124. *Cyclitols. Part I.* iso*Propylidene Derivatives of Inositols and Quercitols. The Structure of Pinitol and Quebrachitol.*

By S. J. Angyal and C. G. Macdonald.

By the use of acetone containing zinc chloride and acetic acid, several cyclitols have been converted into *iso*propylidene derivatives. The presence of at least two contiguous hydroxyl groups in *cis*-position is necessary for reaction to occur. In the case of *epi*- and (−)-inositols, however, both di- and tri-*iso*propylidene compounds have been obtained; in the latter, contiguous hydroxyl groups in *trans*-position have reacted. The stereochemistry of these derivatives is discussed.

Pinitol gave a di*iso*propylidene, and quebrachitol a mono*iso*propylidene derivative, the latter consuming one mole of periodate. It is therefore concluded that pinitol is 3-methyl (+)-inositol, and quebrachitol is 2-methyl (−)-inositol.

In the introduction, proposals are made for the nomenclature and numbering of cyclitols.

Nomenclature and Numbering (with N. K. Matheson).—Although the chemistry of the cyclitols has greatly expanded in the last fifteen years and there are at present many workers active in this important field (see, *e.g.*, Fletcher, *Adv. Carbohydrate Chem.*, 1948, **3**, 45), there exists neither an adequate system of nomenclature nor a generally accepted method of numbering. When naming and numbering the partially substituted cyclitols described in this paper, the lack of a system became particularly apparent; and other work in progress foreshadows further difficulties in nomenclature. In the following paragraphs therefore some rules on nomenclature and numbering are proposed; they will be used in this and in the subsequent papers of this series.

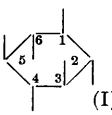
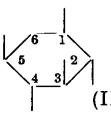
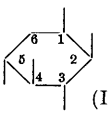
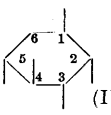
(*A*) To avoid the introduction of many new names, it is proposed that all *cyclo*hexanehexols be called inositols, all *cyclo*hexanepentols quercitols, and all pentahydroxy*cyclo*hexanones inososes, the various isomers being distinguished by prefixes. Cyclitols with

less than five hydroxyl groups will be described as derivatives of *cyclo*hexane, *e.g.*, *cyclo*hexanetetrol. The present names of inositols conform to this proposal, the only exception being scyllitol (I), for which the name *scyllo*inositol is suggested. As there is only one pair of optically active inositols, the symbols (+) and (−) describe them unequivocally.

For the inososes, Posternak (*Helv. Chim. Acta*, 1942, **25**, 746) introduced a system of double prefixes, *e.g.*, *scyllo-meso*-inosose, to indicate the two inositols from which they are theoretically derivable. This proved cumbersome and many authors have dropped one of the prefixes. It is now suggested that only one prefix be used and this be the same as for the corresponding quercitols (derived by replacement of the carbonyl by a methylene group). This is already the case with *epi*quercitol (May and Mosettig, *J. Org. Chem.*, 1949, **14**, 1137) which has the same configuration as *epi*inosose (Posternak, *Helv. Chim. Acta*, 1936, **19**, 1333). Under this scheme Posternak's " desoxyscyllitol " (II) (*ibid.*, 1941, **24**, 1045), having the same configuration as *scyllo*inosose, would be called *scyllo*quercitol. Viburnitol (III) (Power and Tutin's " lævorotatory quercitol ", *J.*, 1904, **85**, 624; Hérissey and Poirot, *J. Pharm. Chim.*, 1937, [viii], **26**, 385; Posternak and Schopfer, *Helv. Chim. Acta*, 1950, **33**, 343) would be called *vibo*quercitol and the enantiomorph of the corresponding keto-compound (insufficiently named " d-inosose " by Magasanik and Chargaff, *J. Biol. Chem.*, 1948, **175**, 929) would be (+)-*vibo*inosose. For the common quercitol (IV) (" acorn sugar ") the name *proto*quercitol (πρωτος, first) is proposed.

Derivatives of cyclitols in which other than hydroxyl groups occur but in which the asymmetry of the carbon atoms is retained, *e.g.*, inosamines (pentahydroxy*cyclo*hexylamines), bromoquercitols, are best described as derivatives of deoxy-cyclitols, *e.g.*, bromodeoxy-inositol.

(*B*) In the past nearly every worker has used a different method of numbering the cyclitols. (For a recent discussion of cyclitol numbering and for references, see Anderson and Lardy, *J. Amer. Chem. Soc.*, 1950, **72**, 3141.) Magasanik and Chargaff (*J. Biol. Chem.*, 1948, **174**, 173) have made the only attempt to introduce a logical system of numbering, but their method is contrary to the accepted usage that carbon atoms bearing functional groups should have the lowest possible numbers; and in their system the equivalent positions in enantiomorphs have different numbers. This is objectionable in principle and makes it impossible to describe racemic compounds by a single expression (see below).


(I)

(II)

(III)

(IV)

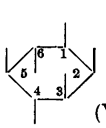
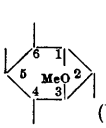
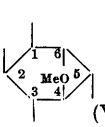
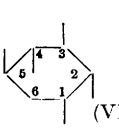
The system proposed in the following paragraphs retains the essential features of Magasanik and Chargaff's method but attempts to eliminate its weaknesses and is more generally applicable, especially to optically active compounds.

For the purposes of numbering, the *cyclo*hexane ring is regarded as a planar hexagon resulting from an imaginary flattening of the puckered ring; the directions of the valencies can then be described as " up " and " down."

