THE CATALYTIC OXIDATION OF INOSITOLS

AND THE SOLVOLYSIS OF THEIR MONOTOSYL ESTERS.

by

MARY E. PITMAN B.Sc. (Hons.) (Tas.).

A Thesis

submitted for the degree of

MASTER OF SCIENCE

at the

UNIVERSITY OF TASMANIA.

May, 1957.

SUMMARY AND CONCLUSIONS.

The oxidation of inositols by aeration in aqueous solution in the presence of a platinum catalyst is described in Part I of this thesis. The six isomers, *epi*-, *cis*-, *scyllo*-, (-)-, *neo*-, and *allo*-inositols, and two methyl ethers, quebrachitol and dambonitol were oxidized and the oxidation products identified. The results are discussed with reference to the corresponding results for oxidation by *Acetobacter suboxydans*. It was established that only axial hydroxyl groups were dehydrogenated. This also holds for oxidation by *Acetobacter suboxydans*.

Catalytic oxidation differs from enzymatic oxidation in two respects. Firstly, the action stops at the monoketone stage except in the case of alloinositol. Aeration of alloinositol in the presence of platinum catalyst gave a diketone and a monoketone which was not an intermediate in the formation of the diketone. Secondly, the presence of adjacent methyl groups, as in dambonitol, does not prevent oxidation.

Two new monotosyl esters of inositols were prepared and the solvolysis of a number of monotosyl esters was studied. This work is described in Part II of this thesis. In all the cases studied, solvolysis occurred, and was mostly accompanied by inversion, but the stereochemical result varied considerably. These solvolysis reactions provide new methods of synthesis for two of the rarer isomers, *cis*-

and muco- inositols. It was found that the solvolysis was accompanied by a novel type of epimerisation reaction, and a preliminary study of this reaction was made.

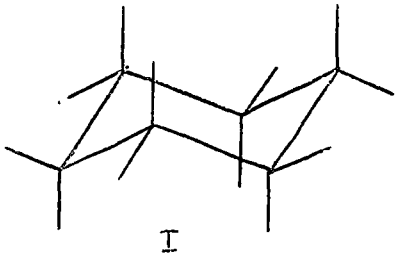
CONTENTS.

GENERAL INTRODUCTION.

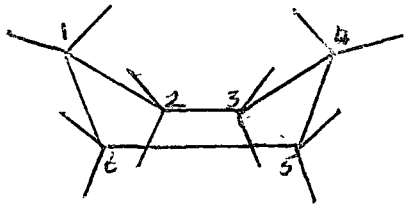
CYCLITOLS AND THEIR STEREOCHEMISTRY.

1. THE CONFORMATION OF CYCLOHEXANE.

The term 'conformation' (1) may be defined as follows : the conformations of a molecule are those arrangements in space of its atoms which are not superposable on each other (2). Sachse (3) and Mohr (4) first postulated the existence of non-planar ring forms with six or more carbon atoms, and showed that for cyclohexane two conformations are possible, the chair (I) and boat (II) forms, in which normal tetrahedral angles are maintained and, consequently, the ring is free from angle strain.



I



II

The chair form has been shown to be the more stable of the two. This may be predicted on theoretical grounds, and physical evidence has established the fact beyond doubt.

Another type of strain, caused by the interaction of the non-bonded atoms, and similar to steric hindrance, must

---

(1) Haworth, "The Constitution of Sugars", E. Arnold & Co., London, 1929, p. 90.

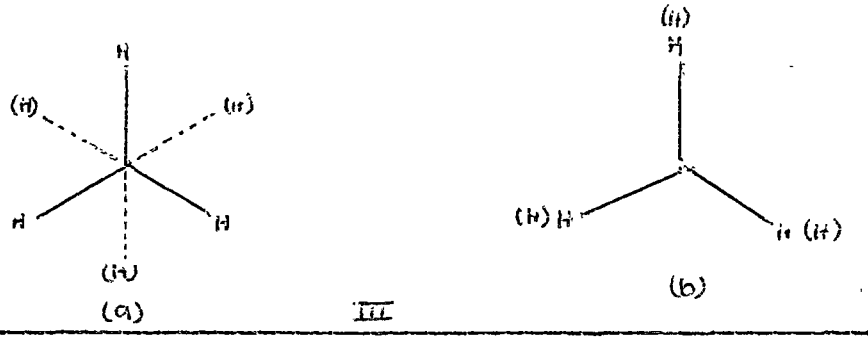
(2) Barton and Cookson, Quart. Rev., 1956, 10, 44.

(3) Sachse, Ber., 1890, 23, 1363.

(4) Mohr, J. Prakt. Chem., 1918, 98, 315.

be considered when determining which of the two conformations is the more stable. If the distance between two neutral non-bonded atoms is greater than the sum of their van der Waals' radii, their interaction is weakly attractive. While, if the distance is less than the sum of their van der Waals' radii, their interaction is repulsive, and the force of the repulsion increases rapidly as the distance decreases. Thus, the interaction of neutral non-bonded atoms is mainly repulsive, and the molecule achieves its lowest energy level when the distances between the non-bonded atoms are at a minimum (5).

For atoms attached to a pair of bonded carbon atoms, these distances will be greatest when the valences on the carbon atoms are in the fully staggered conformation. In ethane, for example, the fully staggered conformation is that in which the C-H bonds attached to the two C-atoms make angles of 60° with each other when projected on a surface perpendicular to the C-C bond, (III a), while the



(a) (b)

III

(5) Angyal and Mills, Revs. Pure Appl. Chem. (Australia) 1952, 2, 185.

conformation produced by rotation through 60° is the eclipsed conformation (III b).

In the chair form (I) of cyclohexane, all the carbon atoms are in the staggered conformation, and so the distances between the non-bonded atoms are at a maximum. The boat form (II) is energetically less favourable, as the two pairs of carbon atoms (2, 3) and (5, 6), which form the sides of the boat, are in an eclipsed conformation, which brings the non-bonded atoms closer together.

These theoretical conclusions are substantiated by much physical evidence, including thermodynamical considerations (6), infra-red (7) and Raman spectroscopy (8), and work on the electron diffraction of cyclohexane and its derivatives (9). Thus, where stereochemically possible, cyclohexane and its derivatives tend to adopt the chair conformation.

The C-H bonds in the chair conformation of cyclohexane belong to two distinct geometrical types. The mid-points of the six C-C bonds define a plane which passes through

---

(6) a) Aston, Schumann, Fink and Doty, J. Amer. Chem. Soc., 1941, 63, 2029.

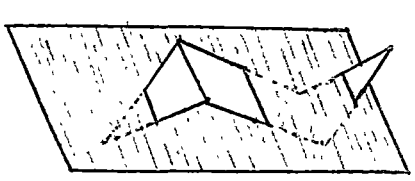
b) Beckett, Pitzer and Spitzer, ibid., 1947, 69, 2488.

(7) Rasmussen, J. Chem. Phys., 1943, 11, 249, and papers there cited.

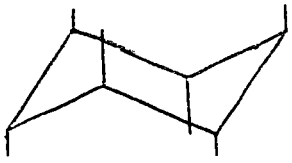
(8) Kohlrausch and Wittek, Z. physikal. Chem., 1941, 48B, 177.

(9) Hassel et al., Acta Chem. Scand., 1947, 1, 149 ; Research, 1950, 3, 504 ; Quart. Rev., 1953, 7, 221.

the centre of the molecule (IV). Six of the C-H bonds are perpendicular to this plane, and are called axial bonds (V). The remaining six C-H bonds are called equatorial, as they radiate out from the ring (VI).



IV

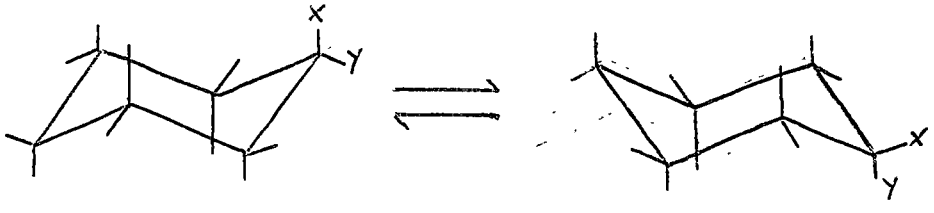


V

VI

A consequence of the chair conformation is that no two adjacent bonds are in the true <u>cis</u> position (oriented at an angle of 0^{o}) in the cyclohexane molecule. Each axial group has two adjacent axial groups in the true <u>trans</u> position (oriented at an angle of 180^{o}), but an equatorial group cannot have an adjacent group in the true <u>trans</u> position.

Theoretically, there are two possible chair conformations for the cyclohexane ring ; one may be changed to the other by passing the ring through a planar conformation. In this way, each axial substituent becomes equatorial and vice versa (VII).



VII

For cyclohexane itself, the two forms are identical. Where the two forms are not identical, the work of Hassel (10) has shown that the larger groups and the larger number of groups occupy equatorial positions preferentially. Normally, the form of the molecule with the maximum number of equatorial substituents predominates.

2. THE INOSITOLS.

Nomenclature.

The system proposed by Angyal and Macdonald (11) for the nomenclature and numbering of inositols and their derivatives has been adopted.

Structure and Conformation of the Inositols.

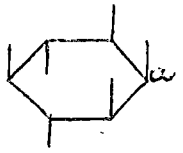
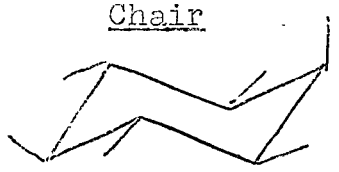
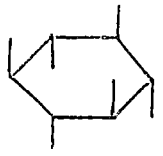
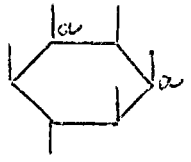
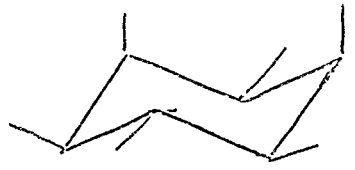
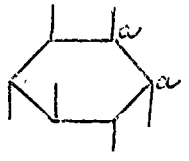
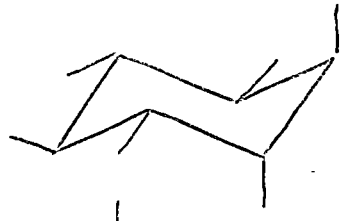
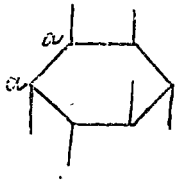
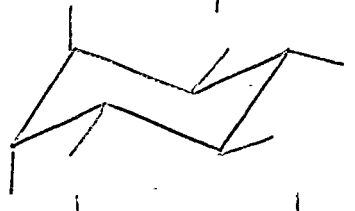
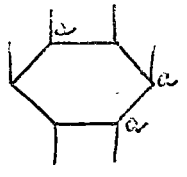
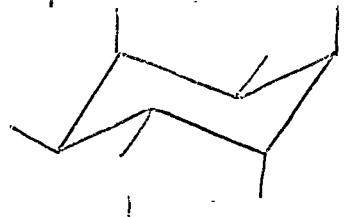
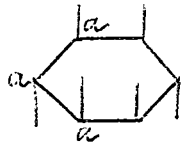
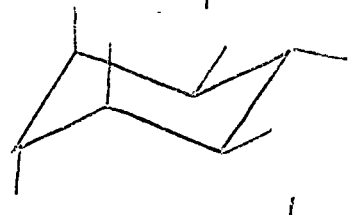
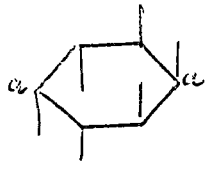
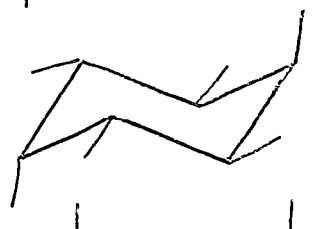
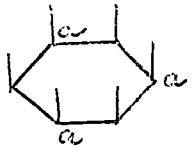
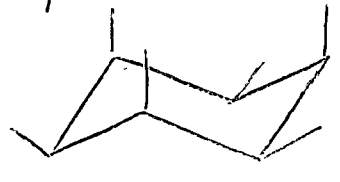
There are nine possible isomers (VIII-XVI) of inositol, two of which, (XI) and (XII), are enantiomorphs. Each inositol can exist in two possible chair conformations, but, in accordance with the principles outlined above, the conformation with the maximum number of equatorial hydroxyl groups is the more stable of the two. The chair formulae illustrated show the more stable conformation, and in the

---

(10) Reviews : Hassel and Ottar, Acta Chem. Scand., 1947, 1, 929 ; Hassel, Research, 1950, 3, 504 ; Quart. Rev., 1953 7, 221.

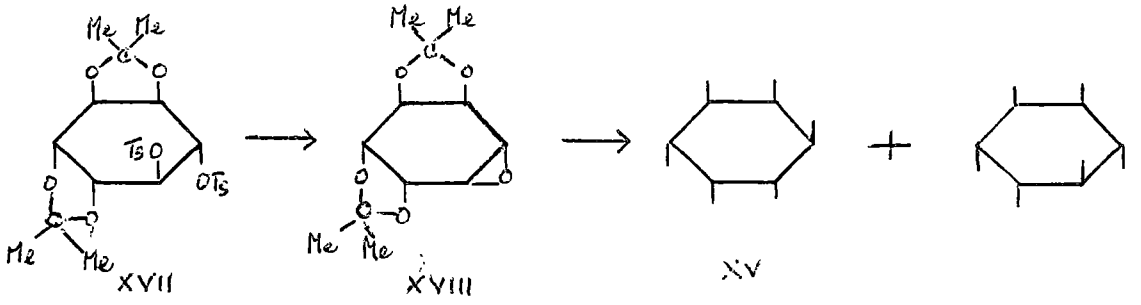
(11) Angyal and Macdonald, J. Chem. Soc., 1952, 686.

THE INOSITALS

	Name	Classical	Chair
(VIII)	meso		
(IX)	scyllo		
(X)	epi		
(XI)	(+)		
(XII)	(-)		
(XIII)	allo		
(XIV)	muco		
(XV)	neo		
(XVI)	cis		

classical formulae, the hydroxyl groups are marked 'a' if they become axial when written in their stable chair form.

Fletcher (12) and Orloff (13) have both reviewed the chemistry of the inositols, and the structures and conformations of the isomers (VIII-XIV) are discussed in these reviews. Since the date of Orloff's review, the remaining two isomers, cisinositol and neoinositol have been isolated, and their configurations established.



neoInositol (XV) was obtained by Angyal and Matheson (14) by acid hydrolysis of the epoxide (XVIII), which was prepared from a ditosyl derivative of (-)-inositol (XVII).

cisInositol (XVI) has been synthesised by the reduction of hexahydroxybenzene in the presence of a palladium catalyst (15). This isomer is of particular interest as it is the first cyclohexane derivative to be prepared with

---

(12) Fletcher, Adv. Carbohydrate Chem., 1948, 3, 46.

(13) Orloff, Chem. Reviews, 1954, 54, 393.

(14) Angyal and Matheson, J. Amer. Chem. Soc., 1955, 77, 4343.

(15) Angyal and McHugh, Chem.and Ind., 1955, 947.

three axial groups on the same side of the molecule, other than hydrogen or fluorine. The corresponding isomer in the hexachlorocyclohexane series is unknown.

Interaction Energies of Axial Hydroxyl Groups.

The interaction between two or three axial hydroxyl groups on the same side of the ring, as in epi and cis-inositols, greatly increases the energy of the molecule. Recently, the values of the interaction energies of some of the non-bonded interactions present have been calculated from a study of the free energy changes in borate complex formation of inositols and quercitols (16). For cyclitols, the principal interactions are those between two axial oxygen atoms, (O_a : O_a) between an axial oxygen and an axial hydrogen (O_a : H_a), and between two oxygen atoms on adjacent carbon atoms, both being equatorial or one equatorial and one axial, (O_1 : O_2). Other non-bonded interactions present in the molecule are small by comparison and may be neglected. The values obtained were :-

(O_1 : O_2) = 0.35 $\pm$ 0.07 kg. cal./mol.

(O_a : H_a) = 0.45 $\pm$ 0.05

(O_a : O_a) = 1.9 $\pm$ 0.1

---

(16) Angyal and McHugh, Chem. and Ind., 1956, 1147.

3. METHYL ETHERS OF INOSITOLS.

Monomethyl Ethers of (+)- and (-)-Inositol.

Quebrachitol, a monomethyl ether of (-)-inositol occurs in a number of latex producing plants, but the most convenient source is from the latex of the rubber tree, Hevea brasiliensis. Quebrachitol forms a monoisopropylidene derivative, which consumes one mole of periodate, and this establishes its structure as 2-O-methyl-(-)-inositol (XIX), (14, 17).

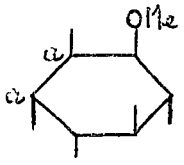
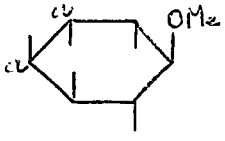
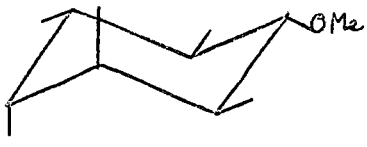
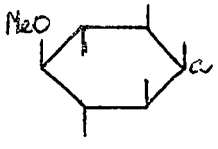
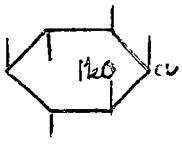
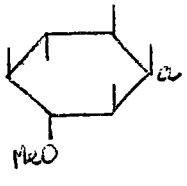
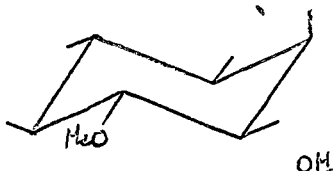
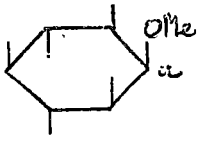
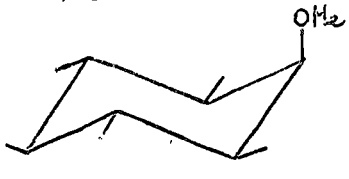
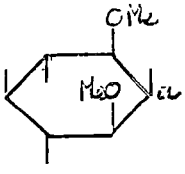
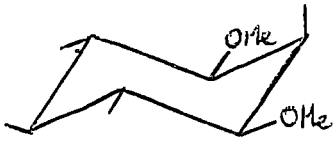
(+)-Pinitol is a monomethyl ether of (+)-inositol, which is not an enantiomorph of quebrachitol. It condenses with acetone to form a diisopropylidene derivative (17, 18). On the assumption that acetal formation occurs only with vicinal cis hydroxyl groups, the structure 3-O-methyl-(+)-inositol (XX) was assigned to pinitol, as the remaining two hydroxyl groups, one of which must carry the methyl group, are equatorial and equivalent. Under certain circumstances trans hydroxyl groups may form acetals, but the above structure was confirmed when the structure of the acetal was proved to be 1:2-5:6-di-O-isopropylidene-(+)-inositol by

---

(17) Posternak, Helv. Chim. Acta, 1952, 35, 50.

(18) Anderson, Macdonald and Fischer, J. Amer. Chem. Soc., 1952, 74, 1479.

