The recovery of diacetal was 8 g (42%).

6-O-Benzoyl-1,2:3,4-di-O-cyclohexylidene-epi-inositol. — To a stirred solution of compound **3** (1.5 g) in dry pyridine (10 ml) at 100° was added benzoyl chloride (0.75 g) dropwise, and heating and stirring were continued for 21 h. The mixture was cooled, and poured onto a slurry of crushed ice and sodium hydrogen carbonate; an oil separated which solidified on standing. The solid was filtered off, well washed with water, and then with 3% hydrochloric acid, and dried. This crude product (1.6 g) was chromatographed on a column of silica gel, with 1:1 (v/v) benzene–chloroform as eluant, during 48 h, 5-ml fractions being collected. The first compound to emerge from the column was 6-*O*-benzoyl-1:2,3:4-di-*O*-cyclohexylidene-*epi*-inositol (0.69 g, 35%). For analysis, it was recrystallized from methanol; m.p. 158–160°. N.m.r. data ($CDCl_3$): δ 1.2–2.0 (20 H), 2.3 (broad signal, OH), 3.50 (broad doublet; on exchange with D_2O, changes to a pair of doublets, H-5, $J_{4,5}$ 4.0, $J_{5,6}$ 11.5 Hz), 4.3–4.7 (4 H, multiplet), 5.76 (pair of doublets, H-6, $J_{1,6}$ 5.8 Hz), and 7.2–8.2 p.p.m. (5 H, Bz).

Anal. Calc. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.25. Found: C, 67.4; H, 7.25.

Subsequent fractions contained compound **4** (0.5 g, 25%).

6-O-Benzoyl-2,3:4,5-di-O-cyclohexylidene-2,3,4,5,6/0-pentahydroxycyclohexanone (**5**). — To compound **4** (10 g) were added benzene (500 ml) and methyl sulphoxide (150 ml). The mixture was heated under reflux until boiling, and acetic anhydride (15 ml) was added dropwise during ~15 min. Refluxing was continued for 17 h, and then most of the benzene was removed by distillation under diminished pressure in a stream of nitrogen. The residue was dissolved in chloroform (400 ml), and the solution was washed successively with water (3 × 400 ml), 1% sodium hydrogen carbonate (2 × 500 ml), and water (3 × 400 ml), dried, and evaporated, and the resulting material freeze-dried to remove methyl sulphoxide. The solid residue (10.4 g) was dissolved in chloroform (54 ml), the solution was heated until boiling, and hot methanol (225 ml) was added. The solution was allowed to cool, and was then kept overnight at 0°. The crystalline material (5.9 g) that was deposited was the desired ketone (**5**), contaminated with 5-*O*-benzoyl-1,2:3,4-di-*O*-cyclohexylidene-6-*O*-[(methyl-thio) methyl]-*epi*-inositol. One recrystallization from 1:2 (v/v) chloroform–methanol (60 ml) gave a sample of the ketone (5.0 g, 50%) which was pure by t.l.c.; m.p. 211–

214°; ν_{max}^{Nujol} 1750 and 1715 cm^{-1}; δ ($CDCl_3$) 1.0–2.0 (20 H, envelope), 4.5–5.2 (5 H, multiplet), 7.2–8.2 (5 H, multiplet).

Anal. Calc. for $C_{25}H_{30}O_7$: C, 67.85; H, 6.85. Found: C, 67.75; H, 6.75.

A total of 39.1 g of compound **4** was thus oxidized, in four batches. Additional crops of ketone **5** were obtained as described next, the total yield being 24.1 g (62%).

The mother liquors from each of the second recrystallizations were combined and evaporated. Recrystallization of the residue from methanol–chloroform gave 1.9 g of ketone **5**.

The mother liquors from each of the first recrystallizations were combined and evaporated. The residue was dissolved in a mixture of benzene (166 ml) and methyl sulphoxide (50 ml), the solution was heated to boiling under reflux, acetic anhydride (5 ml) was added, and refluxing was continued overnight. After the usual processing, the crude product was dissolved in boiling methanol (400 ml), decolourising carbon was added, the suspension was boiled for a few minutes and filtered, and the filtrate was allowed to cool, affording 4.5 g of ketone **5**, which was recrystallized from methanol–chloroform to give 4.0 g of ketone **5** (pure by t.l.c.). The mother liquors from the original crystallization were concentrated and, on cooling, deposited 5-*O*-benzoyl-1,2:3,4-di-*O*-cyclohexylidene-6-*O*-[(methylthio)methyl]-*epi*-inositol (8.1 g, 18%), m.p. 125–127°; δ ($CDCl_3$) 1.0–2.0 (20 H, envelope), 2.07 (3 H, singlet, Me), 4.3–5.1 (8 H, multiplet), 7.4–8.2 (5 H, multiplet).

Anal. Calc. for $C_{27}H_{36}O_7S$: C, 64.25; H, 7.2; S, 6.35. Found: C, 64.55; H, 7.2; S, 6.1.

*5-O-Benzoyl-1,2:3,4-di-O-cyclohexylidene-*cis*-inositol* (**6**). — A solution of ketone **5** (10 g) in 1:1 (v/v) chloroform–methanol (400 ml) was cooled to 5–10° in an ice bath, and a solution of sodium borohydride (0.81 g) in methanol (90 ml) was added dropwise to the cold, well-stirred solution during ~10 min. After 2 h, water (45 ml) was added, the solution was allowed to warm to room temperature, and evaporated, and the residual material was dissolved in chloroform (250 ml). The solution was then washed with water (3 × 150 ml), dried, and evaporated to dryness, giving 9.6 g (96%) of material, m.p. 192–195°. Examination of the product by t.l.c. showed that it consisted of **6** contaminated with a small proportion of **7**. Recrystallization from methanol gave **6**, m.p. 197–198°.

Anal. Calc. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.3. Found: C, 67.3; H, 7.2.

*1,2:3,4-Di-O-cyclohexylidene-*cis*-inositol* (**7**). — To a solution of **6** (9.4 g) in dry methanol (200 ml) was added a small piece of sodium. The solution was kept overnight, and evaporated to dryness, and water (100 ml) and then chloroform (200 ml) were added to the residue. After thorough shaking, the chloroform layer was separated, washed with water until the washings were no longer alkaline, dried, and evaporated, and the residue was freeze-dried to remove methyl benzoate, giving 7.1 g (99%) of **7**, m.p. 139–141°. For analysis, the compound was recrystallized from methanol; m.p. 147–149°.

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.5; H, 8.3. Found: C, 63.65; H, 8.3.

cis-Inositol (**8**). — A mixture of **7** (1.04 g), acetic acid (8 ml), and water (2ml)

was heated for 2 h on a steam-bath. The solution was then steam-distilled until 150ml of distillate had collected. The solution was evaporated to dryness, and the residue was recrystallized from a mixture of ethanol (15 ml) and water (3 ml) to give *cis*-inositol (0.42 g, 76%), m.p. >300°. In order to confirm the identity of the compound and to estimate its purity, a small sample was acetylated with 1:1 pyridine–acetic anhydride. Examination of the reaction mixture by g.l.c.[25], with *epi*-inositol hexaacetate as the reference compound, showed that the sample contained less than 1% of *epi*-inositol.

Evaporation of the mother liquors from the recrystallization, followed by acetylation with 1:1 pyridine–acetic anhydride for 2 h at 100°, permitted the isolation of additional *cis*-inositol (about 10%) as its hexaacetate, m.p. 210–212° (lit.[4] m.p. 205–206°).

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