378. *Cyclitols. Part XIV.*[1] *Formation of* 1,4-*Anhydroepi-inositol by Dehydration of Myoinositol.*

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Condensation of myoinositol with benzaldehyde in the presence of acid has unexpectedly afforded 1,4-anhydroepi-inositol, isolated as its mono- and di-*O*-benzylidene acetal. The structure and configuration of the anhydro-compound were determined by use of the glycol-fission reaction.

The preparation of cyclic ketals from myoinositol has received much attention.[2-4] The formation of analogous cyclic acetals has not hitherto been intensively studied, possibly because of an early report [5] of unsuccessful attempts to condense myoinositol with benzaldehyde. The recent synthesis of 1,2:5,6-di-*O*-benzylidene-(—)-inositol by Shneour and Ballou,[6] coupled with the attractive possibility that the benzylidene moiety could, in a subsequent synthesis, be removed by hydrogenolysis, prompted a reinvestigation of the condensation of myoinositol with benzaldehyde.

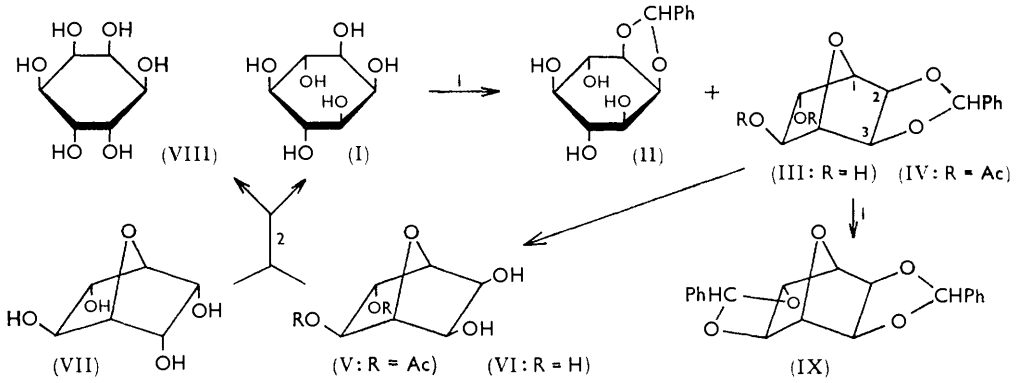
When myoinositol (I), benzaldehyde, toluene, and toluene-*p*-sulphonic acid were heated under vigorous reflux, with accompanying azeotropic distillation, slow condensation occurred. After collection of about 2 moles of water, paper chromatography indicated the formation of two water-soluble products. On acetylation, one product afforded a benzylideneinositol tetra-acetate which on hydrogenolysis gave 1,4,5,6-tetra-*O*-acetyl-myoinositol,[4] thereby demonstrating that the original acetal must have been 1,2-*O*-benzylidenemyoinositol (II). The yield was not reproducible and synthesis of this acetal by the method described is not attractive.

On hydrolysis by dilute acid, the second water-soluble product yielded not inositol but a new polyol of higher chromatographic mobility. Elementary analysis indicated that it was an anhydrobenzylideneinositol (III; the correct structures are shown, in anticipation of their proof); it was clearly not an epoxide since the anhydro-bridge was not cleaved by mild acid hydrolysis. Acetylation gave an anhydrobenzylideneinositol diacetate (IV) which, on hydrogenolysis, afforded an anhydroinositol diacetate (V). Hydrogenolysis of the benzylidene acetal (III) gave the anhydroinositol (VI) which was converted into a non-crystalline tetra-acetate.

Glycol fission was used to determine the structure and configuration of the new anhydroinositol. It had been shown [7] that in diols of rigid five-membered ring systems, like that of camphane, the bond between *cis*-hydroxyl groups is broken with extreme

[1] Part XIII, Angyal and Hoskinson, *J.*, 1962, 2991.
[2] Angyal and Macdonald, *J.*, 1952, 686.
[3] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[4] Angyal, Tate, and Gero, *J.*, 1961, 4116.
[5] Karrer, *Helv. Chim. Acta*, 1926, **9**, 116.
[6] Shneour and Ballou, *J. Amer. Chem. Soc.*, 1958, **80**, 3960.
[7] Angyal and Young, *J. Amer. Chem. Soc.*, 1959, **81**, 5467.