Carbon atoms carrying functional groups have the lowest possible numbers, according to the accepted usage in organic chemistry. Thus, in inososes the ketonic carbon atom will be $C_{(1)}$; in quercitols the methylene group, $C_{(6)}$.

*The larger number of functional groups on one side of the plane of the hexagon shall be described by the lowest possible numbers, e.g., meso*inositol will be numbered as in (V).

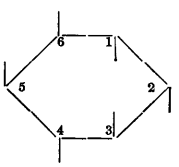
If the hydrogen atom of a hydroxyl group is replaced by another group and if the above rule has not yet determined the numbering unequivocally, then this substituted position shall be given the lowest possible number, *e.g.*, pinitol will be described as 3-methyl (+)-inositol (VI) and not as 4-methyl (+)-inositol (VII).


(V)

(VI)

(VII)

(VIII)

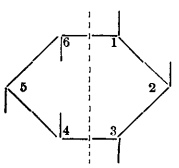
Every cyclitol can be written in two ways depending on which side is " up " and which is " down." It is proposed that the formulæ be written in such a way that the numbering is always clockwise. If, determined according to the above rules, it runs anticlockwise, *e.g.*, in formula (VIII) for (−)-*vibo*quercitol, the formula should be " turned on its back " to give (III). (+)-Inositol and (−)-inositol will then be written and numbered as in (IX) and (X), respectively; the corresponding positions have the same number (contrast Magasanik and Chargaff's method), and each carbon atom in one optical isomer has a configuration opposite to that of the same number in the other. It is further proposed that in symmetrical or racemic cyclitols, for the sake of uniformity, the lowest-numbered asymmetric carbon atom should be written with its functional group upwards, *e.g.*, (II), (XVII), (V).

(*C*) In the past, the enantiomorphs of cyclitols have been differentiated from each other by indicating the actual direction of their optical rotation. This is, obviously, a poor method because the direction of the rotation is not predictable from the structure of the compounds; it is justified only while the configuration of the enantiomorphs has not yet been determined. The configurations of most of the asymmetrical cyclitols are now known, such knowledge being, of course, not absolute but related, by degradation, to carbohydrates, *i.e.*, to the arbitrarily chosen configuration of D-glyceraldehyde. Cahn and Ingold's " sequence rule " (*J.*, 1951, 612) is unfortunately not applicable to inositols. The time therefore seems opportune for the introduction of a convention connecting the structure and the configurational symbol in an unambiguous way, as in the carbohydrate field. Proposals for such a convention have been submitted by us to this *Journal* but, at the Editor's suggestion, their publication will be deferred for further consideration and discussion. As an interim device, until a comprehensive symbolism has been devised, the enantiomorphous cyclitols will be distinguished by the (+) and (−) symbols, indicating the direction of their rotation. Compounds derived from asymmetrical cyclitols will be characterised by the symbol of the parent compound, *e.g.*, tri*iso*propylidene (−)-inositol will describe the compound made from (−)-inositol; but the symbol should not be taken to imply that the tri*iso*propylidene derivative itself is lævorotatory.

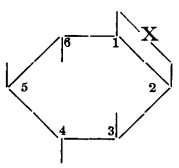
iso*Propylidene Derivatives of Cyclitols.*—The very fruitful technique of cyclic acetal formation has been extensively used in carbohydrate chemistry. In the field of the cyclitols, however, the method has been less successful. It is true that some related compounds, *e.g.*, quinic acid (H. Fischer, *Ber.*, 1921, **54**, 775), shikimic acid (Fischer and Dangschat, *Helv. Chim. Acta*, 1937, **20**, 705), conduritol (Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756), and a nitro-deoxy-inositol (Grosheintz and Fischer, *J. Amer. Chem. Soc.*, 1948, **70**, 1479), gave *iso*propylidene derivatives; but repeated attempts (Böeseken and Julius, *Rec. Trav. chim.*, 1926, **45**, 489; Karrer, *Helv. Chim. Acta*, 1926, **9**, 116; Micheel, Ruhkopf, and Suckfüll, *Ber.*, 1935, **68**, 1523) to condense *meso*inositol or *proto*quercitol with acetone or benzaldehyde failed until Dangschat (*Naturwiss.*, 1942, **30**, 146), working in collaboration with H. O. L. Fischer, reported the preparation of 1 : 2-*iso*propylidene *meso*inositol (XI) by the use of zinc chloride and acetic acid as catalyst. Only a preliminary account of this work has appeared, without experimental details; and Anderson and Wallis reported later (*J. Amer. Chem. Soc.*, 1948, **70**, 2931) that they were unable to repeat it.



(IX)

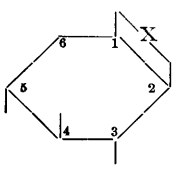


(X)



(XI)

X = $Me_2C<$



(XII)

Recently Posternak (*Helv. Chim. Acta*, 1950, **33**, 350) described the preparation of an *iso*propylidene derivative (XII) from *vibo*quercitol (III), using also a mixture of zinc chloride and acetic acid as catalyst. Following his conditions closely, we attempted the reaction of a number of cyclitols with acetone and were successful with all those compounds—including *meso*inositol—which contained at least two contiguous hydroxyl groups in *cis*-position. But there was found a great difference between the behaviour of *meso*inositol

and that of the other cyclitols. Even after prolonged heating with a large excess of acetone, zinc chloride, and acetic acid, a considerable amount of *meso*inositol remained undissolved; the other cyclitols reacted more readily: we found that the amounts of acetone and catalyst could be reduced considerably below those used by Posternak. It is apparent therefore that of the cyclitols *meso*inositol, the subject of previous attempts at acetal formation, was the least fortunate choice.

