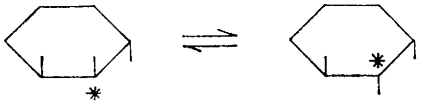
## 334. *Cyclitols. Part XV.*[1] *A Stereospecific Epimerization of Cyclitols: Conformational Free Energies*

By S. J. Angyal, P. A. J. Gorin, and (Miss) M. E. Pitman

When cyclitols are heated in 95% (v/v) acetic acid containing a strong acid, epimerization occurs at the middle carbon atom of each *cis–trans* sequence of hydroxyl groups. Equilibrium constants were determined for eight epimeric pairs, and it was shown that the differences between the free energies of the epimers can be calculated approximately from the non-bonded interaction energies.

In 1956 it was unexpectedly observed [2] that alloinositol (V) was partially converted into epi-inositol (VI) on being heated in a solution of toluene-*p*-sulphonic acid in 95% (v/v) acetic acid. A qualitative investigation indicated that the reaction is general for cyclitols but shows surprising stereo specificity: epimerization occurs only on a carbon atom, marked with an asterisk in the formulæ:

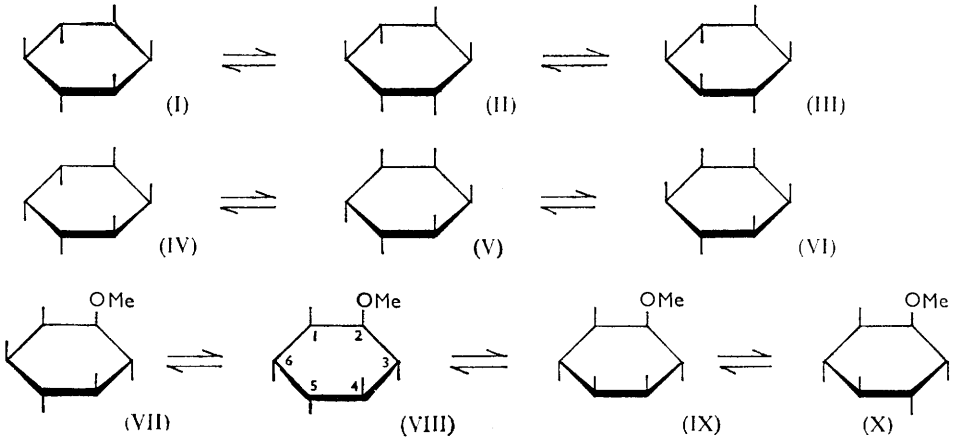


whose hydroxyl group is flanked by a *cis*-hydroxyl group on one side and by a *trans*-hydroxyl group on the other. The mechanism of the reaction appeared of interest; but even more interesting was the prospect that, if equilibria could be established between cyclitols by this reaction, the differences between the free energies of diastereomeric

[1] Part XIV, Angyal and Hoskinson, *J.*, 1963, 2043.
[2] M. E. Pitman, M.Sc. Thesis, University of Tasmania, 1957.

cyclitols could be determined. At that time, however, no method was available for the quantitative determination of mixtures of cyclitols. Now that gas chromatography has been applied to cyclitols,[3] we have reinvestigated the epimerization reaction.[4]

For epimerization to occur, acetic acid is necessary; the rate of reaction varies with acid concentration and appears to be greatest at 95% (v/v) concentration, slower at 90% (v/v), and hardly noticeable at 85% (v/v) concentration. However, glacial acetic acid, with or without acetic anhydride, can also be employed. The free cyclitol or its acetate can be used, since acetylation and deacetylation occur during the reaction. Toluene-*p*-sulphonic acid can be replaced by other strong acids; sulphuric acid (1·5%) has been used in our experiments (at higher concentrations it causes some charring).




*Inositols.*—Under the above conditions, equilibria are reached between inositols, though complete equilibration requires about 12 days at the temperature of reflux (117°). Thus myo- (I), (±)- (II), and muco-inositols (III) epimerize and are found in the proportion of 54 : 41 : 5. Similarly, neo- (IV), allo- (V), and epi-inositols (VI) are equilibrated to a 58 : 21 : 15 mixture; * in this case an unidentified by-product appears after prolonged heating. Analysis of the reaction mixture at intervals showed that the reactions occur in the sequence indicated by the formulæ; thus, for example, epi-inositol is first converted into alloinositol, with subsequent formation of neoinositol. The reaction is suitable for the preparation of neoinositol (IV) which is much less soluble in water than any of the other inositols and was readily obtained in 40% yield from epi-inositol (not necessarily pure). The reaction could also be used for the synthesis of alloinositol, since epi-inositol yields alloinositol (over 40% of the mixture in 21 hours, then declining owing to the formation of neoinositol).

The other two inositols, scyllo, and *cis*-inositol, which do not have hydroxyl groups flanked by one *cis* and one *trans* hydroxyl group, are unaffected under these reaction conditions.