METHYL ETHERS OF INOSITOLS

	Name	Classical	Chair
(XIX)	quebrachitol		
(XX)	pinitol		
(XXI)	sequoyitol		
(XXII)	(-) bornesitol		
(XXIII)	ononitol		
(XXIV)	2-O-methyl-meso		
(XXV)	dambonitol		

degradation of its enantiomorph to L-mannitol (19). (+)-Pinitol occurs extensively in nature in a number of families, including the Sapondaceae and Eleaegonaceae. Recently, (-)-pinitol was isolated from Artemesia dracunculus (20).

Monomethyl Ethers of mesoInositol.

There are four possible monomethyl stereoisomers of mesoinositol (XXI-XXIV), two of which , XXII and XXIII, can exist as optical enantiomorphs.

Sequoyitol, which occurs naturally, is optically inactive. Its structure has been established conclusively as 5-O-methyl mesoinositol (XXI), by synthesis from pinitol (XX) by Anderson et al.(21).

Both enantiomorphs of bornesitol have been found in nature (22, 23). Stacey and Foster (24) first postulated the 1-O-methyl structure (XXII), which has since been proved

---

(19) Angyal, Macdonald and Matheson, J. Chem. Soc., 1953, 3321.

(20) Plouvier, Compt. rend., 1956, 243, 1913.

(21) Anderson, Deluca, Bieder and Post, J.Amer. Chem. Soc., 1957, 79, 1171.

(22) Plouvier, Compt. rend., 1955, 241, 983.

(23) Girard, Compt. rend., 1871, 73, 426; Flint and Tollens, Annalen, 1892, 272, 288 ; King and Jurd, J.Chem. Soc., 1953, 1192.

(24) Stacey and Foster, Chem. and Ind., 1953, 279.

correct by Angyal *et al.* (25). Recently, Anderson (26) synthesised (−)-bornesitol from quebrachitol (XIX); this synthesis established the absolute configuration of (−)-bornesitol as (XXII).

Plouvier (22) has isolated (+)-ononitol from *Ononis natris*; this compound must therefore be one of the enantiomorphs of 4-*O*-methyl*meso*inositol (XXIII), as there are only two possible pairs of optically active monomethyl ethers which can be derived from *meso*inositol.

The last isomer, 2-*O*-methyl*meso*inositol (XXIV) has been isolated as a product of the direct methylation of *meso*-inositol (25).

Dimethyl Ethers of *meso*Inositol.

Two dimethyl ethers of *meso*inositol, dambonitol and liriodendritol, have been isolated from natural sources.

A 2:5-dimethyl structure was first proposed for dambonitol (27), but this was later modified to a 1:3 structure (XXV), (28), which has been confirmed by the work of Angyal *et al.* (25).

---

(25) Angyal, Gilham and (in part) Macdonald, *J. Chem. Soc.*, 1957, 1417.

(26) L. Anderson, private communication.

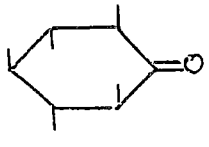
(27) Comollo and Kiang, *J. Chem. Soc.*, 1953, 3319.

(28) Kiang and Loke, *ibid.*, 1956, 480.

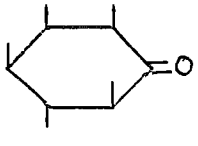
Liriodendritol was recently isolated by Plouvier (29) from Liriodendro tulipifera, but its structure has not yet been established.

4. THE INOSOSES.

The series of monoketone compounds derived from the inositols are called inososes. Fletcher (12) has discussed in his review the structures of scylloinosose and epiinosose, which have been established as (XXVI) and (XXVII) respectively.



XXVI



XXVII

Magasanik and Chargaff (30) obtained an inosose (XXVIII) by partial oxidation of (+)-inositol by Acetobacter suboxydans. The configuration of this inosose was established by further oxidation by the microorganism to a diketone of known structure (XXIX), (31). Catalytic

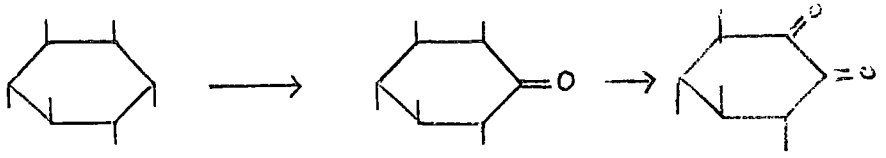
---

(29) Plouvier, Compt. rend., 1955, 241, 765.

(30) Magasanik and Chargaff, J. Biol. Chem., 1948, 175, 929.

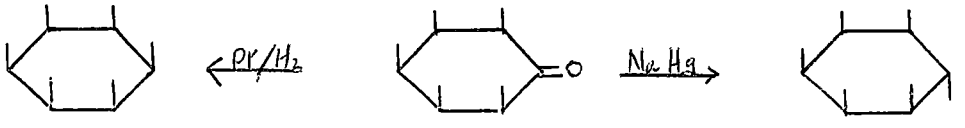
(31) Magasanik and Chargaff, ibid., 1948, 174, 173.

reduction of the inosose gave a mixture of (+)-inositol and mesoinositol, in agreement with structure (XXVIII). Magasanik and Chargaff called this inosose 'd-inosose', but it is now known as (+)-viboinosose.



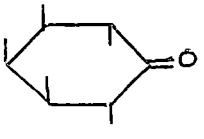
(+) XXVIII XXIX

cisInosose has been isolated as a product of the reduction of hexahydroxy benzene (15). Catalytic reduction of the inosose gave cisinositol, while reduction with sodium amalgam gave epiinositol. These two reactions established the structure of cisinosose as (XXX).



XXX

neoInosose, (XXXI), has been obtained as the product of aerial oxidation of neoinositol in the presence of a platinum catalyst. The proof of the structure of this inosose is contained in this thesis.

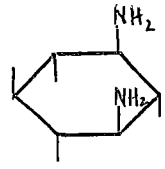


XXXI

5. AMINODEOXYINOSITOLS.

The aminodeoxyinositols are the group of compounds in which one or more hydroxyl groups of an inositol has been replaced by an amino group ; the monoaminodeoxyinositols are frequently called inosamines.

In 1946, the structure of streptamine (XXXII) was established as 1:3-diamino-1:3-dideoxyscylloinositol (32). This work has largely been responsible for the further studies in the synthesis of aminodeoxyinositols, and recently streptamine was synthesised from mesoinositol by Heyns (33).



XXXII

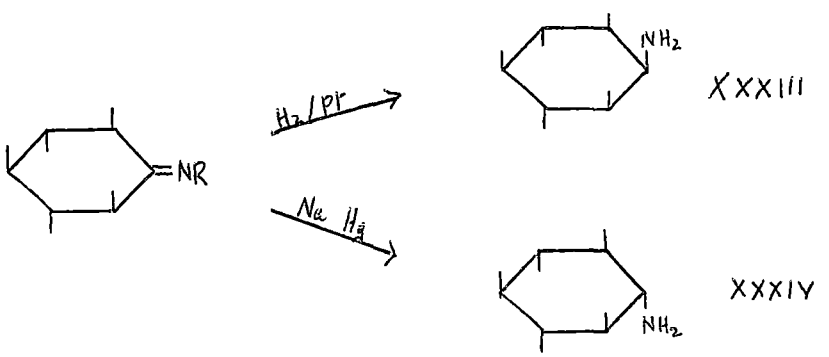
Aminodeoxyinositols are synthesised by the reduction of the phenylhydrazone or oxime of the corresponding inosose. Catalytic reduction leads predominantly to the formation of the isomer with an axial amino group, while reduction with sodium amalgam gives the isomer with an equatorial amino group. In this way, mesoinosamine-2

---

(32) Carter et al., Science, 1946, 103, 53 ; Fried, Boyak, and Wintersteiner, J. Biol. Chem., 1946, 162, 393; Peck et al., J. Amer. Chem. Soc., 1946, 68, 776.

(33) Heyns and Paulsen, Ber., 1956, 89, 1152.

(XXXIII) and scylloinosamine (XXXIV) have been prepared from scylloinosose (34, 35). Studies on the rate of N → O acetyl migration (36) and on the rate of oxidation with lead tetraacetate and periodic acid (37) have confirmed the structures assigned to these two aminodeoxyinositols.



The two aminodeoxyinositols derived from epiinosose, 2-amino-2 deoxyepiinositol (XXXV) and 4-amino-4 deoxy-mesoinositol (XXXVI) have also been prepared (38, 39).

neoInosamine-2 (XXXVII) has been isolated as a product of the hydrolysis of a new antibiotic (1703-18B) similar

---

(34) Carter et al., J. Biol. Chem., 1948, 175, 683.

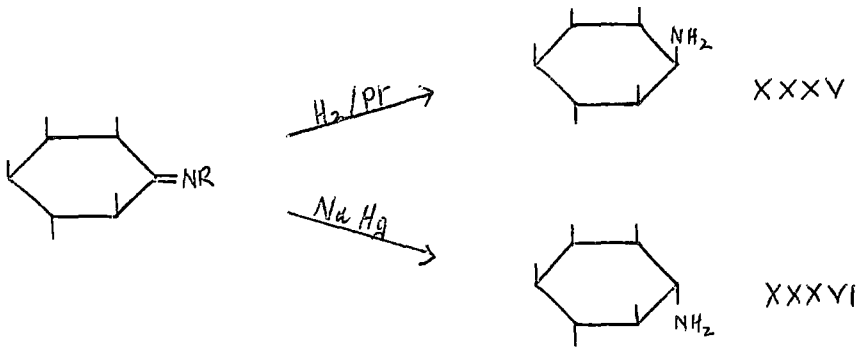
(35) Anderson and Lardy, J. Amer. Chem. Soc., 1950, 72, 3141.

(36) McCasland, ibid., 1951, 73, 2295.

(37) Posternak, Helv. Chim. Acta, 1950, 33, 1597.

(38) May and Mosettig, J. Org. Chem., 1949, 14, 1137.

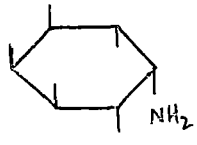
(39) Straube Rieke, Lardy and Anderson, J. Amer. Chem. Soc., 1953, 75, 694.



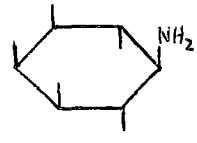
XXXV

XXXVI

to hygromycin (40), and also from hygromycin itself (41). The inosamine was optically inactive, and the phthalimido derivative formed a monoisopropylidene derivative, which consumed only one mole of periodate, and hence only structures (XXXVII) and (XXXVIII) were possible. Deamination with nitrous acid gave mesoinositol (41), and as this reaction is known to proceed with inversion in the aminodeoxyinositol series, the inosamine has structure (XXXVII).



XXXVII



XXXVIII

This inosamine is of particular interest, as it is the

---

(40) Patrick, Williams, Waller and Hutchings, J. Amer. Chem. Soc., 1956, 78, 3652.

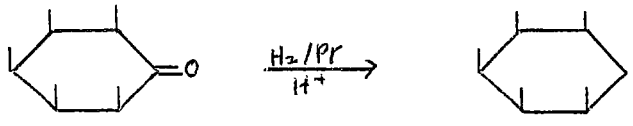
(41) Mann and Woolf, J. Amer. Chem. Soc., 1957, 79, 120.

first time an inositol derivative with the 1:4 diaxial conformation has been found in nature. The synthesis of (XXXVII) from neoinososе is described in Part I of this thesis. A similar synthesis was carried out simultaneously by workers in America (42).

6. THE QUERCITOLS.

Of the ten possible steric isomers of pentahydroxy-cyclohexane, only six are known. In his review, Orloff (13) discusses the chemistry and structures of the four isomers known to that date, which may be represented by structures (XXXIX-XLII).

cisQuercitol has been synthesised by catalytic reduction of hexahydroxybenzene (43). It may also be prepared by catalytic reduction of cisinososе (XXX) in acid solution, and this reaction established its structure as (XLIII).

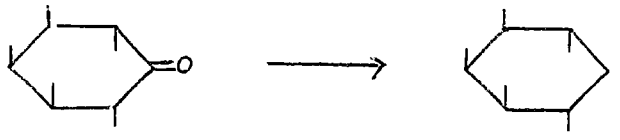


XXX XLIII

(42) Allen, J. Amer. Chem. Soc., 1956, 78, 5691.

(43) D. McHugh, Ph.D. Thesis, Sydney, 1957.

The preparation of neoquercitol (XLIV) by catalytic reduction in acid solution of neoinosose (XXXI) is described in Part I of this thesis.



XXXI XLIV

XXXIX scyllo XL epi

XLI proto XLII vibo

PART I.

CATALYTIC OXIDATION OF INOSITOLS.

INTRODUCTION.

It has been shown that aeration of cyclitols in aqueous solution in the presence of a platinum catalyst causes dehydrogenation in a selective manner, similar to oxidation by Acetobacter suboxydans. Oxidation by the latter has been studied extensively as such selective reactions are of great interest in cyclitol chemistry, and therefore the catalytic oxidation of inositols has been studied in order to establish the similarities and differences between the two reactions.

Biological Oxidation of Inositols.

Magasanik and Chargaff made a study of the action of a particular strain of Acetobacter suboxydans (American Type Culture Collection No. 621.) on a wide variety of inositols and quercitols, and concluded that only axial hydroxyl groups could be oxidized to keto groups, but that not all such hydroxyl groups were affected by the enzyme (31). In 1952, after additional compounds had been studied (44, 45) they postulated the following rules for the steric requirements for oxidation by the microorganism (45).

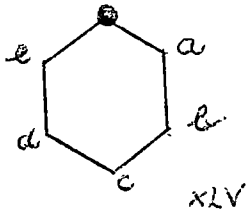
1. Only axial hydroxyl groups are oxidized.
2. The carbon atom in the meta position to the one carrying the axial hydroxyl group,(in clockwise direction if south axial, counterclockwise direction if north axial), must carry an equatorial hydroxyl group.

---

(44) Posternak, Helv. Chim. Acta., 1950, 33, 350, 1594.
(45) Magasanik, Franzl and Chargaff, J. Amer.Chem. Soc., 1952, 74, 2618.

Posternak and Reymond (46) studied the biological oxidation of a large number of cyclitols, including inositols, quercitols, tetrols and triols. They found that the above rules did not apply generally to tetrols and triols, and that epiinositol and epiinosose consumed twice the amount of oxygen stated by Magasanik and Chargaff. Their results, however, are not strictly comparable with those of Magasanik and Chargaff, as they used a different strain of Acetobacter suboxydans (Kluyver and de Leeuw) which does not appear to be so specific.

The rules formulated by Magasanik and Chargaff were based on the study of the effect of substitution of hydroxyl, methylene, and keto groups in positions a, b, d and e of (XLV) ; all the compounds which they studied possessed an equatorial hydroxyl group in position c.



XLV

● = North axial O H

Investigations in these laboratories (47) of the effect of substitution of axial hydroxyl, methylene, and keto groups in position c have shown that, while substitution of these groups does not prevent oxidation, the rate is far

---

(46) Posternak and Reymond, Helv. Chim. Acta., 1953, 36, 260.

(47) D. McHugh, Ph. D. Thesis, Sydney, 1957.

slower than when an equatorial hydroxyl group occupies position c. Thus the microorganism shows a certain degree of specificity at position c. Neither cisinositol nor cisquercitol conforms to Rule 2, but it has been shown that both are slowly oxidized by A. suboxydans, cisquercitol more slowly than cisinositol (47).

Replacement of a hydroxyl group of an inositol by an amino or an acetylamino group yields products which are not oxidized, although they may satisfy both requirements of Magasanik and Chargaff (48).

The only inositol methyl ethers which have so far been found to be oxidized by the bacteria are (+)-bornesitol (49) and (-)-pinitol (47). Both compounds satisfy Rules 1 and 2, but there are other methyl ethers, quebrachitol (31) and sequoyitol (49) for example, which also satisfy both rules, and are not oxidized. The presence of an O-methyl group does not, therefore, prevent oxidation, but the enzyme does not seem able to tolerate the presence of an O-methyl group in many positions.

Magasanik and Chargaff's first requirement still holds, and only axial hydroxyl groups are oxidized by the enzyme, although not all axial hydroxyl groups are attacked. Their second requirement does not appear to be absolute ;

---

(48) Anderson, Tomita, Kussi and Kirkwood, J. Biol. Chem., 1953, 204, 769.

(49) L. Anderson, personal communication.

however, the cyclitol oxidase shows considerable selectivity with respect to the rate at which oxidation takes place.

Catalytic Oxidation of Inositols.

Under suitable conditions, carbohydrates are oxidized in a specific manner by oxygen in the presence of a platinum catalyst (50). The oxidative attack occurs at carbon atom 1 for aldoses and ketoses, and leads to the formation of the corresponding α-ketoacid in good yields. Thus, for example, L-sorbose may be oxidized to 2-keto-L-gulonic acid, and D-fructose to 2-keto-D-gluconic acid by this means. The hydroxyl group at carbon atom 6 may also be oxidized when more vigorous conditions are used, or when the hydroxyl at C_1 is protected by an acetal bridge or a glycosidic link. D-glucuronic acid has been prepared from D-glucose by catalytic oxidation of 1:2-O-isopropylidene D-glucose (51).

In all these cases, either an aldehyde or a primary alcohol group was attacked, the aldehyde preferentially ; the secondary hydroxyl groups present were unaffected. To determine whether, and under what conditions secondary hydroxyl groups were catalytically oxidized, Heyns

---

(50) Heyns,

(51) Mehltretter, Alexander, Mellies and Rist, J.Amer. Chem. Soc., 1951, 73, 2424.

investigated the reaction for mesoinositol (VIII) (52). This compound was particularly suited for the purpose, as it contained only secondary hydroxyl groups. The product of the reaction was a monoketone, identical with scylloinosose (XXVI), the structure of which had been determined by Posternak (53).

VIII XXVI

From (VIII) it can be seen that mesoinositol has five equivalent equatorial hydroxyl groups, and one axial hydroxyl group. scylloInosose could arise only through the specific attack of the axial hydroxyl group in position 2.

Heyns subsequently used this reaction in his synthesis of streptamine (XXXII) from mesoinositol (33). meso-Inositol was converted to DL-mesoinosamine-4 (XLVI) by oxidation to epiinosose (XXVII) with nitric acid (54) followed by reduction of the oxime of the ketone with sodium amalgam. The amino group of (XLVI) was converted

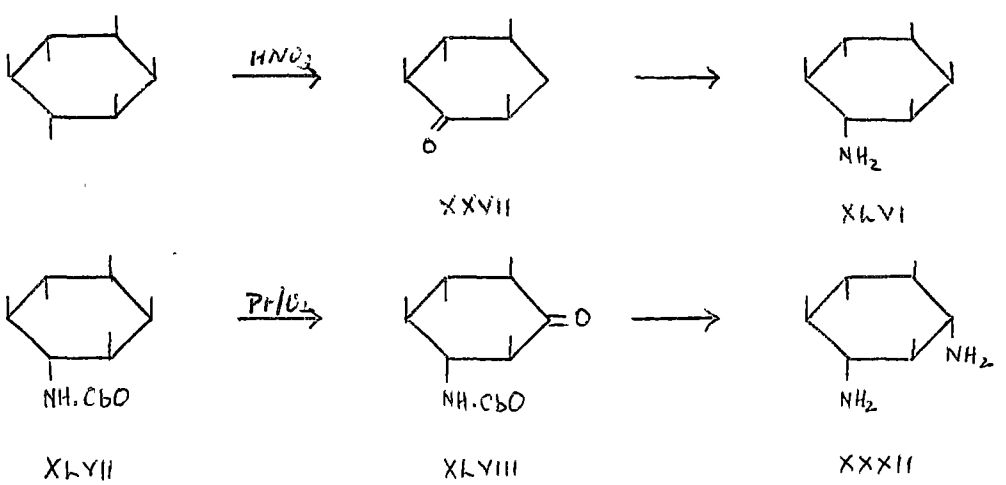
---

(52) Heyns, Ber., 1953, 86, 833.