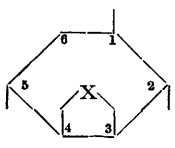
Nevertheless, the failure of Anderson and Wallis (*loc. cit.*) to condense *meso*inositol with acetone is not readily explained. Their conditions were practically the same as ours, yet after 5 days' boiling 96% of the inositol remained undissolved. Several authors (E. Fischer, *Ber.*, 1895, **28**, 2496; Freudenberg, Dürr, and Hochstetter, *ibid.*, 1928, **61**, 1735; Ohle, *ibid.*, 1938, **71**, 562) have reported that pure acetone was less suitable for such reactions than the commercial grade. Anderson and Wallis used "reagent acetone"; accordingly we made parallel runs with commercial acetone and with acetone carefully purified by permanganate oxidation and through the sodium iodide compound, but found no significant difference.

The structure of (XI) has been proved by degradation (Dangschat, *loc. cit.*), but formula (XII) was assigned by Posternak and Schopfer (*loc. cit.*) to *iso*propylidene *vibo*quercitol only on the assumption that the two hydroxyl groups in *cis*-position have reacted with acetone. Consumption of two mols. of periodate supports this structure but does not exclude the possibility of a 4 : 5-*iso*propylidene derivative. The assumption that only *cis*-hydroxyl groups will condense with acetone is based on wide experience in carbohydrate chemistry and particularly on the work of Derx (*Rec. Trav. chim.*, 1922, **41**, 318) who showed that *cis*-, but not *trans*-, 1 : 2-*cyclo*hexanediol gives an *iso*propylidene derivative. This point will be further discussed below.

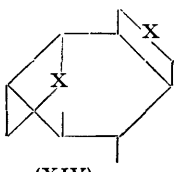
It is necessary to acetylate the water-soluble *iso*propylidene compounds in order to separate them from zinc chloride. Some of the resulting acetates were not obtained in the crystalline state; but after deacetylation every *iso*propylidene derivative crystallised.

*scyllo*Inositol (I) and *scyllo*quercitol (II), two cyclitols without contiguous *cis*-hydroxyl groups, did not react with acetone. The former remained undissolved, the latter dissolved without condensing with acetone. Since the cyclitols have very low solubility in acetone, this indicates that zinc chloride increases their solubility, presumably by complex formation, which may account for part or the whole of its catalytic activity. In the case of *scyllo*quercitol, when the zinc chloride was removed by the addition of pyridine, the cyclitol was also precipitated.

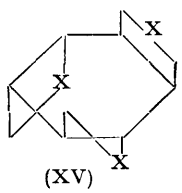
*proto*Quercitol was found to give a mono*iso*propylidene derivative. As there is only one pair of contiguous *cis*-hydroxyl groups in this molecule (Posternak, *Helv. Chim. Acta*, 1932, **15**, 948), structure (XIII) is assigned to it. In agreement with this it consumed one mol. of periodate.



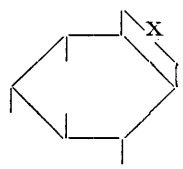
(XIII)



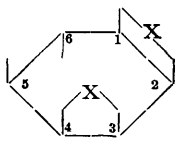
(XIV)



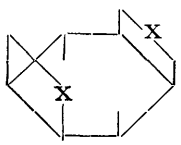
(XV)



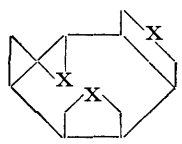
(XVI)



(XVII)



(XVIII)



(XIX)

X = $Me_2C<$

(−)-Inositol (X) gave two *iso*propylidene derivatives. The more soluble, also isolated as the diacetate, is a di*iso*propylidene compound. This inositol contains two pairs of *cis*-

hydroxyl groups and it is assumed that it is these which have reacted giving 1 : 2-5 : 6-di*iso*propylidene (−)-inositol (XIV); in accordance with this structure it consumes one mol. of periodate. The higher-melting, less soluble derivative could not be acetylated and was shown by analysis to be a tri*iso*propylidene derivative. In this compound two of the *iso*propylidene groups are in the same position as in (XIV) since partial hydrolysis of the former compound by dilute acetic acid gave the latter. The structure of the tri*iso*propylidene compound is therefore (XV), in which two hydroxyls in *trans*-position have condensed with the ketone. As a by-product of the hydrolysis a small amount of a mono-*iso*propylidene derivative (XVI) was isolated. It is to be noted that (−)-inositol, though dissymmetrical, has a two-fold axis of symmetry as indicated in (X); positions 1 and 6, 2 and 5, 3 and 4 are therefore equivalent, and removal of either *iso*propylidene group from (XIV) will give the same compound, 1 : 2-*iso*propylidene (−)-inositol (XVI).

The reaction of *epi*inositol with acetone is more complex. After a lengthy and wasteful separation, three crystalline products were obtained: two di- and one tri-*iso*propylidene derivatives. Of the former, the one obtained in larger amounts consumed one mol. of periodate and is therefore 1 : 2-3 : 4-di*iso*propylidene *epi*inositol (XVII); the other was not oxidised by periodate and is thus the 1 : 2-4 : 5-derivative (XVIII). Since the tri*iso*propylidene compound was converted into (XVII) by partial hydrolysis, its structure is (XIX) in which, again, two *trans*-disposed hydroxyl groups have reacted with acetone. As

FIG. 1.