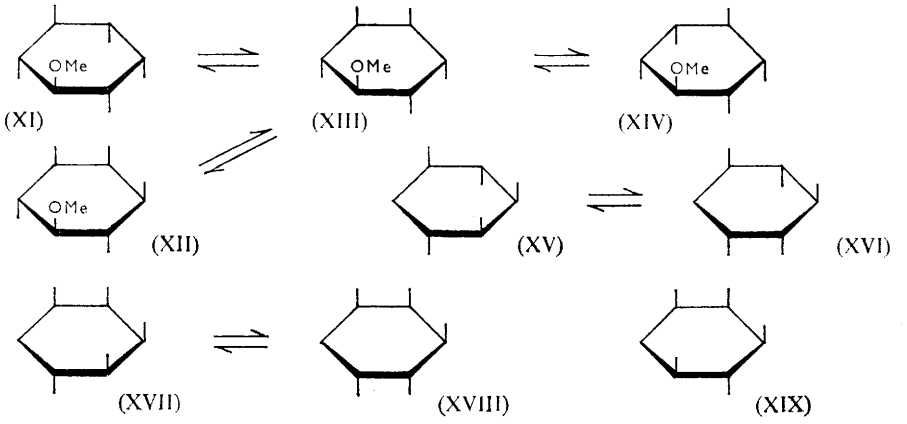
*Inositol Methyl Ethers.*—Further insight was gained into the stereospecificity of the reaction from its application to inositol methyl ethers.[5] 2-*O*-Methyl-(−)-inositol (quebrachitol, VIII) is converted into 1-*O*-methylmyoinositol (bornesitol, VII) and 1-*O*-methyl-(+)-inositol (X), the latter presumably *via* a 1-*O*-methylmucoinositol (IX). Inversion therefore occurs on C-5 and C-6, which each have a *cis* and a *trans* neighbouring hydroxyl group, but not on C-1 where one neighbouring group is a hydroxyl and the other

* In the formulæ the vertical lines represent hydroxyl groups; the hydrogen atoms on the ring carbons are not shown.

[3] Krzeminski and Angyal, *J.*, 1962, 3251.
[4] Angyal, Gorin, and Pitman, *Proc. Chem. Soc.*, 1962, 337.
[5] Angyal and Anderson, *Adv. Carbohydrate Chem.*, 1959, **14**, 135.

a methoxyl group. The 1-*O*-methylmyoinositol was optically active and there was no indication of any racemization.

The reaction was also applied to 3-*O*-methyl-(+)-inositol (pinitol, XIII), a somewhat more complicated case. According to the stereospecificity rule the formation of 4-*O*-methyl- (XI) and 5-*O*-methyl-myoinositol (XII) and of 3-*O*-methylmucoinositol (XIV) would be




expected. Two of these products (XII and XIV) are *meso*-compounds, however, and reversal of the reaction would lead to racemization of the starting material and, subsequently, of all products. 4-*O*-Methyl- and 5-*O*-methyl-myoinositol were isolated from the reaction mixture; the former, after purification, retained its optical activity, indicating that racemization had not yet progressed significantly. The muco-derivative (XIV), a minor product, was not isolated.

Unfortunately, under the conditions of the reaction slow demethylation occurred. After 4 days, about 20% of the methyl ethers were converted into free inositols, and for this reason equilibrium could not be reached.

*Cyclohexanepentaols.*—All of the ten possible diastereomers of cyclohexanepentaol are now known.[6] Samples of the recently synthesized isomers enabled us to test the separation, by gas chromatography, of nine diastereoisomers as the penta-acetates. In general, satisfactory separation was achieved, although one pair of isomers gave coincident peaks and two others were poorly separated. The sequence of retention times parallels that of the inositols;[3] here also, increasing the number of axial acetoxyl groups reduces the retention time except when two such groups are in 1,3-relation to each other. As for the inositols, the all-*cis*-isomer emerges from the column much later than the others.

The epimerization of the lower cyclitols, in contrast to the inositols, is not completely stereospecific. The main reaction, which requires a hydroxyl group to have both a *cis* and a *trans* neighbour, is accompanied by other, slower inversions which seem to occur on the carbon atoms adjacent to the methylene group. It is still possible to determine the position of equilibrium of the main reaction and to isolate the main reaction products but, after prolonged heating, mixtures of many products are obtained.

The two naturally occurring cyclohexanepentaols,[5] the (+)-1,3,4/2,5-isomer (quercitol, XV) and the (−)-1,2,4/3,5-isomer (viburnitol, XVI) are readily interconvertible; equilibration is rapid, and gives a 39 : 54 mixture, with only a minor proportion of by-products. There is no loss of optical activity.

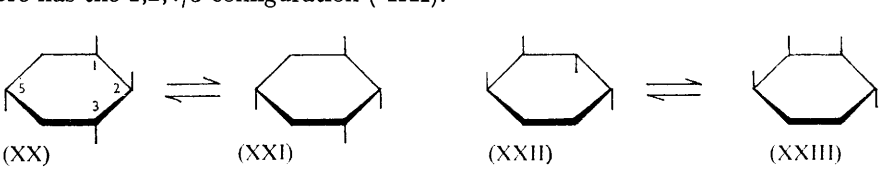
The 1,2,3,4/5- (XVII) and the 1,2,3/4,5-isomers [6] (XVIII) were also found to be interconvertible. Equilibrium was reached in about 24 hours but at least two other cyclohexanepentaols (probably the 1,2,5/3,4- and the 2,3,4/1,5-isomers) were then also present. Paper chromatography showed the presence of 1,2,3,5/4-cyclohexanepentaol (XIX), which is not separable from (XVII) by gas chromatography. The actual proportion of (XVII)

[6] McCasland, Furuta, Johnson, and Shoolery, *J. Amer. Chem. Soc.*, 1961, **83**, 2335, 4243.

to (XVIII) in equilibrium is therefore somewhat lower than that (24 : 65) measured by gas chromatography.