(53) Posternak, Helv. Chim. Acta., 1942, 25, 746.

(54) Posternak, ibid., 1936, 19, 1333.

to its carbobenzoxy derivative and then the axial hydroxyl group present was catalytically oxidized to a keto group. For this reaction he found that the 10% platinum catalyst on a charcoal carrier which he had used previously, was unsatisfactory , and better yields were obtained using freshly reduced Adams catalyst. The keto group formed was converted to an amino group by reduction of the oxime with sodium amalgam, and the product obtained was identical with streptamine (XXXII).

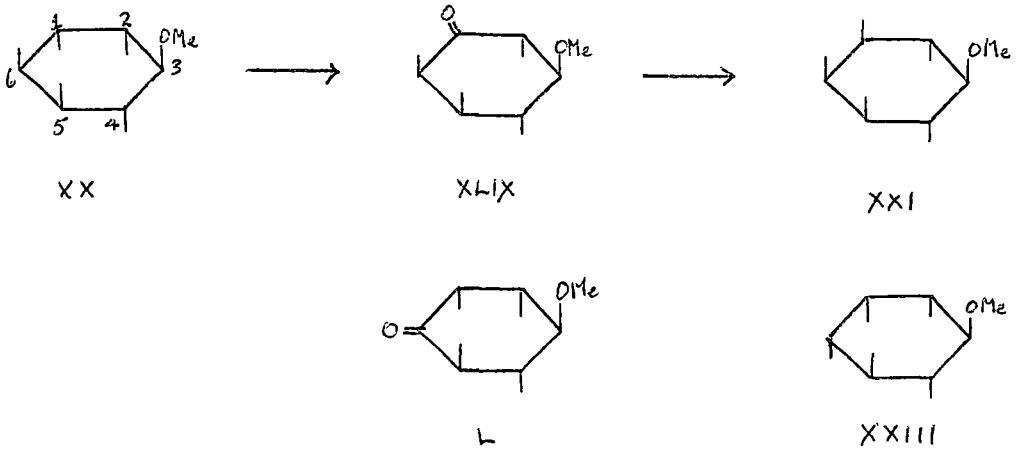


XXVII XLVI

XLVII XLVIII XXXII

The final proof of the structure of sequoyitol (XXI) was its synthesis from pinitol (XX) (21). The configuration of pinitol is such that inversion of the hydroxyl group at position 1 would convert it to 5-O-methyl*meso*-inositol (XXI). (+)-Pinitol was oxidized catalytically with a 10% platinum catalyst, and a monoketone was obtained which gave sequoyitol on reduction with sodium amalgam. The only *meso*inositol derivatives which could be derived from (+)-pinitol by these reactions are 5-O-methyl-*meso*-

inositol (XXI), from the ketone (XLIX), and 4-O-methyl-mesoinositol (XXIII) from the ketone (L). (XXIII) is asymmetric and must therefore correspond to one of the



XX XLIX XXI

L XXIII

ononitols. Thus sequoyitol is 5-O-methylmesoinositol, and the monoketone obtained by catalytic oxidation of (+)-pinitol has structure (XLIX).

As in the case of mesoinositol, the hydroxyl group in pinitol which is oxidized catalytically is an axial one. Here, however, there are two axial hydroxyl groups, in positions 1 and 6, but only the one in position 1 is oxidized. These results suggest that catalytic oxidation of inositols only affects axial hydroxyl groups, and in this respect it would closely resemble biological oxidation by Acetobacter suboxydans where only axial hydroxyl groups are attacked. For mesoinositol the product of oxidation either catalytically or biologically is the same, namely, scyllo-inosose. Of the enantiomorphs of pinitol, A. suboxydans will only oxidize (-)-pinitol to yield a ketone which is

the enantiomorph of (XLIX), since it also yields sequoyitol on amalgam reduction (47). Oxidation by catalytic means cannot discriminate between optical enantiomorphs.

CATALYTIC OXIDATION OF INOSITOLS.

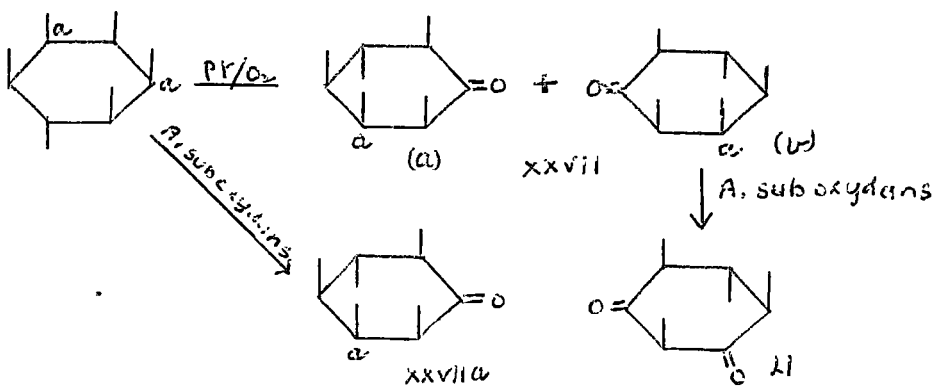
In the earlier work on the catalytic oxidation of inositols the oxidations were carried out using a 10% platinum catalyst on a carbon carrier, as this was the catalyst which Heyns had found satisfactory for the oxidation of aldoses, ketoses and mesoinositol (50, 52). For the oxidation of N-carbobenzoxy-DL-mesoinosamine-4 (XLVII), he found that better yields were obtained if freshly reduced Adams' platinum catalyst was used, in a ratio of 1:1 (W/W). Allen (42) also reported rapid and complete oxidation of neoinositol with Adams' catalyst, and in all later experiments this catalyst was used.

§ 1.1 As the main product of oxidation of mesoinositol, Heyns isolated scylloinosose in 42% yield. In addition, he found small quantities (0.5-1%) of sugar acids present, and, by paper chromatography of the reaction mixture, showed the presence of a second compound with reducing properties. As this product was not isolated, the catalytic oxidation of mesoinositol was repeated under similar conditions. Again, the main product of the reaction was scylloinosose. The reaction mixture was examined by paper chromatography in acetone-water (4:1), phenol-water (4:1), and in pyridine-amyl alcohol-water (7:7:6), the solvent system used by Heyns, but in none of these three solvent systems could any compound with reducing properties other than scylloinosose be detected.

To determine whether the second compound detected by Heyns was a diketone formed by further oxidation of scylloinosose, scylloinosose was subjected to oxidation under the same conditions. After 22 hours the scylloinosose was recovered unchanged, and paper chromatography in the above three solvent systems did not show any traces of a compound such as Heyns described. Thus, scylloinosose is stable under the conditions of oxidation and not readily further oxidized.

Heyns' work on the oxidation of mesoinositol and N-carbobenzoxy-DL-mesoinosamine-4 suggests that only axial hydroxyl groups are affected. In both cases, the products of oxidation (XXVI and XLVIII), could only have arisen through specific attack of the single axial hydroxyl group present. Catalytic oxidation of (+)-pinitol also gives a ketone (XLIX) derived from an axial hydroxyl group. Here, however, there are two axial hydroxyl groups present, in positions 1 and 6, but only one is oxidized.

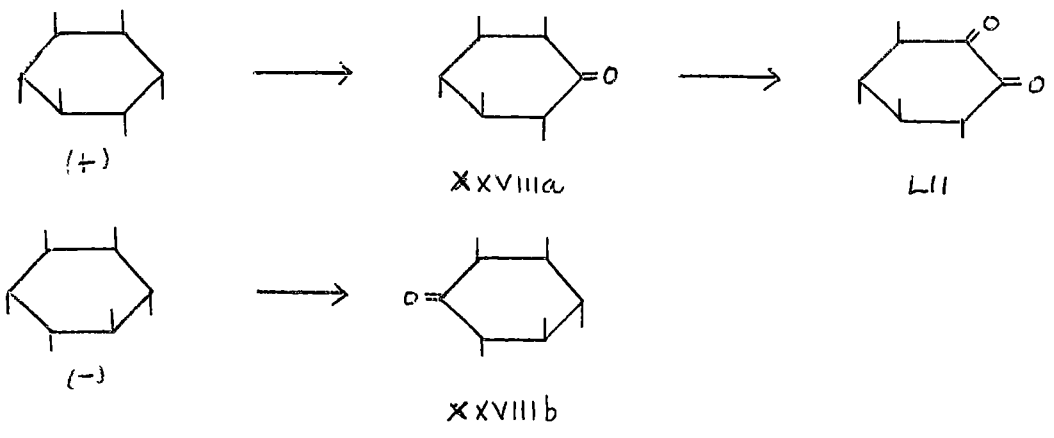
§ 1.2 If equatorial hydroxyl groups are not affected by the reaction, then scylloinositol, the all equatorial inositol isomer would not be oxidized, and this was found to be the case. After 20 hours, the scylloinositol was recovered from the reaction mixture, and no trace of any reducing compound could be detected by paper chromatography of the reaction mixture. scylloInositol is not attacked by A. suboxydans.



§ 1.3 epiInositol (X) was oxidized catalytically, and the product obtained was found to be identical with (±)-epiinosose (XXVII). Paper chromatography of the reaction mixture did not show the presence of any other keto compound, although epiinosose possesses an axial hydroxyl group in position 4. epiInosose itself is quite stable under the conditions of oxidation, as, after having been subjected to oxidation conditions for 30 hours, it was recovered unchanged.

Acetobacter suboxydans shows considerable optical specificity in regard to the oxidation of epiinositol. Only (-)-epiinosose (XXVIIa) is obtained, and this compound is not further attacked by the microorganism. However, (+)-epiinosose (XXVIIb) is oxidized by Acetobacter suboxydans. The oxidation product has not been isolated, but presumably has structure (LI), as the axial hydroxyl group would be attacked (31). These results conform with rules of

Magasanik and Chargaff.



§ 1.4 (+)-Inositol is oxidized by A. suboxydans with the consumption of one mole of oxygen, and the diketone (LII) is the end product. If the reaction is interrupted before the uptake of oxygen is complete, a monoketone can be isolated in addition to the diketone. The monoketone, (+)-viboinosose (XXVIIIa) is further oxidized by the micro-organism to give the diketone (30, 31).

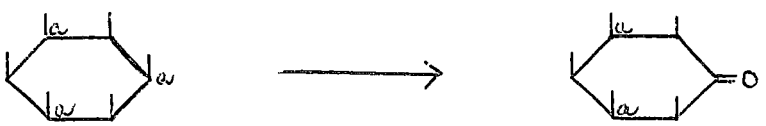
(-)-Inositol was prepared by demethylation of quebrachitol, and subjected to catalytic oxidation. The oxidation product was isolated as its phenylhydrazone, and identified as (-)-viboinosose (XXVIIIb). This result was confirmed by the work of Anderson (55), who also isolated (-)-viboinosose from the catalytic oxidation of (-)-inositol. Thus, catalytic oxidation provides a more direct route to viboinosose, as it terminates at the monoketone stage.

---

(55) L. Anderson, personal communication.

§ 1.5 cisInositol has three axial hydroxyl groups.

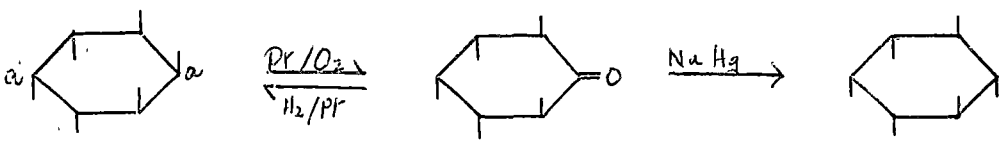
Oxidation of cisinositol by A. suboxydans proceeds slowly but steadily and the product obtained is cisinosose (XXX)(47) Catalytic oxidation of cisinositol also gave cisinosose as the only product.



XXX

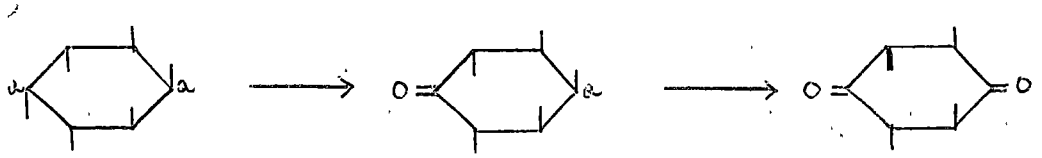
§ 1.6 neoInositol was prepared by the method of Angyal and Matheson (14). Catalytic oxidation of neoinositol gave an inosose, which was isolated as its phenylhydrazone. Considerable difficulty was found in obtaining satisfactory yields of the inosose owing to the low solubility of neoinositol in water, and the poor yields obtained when 10% platinum catalyst was used for the oxidation. Decomposition of the phenylhydrazone with benzaldehyde gave the inosose. The configuration of this inosose was shown to be (XXXI) by reduction ; with sodium amalgam the product obtained was mesoinositol, and catalytic reduction gave neoinositol. Since amalgam reduction is known to give equatorial hydroxyl groups predominantly, while catalytic reduction gives axial hydroxyl groups, the only possible structure is (XXXI). This inosose has been named neoinosose. The oxidation was followed by paper chromatography, but no second oxidation

product could be detected.



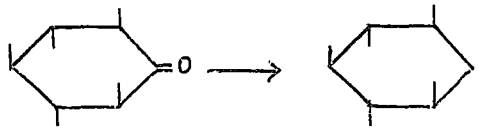
XXXI

Bacterial oxidation of neoinositol yields a tetrahydroxy cyclohexanedione (LIII), as both the axial groups present are attacked. neoInosose cannot be isolated as an intermediate as it is oxidized to (LIII) at a more rapid rate than neoinositol is oxidized to neoinosose(47)

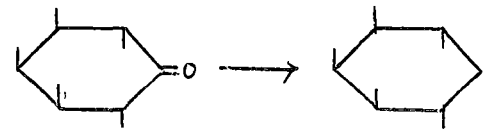


XXXI LIII

Hydrogenation of an inosose using platinum oxide in acid solution has been shown to reduce the keto group to a methylene group, thus forming a quercitol ; for example, scylloinosose gives scylloquercitol (XXXIX). Therefore, catalytic reduction of neoinosose (XXXI) under these conditions should yield the quercitol with the configuration (XLIV). This has been carried out and the quercitol and its acetate were characterized. The quercitol has been named neoquercitol.

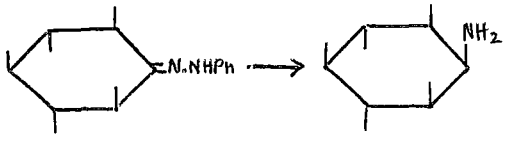


XXXIX

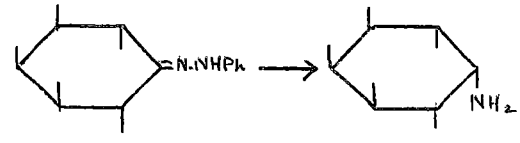


XXXI XLIV

§ 161 It has been shown that catalytic reduction of an inososе phenylhydrazone or oxime gives an aminodeoxyinositol with an axial amino group ; for example, scylloinososе phenylhydrazone (LIV) gives mesoinosamine-2 (XXXIII).



LIV XXXIII



LV XXXVII

Recently the aminodeoxyinositol (XXXVII) was isolated as a hydrolysis product of a new antibiotic (40). The structure of the aminodeoxyinositol was established as 2-amino-2 deoxyneoinositol by its reactions, but the compound was not synthesised. Catalytic reduction of neoinososephenylhydrazone (LV) should,therefore, give the aminodeoxyinositol of this configuration. This has been carried out and the inosamine was isolated as its hexaacetate, which was identical with a sample of hexaacetate prepared from the natural compound. A similar synthesis from neoinososе was carried out at the same time by Allen

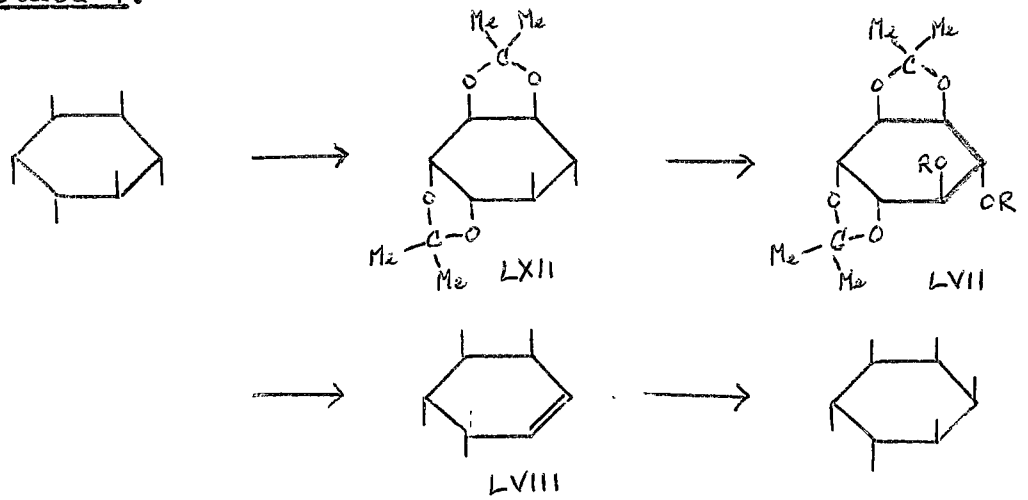
and has recently been published (42).

§ 1.7 alloInositol has been obtained by hydroxylation of a naturally occurring cyclohexenetetrol, conduritol (LVI) (56).

LVI

In the absence of a suitable source of conduritol, it was necessary to develop an alternative method of synthesis. alloInositol is obtained as a product of a number of reactions of tosyl derivatives of (-)-inositol (57). The following three series of reactions were therefore investigated as possible methods of preparation of allo-inositol.

Method 1.