rapidity, whereas fission between *trans*-hydroxyl groups occurs very slowly. The anhydrobenzylideneinositol (III) is a diol but it did not react with sodium metaperiodate at room



temperature; it is a vicinal diol, however, because it reacted with lead tetra-acetate in pyridine solution, a reagent which oxidises even sterically unfavourable glycols.[8] The diol (III) therefore appears to have the *trans*-cyclopentanoid geometry, with a dihedral angle of about 120°. The di-*O*-acetylanhydroinositol (V) is also a diol, in which a different pair of hydroxyl groups is free; it consumed one mole of sodium metaperiodate practically instantly, thereby demonstrating its *cis*-cyclopentanoid nature (dihedral angle of about 0°). The presence of one *cis*- and one *trans*-glycol group, observed in the two derivatives (III and V, respectively), compels the formulation of the parent compound as a 1,4-anhydroinositol and, since the *cis*-diol may have either the *exo*- or the *endo*-configuration, the two possible structures of the tetraol are 1,4-anhydroepi-inositol (VI) and 1,4-anhydro-(±)-inositol (VII).

As this investigation was in progress, the synthesis of several 1,4-anhydroinositols, from furan and ethylene carbonate, was reported by Sarel and Kowarsky [9] and by Yurev and Zefirov.[10] Professor Sarel kindly gave us a sample of tetra-*O*-acetyl-1,4-anhydro-(±)-inositol; this crystalline material, on inoculation, did not cause our oily tetra-acetate to crystallise, and the two compounds were shown to be different by gas chromatography.[11] Our 1,4-anhydroinositol must therefore possess the epi-configuration (VI). This is consistent with the expectation that the thermodynamically more stable isomer would be formed in the cyclisation, *i.e.*, the isomer having the *exo*-configuration of the *cis*-diol group.

Yurev and Zefirov claimed to have obtained inositols by the alkaline hydrolysis of 1,4-anhydroinositols. Ring-opening under these conditions appears unlikely, and our anhydroinositol was not affected by prolonged boiling with 4% barium hydroxide solution. Acidic hydrolysis, however, as suggested by Sarel,[12] afforded, albeit slowly, allo- (VIII) and myo-inositol (I), which were isolated and characterised as their hexa-acetates. This ring-opening, which must proceed with inversion of configuration (otherwise only one inositol would be obtained) confirms our previous assignment of configuration since only the epi- and the (±)-isomer of 1,4-anhydroinositol would give allo- and myo-inositol; but the reaction does not distinguish between these two configurations.

It is presumed that formation of the acetal ring precedes the establishment of the anhydro-bridge, since myoinositol did not undergo dehydration when heated with toluene-*p*-sulphonic acid in an inert solvent. Probably the deformation of the chair form, which

[8] Goldschmid and Perlin, *Canad. J. Chem.*, 1960, **38**, 2280.
[9] Sarel and Kowarsky, *Bull. Res. Council Israel*, 1960, **9**, *A*, 72.
[10] Yurev and Zefirov, *Zhur. obshchei Khim.*, 1961, **31**, 685.
[11] Krzeminski and Angyal, *J.*, 1962, 3251.
[12] Professor S. Sarel, personal communication.

accompanies its fusion to a five-membered ring, facilitates the transannular reaction by bringing the conformation closer to that of the boat form, which is clearly required for the formation of a 1,4-bridge. The reaction occurs with inversion of configuration at C-4. It is interesting to note that the parent ring system, 7-oxabicyclo[2,2,1]heptane, was isolated during the thermal dehydration of the cyclohexane-1,4-diols,[13] but could not be prepared by the classical method of 1,2-anhydride formation, *i.e.*, treatment of the mono-toluene-*p*-sulphonates of *cis*- or *trans*-cyclohexane-1,4-diol with alkali.[14]

The water-insoluble product formed in low yield in the condensation described above was an oil. It proved to be a complex mixture and was not further investigated.