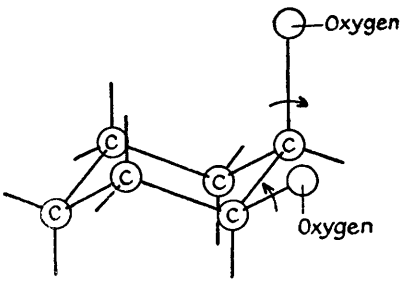
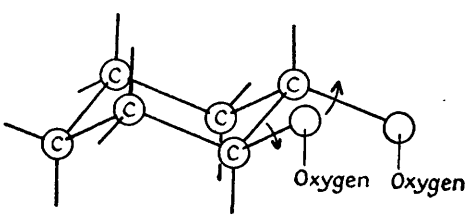


FIG. 2.



the two tri*iso*propylidene inositols are believed to be the first examples of cyclic acetal formation involving *trans*-hydroxyl groups in a *cyclo*hexane derivative, some discussion of their stereochemistry seems warranted.

The Stereochemistry of iso*Propylidene Cyclitols.*—It has been established by thermodynamical calculations (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488) and by electron-diffraction measurements (Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929) that the chair form is the most stable conformation of the *cyclo*hexane ring. In this form, three of the atoms attached to the ring carbon atoms are above, and three below, the ring ("polar" positions) whilst the other six surround the ring in an equatorial belt ("equatorial" positions) (Fig. 1). A twist of the carbon atoms through a single plane to the opposite chair form changes the polar into equatorial groups and *vice-versa*. This picture being kept in mind, the requirement of *cis*-relationship for cyclic acetal formation is far less obvious than the planar formulæ would suggest. The distance between two groups attached to adjacent carbon atoms is the same for two equatorial groups (" *trans* ") as for one equatorial and one polar (" *cis* "). In the case of hydroxyl groups, the distance between the oxygen atoms is 2·86 Å (if all valency angles on carbon are tetrahedral), a distance too large to be bridged by one carbon atom.* This explains why the cyclic acetal formation of cyclitols is more difficult than that of the open-chain sugar alcohols but does not explain the difference between the reactivity of *cis*- and *trans*-groups. To understand this, the deformation of the molecule during the reaction must be considered.

In order to bring two *cis*-disposed hydroxyl groups nearer to each other, the two carbon atoms to which they are attached will have to rotate around their connecting line as shown

* Two *trans*-situated hydroxyl groups may also be both polar, the distance between the oxygen atoms then being much larger, *viz.*, 3·66 Å.

FIG. 3. (−)-*Inositol.*

FIG. 4. *Tri*iso*propylidene* (−)-*inositol.*

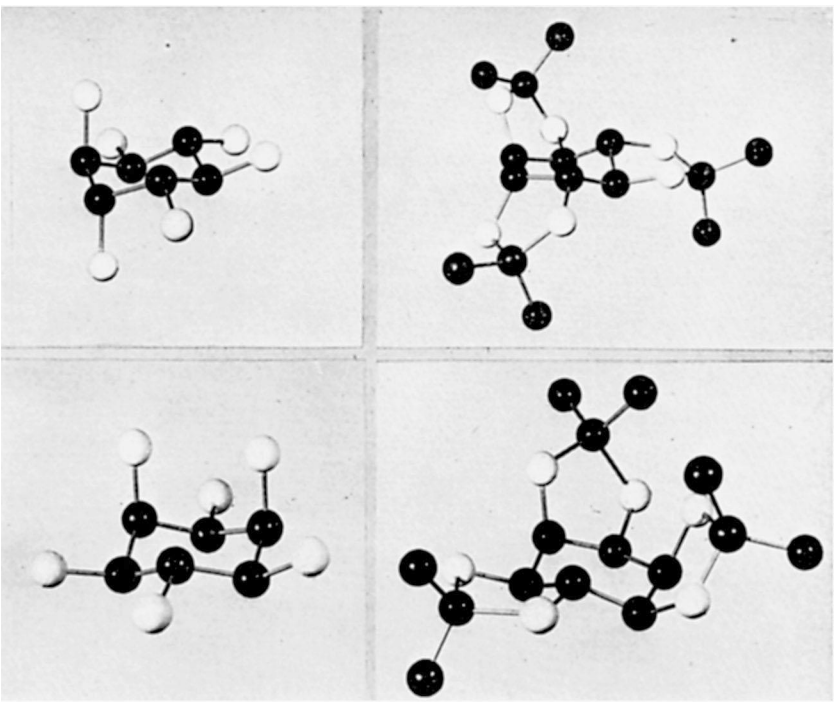


FIG. 5. epi*Inositol.*

FIG. 6. *Tri*iso*propylidene* epi*inositol.*

For clarity, only the carbon and the oxygen atoms are shown in the models.

[*To face p.* 691.

in Fig. 1. There is reason to believe that comparatively little energy is required for this rotation : the strain created is small and the interatomic repulsions are not changed to a considerable extent. This deformation makes the ring less puckered and increases the distances between the polar groups; it must be part of the process whereby one chair form is converted into the other possible chair form, a process which has a low energy of activation since isomers corresponding to the two chair forms have never been isolated.

However, when two *trans*-situated hydroxyl groups are brought nearer to each other by the rotation of the two carbon atoms according to Fig. 2, the ring becomes more puckered and two polar groups are moved nearer to the other polar groups. Very considerable energy will be required for this movement because the distance between the polar groups (2·51 Å), even if they are all hydrogen atoms, is not much larger than the sum of their van der Waals radii. If one of the polar groups is larger than hydrogen the van der Waals radii will touch or even overlap. The energy required to bring the polar groups nearer to each other (cf. the " compression energy," Ingold and Hughes, *J.*, 1946, 157 *et seq.*) will be large and it can be said that the rotation which brings the *trans*-situated hydroxyl groups into a plane is sterically hindered.