1,2,3,5/4-Cyclohexanepentaol [7] (XIX) was epimerized readily but the reaction is rather complex. The formation of three isomers was to be expected but the resulting mixture apparently contained every diastereoisomer except the all-*cis* compound. The 1,2,3/4,5- and the 1,2,5/3,4-isomers were isolated by chromatography.

*Cyclohexanetetraols.*—The epimerization of two pairs of tetraols was investigated. One pair had been obtained by Dangschat and Fischer [8] in the reduction of (+)-3,4-*O*-isopropylidene-3,4/5-trihydroxycyclohexanone, followed by acid hydrolysis. One of these compounds must be the 1,2,5/3- and the other the 1,2/3,5-cyclohexanetetraol but the configurations were not determined. It is possible, however, to assign the configurations by considering the optical rotation of the two tetraols.[9] The method suggested by Whiffen allows the prediction of the optical rotation of polyhydroxycyclohexanes with considerable accuracy.[10] The 1,2/3,5-tetraol would be predominantly in the *ax,eq/eq,eq* conformation for which the calculated value of the molecular rotation is −90°. The tetraol of m. p. 151° has a molecular rotation of −90° and is therefore assigned the 1,2/3,5 configuration (XX). The 1,2,5/3-isomer would be a mixture of the *eq,ax,eq/ax* and the *ax,eq,ax/eq* conformations, the former predominating; the calculated values of the molecular rotations are +45° and −90°, respectively. The tetraol of m. p. 208° has a molecular rotation of −12°, and therefore has the 1,2,5/3 configuration (XXI).




(XX) (XXI) (XXII) (XXIII)

The two tetraols were readily interconvertible by acid-catalysed epimerization. Equilibrium was reached after 7 hours when 50% of (XX) and 29% of (XXI) were present. Two other products were slowly formed but did not hinder the determination of the position of equilibrium.

The position of the equilibrium confirms the assignment of configurations since (XX), with one axial hydroxyl group, is expected to be more stable than (XXI) which has two axial groups in either chair form. Interconversion by epimerization occurs at C-2, but in the original preparation of the tetraols epimers were obtained owing to the establishment of different configurations at C-5. In fact, inversion at either centre will give the same products.

The reaction of one other tetraol was investigated. 1,2/3,4-Cyclohexanetetraol [11] (XXII) was epimerized smoothly to another compound, presumably the 1,2,3/4-isomer (XXIII). The reaction was slow, but the formation of other tetraols much slower. Since much destruction of the tetraols occurred, it must be assumed that they were destroyed at equal rates for the equilibrium composition to have significance. After 6 days equilibrium was probably reached, with 25% of (XXII) and 58% of (XXIII) present.

The reaction of quinic acid, another cyclohexanetetraol, has been reported elsewhere.[12]

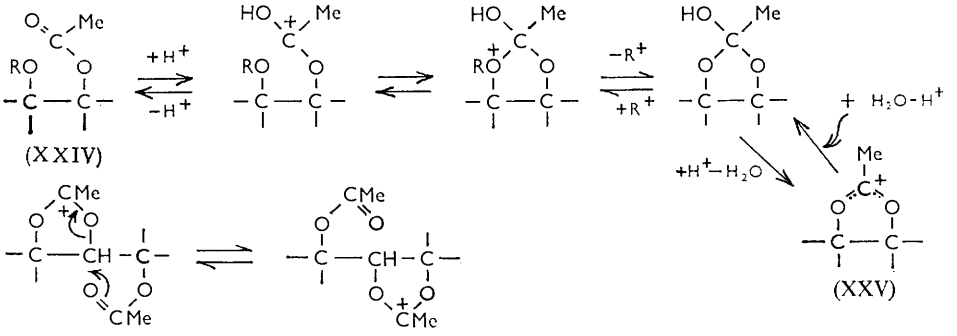
*The Mechanism of the Reaction.*—Acetic acid in high concentration is required for the epimerization, which will not occur in formic acid. Under the conditions of the reaction, acetylation and deacetylation occur; whether the starting material is a cyclitol or its acetate, a mixture of partially acetylated derivatives is formed. The approximate composition of this mixture was determined, in one case, by gas chromatography: after

[7] Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2618.
[8] Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756.
[9] Dr. D. H. Whiffen, personal communication, 18/10/61.
[10] Whiffen, *Chem. and Ind.*, 1956, 964.
[11] Angyal and Gilham, *J.*, 1958, 375.
[12] Gorin, *Canad. J. Chem.*, 1963, **41**, 2417.

refluxing in 95% acetic acid for 4 hours, myoinositol was acetylated to the extent of 3·7 acetyl groups per molecule.

Any mechanism for the epimerization must explain: (i) why it is reversible; (ii) why *cis* and *trans* hydroxyl groups are necessary on the adjacent carbon atoms; and (iii) the role acetic acid plays in the reaction.