When the condensation of myoinositol with benzaldehyde was continued until distillation of water was essentially complete, the two water-soluble products described above were formed in small yield. After removal of benzaldehyde from the non-aqueous phase, and chromatography on alumina with benzene, chloroform, and ethanol, three distinct fractions were obtained as gums. Only the product in the chloroform eluate solidified and this is apparently a dibenzylideneanhydroinositol. Its infrared spectrum did not show free hydroxyl groups; on mild hydrolysis in dilute acid it afforded 1,4-anhydroepi-inositol (VI) and 1,4-anhydro-2,3-*O*-benzylidene-epi-inositol (III). The same amorphous diacetal was formed on treatment of the monoacetal (III) with benzaldehyde. Elementary analysis indicates that it does not contain a trioxepan system analogous to that obtained by Head from *trans*-cyclohexane-1,2-diol.[15]

The diacetal is therefore formulated as 1,4-anhydro-2,3:5,6-di-*O*-benzylidene-epi-inositol (IX). Its failure to crystallise suggests that it may be a mixture of diastereisomers, differing in the configuration of the acetal carbon atom.[16] The diacetal is of particular interest since it contains two mutually *trans*-fused five-membered rings; such a system is rare.[17,18]

No solid product could be recovered from either of the remaining chromatography fractions. These comprise complex mixtures of the higher acetals of myoinositol and 1,4-anhydroepi-inositol, which they yielded on hydrolysis in dilute acid.

The spectrum of the product from this condensation is temperature-dependent; the yield of anhydroinositol derivatives was noticeably lower when heating was provided by an electric mantle rather than a Bunsen burner.

Some difficulties were experienced with the hydrogenolysis of the benzylidene acetals; generally reaction did not occur in neutral solution of organic solvents, as customarily performed.[19] In some cases it did proceed impracticably slowly if the catalyst (palladium chloride on carbon) was not pre-reduced. Hydrogenolysis with Raney nickel under pressure was also slow and was accompanied by some hydrogenation of the benzene ring. Only in glacial acetic acid, with catalyst not previously reduced, was hydrogenolysis satisfactory.

Experimental

All the compounds described in this paper are racemic. M. p.s are uncorrected and were observed in soda-glass capillaries unless otherwise stated. Paper chromatography was performed as previously described,[20] with acetone–water (87 : 13) as solvent. Palladium (5%) on charcoal catalyst was prepared as described by Mozingo.[21]

Condensation of Myoinositol with Benzaldehyde.—(*a*) A suspension of powdered myoinositol (40 g.) in a mixture of benzaldehyde (400 ml.), toluene (30 ml.), and toluene-*p*-sulphonic acid

[13] Olberg, Pines, and Ipatieff, *J. Amer. Chem. Soc.*, 1944, **66**, 1096.
[14] Owen and Robins, *J.*, 1949, 320.
[15] Head, *J.*, 1960, 1778.
[16] Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.
[17] Owen and Peto, *J.*, 1955, 2383.
[18] Wendler, Hirschmann, Slates, and Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 1632.
[19] Hartung and Simonoff, *Org. Reactions*, 1953, **7**, 263.
[20] Angyal, McHugh, and Gilham, *J.*, 1957, 1432.
[21] Mozingo, *Org. Synth.*, 1946, **26**, 77.

(1·0 g.) was heated with a Bunsen flame for 30 min. under a Dean and Stark separator filled with toluene; 4·0 ml. of water collected. Unchanged myoinositol (19 g.) was recovered by decantation of the liquid phase into a solution of sodium hydrogen carbonate (20 g.) in water (800 ml.). Benzaldehyde was then removed by steam distillation and the residual insoluble oil was extracted with chloroform (2 × 150 ml.).

Paper chromatography of the aqueous phase indicated two new compounds, R_F 1·0 and 0·8, together with myoinositol. The compound with R_F 1·0 was extracted by ethyl acetate (4 × 50 ml.); the extracts were combined, washed with water (3 × 20 ml.), dried (K_2CO_3), and evaporated to 20 ml.; 1,4-*anhydro*-2,3-O-*benzylidene-epi-inositol* (2·2 g., 7·5%), m. p. 194°, was deposited (Found: C, 62·4; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). Acetylation with acetic anhydride–pyridine yielded the *diacetate* (1·7 g., 75%), m. p. 109°, as needles from ethanol (Found: C, 61·1; H, 5·5. $C_{17}H_{18}O_7$ requires C, 61·1; H, 5·4%).