The situation is different, however, in the di*iso*propylidene compounds. Formation of two acetal rings from two pairs of *cis*-hydroxyl groups has moved four of the polar groups nearer to the equatorial belt. Their distances from the remaining two polar groups have been increased and, accordingly, the hindrance towards the rotation shown in Fig. 2 has been considerably lessened and acetal formation becomes possible. We conclude that, in agreement with the experimental findings, acetone will condense with a pair of *trans*-hydroxyl groups of a *cyclo*hexane ring only if two *cis*-pairs have already thus reacted. Even then the *trans*-hydroxyl groups react more slowly than the *cis*-groups, as shown by the fact that mixtures of di- and tri-*iso*propylidene derivatives were always obtained.

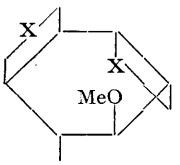
Models of (−)-inositol and of its tri*iso*propylidene derivative are shown in Figs. 3 and 4. In the former, all valency angles are tetrahedral; comparison of the two models shows clearly how the polar hydroxyl groups have been displaced in Fig. 4 (the polar valencies are no longer vertical) and how that part of the six-carbon ring which contains the *cis*-hydroxyl groups has been flattened whilst the other part has been more strongly puckered. Figs. 5 and 6 show a similar comparison between *epi*inositol and its tri*iso*propylidene derivative.

There is another possibility which cannot be overlooked (cf. Derx, *loc. cit.*) : that in the mono*iso*propylidene derivatives the *cyclo*hexane ring is in its boat form. In this form two pairs of carbon atoms, on the opposite side of the " boat," are in eclipsed conformation, *i.e.*, the two carbon atoms and two *cis*-groups attached to them lie in one plane. Cyclic acetal formation can occur, therefore, without deformation. It is to be noted, however, that the boat form has a markedly higher energy than the chair form because of its shorter distances between some of the non-bonded atoms. From our work, the following argument can be advanced against the boat form of *iso*propylidene cyclitols : Mono*iso*propylidene *epi*inositol, in its boat form, would have a *cis*-pair of hydroxyl groups opposite the acetal ring in a favourable position for the formation of another acetal ring. Further reaction should therefore give mainly the 1 : 2-4 : 5-di*iso*propylidene compound; in fact, however, the 1 : 2-3 : 4-derivative (and the triacetal derived from it) was formed predominantly.

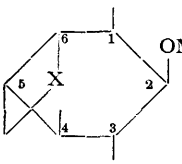
It should be mentioned that 1 : 3-*cis*-hydroxyl groups, when in the polar position, are favourably situated for acetal formation. The distance between them is 2·51 Å if all the inter-bond angles are tetrahedral. This is less than double the van der Waals radius of oxygen, and it is probable therefore that this distance has been increased by mutual repulsion unless there is a hydrogen bond between them.* Such a pair of 1 : 3-*cis*-hydroxyl groups in polar positions exists in *epi*inositol; reaction of these with acetone would give a mono-*iso*propylidene derivative incapable of further condensation. Such a derivative has not been encountered in our work.

* The question whether there is a hydrogen bond between 1 : 3-*cis*-hydroxyl groups in polar positions has been investigated by Drs. Rees and Willis (Commonwealth Scientific and Industrial Research Organisation, Melbourne) by comparison of the infra-red spectra of the *cis*- and *trans-cyclo*hexane-1 : 3-diols, and of *meso*- and *epi*-inositol. The results, however, were inconclusive (private communication).

The Structure of Pinitol and Quebrachitol.—Pinitol, a monomethyl ether of (+)-inositol, which occurs in various conifers, particularly in *Pinus lambertiana* Dougl., gave a di*iso*propylidene derivative. This indicates that the methyl group is not on any of the two pairs of *cis*-oxygen atoms; and as the remaining two positions are equivalent, pinitol must be 3-methyl (+)-inositol (VI), and the diacetal is 3-methyl 1 : 2-5 : 6-di*iso*propylidene (+)-inositol (XX).



(XX)



X = $Me_2C<$

(XXI)

Quebrachitol, a monomethyl ether of (−)-inositol, which occurs in the latex of *Hevea brasiliensis* and in several other plants, is not the enantiomorph of pinitol. The methoxyl group can therefore be only on carbon atoms 1 or 2 (carbon atoms 5 and 6 being equivalent to these). It gave a mono*iso*propylidene compound which consumed only one mol. of periodate; therefore the acetal is 2-methyl 5 : 6-*iso*propylidene (−)-inositol (XXI) and quebrachitol is 2-methyl (−)-inositol.

It is interesting to consider these compounds in the light of their possible biogenesis. It is widely believed that inositols are formed in nature by ring closure of *aldo*hexoses (Fischer, Harvey Lectures, 1944—45, **40**, 174). If such closure gave a methyl inositol the most probable position of the methyl group would be on that carbon atom which was aldehydic in the sugar. Amongst the naturally occurring *aldo*hexoses, D-glucose and D-galactose can give (−)-inositol on ring closure; and, if a methyl group entered the glycosidic hydroxyl group, quebrachitol would be formed in both cases. Similarly, (+)-inositol could be produced from D-mannose and from D-galactose; the methyl inositol formed by methylation on the glycosidic carbon atom would be pinitol in both cases.

Experimental

M. p.s, which are corrected, were taken, unless otherwise stated, by placing the intact crystals on a heated aluminium block. The rotations were determined in a 2 dm.-tube. Microanalyses were carried out in this Department by Mrs. E. Bielski.