Acetic acid was also found [13] necessary in another inversion reaction of glycols, the conversion of *cis*-glycols into *trans*-chlorohydrins, for which Boschan and Winstein [13] suggested a mechanism in which acetic acid formed a cyclic acetoxonium ion; this could similarly explain the stereospecificity of the epimerization of cyclitols, as shown in the formulæ (R = H):




A monoacetate (XXIV) of a vicinal glycol will form a cyclic acetoxonium ion (XXV) in the presence of a strong acid if the steric relationship is favourable; for this, the vicinal oxygen atoms in a cyclohexane system must be *cis*-related. If another acetoxy-group is *trans*-situated on an adjacent carbon atom, the system has the right configuration for nucleophilic attack by the acetoxy-group, involving a shift of an electron-pair towards the positive centre. Since the position of all of the atoms involved changes only slightly and an analogous structure is formed, the reaction would be expected to occur smoothly and reversibly, with an inversion of configuration on the middle carbon atom of a *cis–trans* sequence. *cis*-Hydroxyl groups are required for formation of the cyclic acetoxonium ion, and a *trans*-hydroxyl group for nucleophilic attack; hence this mechanism explains the steric requirements of the reaction.

When the reaction is carried out in glacial acetic acid, the cyclitols would be fully acetylated; acetoxonium ions may then be formed by a similar mechanism, involving loss of acetylium ions, as shown by formulæ (XXIV) to (XXV) (R = Ac).

This epimerization is closely related to a number of other reactions, in particular to the recently described epimerization of cyclitols in liquid hydrogen fluoride.[14] Usually this reaction leads to the same products as described above, but equilibrium is apparently not reached. Acetyl groups are lost, probably by the formation of the volatile acetyl fluoride, and the reaction ceases. Unexpectedly, myoinositol is converted in good yield into the thermodynamically much less stable muco-isomer; the latter, which is rich in axial groups, is perhaps more readily deacetylated and thereby withdrawn from further reaction. The reaction in hydrogen fluoride probably occurs by the mechanism outlined above; Hedgley and Fletcher [14] postulated the initial formation of acetoxonium ions with seven-membered rings but these appear to be less stable than the nearly planar five-membered rings now suggested.

Other related reactions are the epimerizations of some sugar acetates in liquid hydrogen fluoride,[15] the conversion of lactose into " neolactose " under the influence of phosphorus

[13] Boschan and Winstein, *J. Amer. Chem. Soc.*, 1956. **78**, 4921.
[14] Hedgley and Fletcher, *J. Amer. Chem. Soc.*, 1962, **84**, 3726.
[15] Pedersen and Fletcher, *J. Amer. Chem. Soc.*, 1960, **82**, 945; Pedersen, *Acta Chem. Scand.*, 1962, **16**, 1831; 19th I.U.P.A.C. Congress, London, 1963, Abstracts, p. 42.

pentachloride and aluminium chloride,[16] and the epimerization of acetylated 6-deoxy-6-iodo-*aldehydo*-sugars in the presence of zinc chloride and acetic anhydride.[17] The initial step in all these is probably the concurrent formation of a halogen anion and a cyclic acetoxonium ion.

*The Free Energies of Cyclitols.*—From the equilibrium constants of several epimerization reactions we calculated the differences between the free energies of several cyclitols and compared them with the values calculated from the energies of interaction between non-bonded atoms, according to the tenets of conformational analysis. Similar calculations have been attempted by Angyal and McHugh,[18] and by Lemieux and Chü.[19]

The calculations are based on two assumptions: (i) that the cyclohexane ring assumes a geometrically perfect chair form; and (ii) that the interaction energies are additive, *i.e.*, the value of one non-bonded interaction is not affected by other interactions in the molecule. Neither is strictly true, because the chair form of the molecule is slightly distorted by interactions between groups and so the relative positions of other interacting groups are changed. With comparatively small groups, such as hydroxyl, however, the distortion is considered to be negligible.

Only three non-bonded interactions were taken into account: that between two axial oxygen atoms, designated ($O_a$:$O_a$); that between an axial hydrogen and axial oxygen atom, ($O_a$:$H_a$); and that between two oxygen atoms on adjacent carbon atoms, at a dihedral angle of 60°, ($O_1$:$O_2$). In the last, the two atoms may both be equatorial, or one may be axial and the other equatorial. Other interactions, estimated to account for less than 0·05 kcal./mole, were neglected.

Angyal and McHugh [18] determined the interaction energies for free cyclitols in aqueous solution at 25° as ($O_a$:$O_a$) = 1·9, ($O_a$:$H_a$) = 0·45, and ($O_1$:$O_2$) = 0·35 kcal./mole. Lemieux and Chü's values,[19] 2·08, 0·18, and 0·55, respectively, refer to fully acetylated sugars in a 1 : 1 mixture of acetic acid and acetic anhydride. Since our cyclitols are partially acetylated, values intermediate between the above figures should be most appropriate. It was found that best agreement with the experimental results was obtained with the values ($O_a$:$O_a$) = 2·1, ($O_a$:$H_a$) = 0·4, and ($O_1$:$O_2$) = 0·5 kcal./mole.

The difference between the entropies of epimeric cyclitols is regarded as negligible, except as regards two factors. Entropy due to symmetry [20] is $\Delta S_{sym} = -\boldsymbol{R} \ln \sigma$, where $\sigma$ is the " symmetry number " or the number of ways in which the molecule may be rotated to give an equivalent structure. Of the cyclitols here studied, (±)-inositol, neoinositol, and 1,2/3,4-cyclohexanetetraol have symmetry numbers of 2; hence, in the calculations, their free energy has to be increased by $-T\Delta S_{sym} = \boldsymbol{R}T \ln 2 = 0{\cdot}5$ kcal./mole (at 117°).