The aqueous layer, which contained myoinositol and the compound with R_F 0·8, was evaporated to 20 ml., diluted with acetone (80 ml.), and chromatographed on cellulose with 80% acetone. The fractions with R_F 0·8 gave 1,2-*O*-benzylidenemyoinositol (15 g.) as a gum. A solution of the gum (5 g.) in anhydrous ethanol (5 ml.), after six months at 5°, deposited crystals of 1,2-O-*benzylidenemyoinositol* (2·0 g., 18%), m. p. 140—142° (Found: C, 58·0; H, 6·2. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). Acetylation of a second portion (2·4 g.) of the gum afforded the *tetra-acetate* as needles from ethanol (1·2 g., 33%), m. p. 156—158° (Found: C, 57·8; H, 5·5. $C_{21}H_{24}O_{10}$ requires C, 57·8; H, 5·5%). Benzoylation of the gum (3·1 g.) with benzoyl chloride (25 ml.) and pyridine (25 ml.) afforded a semicrystalline solid (4·3 g.) which gave the *tetrabenzoate* (1·8 g., 22%), m. p. 280° (decomp.) (from benzene) (Found: C, 71·8; H, 4·8. $C_{41}H_{32}O_{10}$ requires C, 71·9; H, 4·7%). The yield of 1,2-*O*-benzylidenemyoinositol was not reproducible and has been as low as 10%.

Evaporation of the chloroform-soluble fraction (see above) yielded an oil which was a complex mixture and was not studied.

(*b*) When the same reaction was carried out on half the scale but for 1·5 hr. all the inositol dissolved and 5·2 ml. of water were collected. On working up of the products as above 1,4-anhydro-2,3-*O*-benzylidene-epi-inositol (1·4 g., 5%), m. p. 194°, and 1,2-*O*-benzylidenemyoinositol tetra-acetate (2·0 g., 4%), m. p. 156—158°, were recovered from the aqueous layer.

The contents of the chloroform layer (33 g.) could not be crystallised and were chromatographed on alumina with benzene (3 l.), chloroform (3 l.), and ethanol (3 l.), in turn. The product from chloroform (17 g.), when dissolved in ethanol, deposited 1,4-*anhydro*-2,3:5,6-*di*-O-*benzylidene-epi-inositol* (10·0 g., 26·6%) as a light brown amorphous solid, m. p. 156—170° (Found: C, 70·5; H, 5·3. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·4%). Rechromatography on alumina and many attempts to crystallise this material did not significantly alter the m. p. The products in the benzene and ethanol percolates could not be solidified.

Condensation of Benzaldehyde with 1,4-*Anhydro*-2,3-O-*benzylidene-epi-inositol.*—Benzaldehyde (20 ml.), toluene (3 ml.), and toluene-*p*-sulphonic acid (200 mg.) were heated under a Dean and Stark apparatus until traces of water were removed. 1,4-Anhydro-2,3-*O*-benzylidene-epi-inositol (2·0 g.) was then added and refluxing continued for 40 min. The mixture was poured into sodium hydrogen carbonate solution (10%, 40 ml.) and extracted with benzene (2 × 30 ml.). Paper chromatography showed the absence of monoketal. The benzene solution was dried ($MgSO_4$) and evaporated *in vacuo* to yield a gum; a solution of the gum in ethanol (20 ml.) deposited 1,4-anhydro-2,3:5,6-di-*O*-benzylidene-epi-inositol (0·4 g., 14·8%), m. p. 138—150°, as a light brown amorphous solid (Found: C, 71·3; H, 5·8. Calc. for $C_{20}H_{18}O_5$: C, 71·0; H, 5·4%). The infrared spectrum (Nujol) was identical with that of the diacetal above and showed no hydroxyl band.