Materials.—*meso*Inositol and (+)-*proto*quercitol were commercial preparations. Crude pinitol was obtained through the courtesy of Dr. Arthur B. Anderson, Oregon Lumber Co., Portland, U.S.A. It was purified by treating its aqueous solution with charcoal and adding ethanol to the concentrated solution. Crude quebrachitol was kindly presented to us by Mr. M. W. Philpott, The Rubber Research Institute of Malaya, Kuala Lumpur. It was purified in the same way as the pinitol. (−)-Inositol was obtained by demethylation of quebrachitol with hydriodic acid. (−)-*vibo*Quercitol was isolated in this Department from *Stephania hernandifolia*, Walp., by Mrs. J. Ewing (Ewing, Hughes, and Ritchie, *Austral. J. Sci. Res.*, *A*, 1950, **3**, 514). *scyllo*Inositol and *scyllo*quercitol were prepared by catalytic hydrogenation of *scyllo*inosose (Posternak, 1941, *loc. cit.*), and *epi*inositol by the hydrogenation of *epi*inosose (Posternak, *Helv. Chim. Acta*, 1946, **29**, 1996). The acetone was a commercial grade, made by fermentation, free from reducing impurities; it was kept over anhydrous potassium carbonate.

Reaction of meso*Inositol with Acetone.*—Finely powdered anhydrous *meso*inositol (2·0 g.), anhydrous zinc chloride (24 g.), acetic acid (24 ml.), and dry acetone (180 ml.) were heated under reflux for 9 hours. After the undissolved inositol (1·51 g.) had been filtered off, dry pyridine (90 ml.) was added to the solution, the precipitated complex salt was filtered off after a few hours, and the acetone was removed under reduced pressure at 40°. Acetic anhydride (30 ml.) and dry pyridine (50 ml.) were added to the residue; on the following day a further amount of complex salt was filtered off and washed with a small amount of ice-cold chloroform. More chloroform (15 ml.) was added to the filtrate which was then shaken with iced water (2 × 50 ml.), sodium carbonate solution (2 × 50 ml.; 5%), and again with iced water (2 × 10 ml.). The chloroform layer was dried (Na_2SO_4) and evaporated, and the residue crystallised from ethyl acetate–light petroleum to obtain (±)-3 : 4 : 5 : 6-tetra-acetyl 1 : 2-*iso*propylidene *meso*-inositol (0·5 g.; 47% on inositol not recovered), m. p. 118—121°.

This compound (0·33 g.) was heated under reflux for 10 minutes with anhydrous methanol (6 ml.) containing 1 millimole of sodium methoxide. After the solvent had been removed, crystallisation of the residue from ethanol (4 ml.) gave (±)-1 : 2-*iso*propylidene *meso*inositol (0·12 g., 64%), m. p. 182—183° (Found : C, 48·95; H, 7·25. Calc. for $C_9H_{16}O_6$: C, 49·1; H, 7·35%). Dangschat (*loc. cit.*) reports m. p. 182—183°.

It was of interest to determine the amount of periodate consumed by this compound which has four contiguous hydroxyl groups, since anomalous results were obtained with compounds containing five (Hérissey and Poirot, *loc. cit.*; Riggs, *J.*, 1949, 3199) and six (Fleury, Poirot, and Fievet, *Compt. rend.*, 1945, **220**, 664) hydroxyl groups attached to a *cyclo*hexane ring. From a solution of *iso*propylidene *meso*inositol (22·0 mg. , 0·1 millimole) and sodium meta-periodate (0·75 millimole) in water (25 ml.), kept in the dark, aliquots (5 ml.) were taken at intervals, sodium hydrogen carbonate solution (2 ml.; M.), sodium arsenite solution (15·0 ml.; 0·025N.), and potassium iodide (0·1 g.) were added and, after 5 minutes, the solution was titrated with 0·025N-iodine solution. The results, expressed in moles of periodate consumed per mole of *iso*propylidene inositol were : 0·5 hour, 1·96; 1 hour, 2·18; 2 hours, 2·40; 15 hours, 2·72.

Reaction of (+)-proto*Quercitol with Acetone.*—Finely powdered *proto*quercitol (2 g.), anhydrous zinc chloride (10 g.), acetic acid (10 ml.), and dry acetone (80 ml.) were heated under reflux for 5 hours. The cyclitol dissolved in about 30 minutes. To the cooled mixture dry pyridine (20 ml.) was added to precipitate most of the zinc chloride as a complex salt; after cooling to 0°, the crystals were filtered off and washed with acetone (10 ml.). The mother-liquor was freed from acetone under reduced pressure at 40° and acetic anhydride (10 ml.) was added. After 24 hours the mixture was cooled to 0° and filtered, and the salt washed with ice-cold chloroform (10 ml.). After the addition of more chloroform (20 ml.), the filtrate was repeatedly shaken with 30-ml. portions of iced water until the aqueous layer no longer showed a reaction for zinc with potassium ferrocyanide (4—5 times). The combined aqueous layers were shaken with chloroform (15 ml.) which was then washed with water (15 ml.) and combined with the bulk of the chloroform solution. After further washings with sodium carbonate solution (2 × 10 ml.; 5%) and water (10 ml.), the chloroform layer was dried (Na_2SO_4) and evaporated.

The residue (2·94 g.) was a syrup which could be distilled without decomposition at 130° (bath-temp.)/0·3 mm., but did not crystallise. Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave 3 : 4-iso*propylidene* (+)-proto*quercitol* (1·1 g., 44%), m. p. 158°. For analysis it was recrystallised from ethyl acetate and then had m. p. 159° and $[\alpha]_D^{20}$ + 73·7° (*c*, 1·2 in ethanol) (Found : C, 52·9; H, 7·95. $C_9H_{16}O_5$ requires C, 52·95; H, 7·9%).