The interactions were calculated for both chair forms of each cyclitol.[21] The conformational standard free energy for each cyclitol is then given by the formula $G^\circ = G^\circ_1 N_1 + G^\circ_2 N_2 + \boldsymbol{R}T(N_1 \ln N_1 + N_2 \ln N_2)$, in which the final term represents the free energy due to the entropy of mixing; $G^\circ_1$ and $G^\circ_2$ are the calculated standard free energies of the two chair forms, and $N_1$ and $N_2$ are their mole fractions, which can be calculated from $G^\circ_1 - G^\circ_2 = -\boldsymbol{R}T \ln N_1/N_2$, since $N_1 + N_2 = 1$. When one chair form has a much higher free energy (by about 2·0 kcal./mole) than the other, it can be disregarded because $N_2$ becomes very small and then $G^\circ = G^\circ_1$; this applies to the inositols, except for the two chair forms of alloinositol, which are enantiomorphs and therefore of equal energy: the entropy-of-mixing term then is $\boldsymbol{R}T \times 2 \times 0{\cdot}5 \ln 0{\cdot}5 = -0{\cdot}5$ kcal./mole (at 117°). By contrast, the two chair forms of muco-inositol are equivalent and there is no

[16] Kunz and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1978, 2435; Richtmyer and Hudson, *ibid.*, 1935, **57**, 1716; 1936, **58**, 2534.
[17] Micheel and Böhm, *Tetrahedron Letters*, 1962, 107.
[18] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.
[19] Lemieux and Chü, Abstracts of Papers, *Amer. Chem. Soc.*, 1958, **133**, 31N.
[20] Benson, *J. Amer. Chem. Soc.*, 1958, **80**, 5151.
[21] See, *e.g.*, Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, 1962, p. 214.

entropy of mixing. If a compound is racemic, it is a mixture of two compounds of equal energy and the entropy-of-mixing term is −0·5 kcal./mole at 117°.

Two examples of the calculations are given. For alloinositol, the conformational free energy is $5(O_1{:}O_2) + 4(O_a{:}H_a) + (O_a{:}O_a)$ + (entropy-of-mixing) = 2·5 + 1·6 + 2·1 − 0·5 = 5·7 kcal./mole. For 1,3,4/2,5-cyclohexanepentaol the total of the interaction energies of the *eq-eq-eq-ax-ax* chair form is 3·1, of the *ax-ax-ax-eq-eq* form is 4·7; $N_1/N_2$ is 8, and therefore $G° = 0·889 \times 3·1 + 0·111 \times 4·7 + 2 \times 390\ (0·889 \ln 0·889 + 0·111 \ln 0·111)$ = 3·05 kcal./mole at 117°. The free-energy contents of the other cyclitols were similarly calculated to be inositols: myo; 3·8, (±)-4·1; neo, 5·1; muco, 5·7; epi, 5·9; cyclohexanepentaols: 1,2,4/3,5, 2·8; 1,3,4/2,5, 3·05; 1,2,3/4,5, 3·55; 1,2,3,4/5, 4·55; cyclohexanetetraols: 1,2/3,4, 2·8; 1,2,3/4, 2·3; 1,2/3,5, 1·8; and 1,2,5/3, 2·1 kcal./mole. All these values are relative to imaginary cyclitols, of the same structure, in which there are no non-bonded interactions.

The differences thus calculated between the free energies of epimeric pairs of cyclitols are compared with the experimentally found values (calculated from $\Delta G° = -RT \ln K$, with an estimated precision of ±0·1) in the Table. The agreement is satisfactory and seems to justify the method used for calculating the non-bonded interactions.

Free-energy differences between epimeric pairs of cyclitols

| Compounds | $K$ | $\Delta G°$ found (kcal./mole) | $\Delta G°$ calc. (kcal./mole) |
|---|---|---|---|
| Inositols | | | |
| myo – (±) | 1·3 | 0·2 | 0·3 |
| (±) – muco | 8·3 | 1·65 | 1·6 |
| neo – allo | 2·7 | 0·75 | 0·6 |
| allo – epi | 1·4 | 0·25 | 0·2 |
| Cyclohexanepentaols | | | |
| 1,2,4/3,5 – 1,3,4/2,5 | 1·4 | 0·25 | 0·25 |
| 1,2,3/4,5 – 1,2,3,4/5 | >2·7 | >0·75 | 1·0 |
| Cyclohexanetetraols | | | |
| 1,2,3/4 – 1,2/3,4 | 2·3 | 0·65 | 0·5 |
| 1,2/3,5 – 1,2,5/3 | 1·7 | 0·4 | 0·3 |

A few epimerizations were carried out in acetic acid containing 10% of acetic anhydride. The equilibrium constants were somewhat different from those obtained in 95% acetic acid, being 0·92 for the myoinositol–(±)-inositol pair, 7·0 for the (±)-inositol–mucoinositol pair, and 1·0 for the 1,2,4/3,5-cyclohexanepentaol–1,3,4/2,5-cyclohexanepentaol system. From these the interaction energies of acetoxy-groups were calculated: $(O_1{:}O_2)$ 0·6, $(O_a{:}H_a)$ 0·3, and $(O_a{:}O_a)$ 2·1 kcal./mole. These values, which now refer to fully acetylated cyclitols, are close to those given by Lemieux and Chü.[19]

## Experimental

Evaporations were carried out under reduced pressure below 50°. Unless otherwise stated, acetone–water (4 : 1 v/v) was used as solvent for paper chromatography.[22] For chromatography on cellulose powder columns, acetone–water (10 : 1 v/v) was used as eluant.

