## 1235. *Cyclitols. Part XX.*[1] *Cyclohexylidene Ketals of Inositols*

By S. J. Angyal, G. C. Irving, D. Rutherford, and M. E. Tate

In Part IX of this Series [2] the preparation of some cyclohexylidene derivatives of myo-inositol was described. These derivatives proved to be easier to prepare, and were obtained in better yield, than the corresponding isopropylidene ketals previously used as intermediates.[3] Moreover, the reaction with cyclohexanone can be forced by azeotropic removal of water, and even myoinositol can be converted into a tricyclohexylidene derivative (I), containing one *cis*- and two *trans*-fused ketal rings. In our laboratories, cyclohexylidene ketals have replaced the isopropylidene derivatives; this Note describes the preparation of five new inositol ketals.

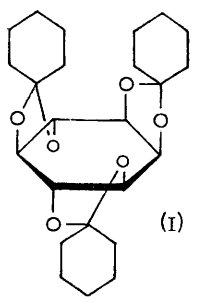
Several personal Communications have been received indicating that difficulties were experienced in reproducing successfully the procedure previously published [2] for the synthesis of 1,2-*O*-cyclohexylidenemyoinositol. We therefore now give fuller details of this preparation which has been carried out many times in the last few years.

It was found advantageous to reduce the amount of toluene-*p*-sulphonic acid used as catalyst because in larger concentration it promotes the self-condensation of cyclohexanone, producing water which actually represses the formation of the desired ketal.

*Experimental.*—(±)-1,2-O-*Cyclohexylidenemyoinositol.* In a flask fitted with an efficient stirrer, a wide condenser, and a Dean and Stark separator connected to the flask by a tube at least 2 cm. in diameter, finely powdered myoinositol (50 g.) is heated with purified cyclohexanone

[1] Part XIX, S. J. Angyal and G. J. Melrose, *J.*, 1965, 6501.
[2] S. J. Angyal, M. E. Tate, and S. D. Gero, *J.*, 1961, 4116.
[3] S. J. Angyal and C. G. Macdonald, *J.*, 1952, 686.

(500 ml.) and benzene (130 ml.) until no more water distils. Toluene-*p*-sulphonic acid (0·5 g. of monohydrate) is then added and the solution is boiled vigorously with rapid stirring until the separation of water becomes slow and nearly all the inositol has dissolved (about 4 hr.). The success of the reaction at this stage is indicated by the disappearance of the solid; the amount of water collected in the separator (usually about 20 ml.) is not a true indication since it exceeds the theoretical, owing to the inevitable self-condensation of cyclohexanone. The solution is cooled and decanted from the solid which is washed with benzene (50 ml.); more benzene (200 ml.), light petroleum (b. p. 60—80°) (250 ml.), ethanol (50 ml.), and cyclohexylidene-myoinositol (0·5—1 g., for seeding) are added, in this order, to the solution. Hydrolysis of the tri- and di-ketals begins as soon as ethanol is added; the cyclohexylidene groups are removed as cyclohexanone diethyl ketal. The monoketal is readily hydrolysed further to myoinositol if it remains in solution; hence it is essential to remove it from solution as soon as possible. This aim is achieved by generous inoculation and stirring; a copious precipitate appears within 10 min. After storage at 0° overnight, triethylamine (1 ml.) is added with stirring, the solution is filtered, and the solid (*ca.* 66 g.) is well washed with benzene. To remove the myoinositol, the solid is extracted with boiling ethanol (1000 ml.) containing triethylamine (1 ml.) to neutralise any acid which may be present; if the reaction is successful only a small amount of myoinositol remains undissolved. On cooling, 1,2-*O*-cyclohexylidenemyoinositol, (*ca.* 54 g., 74%), m. p. 181—183° (with transition at 158—160°), crystallises; it usually contains a trace of myoinositol. To obtain the compound free from myoinositol, it is recrystallised from three parts of water.



(I)

(±)-1,2:3,4:5,6-*Tri*-O-*cyclohexylidenemyoinositol* (I). Powdered mylinositol (2·0 g.) was heated with cyclohexanone (25 ml.) and benzene (10 ml.) under a Dean and Stark separator until no more water separated. Toluene-*p*-sulphonic acid (100 mg.) was added and vigorous boiling continued for 3·5 hr. After the addition of an aqueous solution (20 ml.; 10%) of potassium carbonate, steam was passed through the mixture until 250 ml. of distillate was collected. The oily residue in the flask was extracted with cold water (5 × 100 ml.). The insoluble residue was then dissolved in methanol (35 ml.) from which crystals separated overnight. After 24 hr. at 0° the crystals of the *triketal* (0·73 g.; 16%), m. p. 149—152°, were collected by filtration. Recrystallisation from methanol raised the m. p. to 154—156° (Found: C, 68·7; H, 8·55. $C_{24}H_{36}O_6$ requires C, 68·55; H, 8·6%).