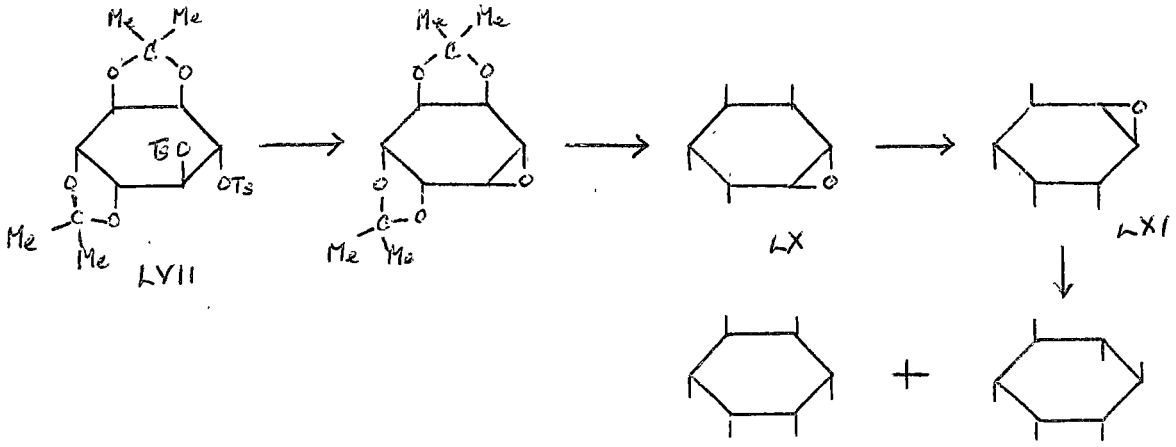
---

(56) Dangschat and Fischer, Naturwiss., 1939, 27, 756.

(57) P.T. Gilham, Ph. D. Thesis, Sydney, 1956.

In this method a disulfonyl ester of (-)-inositol (LVII) was reacted with sodium iodide to yield (+)3:4/ 5:6-cyclohexenetetrol (LVIII), which was then oxidized to alloinositol with silver chlorate and osmium tetroxide. The reaction of (LVII) with sodium iodide did not give a very good yield, although the dinisyl ester (LVII, R = Ns) gives a better yield (46%) than the ditosyl ester (LVII, R = Ts, 30%). The hydroxylation of (LVIII) also gave a poor yield (35-40%) for a preparative method.

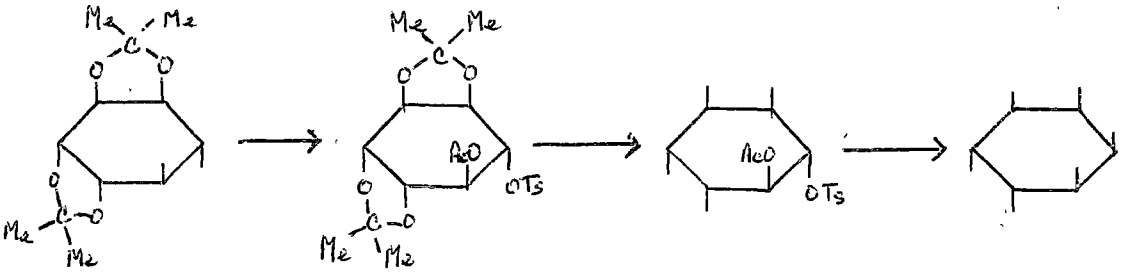
Method 2.



1:2-Anhydroalloinositol (LX) was formed from the ditosyl ester of (-)-inositol (LVII). This epoxide was then rearranged in alkaline solution to give the epoxide (LXI), which, on hydrolysis with alkali gave a mixture of allo- and mesoinositol. This method has the disadvantage that it leads to the formation of mesoinositol in addition to alloinositol, although more of the latter is formed. These two inositols could not be satisfactorily separated

except by cellulose column chromatography, which was only practicable on a relatively small scale. In addition, the epoxide (LX) was only formed in yields of approximately 50%.

Method 3.



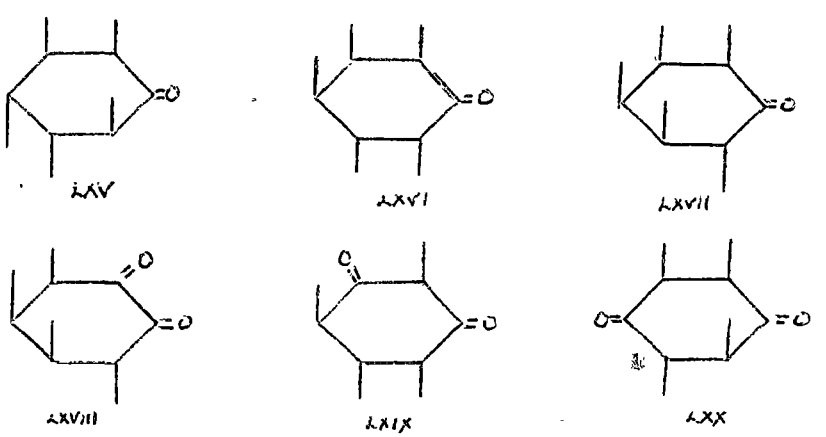
LXII LXIII LXIV

This method has finally been adopted as the most satisfactory means of preparation of alloinositol. Diisopropylidene-(-)-inositol (LXII) was partially tosylated, and the monotosyl derivative (LXIV) solvolysed in 95% acetic acid for 30 hours to give alloinositol. Although the monotosyl derivative (LXIII) was obtained in poor yields, (20%), it is not difficult to prepare and the starting material, diisopropylidene-(-)-inositol is readily available. The remainder of the reaction is straight forward and 50% yields of alloinositol have been obtained from the monotosyl derivative. Under the conditions of solvolysis, an isomerisation reaction occurred and 5-10% epiinositol was also formed. It was found that the formation of epiinositol could be avoided by the addition of 1 mole of sodium acetate to the solvolysis. The sodium acetate reacted with the toluenesulfonic acid formed during the

reaction. This isomerisation reaction is discussed in Part II of this thesis.

alloInositol was oxidized catalytically and paper chromatography of the reaction mixture showed the presence of two reducing compounds. Cellulose column chromatography of the mixture gave two fractions, A and B, neither of which could be obtained crystalline.

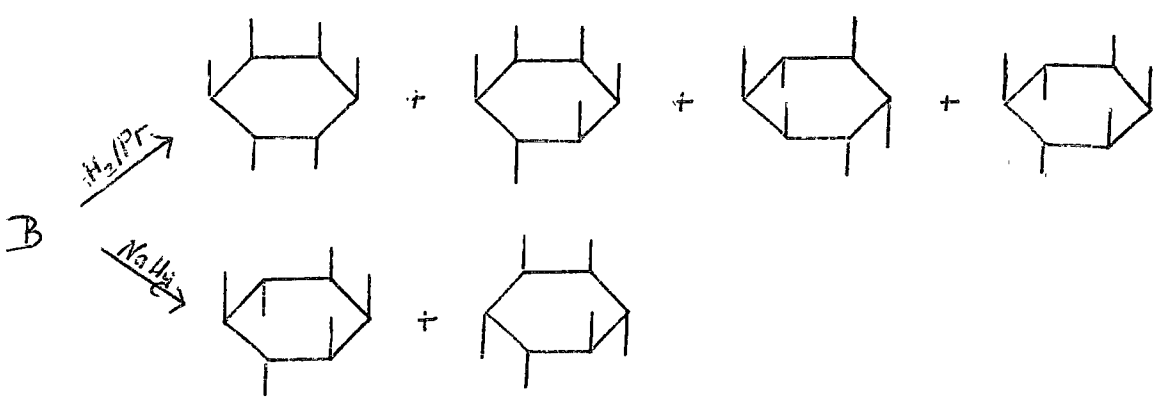
Fraction A had a high R_I value, suggestive of a monoketone. Reduction of this fraction with sodium amalgam gave neoinositol as the main product, together with a small amount of (±)-inositol, but no mesoinositol could be detected in the reaction mixture. Oxidative attack of the axial hydroxyl groups present in alloinositol could give rise to three monoketones (LXV to LXVII), and three diketones (LXVIII to LXX).



If fraction A consisted principally of any one of the three diketones, reduction with amalgam should give rise principally to mesoinositol, in which both keto groups

are replaced by equatorial hydroxyl groups. The isolation of neoinositol as the major product suggests that fraction A consists largely of the monoketone (LXVI), which is the only monoketone which could give neoinositol. The traces of (±)-inositol probably arose from small amounts of a second monoketone present, although fraction A could not be separated into two components by paper chromatography in any of the three solvent systems used.

Fraction B, which had a low R_f value, was reduced with sodium amalgam and mesoinositol was isolated as the main product, which suggested that fraction B was a diketone fraction. Paper chromatography of the reduction mixture showed the presence of traces of (±)-inositol, but no neo-inositol. Further oxidation of fraction A did not give fraction B, and thus A is not an intermediate in the formation of B. Fraction B was reduced catalytically on a small scale, and paper chromatography of the reaction mixture showed that, in addition to alloinositol which was formed as the principle product, small amounts of epi-, (±)- and mesoinositols were formed.



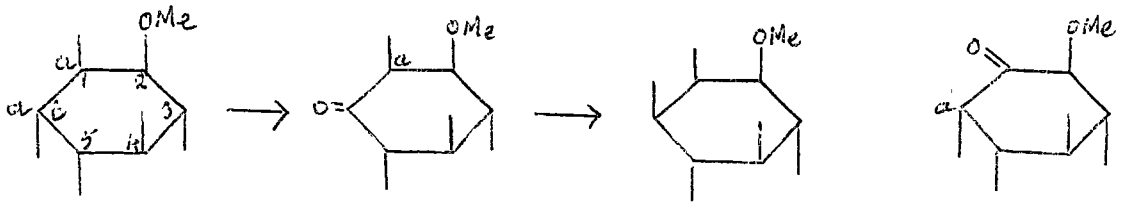
These facts suggest that B is a diketone, and since no neo-inositol was found, and (±)- and epi- both were found, that the diketone has structure (LXX).

§ 1.8 The action of A. suboxydans on a wide variety of inositol methyl ethers has been studied, and it has been found that the microorganism cannot tolerate the presence of methoxy groups in many positions, even though the methyl ethers may fulfil Magasanik and Chargaff's requirements. The presence of equatorial methoxy groups does not, however, prevent oxidation by catalytic means.

Quebrachitol was oxidized with platinum catalyst and the ketone obtained was reduced with sodium amalgam. This reduction was very slow, and gave a very poor yield; the major product isolated was quebrachitol. Bornesitol was identified as the other product of reduction by paper chromatography in two solvent systems and paper ionophoresis in 0.15 M. borate solution. The bornesitol was not isolated as it could not be separated from the scylloquercitol which accompanied it; the latter was isolated in small quantities and identified as its acetate. The scylloquercitol presumably arose from reduction of scylloinosose, which would have been formed in small amounts from the meso-inositol which is always present in quebrachitol as an impurity.

There are two possible monoketones (LXXI, LXXII) which could be formed from quebrachitol. Oxidation of the axial

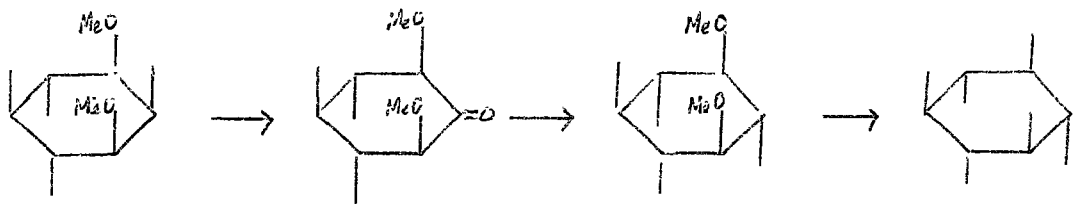
hydroxyl group in position 1 would give (LXXII), which would give ononitol on amalgam reduction, while bornesitol must be derived from (LXXI), which would be formed by oxidation of the axial hydroxyl group in position 6.



LXXI LXXII

No trace of ononitol was found, and so the ketone formed by catalytic oxidation must have structure (LXXI). This work has been confirmed by the work of Anderson (26), who isolated (-)-bornesitol. He found sodium amalgam reduction did not give satisfactory results, and the bornesitol was isolated when sodium borohydride was used as a reducing agent. Quebrachitol is not oxidized by A. suboxydans.

§ I.9 Dambonitol, the 1:3 dimethyl ether of mesoinositol is also not attacked by the microorganism. Catalytic oxidation of dambonitol gave a single oxidation product, a monoketone. The ketone was reduced with sodium borohydride, and from the reduction mixture an inositol dimethyl ether was isolated and characterised as its acetate. Demethylation of this dimethyl ether gave scylloinositol, which was identified as its hexaacetate. Thus, the ketone must have structure (LXIII) and the initial reduction product was the 1:3 dimethyl ether of scylloinositol (LXXIV).



XXXIII XXXIV

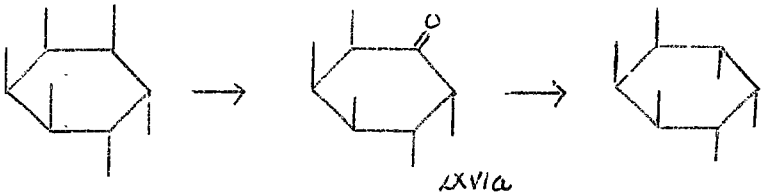
Dambonitol was oxidized catalytically at a much slower rate than the other inositols and inositol methyl ethers under the same conditions. This slower rate of oxidation could be accounted for by steric hindrance caused by the two methoxyl groups, both of which are adjacent and cis to the axial hydroxyl group.

APPENDIX.

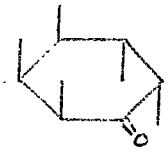
Oxidation of alloInositol by Acetobacter suboxydans.

The study of the oxidation of alloinositol by A. suboxydans was commenced by D.J. McHugh who carried out a large scale fermentation of alloinositol with the micro-organism for seven days.

The ketone produced was shown to have the same R_f value as the monoketone obtained by catalytic oxidation of alloinositol and has been named alloinosose. Reduction of the ketone with sodium amalgam also gave neoinositol, together with traces of either (+) or (-)- inositols and mesoinositol. These latter products could only be identified by paper chromatography and were probably due to traces of impurity in the inosose. The inosose was optically active with negative rotation and must therefore be one of the enantiomorphs of (LXVI).



LXVIa



LXVIb.

By analogy with Magasanik and Chargaff's work on the oxidation of epiinositol and (+) and (-) epiinosose it is probable that (-)-alloinosose has the structure (LXVI b).

PART II.

THE SOLVOLYSIS OF MONOTOSYL ESTERS OF INOSITOLS.

INTRODUCTION.

The sulphonic esters form one of the most useful groups of carbohydrate derivatives. Comparative study of the esters of some simple aliphatic alcohols has shown that, whereas, in general, esters of carboxylic acids react by acyl-oxygen fission, those of sulphonic acids react by alkyl-oxygen fission. This latter type of fission leads to displacement reactions on the carbon atom, which may be accompanied by Walden inversion. This explains the extensive use of sulphonic esters in carbohydrate chemistry, and in particular, in the synthesis of some of the rarer sugars ; in these syntheses an epoxide ring is formed and opened, which causes a double inversion (58). A similar set of reactions occurs in the cyclitol series.

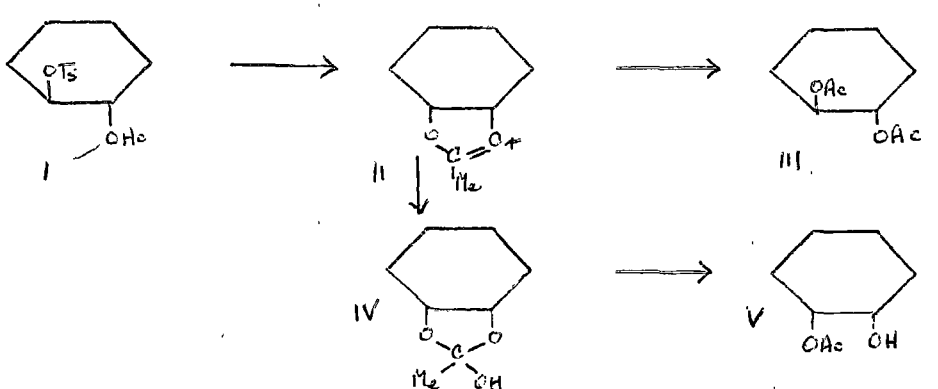
The solvolysis of monotosyl esters of the higher cyclitols has not been studied extensively, but it may be accompanied by a single inversion (57) ; this reaction would be very useful if the conditions for its occurrence could be established. In the sugar series, there appears to be no case recorded where a secondary tosyl group has been removed with inversion without the formation of epoxides owing to the influence of neighbouring groups.

The effect of neighbouring groups in the solvolysis of

---

(58) Tipson, Adv. in Carbohydrate Chem, 1953, 8, 107.

the monotosyl esters of cyclohexanediols has been studied by Winstein et al. (59). They found that trans 1-O-acetyl-2-O-tosylcyclohexanediol (I) was converted to trans 1:2-di-O-acetylcyclohexanediol (III) by heating it with dry acetic acid in the presence of potassium acetate. If optically active trans-tosylacetylcyclohexanediol was used, the product was a racemate. If the reaction was carried out with sufficiently wet acetic acid, or in the absence of potassium acetate, the product obtained was mainly of the cis configuration. Hence, they proposed that the intermediate in the reaction must have structure (II), which reacts with acetate ion to form the trans compound (III) in the first case, and in the presence of water forms the ortho-ester (IV), which in turn opens to give the cis product (V).

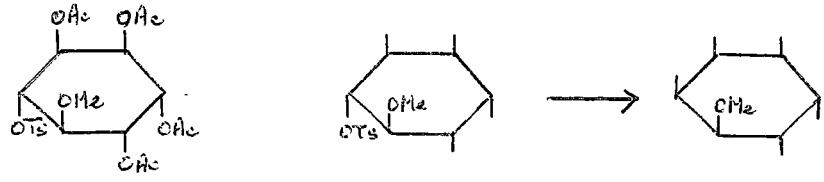


Gilham (57) prepared several monotosyl acetyl derivatives of (+)-, (-)- and epi- inositols and subjected them to solvolysis. He found that no reaction occurred when

---

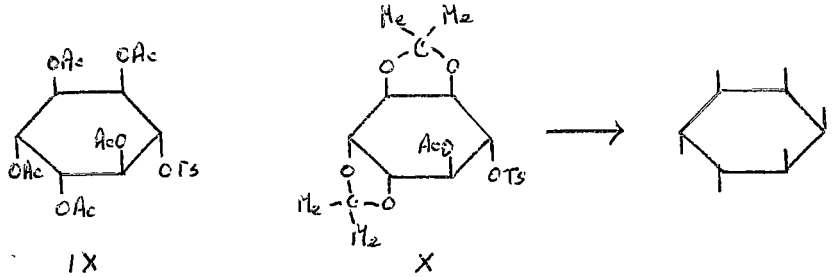
(59) Winstein et al., J. Amer. Chem. Soc., 1942, 64, 2796.

3-O-methyl-4-O-tosyl-(+)-inositol tetraacetate (VI) was heated under reflux with dry acetic acid, although there was an acetyl group present trans to the tosyl group. If, however, 3-O-methyl-4-O-tosyl-(+)-inositol (VII) was heated under reflux for 30 hours with wet acetic acid a good yield of the methylalloinositol (VIII) was obtained. This result is not explained by the mechanism proposed by Winstein.



VI VII VIII

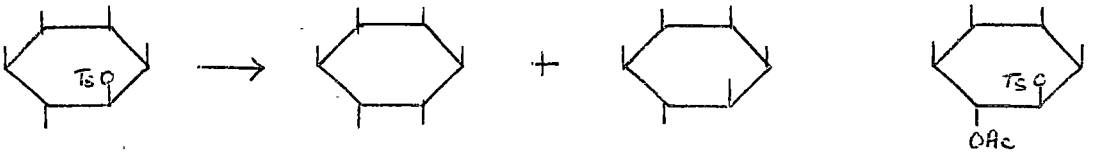
Gilham also found that 3-O-tosyl-(-)-inositol penta-acetate (IX) gave no result when heated with dry acetic acid, but that the diisopropylidene monoacetyl derivative (X) gave alloinositol when solvolysed in dry acetic acid and subjected to mild acid hydrolysis.