*Gas Chromatography.*—For most of the gas-chromatographic separations LAC I-R-296 (manufactured by Cambridge Industries Co., Massachusetts) was used as the stationary phase.[3] The polyester (1½%) was supported on Celite, which had been washed with acid and then with alkali, and heated overnight at 800°. The carrier gas was nitrogen with a flow rate of 30—40 ml./min. The column temperature was usually 210° but for the acetates of the cyclohexanetetraols 199° proved satisfactory. No attempt was made to reproduce emergence times from run to run, since comparison with known materials was far more reliable. Quantitative estimations of mixtures were made by triangulation of the signals.

[22] Angyal, McHugh, and Gilham, *J.*, 1957, 1432.

The following emergence times were found for the cyclohexanepentaol penta-acetates; 1,2,3/4,5, 7·2; 1,2,5/3,4, 8·4; 1,3,4/2,5, 8·4; 1,2,4/3,5, 9·5; 2,3,4/1,5, 9·9; 1,2,3,4/5, 11·9; 1,2,3,5/4, 12·4; 1,3,5/2,4, 13·7; *cis*, 18·2 min. 1,2,4,5/3-Cyclohexanepentaol was not available. As a standard, (−)-inositol hexa-acetate emerged at the same time as 1,2,3,4/5-cyclohexanepentaol penta-acetate.

The acetates of myo- and muco-inositol cannot be separated in this way. Mixtures containing these cyclitols were analysed on a 4-ft. column of 1·5% of GP91A G.E. Nitrile Silicone Gum XE-60 (Analytical Engineering Laboratories, Hamden, Connecticut) on silanized Chromosorb W (60—80 mesh) at 220° with helium as carrier gas. Mucoinositol emerged after the myo-isomer.

*Materials.*—The inositols and most of the cyclohexanepentaols were prepared by methods previously described.[5] Dr. G. E. McCasland generously supplied us with samples of 1,2,3/4,5-, 1,2,5/3,4-, and 1,2,3,4/5-cyclohexanepentaols.[6] (+)-1,2/3,4-Cyclohexanetetraol was prepared by Angyal and Gilham's method.[11] Our preparation of the other two tetraols is described, since it differs from those of Dangschat and Fischer.[8]

(+)-3,4-*O*-Isopropylidene-3,4/5-trihydroxycyclohexanone [23] (180 mg.) in ethyl acetate (10 ml.) was shaken overnight with platinum catalyst (50 mg.) in an atmosphere of hydrogen. The mixture was then filtered; the syrup obtained on evaporation was heated for 1 hr. at 100° with water (50 ml.) containing a drop of formic acid. The product obtained on evaporation was a mixture of 77% of 1,2,5/3-cyclohexanetetraol and 23% of the 1,2/3,5-isomer (gas chromatography). Two crystallizations from ethanol–ethyl acetate yielded the (−)-1,2,5/3-tetraol (80 mg.), m. p. 200° (Found: C, 48·4; H, 8·05. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%). Dangschat and Fischer, who prepared the compound by hydrogenation over Raney nickel at high pressure, reported [8] m. p. 208°.

The isopropylidene ketone (150 mg.) was dissolved in a solution of sodium borohydride (100 mg.) in water (10 ml.). Next day, an excess of acetic acid was added and the solution was shaken with Amberlite IR120. Filtration and evaporation gave a solid residue which was dissolved in methanol and recovered by evaporation four times, to remove the boric acid. The resulting mixture was shown by gas chromatography to consist of 56% of the 1,2,3,5-tetraol and 44% of the 1,2,5/3-isomer, which were separated by chromatography on cellulose powder, with 2-methylpropanol–water (19 : 1) as eluant. The material in the slower-moving fractions yielded (−)-1,2,/3,5-cyclohexanetetraol (25 mg.), m. p. 152—154° on crystallization from ethanol–ethyl acetate. Dangschat and Fischer, who prepared the compound by the Meerwein–Ponndorf reaction, reported [8] m. p. 151°.

*Standard Conditions for Epimerizations.*—Epimerizations were carried out by refluxing a 1% solution of a cyclitol in 95% (v/v) acetic acid containing 1·5% by vol. of sulphuric acid. For experiments carried out on a small scale, sealed tubes were immersed for a time in boiling 95% acetic acid (113°). The solution was then cooled and mixed with an equal volume of acetic anhydride. After 4 hr. the solution was poured into a solution of sodium hydrogen carbonate strong enough to neutralize the sulphuric acid; after a further 3 hr. the mixture was shaken with chloroform and the extract washed, dried, and evaporated. Samples were then analysed by gas chromatography.