Periodate oxidations. In determining the amount of periodate consumed by this compound, we at first reduced the excess of periodate with iodide and titrated the liberated iodine with arsenite. Erratic results, varying between 1 and 2 mols., were thus obtained. It is suspected that the oxidation product reacts with iodine, probably by the iodoform reaction (quercitols give the iodoform reaction). Consistent results were obtained, however, when the unchanged periodate was reduced by excess of arsenite in the presence of iodide—no free iodine being then present in the solution—and the excess of arsenite was titrated by an iodine solution as described under *meso*inositol (Method A). Thus, aliquots from a solution of *iso*propylidene *proto*quercitol (81·6 mg., 0·4 millimole) and sodium metaperiodate (0·9 millimole) in water (25 ml.) gave the following results : 0·5 hour, 1·01; 1 hour, 1·02; 4 hours, 1·04 mols. With most of the other *iso*propylidene derivatives, however, the simple titration of the liberated iodine by arsenite (Method B) gave consistent results.

Reaction of scyllo*Inositol with Acetone.*—Treated under the conditions described for *proto*quercitol, *scyllo*inositol remained completely undissolved.

Reaction of scyllo*Quercitol with Acetone.*—When *scyllo*quercitol (0·49 g.) was treated as described under *proto*quercitol, 0·29 g. did not dissolve. Evaporation of the chloroform solution gave only 0·05 g. of material. The rest of the quercitol was found in the zinc chloride–pyridine complex (4·7 g.); by acetylation with acetic anhydride (2·5 ml.) and pyridine (2·5 ml.) and working up as usual, penta-acetyl *scyllo*quercitol (0·27 g.), m. p. 193—194°, was obtained. Posternak (1942, *loc. cit.*) reports m. p. 190°.

Reaction of (−)-vibo*Quercitol with Acetone.*—When *vibo*quercitol was treated as described under *proto*quercitol, crystallisation from aqueous ethanol gave a 60% yield of 3 : 4 : 5-triacetyl 1 : 2-*iso*propylidene (−)-*vibo*quercitol, m. p. 104° (Posternak, 1950, *loc. cit.*).

Reaction of (−)-*Inositol with Acetone.*—When (−)-inositol (2 g.) was treated as described under *proto*quercitol, evaporation of the chloroform solution gave 4·6 g. of a semi-solid material. Crystallisation from ethanol (8 ml.) yielded 1 : 2-3 : 4-5 : 6-*tri*iso*propylidene* (−)-*inositol* (1·0 g., 30%), m. p. 211°. For analysis it was recrystallised from ethanol and then had m. p. 213—

214° (capillary), $[\alpha]_D^{25}$ + 38·1° (*c*, 1·0 in chloroform) (Found: C, 59·85; H, 8·2. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·05%).

The mother-liquor of the triacetal was evaporated and the residue crystallised twice from ethanol–water (1 : 2): needles of 3 : 4-*diacetyl* 1 : 2-5 : 6-*di*iso*propylidene* (−)-*inositol* (1·65 g., 43%), m. p. 126°, were obtained. Another crystallisation raised the m. p. to 129°, $[\alpha]_D^{22}$ −116·5° (*c*, 2·1 in chloroform) (Found: C, 55·55; H, 7·05. $C_{16}H_{24}O_8$ requires C, 55·8; H, 7·0%).

Catalytic deacetylation, followed by crystallisation from ethyl acetate–light petroleum (2 : 1), gave 1 : 2-5 : 6-*di*iso*propylidene* (−)-*inositol*, m. p. 153°, $[\alpha]_D^{20}$ −4·7° (*c*, 1·2 in ethanol) (Found: C, 55·25; H, 7·85. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). Periodate oxidation (Method B): 0·4 millimole (104·0 mg.), and 0·6 millimole of sodium metaperiodate in water (25 ml.): 1 hour, 1·01; 2 hours, 1·01; 4 hours 1·01 mols.

Partial Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tri*iso*propylidene* (−)-*Inositol.*—A solution of tri*iso*propylidene (−)-inositol (0·7 g.) in a mixture of chloroform (3·0 ml.), acetic acid (3·5 ml.), and water (1·0 ml.) was set aside for 24 hours and then was evaporated to dryness under reduced pressure. The residue was extracted with water, leaving unchanged triacetal (0·12 g., m. p. after recrystallisation from ethanol, 208—210°) undissolved. The aqueous extract was evaporated to dryness under reduced pressure and extracted with ethyl acetate (2 × 5 ml.) which left impure (−)-inositol (0·04 g.) undissolved. The extracts were evaporated and the residue re-extracted with benzene (20 ml.); the undissolved 1 : 2-iso*propylidene* (−)-*inositol* (50 mg., 10%), after recrystallisation from ethyl acetate (1 ml.), had m. p. 157·5—158° (Found: C, 49·5; H, 7·4. $C_9H_{16}O_6$ requires C, 49·1; H, 7·35%).

The benzene solution, on cooling, deposited 1 : 2-5 : 6-di*iso*propylidene (−)-inositol (0·25 g., 41%), m. p. 149—150°, mixed m. p. with an authentic sample, 150—151°.