IX X

Paper chromatography showed that traces of allo- and epi-inositols were formed when 1-O-tosylepiinositol (XI) was heated with wet acetic acid, but the monoacetyl derivative

(XII) was recovered unchanged when heated under reflux with wet acetic acid.



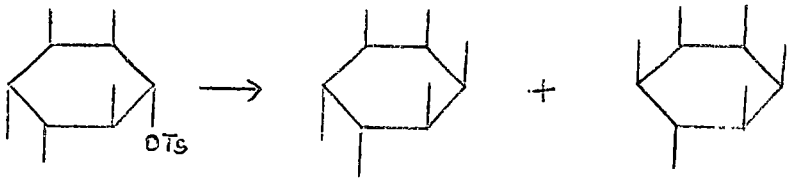
XI XII

Wet acetic acid was used for the solvolysis of those compounds carrying free hydroxyl groups in order to prevent complete acetylation as the fully acetylated derivatives did not undergo solvolysis. The solvolysis of <u>iso</u>propylidene derivatives was carried out in dry acetic acid in order to prevent hydrolysis.

THE SOLVOLYSIS OF MONOTOSYL ESTERS OF INOSITOLS.

§2.1 Epimerisation Reaction.

The solvolysis of 3-O-tosyl-4-O-acetyl-(-)-inositol (XIII) and of 3-O-tosyl-(-)-inositol (XIV) in 95% acetic acid was studied as a method of preparation of alloinositol. Paper chromatography showed that the alloinositol obtained in this way from these two compounds was always accompanied by an impurity with an R_f value similar to that of epiinositol. This second product was isolated by column chromatography and shown to be identical with epiinositol. If 3-O-tosyl-(-)-inositol was heated under reflux in water, solvolysis occurred and alloinositol was formed, but there was no trace of epiinositol in the reaction mixture.

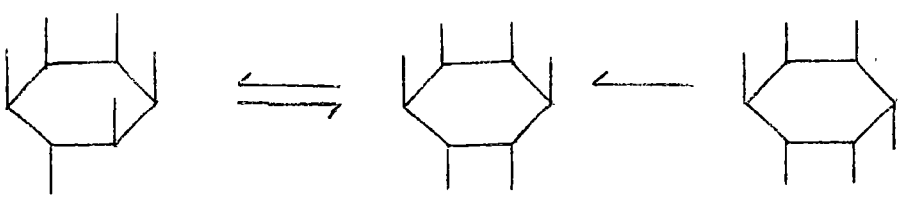


Examination of Gilhams samples of alloinositol, prepared from 3-O-methyl-4-O-tosyl (+)-inositol (VII) showed that these also contained epiinositol. If solvolysis of these compounds occurred without inversion, the product of the reaction would be either (+)- or (-)- inositol, and thus it seemed most probable that the epiinositol was formed from alloinositol by an isomerisation reaction, and this was found to be the case.

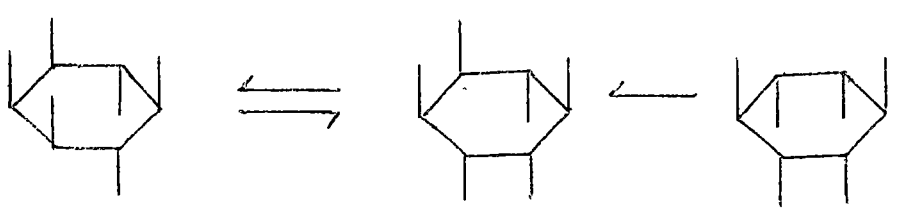
If pure alloinositol was heated under reflux with one mole of toluenesulphonic acid in 95% acetic acid for 12 hours, epiinositol could be identified in the reaction mixture.

This result was unexpected, as rearragements do not usually occur in acid solution in carbohydrate chemistry, and no other reaction of this type occurs in the inositol series. In view of the unexpected nature of this reaction, a brief chromatographic survey of this isomerisation reaction for the other inositol isomers was made, and the following sets of relationships were established :

1. epiinositol ⇌ alloinositol ← neoinositol.



2. mesoinositol ⇌ (±)-inositol ← mucoinositol



3. scylloinositol , cisinositol . . N.R.

No neoinositol could be detected in the alloinositol

reaction mixture or mucoinositol in the (∓)-inositol reaction mixture, but it would seem probable that both these two isomers were formed in small quantities, and would be detected if the reaction were carried out on a larger scale.

An examination of the structural formulae of the inositols shows that, in each case where epimerisation occurs, the hydroxyl group which undergoes inversion has one cis and one trans adjacent hydroxyl group. The two isomers which do not contain three hydroxyl groups in this arrangement, cis- and scylloinositol, do not isomerise.

As mesoinositol hexaacetate gave (∓)-inositol when heated under reflux in 95% acetic acid in the presence of toluenesulphonic acid, it is possible that the epimerisation occurs through an acetylated intermediate. Thus it appears that the necessary condition for this isomerisation to occur is that an inositol which possesses two contiguous cis hydroxyl groups with an adjacent trans hydroxyl group should be heated in wet acetic acid in the presence of a strong acid, such as toluenesulphonic acid or sulphuric acid (60). Further study is required to establish the nature and mechanism of this reaction.

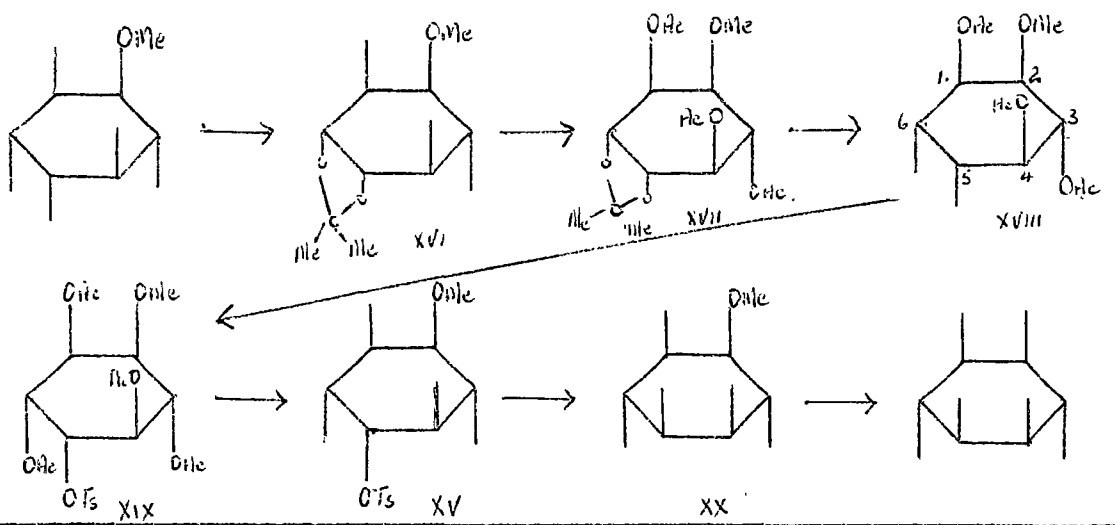
In the study of the solvolysis of monotosyl esters of inositols, this isomerisation reaction is undesirable, as it leads to the formation of additional products. It has been found, however, that the isomerisation may be prevented by the addition of sodium acetate to react with the liberated toluenesulphonic acid.

---

(60) S. Johns, personal communication.

§ 2.2 Preparation of Monotosyl Esters of Inositols.

2-O-Methyl-5-O-tosyl-(-)-inositol (XV) was prepared from quebrachitol. Quebrachitol was reacted with acetone to give the monoisopropylidene derivative (XVI). This reaction gave poor yields ; the most satisfactory method used was similar to that used by Ballou and Fischer (61). The monoisopropylidene derivative was acetylated to give the triacetate (XVII), which could not be obtained crystalline. Mild acid hydrolysis of (XVII) gave 1:3:4-tri-O-acetyl-quebrachitol (XVIII), which on treatment with tosyl chloride gave a monotosyl derivative, which was isolated as the tetra-acetate (XIX). (XVIII) did not react readily with tosyl chloride, and it was necessary to use an excess of tosyl chloride in a concentrated pyridine solution and heat the reaction mixture at 100° for 2 hours. Deacetylation of (XIX) gave the free monotosyl compound. It was assumed that the



(61) Ballou and Fischer, J. Amer. Chem. Soc., 1953, 75, 3673.

tosyl group was in position 5 since it is improbable that monotosylation of (XVIII) would occur on the axial hydroxyl group at C_6 in preference to the equatorial hydroxyl group at C_5. The isolation of mucoinositol by demethylation of the product of solvolysis (XX) confirmed the structure of (XIX) as 2-O-methyl-5-O-tosyl-1:3:4:6 tetra-O-acetyl (-)-inositol.

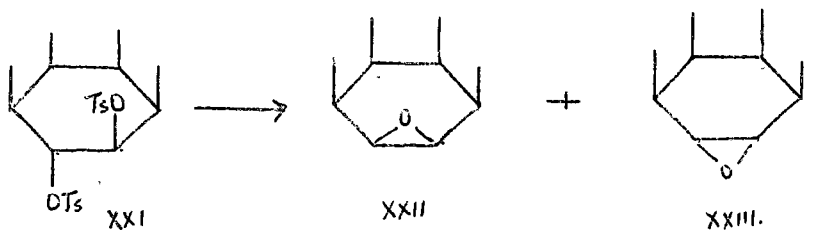
Another method of preparation of monotosyl compounds would be provided by the opening of anhydro inositols with toluenesulphonic acid. For cyclohexene oxide itself, this may be done with anhydrous toluenesulphonic acid in ethereal solution in the cold (62). Since inositols are insoluble in inert solvents such as ether, an attempt was made to open the epoxide ring of the tetraacetyl derivative of 1:2 anhydroallo-inositol, in dioxan, but no reaction occurred. However, it was found that the diisopropylidene derivative, or the free compound itself, both would react slowly in anhydrous dioxan at 100°. Paper chromatograms of the reaction mixture after 3 hours showed the presence of a compound with the R_f value of tosyl derivatives. In this case, two tosyl compounds could be formed, and so the product was not isolated.

In the case of 1:2-anhydrocisinositol, only one possible monotosyl compound could be formed. The diisopropylidene derivative of 1:2-anhydrocisinositol was prepared from 1:2-3:4-diisopropylidene 5:6-ditosylepiinositol.(XXI)Theoretically, two

---

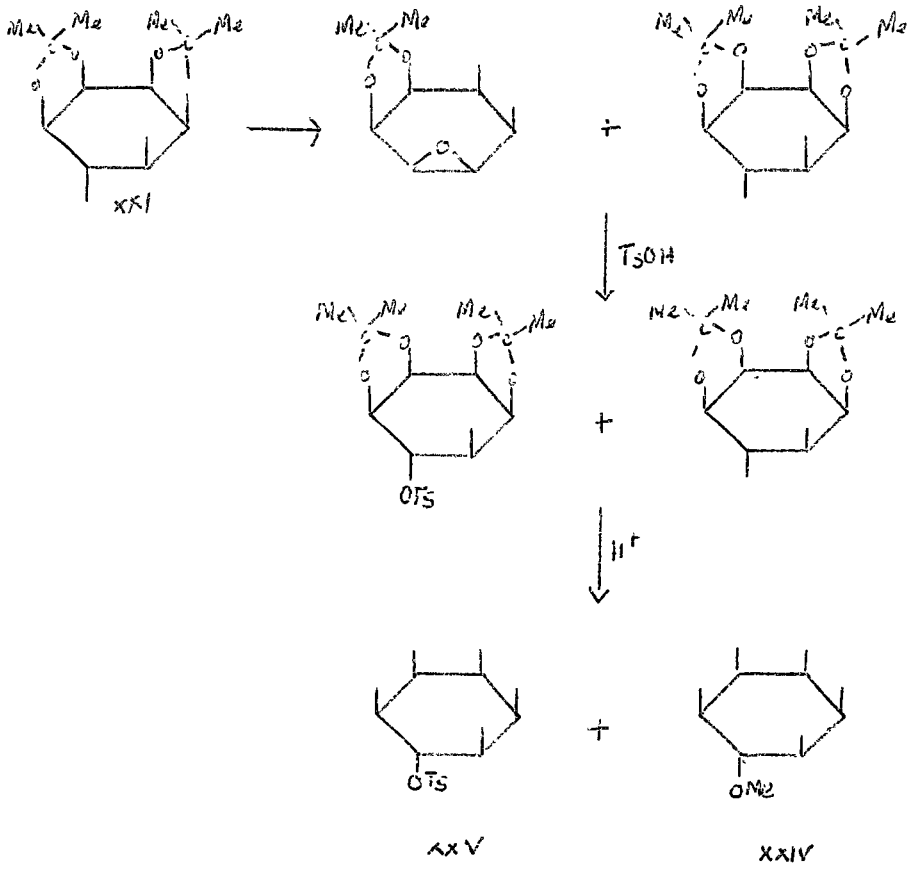
(62) Owen and Clarke, J. Chem. Soc., 1949, 315.

possible epoxides, (XXII) and (XXIII), could be formed from this ditosyl compound by reacting it with sodium in anhydrous methanol.



XXI XXII XXIII.

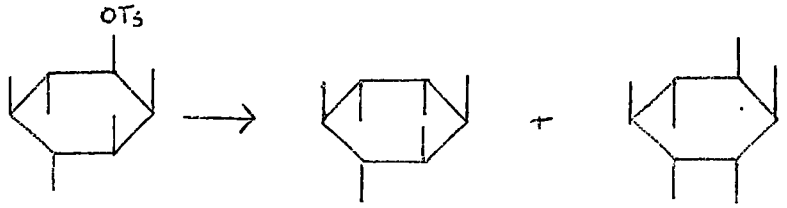
Gilham (57) found that only (XXII) was formed. In this instance, two compounds were obtained from the reaction. Paper chromatography showed that (XXII) was formed, but that the second compound was not (XXIII). A small amount of the compound was isolated by fractional crystallisation from petroleum ether, and analysis showed it to be the di<u>iso</u>-propylidene derivative of an inositol methyl ether. This methyl ether was isolated and characterised as its acetate. This methyl ether arose presumably from the reaction of (XXII) with sodium methoxide, and thus would be 6-<u>O</u>-methyl<u>epi</u>-inositol (XXIV). Since the methyl ether would not interfere in the tosylation reaction, the mixed product was reacted with toluenesulphonic acid in dioxan at 100°, and the product hydrolysed in mild acid conditions and the monotosyl compound separated from the methyl ether and unreacted epoxide on a cellulose powder column. The 6-<u>O</u>-tosyl<u>epi</u>inositol (XXV) obtained in this way was characterised as its acetate.



XXV XXIV

The Solvolysis of some Monotosyl Esters of Inositols.

1-O-Tosylmesoinositol (XXVI) was prepared by Gilham (57) who also subjected this compound to solvolysis in wet acetic acid. After 40 hours, he recovered the greater portion of the starting material (63). The solvolysis of this compound was repeated, as it was thought that solvolysis probably took place, but at a very slow rate. This proved to be the case, as paper chromatography of the reaction mixture after 40 hours showed the presence of a small amount of (±)-inositol. Hence, solvolysis took place, albeit slowly, with inversion.



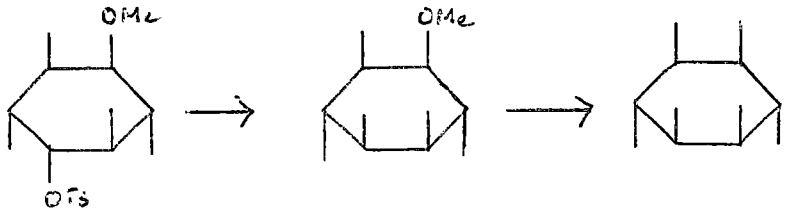
XXVI

2-O-Methyl-5-O-tosyl-(-)-inositol (XV) was prepared and subjected to solvolysis. In a run without sodium acetate, paper chromatography revealed the presence of a large number of products, formed undoubtedly by the epimerisation reaction, but the principal product was a compound with the R_f value of a methyl ether. The same methyl ether was obtained as the main product when the

---

(63) P.T. Gilham, personal communication.

reaction was carried out in the presence of sodium acetate. This methyl ether on demethylation gave mucoinositol, which was identified by paper chromatography in acetone-water (4:1) and by the preparation of the hexaacetate.



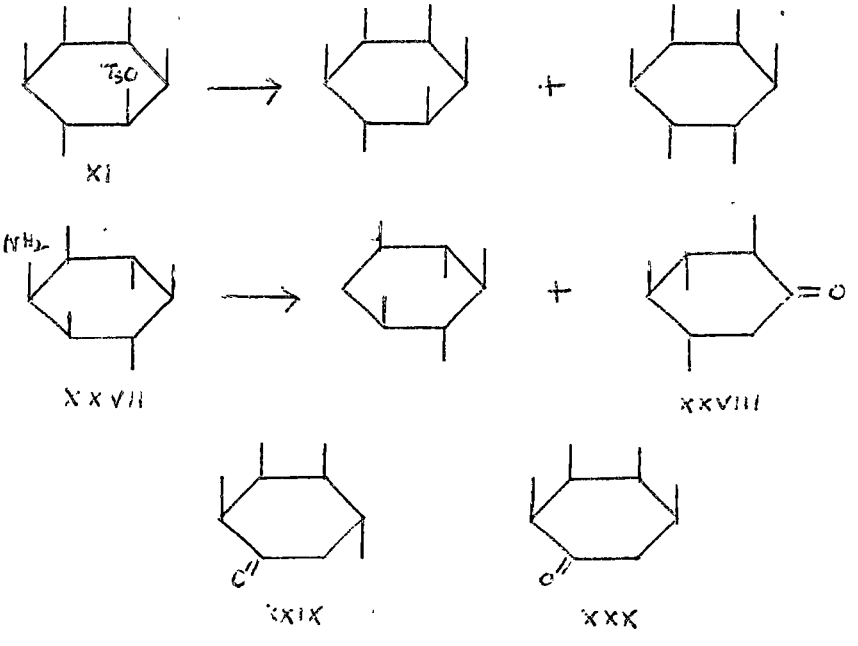
XV XX

The isolation of mucoinositol proves that solvolysis took place with inversion, and also establishes the structure of the initial product of solvolysis (XX) as one of the enantiomorphs of 1-O-methylmucoinositol. This reaction constitutes an alternative synthesis of mucoinositol, starting from quebrachitol, which is readily available. In the past, mucoinositol has been obtained by hydroxylation of conduritol (56), which is not easily obtainable.