*Interconversion of Myo-, Muco-, and* (±)-*Inositol*—Starting with myoinositol, the following results were obtained [time in hr., % of myo + muco, % of (±)]: 25, 84, 16; 73, 78, 22; 121, 66, 34; 336, 55, 44%. With (−)-inositol, the racemization was also followed by determining the optical rotation after deacetylation of the mixture [hr., myo + muco, (±), (−)]: 5, 14, 86, 77; 18·5, 29, 71, 53; 60, 59, 41, 26; 336, 55, 44, 0%. Reactions followed by means of the Silicone Gum column, in 95% (v/v) acetic acid [days, muco, myo, (±)]: 8, 3·4, 65, 32; 14, 4·3, 57, 39; 21, 4·9, 54, 41%; in acetic acid containing 10% acetic anhydride: 2, 5·8, 56, 38; 5, 6·4, 45, 49; 8, 6·7, 43, 50; 11, 7·0, 45, 47%.

After epimerization of (±)-inositol for 190 hr., two crystallizations from ethanol gave hexa-*O*-acetylmyoinositol, m. p. and mixed m. p. 208—211°. Myoinositol under similar conditions gave a mixture, which was deacetylated and chromatographed on cellulose powder. Two crystallizations of the appropriate fraction from aqueous ethanol gave (±)-inositol, m. p. and mixed m. p. 247—249°. (−)-Inositol was epimerized for 20 hr. and the resulting mixture was deacetylated and fractionated on a cellulose powder column; the mucoinositol fraction was acetylated to yield hexa-*O*-acetylmucoinositol, m. p. and mixed m. p. 179—182°.

[23] Fischer and Dangschat, *Ber.*, 1932, **65**, 1009.

*Interconversion of Epi-, Allo-, and Neo-inositol.*—The following analyses were obtained [hr., neo, allo, epi]: starting with epi-inositol: 2, 1, 12, 85; 6, 3, 29, 64; 10·5, 9, 40, 48; 21, 22, 43, 32; 45, 48, 31, 19%. Starting with alloinositol: 2, 11, 82, 7; 4·5, 18, 68, 14; 10, 28, 50, 22; 55, 61, 28, 10; 288, 54, 21, 18, impurity (myo?) 7%. Starting with neoinositol: 6, 92, 7, 1; 14, 83, 12, 4; 61, 65, 24, 11; 288, 62, 22, 11, impurity (myo?) 5%.

Hexa-*O*-acetylepi-inositol (2·3 g.) was heated in the isomerization reagent (50 ml.) for 80 hr. The product was acetylated, and to the mixture of acetates (2·38 g.) in chloroform (30 ml.) 0·1N-methanolic sodium methoxide solution (40 ml.) was added. After 2 hr., excess of acetic acid was added, the solution evaporated, and the residue stirred with hot water (15 ml.); next day, filtration gave neoinositol (0·42 g., 41%). On acetylation hexa-*O*-acetylneoinositol, m. p. and mixed m. p. 262°, was obtained.

After a similar isomerization, the free polyols were chromatographed on cellulose powder. Alloinositol was obtained from the first fractions and on acetylation yielded the hexa-acetate, m. p. and mixed m. p. 137—139°.

*Isomerization of Pinitol.*—The following results were obtained [hr., pinitol, 3-*O*-methylmucoinositol (?), (+)- and (±)-inositol, sequoyitol, ononitol, myoinositol]: 24, 66, 14, 4, 8, 5, 2; 90, 23, 9, 9, 23, 20, 13; 336, 7, 2, 19, 6, 9, 52%. Small amounts of two unidentified compounds emerged before pinitol.

Pinitol (3·8 g.) was heated in the isomerization reagent (38 ml.) for 48 hr. After acetylation and deacetylation (NaOMe), $Na^+$ was removed with Amberlite IR120 and the product fractionated on a cellulose-powder column. Pinitol and faster-moving materials (1·29 g.) were obtained first, followed by a mixture of myoinositol methyl ethers (0·66 g.), and then free inositols (0·38 g.). The mixture of methyl ethers was fractionally crystallized from ethanol. The first fraction (0·28 g.) consisted of sequoyitol and after recrystallization from aqueous ethanol had m. p. and mixed m. p. 237—239°. The residue from the contents of the mother-liquors, on slow crystallization from ethanol–ethyl acetate, gave ononitol (166 mg., m. p. 165—170°, then 60 mg., m. p. 155—160°). After recrystallization from aqueous ethanol it had m. p. 170—172°, $[\alpha]_D$ +4° ± 1° (*c*, 0·9 in $H_2O$). The penta-acetate, crystallized from ethanol–hexane, had m. p. 127—130°, $[\alpha]_D$ −11° (*c* 0·7 in $CHCl_3$). Plouvier reported [24] m. p. 172°, $[\alpha]_D$ +6·6°; and m. p. 122 and 131°, $[\alpha]_D$ −12°, respectively.

*Isomerization of Quebrachitol.*—The results were [hr., 1-*O*-methyl-(+)-inositol (?), quebrachitol, bornesitol, and 2-*O*-methylmucoinositol, (−)- and (±)-inositol, myoinositol]: 29, 3, 78, 12, 6, 0; 101, 16, 46, 23, 10, 6; 336, 17, 14, 20, 19, 31%.

Quebrachitol (3·0 g.) was isomerized for 1 week in the isomerization reagent (100 ml.). The deacetylated polyols were separated on a cellulose powder column. From the appropriate fractions (−)-bornesitol (0·3 g.) was obtained; its penta-acetate, crystallized from ethanol, had m. p. and mixed m. p. 141—143°, $[\alpha]_D$ −10° (*c* 1·6 in acetone).