Hydrogenolysis of Benzylidene Acetals.—(*a*) 1,4-Anhydro-2,3-*O*-benzylidene-epi-inositol (0·5 g.), dissolved in glacial acetic acid (15 ml.), was shaken under hydrogen for 3 hr. with 5% palladium–carbon catalyst (250 mg.). Total hydrogen consumption was 130 ml. The catalyst was filtered off and washed with hot water (30 ml.). The combined filtrates were evaporated to dryness *in vacuo* to yield an oil which, from ethanol, deposited 1,4-*anhydroepi-inositol* (200 mg., 61·8%), m. p. 163—164° (Kofler block) (Found: C, 44·7; H, 6·3. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%). Acetylation of the tetraol (100 mg.) with acetic anhydride–sulphuric acid (95 : 5) afforded the *tetra-acetate* which was distilled *in vacuo* (1 mm.) from a Wood's metal bath (280°) and obtained as a glass (60 mg., 29%) (Found: C, 50·5; H, 5·6. $C_{14}H_{18}O_9$ requires C, 50·9; H, 5·5%).

(*b*) Hydrogenolysis of 1,4-anhydro-2,3-*O*-benzylidene-epi-inositol diacetate (0·87 g.) in a similar manner for 6 hr. afforded 5,6-*di*-O-*acetyl*-1,4-*anhydroepi-inositol* (0·55 g., 86%), m. p. 105—107° (Kofler block) (from benzene). One recrystallisation raised the m. p. to 107° (Found: C, 48·6; H, 5·8. $C_{10}H_{14}O_7$ requires C, 48·8; H, 5·7%).

(*c*) Hydrogenolysis of 1,2-*O*-benzylidenemyoinositol tetra-acetate (1·5 g.) resulted in an oil (0·95 g.) which, on crystallisation from water (3 ml.) at 5°, gave 1,4,5,6-tetra-*O*-acetylmyoinositol monohydrate (0·4 g., 33·7%). After the acetate had been dried over phosphoric anhydride (5 hr., 60°/1 mm.), the m. p. was 78—82°. The mixed m. p. with an authentic specimen (m. p. 84—86°) was 78—82° (hot stage). The infrared spectrum was superimposable on that of the authentic specimen. The anhydrous tetra-acetate had m. p. 126—128° (Kofler block) (from ethanol). The mixed m. p. with an authentic specimen (m. p. 125—127°) was undepressed.

Glycol Fission.—The undermentioned compounds (40 mg. of each), dissolved in ethanol (5 ml.), were added to sodium metaperiodate solution (0·03M; 50 ml.). At intervals portions (5 ml.) of these solutions were added to a mixture of sodium hydrogen carbonate (M; 2 ml.), potassium iodide (10%, 1 ml.), and sodium arsenite (0·025N, 15 ml.) solution. After 15 min., the final solutions were titrated with iodine (0·025N).

1,4-Anhydro-2,3-*O*-benzylidene-epi-inositol did not react; 5,6-di-*O*-acetyl-1,4-anhydroepi-inositol consumed one mole of periodate instantly; and 1,4-anhydroepi-inositol consumed 1·0, 1·04, 1·18, 1·21, 1·30, 1·48, and 1·81 moles after reaction times of 1, 5, 15, 20, 36, 63, and 123 min., respectively.

When treated with lead tetra-acetate in dry pyridine solution [8] 1,4-anhydro-2,3-*O*-benzylidene-epi-inositol consumed 0·45 mole after 20 min. and thence continued to react slowly, 1·75 moles being consumed after 4 hr., in accordance with the known tendency of this reagent to " overoxidise."

Ring-opening of 1,4-*Anhydroepi-inositol.*—1,4-Anhydroepi-inositol (0·4 g.) in a mixture of acetic acid (16 ml.), water (4 ml.), and sulphuric acid (0·2 ml.) was refluxed for 42 hr. Evaporation of the solution to 5 ml., followed by dilution with water (15 ml.), hydrolysis at 100° for 2 hr., re-evaporation to 2 ml., and chromatography on cellulose powder with acetone–water (4 : 1) afforded alloinositol (50 mg.), characterised as its hexa-acetate, m. p. 140—142°, and myoinositol (35 mg.), characterised as its hexa-acetate, m. p. 216—217°. Unchanged 1,4-anhydroepi-inositol was also present but was not isolated.

Attempted Dehydration of Myoinositol.—A mixture of myoinositol (5 g.), isopentyl ether (50 ml.), toluene (15 ml.), and toluene-*p*-sulphonic acid (2 g.) was refluxed vigorously under a Dean and Stark separator for 5 hr. After cooling, myoinositol was quantitatively recovered by filtration. The presence of an anhydro-inositol could not be demonstrated by paper chromatography.

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