Gilham attempted the solvolysis of 1-O-tosylepiinositol (XI), and found that after 37 hours the reaction mixture contained mainly unchanged compound together with traces of allo- and epi- inositols. This solvolysis was repeated in the presence of sodium acetate to prevent epimerisation of the products. After 30 hours, paper chromatography showed the presence of epiinositol and a small amount of allo-

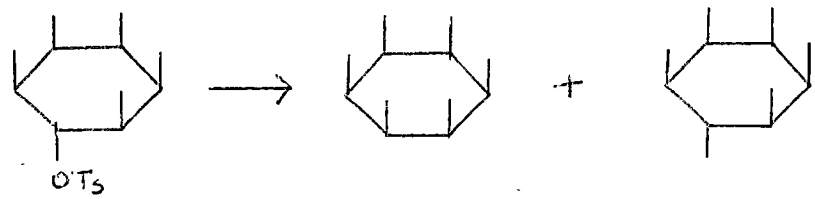
inositol, and in addition to some unchanged tosyl compound, a third product with an R_f value of approximately 0.4. This compound was stable in hot dilute acid solution, but was destroyed in alkaline solution. The products of solvolysis were isolated by column chromatography, and it was found that the third product reduced Fehling's solution.

Two types of reducing compounds could be formed during the reaction, either a tetrahydroxycyclohexanone or a tetrahydroxycyclopentanealdehyde. In the nitrous acid deamination of mesoinosamine-2 (XXVII), Posternak found that, although scylloinositol was formed, the principal product was a quercose (XXVIII)(37). He also showed that ring expansion and contraction by this type of reaction did not occur readily in cyclohexylamines carrying a large number of hydroxyl groups. By analogy with this work, it is more probable that the reducing compound is a quercose, either



(XXIX) or (XXX). Thus, in this case solvolysis leads to a more complex set of products, but largely occurs without inversion.

6-O-Tosylepiinositol (XXXI) was prepared and subjected to solvolysis. The products of solvolysis were separated by column chromatography, and cis- and epi- inositols were identified together with a compound which reduced Fehling's solution with an R_f value similar to the one obtained from 1-O-tosylepiinositol. In this instance, if a quercose were formed it could only have structure (XXX). From the paper chromatograms, it would appear that about equal quantities of epi and cis inositols were formed, and, as these two isomers are not interconvertible, solvolysis occurs partly with retention and partly with inversion of configuration. This reaction constitutes a new synthesis of cisinositol, which has so far only been obtained in small yields from the reduction of hexahydroxybenzene (15).



XXXI

From the examples studied, it would appear that solvolysis of monotosyl esters of inositols is accompanied by inversion, but may also be accompanied by retention and

by elimination. Further study is required to determine what factors govern the nature of the products.

EXPERIMENTAL.

EXPERIMENTAL

General.

Melting Points.

All melting points were carried out in a heated copper block (Townsend and Mercer), and are corrected, unless otherwise stated.

Paper Chromatography.

All paper chromatograms were carried out on Whatman No. 1 chromatographic paper with one of the following solvent systems :- acetone-water (4:1, v/v), phenol-water (4:1, w/w) and ethyl acetate-acetic acid-water (3:1:1, v/v). Generally, acetone-water (4:1) was used as the solvent, as this system gives good separation for most inositols and inososes, and chromatograms can be completed in 3-4 hours. For routine identification purposes, the ascending technique without equilibration was used.

The cyclitols were detected with the $AgNO_3$-NaOH reagent of Trevelyan et al. (64) as modified by Anet and Reynolds (65) ; the latter use fixation by thiosulphate, which gives

---

(64) Trevelyan, Proctor and Harrison, Nature, 1950, 166, 444.

(65) Anet and Reynolds, ibid., 1954, 174, 930.

(66) Magasanik, Franzl and Chargaff, J. Amer. Chem. Soc., 1952, 74, 2621.

black spots which provide a permanent record. For the inositols, 1 drop of a 1% solution of the compound was sufficient for detection, but for the inositol methyl ethers 1 drop of a 2-5% solution was generally required.

The inososes were detected with the alkaline ferricyanide spray used by Magasanik et al. (66). This reagent gives blue spots with compounds which reduce Benedicts' solution in the cold ; it is not as sensitive as the $AgNO_3$-NaOH spray.

Cellulose-Column Chromatography.

(a) Preparation of Column. A uniform suspension of powdered cellulose was obtained by mixing Whatman Cellulose Powder (Standard Grade) with the solvent, acetone-water (4:1, v/v) in a "Waring Blender" for 3 minutes. The resulting slurry was poured into a chromatographic column containing solvent which was running out at a medium rate. A more uniform column was obtained if the slurry was added fairly rapidly. The column was tapped gently as it settled to remove any large air bubbles. The top of the column was protected by 2-3 circles of hardened filter paper. Newly packed columns were allowed to stand overnight to complete settling, and were tested for uniformity by trial runs using dyes ; Methyl Orange and Lissamine red 6 BS. were used for this purpose.

(b) Operation of Column. The mixture to be chromatographed

was dissolved in a minimum quantity of water, which was then diluted with 4 volumes of acetone. If the addition of the acetone caused precipitation of an oil, cellulose powder was added to absorb it. A few drops of Methyl Orange (R_f 1.00) were added to the solution to mark the solvent front, and the solution, together with any added cellulose powder was poured on to the top of the column.

The column was developed with acetone-water (4:1, v/v) ; no fractions were collected until the dye marking the solvent front appeared in the effluent. The fractions that were collected were examined by paper chromatography, and combined accordingly.

Acetyl Derivatives.

The acetyl derivatives of a number of cyclitols were prepared in the course of this work, and generally one of the following two methods was used.

Acetylation in Pyridine.

The cyclitol was dissolved in a mixture of pyridine-acetic anhydride (1:1), containing approximately three times the theoretical quantity of acetic anhydride. The mixture was then heated on a steam bath for three hours, cooled, poured into water and extracted with chloroform. The chloroform extracts were washed with dilute HCl and water, and dried (Na_2CO_3). The solvent was removed by distillation, and the residue crystallised from ethanol or ethanol-water.

Acetylation in the presence of H_2SO_4.

The cyclitol was suspended in acetic anhydride (approx. ten times theoretical, to provide adequate solvent) to which was added 36N H_2SO_4 (5% of total volume). The reaction mixture was heated on a steam-bath for half an hour, cooled, and diluted carefully with water. The reaction mixture was allowed to stand for 1-2 hours, and any product which had crystallized was then filtered off, and the filtrate extracted with chloroform. The chloroform extracts were washed with water, filtered through absorbent cotton-wool, and the solvent removed by distillation. The residue was crystallised from ethanol or ethanol-water.

EXPERIMENTAL PART I.

Apparatus for Catalytic Oxidations.

Large-scale catalytic oxidations were carried out by the method of Heyns (33) in a 750 ml. round-bottomed flask fitted with a reflux condenser, a mechanical stirrer and a gas inlet tube. The gas inlet tube was bent in such a way that it reached the base of the flask, and the stream of air emerged below the blades of the stirrer.

Small-scale oxidations were carried out using round-bottomed flasks fitted with a reflux condenser and a gas inlet tube, which terminated in a bulb approximately 1 inch in diameter. The surface of this bulb was evenly pierced with small holes ; this distributed the stream of air passing through the solution and provided adequate stirring. A rapid stream of air was forced through the solution with the aid of a pump.

Preparation of 10% Platinum Catalyst.

The catalyst was prepared according to the method given by Heyns (50).

Platinum (1 g.) was dissolved in aqua regia, and the solution evaporated to dryness three times with 10N HCl. The residue was taken up in water (20 ml.). Animal carbon (9 g.) and 10N HCl (2 ml.) were added and the mixture hydrogenated at atmospheric pressure. The reduction was

complete after 7 hours. The catalyst was collected by filtration, and washed with water until the washings were neutral. The catalyst was then dried at 100° for 2 hours.

Willstätter Schudel Method of Determination of Inosose (67).

An aliquot of inosose solution containing ca. 10 mg. inosose was treated with N/100 iodine solution (25 ml.). N/100 (approx.) sodium hydroxide solution (15 ml.) was added dropwise and the solution allowed to stand for 15 minutes. The solution was acidified with dilute H_2SO_4 and the liberated iodine titrated with N/100 sodium thiosulphate solution.

10 ml. N/100 I_2 = 8.9 mg. inosose.

§ 11 Catalytic Oxidation of mesoInositol.

mesoInositol (0.5 g.) was dissolved in water (50 ml.) and 10% platinum catalyst (0.5 g.) added. A rapid stream of air was passed through the reaction mixture which was maintained at 70-75°. The course of oxidation was followed by paper chromatography in acetone-water (4:1). A compound with an R_f value identical with that of scyllo-inosose was present, but no second reducing spot such as Heyns (52) mentions could be detected in either acetone-water (4:1) or in pyridine-amyl alcohol-water (7:7:6, v/v),

---

(67) Brown and Zerban, "Physical and Chemical Methods of Sugar Analysis", (Wiley, New York, 1941), p. 896.

which was the solvent used by Heyns.

The amount of inosose present in the solution was determined at 3 hourly intervals by the Willstatter Schudel Method. After 18 hours, 66% of the inositol had been oxidized, and this value was not significantly increased by oxidation for a further 3 hours. The reaction was stopped, the catalyst removed by filtration, and the filtrate concentrated to a volume of 5 ml. A solution of phenylhydrazine (0.75 ml.) in 50% acetic acid (1.5 ml.) was added to the concentrated oxidation solution, and the resulting solution cooled at 0° and stirred for 30 minutes. At the end of this time the phenylhydrazone (0.294 g., 39.7%) was removed by filtration, and washed with alcohol and ether. A sample of phenylhydrazone after recrystallisation from pyridine-water had m.p. 174-6° (decomp.).

Heyns records m.p. 176° d. for scylloinosose-phenylhydrazone.

Isolation of scylloInosose.

The scylloinosose phenylhydrazone was decomposed by the method of Carter et al. (68).

The phenylhydrazone (0.2 g.) was heated under reflux for 5 minutes with benzaldehyde (0.2 ml.), ethanol (2 ml.) water (8 ml.) and acetic acid (0.2 ml.). The reaction mixture was cooled and extracted with ether (3 x 10 ml.).

---

(68) Carter et al., J. Biol. Chem., 1948, 174, 422.

The aqueous solution was decolourised with charcoal and concentrated *in vacuo* to a low volume, and methanol (10 ml.) added. The solution was allowed to stand at 0° overnight, and the product (0.107 g, 95%) collected by filtration. After recrystallisation from methanol-water, the *scyllo*-inosose had m.p. 198° (decomp., rapid heating).

Attempted Oxidation of scylloInosose.

scylloInosose (100 mg.) was dissolved in water (20 ml.) and 10% platinum catalyst (100 mg.) added. A rapid stream of air was passed through the reaction mixture which was maintained at 70-75°. The course of oxidation was followed by paper chromatography in acetone-water (4:1) and in pyridine-amyl alcohol-water (7:7:6). No second reducing compound could be detected in either solvent. After 22 hours the reaction was discontinued and the *scyllo*-inosose recovered from the reaction mixture by filtration and evaporation of the filtrate. The residue was crystallised from methanol-water to yield *scyllo*inosose (85 mg., 85%) m.p. 197-8° (decomp., rapid heating).

§ 1.2 *Attempted Oxidation of* scylloInositol.

scylloInositol (50 mg.) was dissolved in water (20 ml.) and 10% platinum catalyst (50 mg.) was added to the solution. A rapid stream of air was passed through the solution which was kept at a temperature of 75-8°. The reaction was examined at intervals by paper chromatography

in acetone-water (4:1). No trace of a reducing compound could be detected and after 20 hours the reaction was discontinued. The catalyst was removed by filtration, washed with water and the filtrate evaporated to dryness and crystallised from aqueous ethanol to yield colourless crystals (40 mg.), m.p. 335-40°, which had an R_f value identical with scylloinositol. Acetylation of this product in acetic anhydride-H_2SO_4 mixture gave an acetate m.p. 294° and mixed m.p. 294° with a sample of pure scylloinositol-hexaacetate (m.p. 294-5°).

§ 1.3 Oxidation of epiInositol.

epiInositol (0.5 g.) was dissolved in water (50 ml.) and platinum catalyst (0.5 g.) was added. A rapid stream of air was passed through the solution which was maintained at 60-65°. After 2 hours paper chromatography in acetone-water (4:1) showed the absence of epiinositol and the presence of an inosose with an R_f value identical with that of epiinosose. The oxidation mixture was filtered and the filtrate treated with decolourising carbon and filtered through a bed of kieselguhr. The clear filtrate was concentrated in vacuo on the steam bath to a volume of 5 ml. Ethanol was added to the concentrate and the solution cooled overnight at 0°. The product (0.42 g., 84%) was collected by filtration and after recrystallisation from ethanol-water had m.p. 193° (decomp.) and was optically inactive.

A sample of the product (0.1 g.) was acetylated in acetic anhydride-H_2SO_4 mixture. After recrystallisation from ethanol, the epiinososepentaacetate (0.15 g.) had m.p. 106° and mixed m.p. 106° with an authentic sample of epiinososepentaacetate (m.p. 106-7°).

Therefore, the product of oxidation was dl-epiinosose.

Attempted Oxidation of epiInosose.

epiInosose (100 mg.) was dissolved in water (20 ml.) and 10% platinum catalyst (100 mg.) was added. A rapid stream of air was passed through the solution which was maintained at 70-75°. The course of oxidation was followed by paper chromatography in acetone-water (4:1). No reducing spot apart from epiinosose could be detected with the 'alkaline ferricyanide' reagent. The reaction was stopped after 30 hours and the catalyst filtered off. The filtrate was evaporated to a volume of ca. 2 ml., and ethanol added, and the solution allowed to stand at 0° overnight. White crystals (80 mg.) of epiinosose were obtained, m.p. 193° (decomp.).

§ 1.4 (-)-Inositol.

Quebrachitol was demethylated by the method of Gilham (57). Quebrachitol (100 g.) was placed in a flask fitted with an air condenser and heated under reflux with 57% hydriodic acid (250 ml.) for 2 hours. While still hot the solution was poured into boiling ethanol (1.6 l.) and cooled. The colourless crystalline product was collected

by filtration and washed with ethanol. The yield of (-)-inositol (m.p. 242-4°) was 85 g.

Catalytic Oxidation of (-)-Inositol.

(-)-Inositol (1 g.) was dissolved in water (250 ml.) and 10% platinum catalyst (1 g.) was added. A rapid stream of air was passed through the solution which was stirred vigorously and maintained at 70-75°. Paper chromatography of the reaction mixture showed the presence of one compound with reducing properties. After 15 hours the reaction was stopped, as estimation showed that 21% of the inositol had been oxidized, and the rate of oxidation was slow. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a volume of 10 ml. The concentrate was cooled, and a solution of phenylhydrazine (1.5 ml.) in 50% acetic acid (3 ml.) was added and the mixture cooled and stirred for 30 minutes. The phenylhydrazone (0.253 g., 17%) was collected by filtration and washed with ice-cold ethanol and ether.

A portion of the product was recrystallised from pyridine-water to give white crystals, m.p. 198° (decomp.). Magasanik and Chargaff (30) record m.p. 196-7° (decomp.) for (+)-*vibo*inososephenylhydrazone.

The *vibo*inososephenylhydrazone was converted to the inosose by the method of Carter *et al.*, but the (-)-*vibo*-inosose could not be crystallised.

1.5 Catalytic Oxidation of cisInositol.

cisInositol (0.2 g.) was dissolved in water (25 ml.) and platinum catalyst (0.2 g.) was added. A rapid stream of air was passed through the solution which was maintained at 65-70°. After 2 hours the reaction was stopped, as paper chromatography in acetone-water (4:1) showed the absence of cisinositol and the presence of a reducing compound with an R_f value identical with that of cisinosose. The catalyst was removed by filtration, and the filtrate treated with decolourising carbon and filtered through a bed of kieselguhr. The clear filtrate was concentrated *in vacuo* on the steam bath to a volume of *ca.* 10 ml. and further concentrated by storing *in vacuo* over 36N H_2SO_4. The residual gum was crystallised from aqueous ethanol, and the product collected by filtration. After recrystallisation the product (0.12 g., 60%) had m.p. 177-8° decomp. cis-Inosose has m.p. 179° decomp.

An unsuccessful attempt was made to prepare a phenylhydrazone, and so the product was reduced with sodium amalgam. The product (0.1 g.) was dissolved in water (10 ml.) and sodium amalgam (1.7 g.) was added in small batches with shaking until the solution no longer reduced Fehling's solution. The pH of the reaction mixture was kept at 5-7 by the addition of glacial acetic acid. When reduction was complete, the mercury was filtered off, and the filtrate evaporated to dryness, and the residue heated with acetic anhydride (5 ml.). The acetyl derivative so obtained was

recrystallised from ethanol to give colourless crystals (64 mg.) m.p. 188-9° and mixed m.p. 188-9° with a sample of pure epiinositolhexaacetate (m.p. 189°).

§ 1.6 Preparation of neoInositol.

neoInositol was synthesised by the method of Angyal and Matheson (14).

1:2-5:6-Di-O-isopropylidene-(-)-inositol.

Anhydrous zinc chloride (330 g.) was dissolved in dry acetone (1.6 l.) and heated under reflux with dry powdered (-)-inositol (55 g.) for 24 hours. The solution was then filtered and poured slowly into a mixture of potassium carbonate (385 g.) dissolved in water (385 ml.) and ether (1650 ml.). The mixture was stirred vigorously for one hour and then the solution was filtered from the precipitated salts. The filtrate was evaporated *in vacuo* to a semi-crystalline mass, which was extracted with hot benzene. On cooling, the benzene extracts deposited crystals of the crude diisopropylidene derivative. The product was recrystallised from benzene, and had m.p. 150°. Yield 38 g.

The benzene extracts were then evaporated to dryness to yield crude 1:2-3:4-5:6-tri-O-isopropylidene-(-)-inositol. After recrystallisation from ethanol, this product (20 g.) had m.p. 214°.

The triisopropylidene derivative was partially hydrolysed by the method of Angyal and Macdonald (11). The triisopropylidene inositol (20 g.) was dissolved in a mixture of chloroform (85 ml.), acetic acid (100 ml.) and water (27 ml.), and allowed to stand at room temperature for 24 hours. The solution was then evaporated to dryness under reduced

pressure. The residue was extracted with hot benzene, and on cooling, the benzene extracts deposited crystals of the diisopropylidene-(-)-inositol (11 g.) m.p. 148-50°.

3:4-Di-O-tosyl-1:2-5:6-di-O-isopropylidene-(-)-inositol. 1:2-5:6-Di-O-isopropylidene-(-)-inositol (35 g.) and tosyl-chloride (76.5 g.) were dissolved in anhydrous pyridine (350 ml.) and allowed to stand at room temperature for one week. Water was then added, slowly at first to decompose the excess tosyl chloride, and then until no more product came out of solution. The product was collected by filtration and washed with water. Recrystallisation from ethanol gave 3:4-ditosyl derivative (52 g., 67%) m.p. 145-6°.

1:2-Anhydro-3:4-5:6-di-O-isopropylidenealloinositol.

Ditosyldiisopropylidene-(-)-inositol (23 g.) was added to a solution of sodium (5.7 g.) in anhydrous methanol (230 ml.). The mixture was heated under reflux for 5 hours. The solution was then cooled, and chloroform (460 ml.) added, and the resulting dark precipitate removed by filtration. The filtrate was washed with water (2 x 400 ml.), dried ($Na_2 SO_4$) and evaporated. The crystalline residue was recrystallised from light petroleum and gave 1:2-anhydro-3:4-5:6-di-O-isopropylidenealloinositol (6.1 g., 50%), m.p. 108-9°.

neoInositol.