1,2:3,4:5,6-*Tri*-O-*cyclohexylidene*-(−)-*inositol*. (−)-Inositol (1·0 g.), cyclohexanone (25 ml.), benzene (15 ml.), and toluene-*p*-sulphonic acid (50 mg.) were heated to vigorous boiling in a flask fitted with a Dean and Stark separator. After 75 min. only traces of inositol remained undissolved and a total of 0·35 ml. of water had collected in the separator. An aqueous solution (20 ml.; 10%) of potassium carbonate was added, and the mixture was steam-distilled. Towards the end of the distillation crystals (2·27 g.), m. p. 188—190°, appeared in the flask; filtration and recrystallisation from methanol gave needles of the *triketal* (1·8 g.; 77%), m. p. 191—192°, $[\alpha]_D^{25}$ +13·1° (*c* 2·1 in dioxan) (Found: C, 68·8; H, 8·9. $C_{24}H_{36}O_6$ requires C, 68·55; H, 8·6%).

1,2:5,6-*Di*-O-*cyclohexylidene*-(−)-*inositol*. The triketal (30 g.) was dissolved in a mixture of benzene (160 ml.) and ethanol (16 ml.; 95%), and a solution of hydrogen bromide in acetic acid (2 ml.; 40%) was added. After 1 hr. the crystalline solid which had separated was filtered off and washed with light petroleum (300 ml.). The combined filtrates deposited further crystals after 2 hr. The combined crystals (23·5 g.; 96%), m. p. 204—206°, were recrystallised from ethanol, to give needles of the *diketal*, m. p. 209—210°, $[\alpha]_D^{27}$ −16° (*c* 1·4 in $CHCl_3$), $[\alpha]_D^{25}$ +4·5° (*c* 0·6 in dioxan) (Found: C, 63·3; H, 8·3. $C_{18}H_{28}O_6$ requires C, 63·5; H, 8·3%).

1,2:3,4-*Di*-O-*cyclohexylidene*-5-O-*methyl*-(−)-*inositol*. Finely powdered quebrachitol [4] [2-*O*-methyl-(−)-inositol] (10·0 g.) was heated in a flask, equipped with a Dean and Stark separator, with cyclohexanone (50 ml.) and benzene (26 ml.) until no more water distilled. Toluene-*p*-sulphonic acid (0·2 g.) was then added and vigorous boiling continued for 3 hr. by which time almost all the cyclitol had dissolved and 2·0 ml. of water had collected. The mixture was washed with sodium hydrogen carbonate solution, steam-distilled to remove cyclohexanone, and

[4] S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, 1959, **14**, 169.

extracted with chloroform (3 × 30 ml.). The extract was dried ($K_2CO_3$) and evaporated; the residual syrup was dissolved in warm light petroleum (75 ml.; b. p. 60—80°) from which the *diketal* (11·1 g.; 61%), m. p. 115—117°, crystallised. Repeated recrystallisation from light petroleum raised the m. p. to 118—119°, $[\alpha]_D^{20}$ −18·2° (*c* 1 in $CHCl_3$) (Found: C, 64·7; H, 8·55. $C_{19}H_{30}O_6$ requires C, 64·4; H, 8·55%).

1,2:5,6-*Di*-O-*cyclohexylidene*-3-O-*methyl*-(+)-*inositol*. This compound was prepared in the same way as the preceding one except that benzene, rather than chloroform, was used for the extraction. Pinitol [4] [3-*O*-methyl-(+)-inositol] (10 g.) gave 13·8 g. (78%) of the *diketal*, m. p. 109—110°, $[\alpha]_D^{22}$ −302° (*c* 1·1 in $CHCl_3$) (Found: C, 64·5; H, 8·5. $C_{19}H_{30}O_6$ requires C, 64·4; H, 8·55%).

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School of Chemistry, The University of New South Wales,
Kensington, N.S.W., Australia. [*Received, May 24th*, 1965.]