*Interconversion of* (+)-1,3,4/2,5- *and* (−)-1,2,4/3,5-*Cyclohexanepentaol.*—The results were [hr., 1,2,3/4,5-, 1,3,4/2,5- (or 1,2,5/3,4-), 1,2,4/3,5- (or 2,3,4/1,5-), 1,2,3,4/5- or 1,2,3,5/4, 1,3,5/2,4-pentaol]: starting with 1,3,4/2,5-pentaol: 2·75, 0, 85, 15, 0, 0; 6, 0, 66, 34, 0, 0; 20, 0, 44, 52, 1, 2; 37, 0, 41, 54, 1, 4; 288, 7, 29, 39, 9, 17%; starting with 1,2,4/3,5-pentaol: 6, 0, 27, 74, 0, 0; 13, 0, 35, 61, 0, 3; 47, 0, 37, 54, 2, 9; 288, 7, 29, 38, 9, 17%.

In acetic acid with 10% of acetic anhydride, the 1,3,4/2,5-pentaol readily isomerized into the 1,2,4/3,5-isomer; after 10, 19, 27, 40, and 57 hr., 65, 62, 52, 48, and 50%, respectively, of the former remained, the amount of by-products being negligible.

(+)-1,3,4/2,5-Cyclohexanepentaol (0·6 g.) was heated with the isomerization reagent for 24 hr. The fully acetylated mixture deposited crystals from ethyl acetate–hexane which on recrystallization yielded the penta-acetate of (−)-1,2,4/3,5-cyclohexanepentaol, m. p. and mixed m. p. 122—124°. The free pentaol had m. p. 179—180°, $[\alpha]_D$ −44° (*c* 0·6 in $H_2O$).

*Interconversion of* 1,2,3,4/5- *and* 1,2,3/4,5-*Cyclohexanepentaol.*—The following results were obtained [hr., 1,2,3/4,5-, 1,2,5/3,4- or 1,3,4/2,5-, 1,2,4/3,5- or 2,3,4/1,5-, 1,2,3,4/5- or 1,2,3,5/4-, 1,3,5/2,4-pentaol): starting with the 1,2,3,4/5-pentaol: 2, 28, 1, 2, 69, 0; 5, 47, 4, 4, 44, 0; 42, 56, 9, 8, 24, 2; 90, 47, 13, 12, 26, 2; 168, 49, 12, 11, 26, 3%; starting with the 1,2,3/4,5-pentaol: 6, 82, 4, 0, 14, 0; 18, 64, 9, 4, 22, 0; 42, 58, 9, 7, 25, 1; 144, 43, 15, 13, 25, 4%.

*Isomerization of* 1,2,3,5/4-*Cyclohexanepentaol.*—The results were (figures as in the previous example): 6, 2, 5, 0, 86, 6; 29, 6, 14, 7, 66, 6; 120, 13, 21, 17, 41, 8%. The solution darkened rapidly.

[24] Plouvier, *Compt. rend.*, 1955, **241**, 983.

*Isomerization of* (+)-1,2/3,4-*Cyclohexanetetraol.*—The proportions of 1,2/3,4- to 1,2,3/4-isomer were 55 : 45 after 5·5 hr., 39 : 55 after 24 hr., 25 : 58 after 144 hr. Three other products were observed in small amounts.

The 1,2/3,4-tetraol (0·25 g.) was isomerized for 5 hr. The mixture of the deacetylated tetraols was fractionated on a cellulose-powder column with 2-methylpropanol containing 5% water as eluant. From the slower-running fractions 3 mg. of material, m. p. 157—160°, was obtained. Posternak and Reymond recorded [25] m. p. 159—160° for (−)-1,2,3/4-cyclohexanetetraol.

*Interconversion of* (−)-1,2/3,5- *and* 1,2,5/3-*Cyclohexanetetraol.*—The following results were obtained (hr., unknown, 1,2/3,5-, 1,2,5/3-tetraol, unknown): starting with the 1,2/3,5-tetraol: 7, 8, 55, 33, 4; 17, 12, 50, 29, 9; 48, 14, 46, 26, 14%. Starting with the 1,2,5/3-tetraol: 7, 7, 54, 35, 4; 17, 11, 50, 30, 9; 48, 15, 46, 25, 14%.

(−)-1,2,5/3-Cyclohexanetetraol (250 mg.) was isomerized for 6 hr. and the deacetylated product was fractionated on a cellulose column, 2-methylpropanol with 5% water again being the eluant. The material in the slower-running fractions, after two crystallizations from ethyl acetate–ethanol, gave the (−)-1,2/3,5-tetraol, m. p. 146—149°, undepressed by an authentic sample.

The authors are grateful to Dr. G. E. McCasland, University of San Francisco, for his gift of several cyclohexanepentaols and to Dr. S. R. Johns for his assistance with exploratory experiments. One of us (M. E. P.) is indebted to the Commonwealth Scientific and Industrial Research Organization (Australia) for a studentship.

School of Chemistry, University of New South Wales,
Sydney, Australia. [*Received, April 3rd,* 1964.]

[25] Posternak and Reymond, *Helv. Chim. Acta,* 1955, **38**, 195.