1:2-anhydro-3:4-5:6-di-O-isopropylidenealloinositol

(6.1 g.) was heated on a steam bath with 0.1N H_2SO_4 (30 ml.) for 3 hours. The substance dissolved in a few minutes with loss of acetone, and after about 30 minutes crystals began to separate out. The mixture was cooled overnight and the product collected by filtration and washed with water, giving 2.32 g. (51.7%) of neoinositol.

Catalytic Oxidation of neoInositol.

neoInositol (2 g.) was suspended in boiling water (500 ml.) and the suspension cooled to 70° and placed in the reaction flask. 10% Platinum catalyst (2 g.) was added and a stream of air was passed through the reaction mixture, which was stirred vigorously and maintained at a temperature of 70-75°. After 8 hours the reaction was stopped, the reaction mixture filtered to remove the catalyst and undissolved neoinositol, which were returned to the reaction flask. The filtrate was cooled overnight at 0° and the neoinositol which crystallised was collected by filtration and returned to the reaction flask while the filtrate was set aside. Boiling water (500 ml.) was added to the reaction flask and the oxidation continued as before for a further 8 hours. This procedure was repeated until no further neo-inositol crystallised from the oxidation solution.

The combined oxidation solutions (2.5 l.) were concentrated *in vacuo* on the steam bath to a volume of 200 ml., and cooled overnight at 0°. The neoinositol was removed by filtration and the oxidation solution further concentrated

to a volume of 10 ml. The solution was again cooled overnight and the neoinositol removed by filtration. The total amount of neoinositol recovered in this way was 0.983 g. The concentrate was treated with a solution of phenylhydrazine (1 ml.) in 50% acetic acid (2 ml.) ; after cooling and scratching for 15 minutes brown crystals separated. The solution was cooled for an additional 15 minutes, and the phenylhydrazone (0.647 g.) collected by filtration, and washed with ethanol and ether.

A portion of this material was recrystallised from pyridine-water, and methanol-water, to yield white crystals m.p. 199-202° (decomp.).

Allen (42) records m.p. 201-4° (decomp.) for neoinososephenylhydrazone.

Isolation of neoInosose.

The neoinososephenylhydrazone (160 mg.) was converted to the inosose by the method of Carter et al. (68). The crude product was recrystallised from ethanol-water to give colourless crystals (88 mg., 80%), m.p. 217-20° (decomp.).

Allen (42) records m.p. 218-20° (decomp.) for neoinosose.

Configuration of neoInosose.

a) Isolation of mesoInositol.

neoInosose (50 mg.) was dissolved in water (5 ml.), and phenol red indicator (2 drops) was added to the solution.

6° and mixed m.p. 255-7° with pure sample of neoinositol-hexaacetate (m.p. 257°).

Synthesis of neoQuercitol.

neoInosose (55 mg.) was dissolved in a solution (5 ml.) containing 95% water and 5% conc. H_2SO_4 by volume and shaken with platinum oxide (15 mg.) under hydrogen for 3 hours. Paper chromatography in acetone-water (4:1) showed the presence of a quercitol and neoinositol, and the absence of inosose. The solution was neutralised by the addition of a hot solution of barium hydroxide, and allowed to stand overnight. The precipitated barium sulphate was filtered off, and the filtrate taken to dryness. The residue (38 mg.) was taken up in acetone-water (4:1) and the components separated by chromatography on a small cellulose powder column.

The quercitol fraction (27 mg.) was sublimed in vacuo to give colourless crystals, m.p. 238-9° decomp. which analysed for a quercitol.

Found	C, 43.89%	H, 7.35%
$C_6H_{12}O_5$ requires	C, 43.90%	H, 7.37%

A portion of the neoquercitol was acetylated in acetic anhydride-H_2SO_4 mixture, and the product after sublimation at reduced pressure had m.p. 182°; the analysis was correct for a quercitolpentaacetate.

Sodium amalgam (1.6 g.) was added in small batches and the mixture shaken until the solution no longer possessed reducing properties, the solution was kept at pH 5-7 during the reduction by the addition of glacial acetic acid. The mercury was filtered off and the filtrate taken to dryness and heated with acetic anhydride (5 ml.) at 100° for 3 hours. The acetyl derivative so obtained was recrystallised from ethanol to give colourless crystals (30 mg.) of mesoinositol hexaacetate, m.p. 211-12°, and mixed m.p. 211-12° with sample of pure mesoinositolhexa-acetate (m.p. 212-13°).

b) Isolation of neoInositol.

The purity of the sample of neoinosose was checked by paper chromatography, and no neoinositol was present ; it was then reduced catalytically.

neoInosose (30 mg.) was dissolved in water (10 ml.) and shaken with platinum oxide (15mg.) under hydrogen for 3 hours. At the end of this time the solution no longer reduced Fehling's solution. Paper chromatography in acetone-water (4:1) showed the presence of neoinositol, and traces of mesoinositol. The filtered solution was concentrated to a volume ca. 2 ml., cooled overnight, and filtered to yield colourless crystals of neoinositol (15 mg.) m.p. 313-15° when dropped on a preheated stage.

The product was acetylated in acetic anhydride-H_2SO_4 mixture and the neoinositol acetate so obtained had m.p. 255-

Found :	C, 51.42%	H, 5.94%
$C_{16}H_{22}O_{10}$ requires :	C, 51.33%	H, 5.92%

§ 1.61 Synthesis of neoInosamine-2.

The phenylhydrazone of neoinosose was reduced catalytically by the method of Anderson and Lardy (35).

neoInososephenylhydrazone (180 mg.) was dissolved in glacial acetic acid (10 ml.) and shaken with platinum oxide (45 mg.) under hydrogen for 5 hours, when the uptake of hydrogen had ceased. The catalyst was removed by filtration and excess acetic acid evaporated from the filtrate *in vacuo*. The residue was taken up in 1.0N H_2SO_4 (0.5 ml.), and the remaining acetic acid expelled from the solution by steam distillation. The liquid in the still-pot was made alkaline with saturated barium hydroxide solution, added at boiling point, and allowed to stand overnight. The barium sulphate was removed by filtration and the filtrate steam distilled to remove any cyclohexylamine present. The excess barium was precipitated with carbon dioxide, and the solution filtered, and the filtrate evaporated to dryness. The residue (68 mg.) which would not crystallise, was acetylated by heating for 4 hours at 100° with anhydrous sodium acetate (40 mg.) and acetic anhydride (5 ml.). The acetyl derivative was recrystallised from ethanol to give white crystals (53 mg.) m.p. 276-8°. A mixture with authentic neo-inosamine-2 hexaacetate (m.p. 277-8°) melted at 275-77°.

§ 1.7 Preparation of alloInositol.

Method 1.

3:4-Di-O-nisyl-1:2-5:6-di-O-isopropylidene-(-)-inositol. (LVII, R = Ns).

1:2-5:6-Di-O-isopropylidene-(-)-inositol (2.3 g.) and nisyl chloride (7 g.) were dissolved in anhydrous pyridine (20 ml.) and allowed to stand at room temperature for 3 days. The reaction mixture was then poured into water and the resulting gum separated, washed with water, and crystallised from ethanol. Recrystallisation from that solvent gave the pure 3:4-dinisyl derivative (5 g., 89%) m.p. 171°.

(+) 3:4/5:6 Cyclohexenetetrol (LVIII).

Method A. 3:4-Di-O-nisyl-1:2-5:6-di-O-isopropylidene-(-)-inositol (LVII, R = Ns) (5 g.) and anhydrous sodium iodide (12 g.) were dissolved in anhydrous acetone (80 ml.) and heated in a sealed tube at 100° for 13 hours. The reaction mixture was poured into chloroform (60 ml.) and the chloroform solution was washed with water to remove sodium-p-nitrobenzenesulphonate, and then with sodium thiosulphate solution to remove iodine. The chloroform solution was dried (Na_2SO_4) and evaporated to dryness, and the oily residue extracted with light petroleum. The extracts were evaporated to dryness, and the residue was hydrolysed by heating with 20% acetic acid (20 ml.) at 100° for 2 hours. The solution was evaporated and the residue crystallised

from methanol to yield (+) 3:4/5:6-cyclohexenetetrol dideoxy-alloinositol (0.54 g., 46%), m.p. 192-3°.

Method B. 3:4-Di-O-tosyl-1:2-5:6-di-O-isopropylidene-(-)-inositol (LVII, R = Ts) (8 g.) and anhydrous sodium iodide (12 g.) were dissolved in anhydrous acetone (80 ml.) and heated in a sealed tube at 100° for 23 hours. The precipitated sodium p-toluenesulphonate was separated by filtration, and the filtrate was added to light petroleum (b.p. 40-60°, 400 ml.) and the solution filtered to remove the precipitated iodine. The filtrate was hydrolysed by heating it in 20% acetic acid (30 ml.) for 3 hours at 100°. The solution was then evaporated to dryness and the residue extracted with cold water (2 x 10 ml.). Evaporation of the extracts gave crude (+) 3:4/5:6-cyclohexenetetrol which was recrystallised from methanol to give the pure product (0.6 g., 29.6%) m.p. 192-3°.

Hydroxylation of (+) 3:4/5:6-Cyclohexenetetrol (LVIII). (+) 3:4/5:6-Cyclohexenetetrol (1.12 g.) and silver chlorate (0.50 g.) were dissolved in water (55 ml.) and 1% osmium tetroxide solution (1.1 ml.) was added. The mixture was allowed to stand in the dark for 4 days, and was then filtered from the precipitated silver chloride, and the filtrate evaporated to dryness *in vacuo*, and the residue crystallised from ethanol-water to yield alloinositol (0.52 g., 37%) m.p. 310-20° (decomp.).

Method 2.

1:2-AnhydroalloInositol (LX).

1:2-Anhydro-3:4-5:6-di-O-isopropylidenealloinositol (2 g.) (LIX) was dissolved in 50% acetic acid (10 ml.) and the mixture was heated at 100° for 30 minutes. The mixture was cooled, and the product collected by filtration and washed with ethanol. The product was recrystallised from ethanol-water to give 1:2-anhydroalloinositol (0.82 g.)

Alkaline Hydrolysis of 1:2-Anhydroalloinositol (LX).

1:2-Anhydroalloinositol (0.5 g.) was dissolved in 0.5 N barium hydroxide solution (30 ml.) and the mixture was allowed to stand overnight at room temperature, and then heated at 100° for 3 hours. Carbon dioxide was then passed through the solution, and the precipitated barium carbonate removed by filtration. The filtrate was evaporated in vacuo, and the residual oil, which contained allo- and mesoinositol, was passed through a cellulose column with acetone-water (4:1) solvent mixture. The fractions containing alloinositol were combined and taken to dryness. The residual gum was crystallised from aqueous ethanol to yield alloinositol (0.183 g.). The fractions containing mesoinositol were treated similarly, to yield 0.127 g. of mesoinositol.

Method 3.

Solvolysis of 3-O-Tosyl-4-O-acetyl-(-)-inositol (LXIV).

3-O-Tosyl-4-O-acetyl-1:2-5:6-di-O-isopropylidene-(-)-inositol

(LXII) (4 g.) was heated at 100° for 1 hour with 50% acetic acid (40 ml.). The solution was evaporated to dryness *in vacuo* and the residue was heated under reflux with 95% acetic acid (50 ml.) and anhydrous sodium acetate (0.75 g.) for 40 hours. The reaction mixture was concentrated to a volume of 10 ml. and pyridine (7 ml.) and acetic anhydride (7 ml.) were added and the mixture heated at 100° for 2 hours. The reaction mixture was poured into water, extracted with chloroform, and the chloroform extract washed with dilute HCl and water, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallised from ethanol to yield *allo*-inositolhexaacetate (1.94 g.) m.p. 142° and mixed m.p. 142° with an authentic sample of *allo*inositol acetate of m.p. 142°.

The acetate was heated with 2N HCl (20 ml.) at 100° for 3 hours, and the solution evaporated *in vacuo*. The residue was crystallised from ethanol-water to give *allo*inositol (0.79 g., 51%).

Catalytic Oxidation of alloInositol.

alloInositol (1 g.) was dissolved in water (250 ml.) and platinum catalyst (1 g.) was added, and the solution stirred vigorously while a rapid stream of air was passed through for 1½ hours. During the oxidation the temperature of the reaction was held at 65-70°. Paper chromatography of the reaction mixture showed the presence of two compounds with reducing properties. The catalyst was removed by filtration through a bed of kieselguhr, and the filtrate concentrated *in vacuo* on the steam bath to a volume of *ca.* 15 ml., and further concentrated by standing *in vacuo* over 36N H_2SO_4. The residual gum was taken up in acetone-water (4:1) and run through a cellulose powder column to separate the products. The fractions were examined by paper chromatography and combined accordingly into three homogeneous groups, fraction A (0.37 g.) which contained an oxidation product with a high R_f value, a middle fraction with unoxidized allo-, and fraction B (0.26 g.) which contained a second oxidation product with an R_f value less than that of alloinositol. The fractions containing alloinositol were taken to dryness and the residue crystallised from ethanol to give 0.23 g. of alloinositol.

An attempt was made to prepare phenylhydrazones from fractions A and B, but in neither case could a crystalline product be obtained. Neither fraction A nor fraction B could be obtained crystalline.

Sodium Amalgam Reduction of Fraction A.

Fraction A (150 mg.) was dissolved in water (10 ml.) and sodium amalgam (4 g.) was added in small batches with shaking till the solution no longer reduced Fehling's solution. The reaction mixture was kept at pH 5-7 by the addition of glacial acetic acid. The solution was decanted from the mercury and passed through a column of Zeocarb 225 to remove sodium ions. The solution was concentrated and the crystals which separated collected by filtration. This product (90 mg.) was acetylated in acetic anhydride-H_2SO_4 mixture, and the acetate so obtained had m.p. 255° and mixed m.p. 255-6° with a sample of pure neoinositol hexaacetate (m.p. 257°). The filtrate was taken to dryness and dissolved in acetone-water (4:1) and run through a cellulose powder column in acetone-water (4:1). Paper chromatography of the fraction showed the presence of allo-, (±)- and neoinositols.

The fraction containing (±)-inositol was taken to dryness, and the residue (71 mg.) was acetylated in acetic anhydride-H_2SO_4 mixture to yield an acetate of m.p. 104-5° and mixed m.p. 104-6° with a sample of pure (±)-inositol hexaacetate.

The fractions containing neoinositol were combined and acetylated to give 30 mg. neoinositol hexaacetate, m.p. and mixed m.p. 254-6°.

Sodium Amalgam Reduction of Fraction B.

Fraction B (150 mg.) was reduced with sodium amalgam

(7.5 g.) in a similar manner to fraction A, and the reduction products separated on a cellulose powder column. Paper chromatography of the fractions showed traces of allo- and (±)-inositols, but the main product on acetylation gave an acetate (190 mg.) of m.p. 210° and mixed m.p. 210-11° with a sample of pure mesoinositolhexaacetate (m.p. 212°).

Catalytic Reduction of Fraction B.

Fraction B (20 mg.) was dissolved in water (5 ml.) and shaken with platinum oxide (15 mg.) in an atmosphere of hydrogen for 3 hours. The solution then no longer possessed reducing properties. Paper chromatography in acetone-water and phenol-water showed the presence of allo-, (±)-, epi- and mesoinositols.

Catalytic Oxidation of Fraction A.

Fraction A (50 mg.) was dissolved in water (10 ml.) and platinum catalyst (50 mg.) added. The solution was kept at 65-70° while a stream of air was passed through for 2 hours. Paper chromatograms did not show the presence of any other compound. alloInositol (50 mg.) was added to mixture and the oxidation continued for 1 hour. Paper chromatograms of the reaction mixture showed the presence of a reducing compound with an R_f identical with fraction B.

§ 1.8 Catalytic Oxidation of Quebrachitol.

Quebrachitol (1 g.) was dissolved in water (200 ml.) and platinum catalyst (1 g.) was added. A rapid stream of air was passed through the reaction mixture, which was stirred vigorously, and maintained at a temperature of 60-65°. After 3 hours, paper chromatography showed the absence of quebrachitol, and the presence of a compound which reduced the 'alkaline ferricyanide' reagent. The filtered solution was concentrated *in vacuo* to a volume of *ca.* 10 ml. An attempt to prepare a phenylhydrazone was unsuccessful, so the oxidation product was reduced with sodium amalgam (50 g.) ; the amalgam was added gradually while the mixture was shaken, and glacial acetic acid was added, as required, to keep the pH at 5-7. When the solution no longer possessed reducing properties, it was decanted from the mercury, and the sodium ions removed by running the solution through a column of Zeo-carb 225. Paper chromatography in acetone-water (4:1) showed the presence of quebrachitol, a compound with R_I similar to bornesitol, and small amounts of *meso*- and (-)-inositol. The solution was therefore concentrated to a low volume, diluted with acetone, and run through a cellulose column using acetone-water (4:1) as solvent. The fractions containing quebrachitol were taken to dryness and the residue (630 mg.) was dissolved in ethanol containing very little water ; colourless crystals of quebrachitol separated, m.p. 186-8°.

The fractions containing the compound with R_f value of bornesitol were combined and taken to dryness. The residue (52 mg.) could not be crystallised, and was acetylated in acetic anhydride-H_2SO_4 mixture. The acetyl compound (78 mg.) so obtained had m.p. 118-21° after recrystallisation from ethanol-water. A further recrystallisation from ethanol-water did not increase the melting point, and so a sample was deacetylated and paper chromatography in phenol-water (4:1, w/w) showed the presence of two compounds, one of which had an R_f value identical with bornesitol.

Fractional crystallisation of the mixed acetates from ethanol gave a small yield (7 mg.) of crystals of m.p. 191-2°. A mixed melting point of this compound with methyl*scyllo*-inositol (m.p. 192-4°) depressed, and paper chromatography of deacetylated samples in phenol-water (4:1, w/w) showed the two compounds were not identical. A mixture of the compound with *scyllo*quercitol acetate (m.p. 193°) had m.p. 190-92°. Paper chromatography in acetone-water (4:1) and in phenol-water (4:1, w/w) showed that the deacetylated compound had R_f values identical with *scyllo*quercitol in both solvent systems.

The bornesitol acetate could not be isolated by fractional crystallisation, and therefore the combined mother liquors were deacetylated, concentrated to a small volume, and run through a cellulose column using acetone-water (5:1) as solvent. The fractions were identified by paper chromatography in phenol-water (4:1, w/w) but no separation

was achieved. The presence of bornesitol in the reduction mixture was confirmed by paper ionophoresis. The paper ionophoresis was carried out on Whatman No. 1 chromatographic paper in 0.15 M sodium tetraborate solution. A potential of 550 V. was applied for 4 hours. The cyclitols were detected with the permanganate-periodate spray of Lemieux and Bauer. A compound with M_G value identical with bornesitol was present in the solution. Paper ionophoresis in 0.15 M borate solution gives good separation of the methyl ethers formed as possible products of the reduction reaction, as may be seen from their M_G values.

Methyl Ethers	M_G value in 0.15 M borate solution.
Bornesitol	0.15
Ononitol	0.60
Quebrachitol	0.29

Catalytic Oxidation of Dambonitol.