Reaction of epi*Inositol with Acetone.*—When *epi*inositol (4 g.) was treated as described under *proto*quercitol, evaporation of the chloroform solution yielded 7·9 g. of an oil. Crystalline acetates can be obtained from this oil but their separation is difficult. Therefore the oil was catalytically deacetylated and then taken up in chloroform (10 ml.) which was repeatedly extracted with water (25, 10, 10 ml.). The combined aqueous layers were shaken with chloroform (5 ml.) and this with water (5 ml.). The combined chloroform layers were evaporated and the residue (1·0 g., 15%) was recrystallised several times from light petroleum, to give (±)-1 : 2-3 : 4-5 : 6-*tri*iso*propylidene* epi*inositol* (Found: C, 59·55; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·05%). It melted at 121°, resolidified and melted again at 127—128°. This compound, in contrast to tri*iso*propylidene (−)-inositol, is soluble in water.

The combined aqueous layers were evaporated, and the residue was extracted with ethyl acetate (30, 15, 15 ml.). The extracts were concentrated to 15 ml. and on storage at 0° deposited impure (±)-1 : 2-3 : 4-*di*iso*propylidene* epi*inositol* (1·85 g., 32%), m. p. about 176°. (Mother-liquor: see below.) Repeated crystallisation from ethyl acetate gave the pure compound, m. p. 181° (Found: C, 55·15; H, 7·95. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). Periodate oxidation (Method B): 0·2 millimole (52·0 mg.) and 0·5 millimole of sodium periodate in water (25 ml.): 0·5 hour, 1·01; 1 hour, 1·01; 2 hours, 1·01 mols.

Acetylation of this compound with acetic anhydride and pyridine gave (±)-5 : 6-*diacetyl* 1 : 2-3 : 4-*di*iso*propylidene* epi*inositol* which crystallised from ethanol in fine needles, m. p. 138° (Found: C, 55·45; H, 7·2. $C_{16}H_{24}C_8$ requires C, 55·8; H, 7·0%).

The mother-liquor from 1 : 2-3 : 4-di*iso*propylidene *epi*inositol (see above) was evaporated to dryness and heated for 1 hour on the steam-bath with acetic anhydride (4 ml.) and pyridine (4 ml.). It was then poured into water and extracted with chloroform (3 × 8 ml.). After evaporation of the solvent and crystallisation from light petroleum (200 ml.), crude 3 : 6-*diacetyl* 1 : 2-4 : 5-*di*iso*propylidene* epi*inositol* (0·43 g., 5·5 %), m. p. 187—192°, was obtained. Repeated crystallisation from light petroleum gave the pure compound, m. p. 201—203° (Found: C, 55·65; H, 6·95. $C_{16}H_{24}O_8$ requires C, 55·8; H, 7·0%).

Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave 1 : 2-4 : 5-*di*iso*propylidene* epi*inositol*, m. p. 181° (Found: C, 54·9, 55·75; H, 7·8, 7·9. $C_{12}H_{20}O_6$ requires C, 55·35; H, 7·75%). The mixed m. p. with 1 : 2-3 : 4-isomer (m. p. also 181°) was depressed by more than 10°. This compound did not reduce sodium metaperiodate under the usual conditions.

This separation of the di*iso*propylidene isomers is unsatisfactory and will be further studied.

Partial Hydrolysis of 1 : 2-3 : 4-5 : 6-*Tri*iso*propylidene* epi*Inositol.*—On being kept for 24 hours, a solution of tri*iso*propylidene *epi*inositol (0·39 g.) in a mixture of acetic acid (2·0 ml.) and water (0·5 ml.) deposited prisms of *epi*inositol (0·13 g., 56%), m. p. 303—304°. This m. p. is higher than that of our initial *epi*inositol, m. p. 297—298°. Posternak (*Helv. Chim. Acta*,

1936, **19**, 1340) records m. p. 285° (uncorr.; capillary); but because of decomposition we found it impossible to observe a definite m. p. in the capillary.

The mother-liquor was evaporated to dryness under reduced pressure and was extracted with ethyl acetate (4 ml.). On cooling, (±)-1 : 2-3 : 4-di*iso*propylidene *epi*inositol (50 mg., 15%), m. p. and mixed m. p. 181°, crystallised.

Reaction of Pinitol with Acetone.—When pinitol (2 g.) was treated as described for *proto*-quercitol, evaporation of the chloroform solution gave a syrup (3·4 g.) which failed to crystallise. Catalytic deacetylation, followed by two crystallisations from light petroleum, gave 3-*methyl* 1 : 2-5 : 6-*di*iso*propylidene* (+)-*inositol* (1·8 g., 64%), m. p. 99—100°. Further crystallisations raised the m. p. to 103—104°, $[\alpha]_D^{23}$ −22·0° (*c*, 3·4 in water) (Found: C, 56·95; H, 8·0. $C_{13}H_{22}O_6$ requires C, 56·85; H, 8·05%).

Reaction of Quebrachitol with Acetone.—When quebrachitol (2 g.) was treated as described for *proto*quercitol, evaporation of the chloroform solution gave a syrup (2·7 g.) which failed to crystallise. Catalytic deacetylation, followed by crystallisation from ethyl acetate, gave 2-*methyl* 5 : 6-iso*propylidene* (−)-*inositol* (0·55 g., 22%), m. p. 131—132°. Further crystallisation raised the m. p. to 134—135·5°, $[\alpha]_D^{23}$ −88·8° (*c*, 1·6 in water) (Found: C, 51·0; H, 7·65. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75%). Periodate oxidation (Method A): 0·4 millimole (93·6 mg.) and 0·9 millimole of sodium metaperiodate in water (25 ml.): 0·5 hour, 1·01; 1 hour, 1·01; 2 hours, 1·01; 4 hours, 1·03 mols.

CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY, N.S.W. [*Received, June 11th*, 1951.]