§19 Dambonitol (0.5 g.) was dissolved in water (150 ml.) and platinum catalyst (0.5 g.) was added. A rapid stream of air was passed through the solution which was maintained at 75-80° for five hours. At the end of this time paper chromatography in acetone-water (4:1) still showed the presence of unoxidized dambonitol in addition to a single oxidation product. The reaction was terminated and the solution filtered through a bed of kieselguhr and the

filtrate concentrated to a volume of approx. 10 ml. *in vacuo* on the steam bath. The solution was further concentrated to a volume of approx. 2 ml. by standing *in vacuo* over 36N H_2SO_4. The oxidation product was separated from unchanged dambonitol by passing the solution through a cellulose column in acetone-water (4:1). The fractions were examined by paper chromatography, and those which reduced the 'alkaline ferricyanide' reagent were combined and taken to dryness *in vacuo*. The brown residual gum was crystallised from ethyl-acetate-petroleum ether to yield crystals m.p. 120° (0.12 g.) which analysed for the hemi-hydrate of a dimethyl ether of an inosose.

Found :	C, 44.73%	H, 6.87%
$C_8H_{14}O_6 \cdot \frac{1}{2}H_2O$ requires :	C, 44.65%	H, 7.03%

The ketone (50 mg.) was dissolved in water (2 ml.) and sodium borohydride (30 mg.) was added. The solution was allowed to stand for three hours and at the end of this time it no longer possessed reducing properties. The excess borohydride was decomposed with acetic acid, and the solution then passed through a column containing zeocarb 225. The effluent was evaporated to dryness, taken up in acetone-water (4:1) and run through a small cellulose column to separate the reduction products. The first group of fractions contained dambonitol, and the second group of fractions were taken to dryness and acetylated in acetic-

anhydride-H_2SO_4 mixture. The crude acetate was sublimed *in vacuo* to yield 10 mg. of acetylated product, of m.p. 155-6° which analysed for the tetraacetate of an inositol dimethyl ether.

Found :	C, 51.2%	H, 6.8%
$C_{16}H_{24}O_{16}$ requires :	C, 51.06%	H, 6.43%

The acetate appeared to be dimorphous, changing form at 140-145°.

The remainder of this compound was demethylated by heating in 57% hydriodic acid for 2 hours, and the demethylated product was acetylated in acetic anhydride-H_2SO_4 mixture. After recrystallisation from ethanol the acetate had m.p. 294° and mixed m.p. 294-5° with a sample of pure *scyllo*inositol acetate (m.p. 294-5°).

EXPERIMENTAL : APPENDIX.

Oxidation of alloInositol by Acetobacter suboxydans.

A solution containing alloinositol (0.7 g.) in water (15 ml.) was oxidized with a culture of Acetobacter suboxydans for 7 days.

At the end of this time, paper chromatography showed the presence of alloinositol and a compound with an R_f value identical with that of the monoketone fraction obtained from alloinositol by catalytic oxidation.

The solution was filtered through a bed of kieselguhr and the filtrate concentrated to dryness in vacuo and the oxidation product separated from alloinositol by chromatography on a cellulose powder column in acetone-water (4:1). The monoketone fraction was taken to dryness in vacuo and the residue crystallised from aqueous ethanol to yield crystals (81 mg.) of m.p. 141-2° and $\alpha_D^{20} = -24^\circ$ (c= 1.55, H_2O, l= 0.5).

The product was reduced with sodium amalgam (3 g.) in a similar manner to Fraction A obtained from the catalytic oxidation of alloinositol, and the products of reduction separated on a cellulose powder column. The main product was neoinositol, which was acetylated to give neoinositol hexaacetate (103 mg.) m.p. 255° and mixed m.p. 254-6° with pure neoinositol hexaacetate. Traces of meso and (+) or (-) inositol were identified by paper chromatography in acetone-water and phenol-water.

EXPERIMENTAL PART II.

§ 2.1 Isolation of epiInositol from the Solvolysis of 3-O-Tosyl-4-O-acetyl-(-)-inositol.

3-O-Tosyl-4-O-acetyl-(-)-inositol (4 g.) was dissolved in 95% acetic acid (100 ml.) and heated under reflux for 32 hours. At the end of this time, paper chromatography of a deacetylated sample of the reaction mixture showed the presence of alloinositol together with a small amount of a compound with an R_f value identical with that of epiinositol. The reaction mixture was evaporated *in vacuo* and the residue acetylated in pyridine-acetic anhydride mixture. The crude acetyl derivative was heated for 3 hours with 2N HCl (30 ml.) at 100°, and the mixture evaporated to dryness *in vacuo*. The residue (1.08 g.) was taken up in acetone-water (4:1) and run through a cellulose powder column in acetone-water (4:1). The fractions were examined by paper chromatography and combined accordingly. The combined fractions containing alloinositol were taken to dryness and the residue crystallised from aqueous ethanol to yield alloinositol (0.905 g.). The combined fractions containing the compound with an R_f value of epiinositol were evaporated to dryness and the residue crystallised from aqueous ethanol to give white crystals (0.132 g.) of m.p. 283° d. Pure epi-inositol has m.p. 285° d. This product had an R_f value

identical with that of epiinositol in the three solvent systems : acetone-water, phenol-water, and ethyl acetate-acetic acid-water. A sample of the product was acetylated in acetic anhydride-H_2SO_4 mixture, and the acetyl derivative, after recrystallisation from ethanol-water, had m.p. 185-6° and mixed m.p. 185-7° with a sample of pure epiinositol-hexaacetate (m.p. 187-8°).

Epimerisation of Inositols.

alloInositol (10 mg.) was heated under reflux with toluene sulphonic acid (10 mg.) in 95% acetic acid (2 ml.) for 30 hours. The reaction mixture was diluted with one volume of water and 5N HCl(0.5 ml.) was added and the mixture heated at 100° for 3 hours, and then examined by paper chromatography in acetone-water, ethyl acetate-acetic acid-water, and phenol-water to identify the products. epi- , scyllo-, muco-, neo-, cis-, (-)-, and meso- Inositols were treated in a similar manner, and also mesoinositolhexa-acetate. The following products were identified from the reaction mixtures :-

Initial Isomer	Isomers present after 30 hours.
alloinositol	allo-, epi- inositols
epiinositol	epi-, allo- inositols
neoinositol	neo-, allo-, epi- inositols
mesoinositol	meso-, $(\pm)$-inositol
(-)-inositol	(-)-, meso- inositols
mucoinositol	muco-, $(\pm)$-, meso- inositols

Initial Isomer.	Isomers present after 30 hours.
cisinositol	cisinositol
scylloinositol	scylloinositol
mesoinositol-hexaacetate	meso-, (±)- inositols.

§ 2.2 2-O-Methyl-5:6-O-isopropylidene-(-)-inositol.

Quebrachitol (2.5 g.) was heated under reflux with anhydrous zinc chloride (12.5 g.) in anhydrous acetone (125 ml.) for 24 hours. A solution of potassium carbonate (15 g.) in water (12 ml.) was added dropwise with shaking. The acetone was filtered from the precipitated potassium and zinc salts, and these were washed with acetone. The combined filtrates were dried over potassium carbonate and evaporated to dryness to give a semi-crystalline residue. This product was recrystallised from ethyl-acetate to give 2-O-methyl-5:6-O-isopropylidene-(-)-inositol (0.773 g., 28.5%) m.p. 124-126°

The product was identical with that obtained by Angyal and Macdonald by a different procedure (11).

2-O-Methyl-1:3:4-tri-O-acetyl-(-)-inositol.

2-O-Methyl-5:6-O-isopropylidene-(-)-inositol (0.5 g.) and anhydrous sodium acetate (0.2 g.) were heated with acetic anhydride (10 ml.) at 100° for 3 hours. The solution was poured into water and extracted with chloroform. The chloroform extracts were washed with water, dried, and evaporated to dryness. The residual gum could not be crystallised, and so was heated at 100° for 1 hour with 80% acetic acid (15 ml.). The solution was then evaporated to dryness *in vacuo* and the residual gum crystallised from ethyl acetate-petroleum ether to give 2-O-methyl-1:3:4-tri-O-acetyl-(-)-inositol (0.47 g., 62%) m.p. 129-30°. The

product was identical with that obtained by Gilham (63) by a different procedure.

2-O-Methyl-5-O-tosyl-(-)-inositol Tetraacetate.

2-O-Methyl-1:3:4-tri-O-acetyl-(-)-inositol (0.7 g.) tosyl chloride (0.66 g.) and pyridine (0.5 ml.) were heated together at 100° for 3 hours. Pyridine (5 ml.) and acetic anhydride (5 ml.) were added, and the reaction mixture was heated at 100° for a further 3 hours. Water was then added and the product extracted into chloroform. The chloroform extract was washed with dilute HCl, and water and dried (Na_2CO_3). The solvent was removed by distillation and the residue crystallised from ethyl acetate-petroleum ether to give 2-O-methyl-5-O-tosyl-(-)-inositol tetra-acetate (0.58 g., 51%), m.p. 138-40°. Recrystallisation from the above solvent mixture gave the pure compound as needles, m.p. 140-41°.

Found:	C, 50.95%	H, 5.46%
$C_{22}H_{28}O_{12}S$ requires :	C, 51.15%	H, 5.46%

2-O-Methyl-5-O-tosyl-(-)-inositol.

2-O-Methyl-5-O-tosyl-(-)-inositol tetraacetate (0.3 g.) was heated with 2N hydrochloric acid (10 ml.) at 100° for one hour. The solution was taken to dryness in vacuo and

---

(63) P.T. Gilham, personal communication.

the residue recrystallised from ethyl acetate to give 2-O-methyl-5-O-tosyl-(-)-inositol as needles (0.16 g.) m.p. 172-3° (decomp.).

Found :	C, 48.52%	H, 5.78%
$C_{14}H_{20}O_8S$ requires :	C, 48.26%	H, 5.8%

Solvolysis of 2-O-Methyl-5-O-tosyl-(-)-inositol.

2-O-Methyl-5-O-tosyl-(-)-inositol (80 mg.) was dissolved in 95% acetic acid (10 ml.) and heated under reflux for 30 hours. The solution was concentrated *in vacuo* to a small volume and heated for 3 hours at 100° with 2N HCl (5 ml.). Paper chromatography of the reaction mixture showed the presence of a compound with an R_f value of a new methyl ether, together with traces of other methyl ethers. The reaction mixture was taken to dryness *in vacuo* and the residue was dissolved in acetone-water (4:1) and run through a cellulose powder column. The fractions containing the new methyl ether were taken to dryness and the residue heated under reflux with 57% hydriodic acid for 2 hours. The solution was evaporated to dryness and paper chromatography of the residue in acetone-water (4:1) showed the presence of a compound with an R_f value identical with that of *muco*inositol. The residue was acetylated in acetic anhydride-H_2SO_4 mixture to yield an acetate (23 mg.) of m.p. 176 and mixed m.p. 178-9° with *muco*inositol hexaacetate (m.p. 180°).

1:2-Anhydro-3:4-5:6-di-O-isopropylidene-cisInositol.

5:6-Di-O-tosyl-1:2-3:4-di-O-isopropylideneepiinositol (14 g.) was added to a solution of sodium (3.5 g.) in anhydrous methanol (140 ml.), and the mixture heated under reflux for 10 hours. Chloroform (250 ml.) was added, and the solution washed with water. The chloroform extract was dried (Na_2SO_4) and evaporated to dryness. The residue was crystallised from light petroleum (b.p. 40-60°) to yield a product of m.p. 95-110° (3 g.). Paper chromatography in acetone-water (4:1) showed that the product was a mixture of two compounds ; one of these compounds had an R_f value identical with that of 1:2-anhydro-cisinositol, while the other had an R_f value different from that of 5:6-anhydroalloinositol. By fractional crystallisation from light petroleum, small quantities of both compounds were obtained pure. From the less soluble fraction a compound of m.p. 139-41° was isolated, which had mixed m.p. 139-42° with a sample of pure diisopropylidene 1:2-anhydrocis-inositol (m.p. 142-3°). The second fraction isolated had m.p. 104-5°, and gave an analysis for the diiso-propylidene derivative of an inositol methyl ether.

Found :	C, 57.01%	H, 7.87%
$C_{13}H_{22}O_6$ requires :	C, 56.92%	H, 8.08%

The separation was not carried further as it was found easier to separate the two products at a later stage.

6-O-Tosylepiinositol.

A mixture of 1:2 anhydro-3:4-5:6-di-O-isopropylidenecis-inositol and 1:2-3:4-di-O-isopropylidene-6-O methyl epi-inositol (0.8 g.) of m.p.> 110° was dissolved in anhydrous dioxan (50 ml.) containing anhydrous toluenesulphonic acid (0.65 g.). The mixture was heated at 100° for 2 hours, and the dioxan removed by distillation *in vacuo*. The residue was heated for 1 hour with 50% acetic acid (20 ml.), and the acetic acid removed by distillation *in vacuo*. The residual gum was taken up in acetone-water (4:1) and run through a cellulose column in acetone-water (4:1). The early fractions with an R_f of a tosyl compound were evaporated to dryness and the residue acetylated in pyridine-acetic anhydride mixture to give 6-O-tosylepiinositolpentaacetate (0.34 g.) m.p. 227°.

Found :	C, 50.88%	H, 5.32%
$C_{23}H_{28}O_{13}S$ requires :	C, 50.75%	H, 5.2%

6-O-Methylepiinositolpentaacetate.

The fractions from the above column with an R_f value of 6-O-methylepiinositol were combined and taken to dryness. The residue was acetylated in acetic anhydride-H_2SO_4 mixture to give an acetyl derivative, which, after recrystallisation from ethanol had m.p. 171-2°.

Found :	C, 50.77%	H, 5.90%
$C_{17}H_{24}O_{11}$ requires :	C, 50.49%	H, 5.98%

Solvolysis of 1-O-Tosylmesoinositol.

(±)-1-O-Tosylmesoinositol (100 mg.) was dissolved in 95% acetic acid (10 ml.) containing anhydrous sodium acetate (30 mg.) and heated under reflux for 40 hours. The reaction mixture was deacetylated and paper chromatography with acetone-water (4:1) as solvent showed that the solution contained mainly unchanged compound together with a little (±)-inositol. If solvolysis was carried out in the absence of sodium acetate, both (±)- and meso- inositols could be identified in the reaction mixture.

Solvolysis of 1-O-Tosylepiinositol.

(±)-1-O-Tosylepiinositol (80 mg.) was dissolved in 95% acetic acid (7 ml.) with sodium acetate (20 mg.) and heated under reflux for 30 hours. The reaction mixture was diluted with one volume of water and heated for 3 hours with 5N HCl (7 ml.). Paper chromatography of the reaction mixture showed the presence of epiinositol, together with traces of alloinositol and some unchanged starting material and a compound with a higher R_f value. The reaction mixture was evaporated to dryness in vacuo and run through a cellulose powder column in acetone-water (4:1). The early fractions containing the unknown compound were combined and evaporated to dryness. The residue could not be crystallised, but reduced Fehling's solution and was destroyed by alkaline hydrolysis. The fractions containing alloinositol were combined and acetylated in acetic anhydride

H_2SO_4 mixture to yield 8 mg. of alloinositol hexaacetate m.p. and mixed m.p. 140-41° with a pure sample of alloinositol hexaacetate (m.p. 142-43°).

The fractions containing epiinositol were acetylated to yield 20 mg. of epiinositol acetate, m.p. 185-6° and mixed m.p. 185-7° with pure epiinositol acetate (m.p. 187-8°).

Solvolysis of 6-O-Tosylepiinositol.

(±) 6-O-Tosylepiinositol (80 mg.) was dissolved in 95% acetic acid (5 ml.) with anhydrous sodium acetate (20 mg.) and heated under reflux for 30 hours. The reaction mixture was deacetylated and evaporated to dryness in vacuo, and run through a cellulose powder column in acetone-water (4:1). A small amount of a reducing compound with a high R_f value, similar to that of the compound from 1-O-tosylepiinositol was present in the early fractions. Fractions 9-17 contained a compound with an R_f value of epiinositol in acetone-water (4:1). Fractions 9-12 were combined, and also fractions 13-17. Paper chromatography in ethyl acetate-acetic acid-water (3:1:1) showed that 9-12 (9 mg.) contained mainly cisinositol, while 13-17 (12 mg.) contained a mixture of cis and epi inositols. Fractions 9-12 were acetylated in acetic anhydride-H_2SO_4 mixture to yield an acetate, which after several recrystallisations from ethanol gave cisinositol hexaacetate (5 mg.), m.p. 203-4° and mixed m.p. 203-5° with a sample of pure cisinositol acetate (m.p. 205-6°).

ACKNOWLEDGEMENTS.

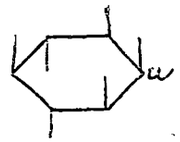
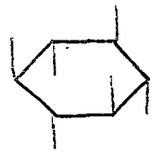
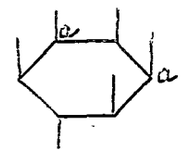
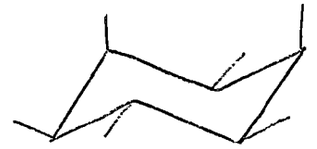
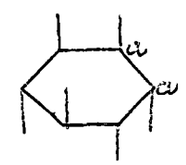
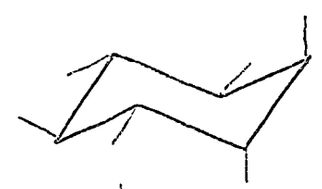
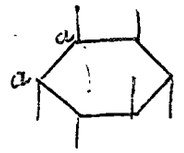
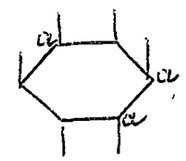
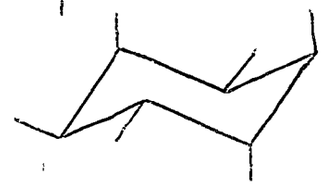
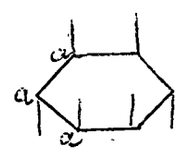
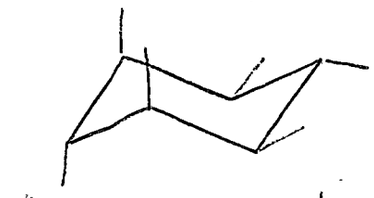
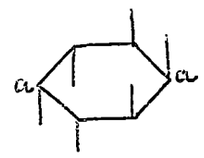
I wish to thank Professor S.J. Angyal of the New South Wales University of Technology for his valuable help and guidance throughout the course of this work.

I am grateful to Mrs. V. Bender and Mr. J. Curtin, who prepared some of the compounds used ; and also to Dr. G.R. Allen of the American Cyanamid Company, who supplied a sample of neoinosamine hydrochloride.

The microanalyses were done by Dr. E. Challen and Dr. K.W. Zimmerman, to both of whom I express my thanks.

The work for this thesis was carried out while I held a Commonwealth Scientific and Industrial Research Organisation Australian Post-Graduate Studentship.

THE INOSITALS

	Name	Classical	Chair
(VIII)	meso		
(IX)	scyllo		
(X)	epi		
(XI)	(+)		
(XII)	(-)		
(XIII)	allo		
(XIV)	muco		
(XV)	neo		
(XVI)	cis