728. *Cyclitols. Part VII.* Anhydroinositols and the "Epoxide Migration."*

By S. J. Angyal and P. T. Gilham.

Several 1 : 2-anhydroinositols have been prepared by the action of strong bases on appropriate toluene-*p*-sulphonyl compounds. In those anhydrides which have a hydroxyl group adjacent and *trans* to the epoxide ring, the epoxide is opened in alkaline solution by the hydroxyl group's attacking from the rear with the formation of a new epoxide ring ("epoxide migration"). The position of the equilibrium between two anhydroinositols has been established and has been shown to be governed by steric interactions.

The configuration of conduritol oxide has been determined.

A proposal is made for specifying the configuration of asymmetric cyclitols by a modified use of the sequence rule.

The Specification of Asymmetric Configuration in Cyclitols.—Several different proposals have recently been made [1,2,3] for logical naming and numbering of cyclitols; in consequence the nomenclature of cyclitols is in a confused state. It was hoped that a body of authority would put forward official proposals, but this hope has, so far, not materialised; in the meanwhile each proposed nomenclature is in limited use.

Whereas the method of nomenclature [2] employed in this Series of papers is unambiguous in its numbering and naming, it does not yet provide for the distinction between enantiomers (other than by structural formulæ). Rules to cover this point were submitted in Part I [2] but were withheld at the Editor's request. In the present paper it is necessary to specify the configuration of asymmetric cyclitols. The other proposed nomenclatures [1,3] provide such methods, but their adoption involves the fundamental objection

* Part VI, preceding paper.

[1] Fletcher, Anderson, and Lardy, *J. Org. Chem.*, 1951, **18**, 1238.
[2] Angyal, Macdonald, and Matheson, *J.*, 1952, 686.
[3] MacCasland, pamphlet available from Chemical Abstracts, Ohio State University, Columbus 10, Ohio.

that their use of *D* and *L* depends on the method of enumeration employed and would necessitate altering the names and numbering used in this Series. Our original, unpublished, proposals do not now appear to offer any advantage.

A method of specifying configurations independent of a numbering system is provided by the "sequence rule." Its recent modification,[4] in contrast to its original form,[5] can deal with cyclitols; but its application to this field is cumbersome, requiring specification of the configuration of every carbon atom, and it completely obscures the *cis–trans*-relation of substituent groups which is the salient feature of cyclitol chemistry. Nevertheless, the sequence rule has the advantage that its specification of asymmetric configuration is independent of any other convention, such as numbering rules.

In the hope that international agreement on cyclitol nomenclature will eventually be reached, any method now advocated is regarded as temporary and should therefore introduce the minimum of new rules or conventions. It is now proposed, after discussion with the Editor, to use the modified sequence rule to distinguish between enantiomers, in a simplified way, namely, by specifying the configuration of only *one* carbon atom with its aid. By using the nomenclature proposed in Part I, *i.e.*, trivial prefixes as used in carbohydrate chemistry, only *one* specification is required to distinguish between enantiomers and therefore to describe the configuration of an asymmetric cyclitol fully.

In Part I [2] we proposed two rules for the numbering of cyclitols, *viz.*: (i) that the larger number of functional groups on one side of the hexagon be described by the lowest possible numbers; and (ii) if the hydrogen atom of a hydroxyl group is replaced by another group and if rule (i) has not by itself determined the numbering of this derivative unequivocally, then this substituted position shall be given the lowest number which remains available. It is now further proposed that the configuration of the *lowest numbered asymmetric carbon atom* (not always $C_{(1)}$) be specified by the modified sequence rule [4] as *R* or *S*. The label shall be written in parentheses preceded by the number of the carbon atom thus labelled, *e.g.*, (1*R*)-inositol; it is not strictly necessary to use this number but we propose to print it for clarity, in accordance with the proposals of Cahn, Ingold, and Prelog.[4]

This application of the sequence rule in the cyclitol series is very simple. Essentially, it requires the four groups attached to the carbon atom to be arranged in a priority sequence; if that sequence for the assemblage Cabcd is a,b,c,d, then it will be denoted as *R* if the sequence a→b→c traces a right-handed turn when viewed from a point on the side remote from d. (The sequence can be conveniently visualised by the use of an imaginary steering wheel.[4]) The opposite arrangement is denoted as *S*.

The priority sequence is, in the first instance, decided by the rule that higher atomic number precedes the lower. In most cases in cyclitol chemistry, oxygen will have the highest and hydrogen the lowest priority; the priority between the two carbons in the ring is determined by the atomic numbers of the atoms attached to them, or, if this fails, to the next atoms, etc. If this procedure fails to establish priority—as in the case of an unsubstituted inositol—it is decided by the rule that *cis* precedes *trans*.

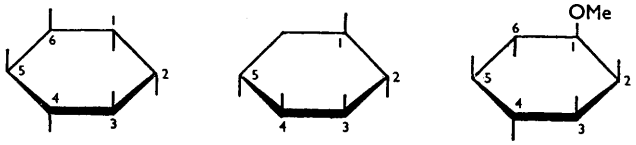
By this method, (+)-inositol (I) * becomes (1*S*)-inositol, the common natural quercitol, (+)-*proto*quercitol (II), is written as (1*R*)-*proto*quercitol, and (+)-bornesitol [6] (III) is named as (1*R*)-1-*O*-methyl*myo*inositol. Other examples appear in this paper.

"*Epoxide Migration.*"—Sugar epoxides (1 : 2-anhydro-sugars) have been extensively used as intermediates in carbohydrate chemistry: opening of the epoxide ring, which always occurs with inversion, yields epimeric sugars and their derivatives.[7] The method is of obvious use in cyclitol chemistry but until recently only one anhydroinositol had been

* Hydroxyl groups are indicated by their bonds, but not shown, in formulæ.

[4] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[5] Cahn, and Ingold, *J.*, 1951, 612.
[6] Angyal and Pitman, unpublished work.
[7] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37.

reported, that made by epoxidation [8] of conduritol, a naturally occurring *cyclo*hexene-tetrol.[9] The configuration of this anhydroinositol has not been determined and it has not been used for the synthesis of other cyclitol derivatives. Recently, in Part III of this series,[10] two anhydroinositols were described and their cleavage utilised to prepare a new inositol and a new inositol methyl ether. The present paper extends this work, making



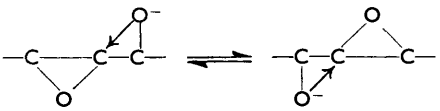
(I) (II) (III)

five of the possible ten 1 : 2-anhydroinositols known; work is in progress on two other anhydrides. No 1 : 3- or 1 : 4-anhydroinositol has yet been described.

The anhydroinositols were prepared in the usual way,[7] by treatment of *trans*-1 : 2-diol monotoluene-*p*-sulphonates with alkali. The epoxide ring is readily opened by nucleophilic reagents; thus alkalis give inositols, sodium methoxide gives inositol methyl ethers, ammonia gives inosamines,[11] etc.

In nucleophilic opening, the group which cleaves the epoxide ring may be within the molecule itself; for example, a suitably placed hydroxyl group, in the presence of bases, may attack the epoxide giving a cyclic ether. The best known example of this reaction is the rearrangement of scopine to scopoline.[12] In carbohydrate chemistry there are several known cases of 1 : 4-anhydride formation from epoxides.[7]

A hydroxyl group on a carbon atom adjacent to an epoxide ring could also carry out the intramolecular nucleophilic displacement: in this case the epoxide ring would open with the formation of another epoxide ring. This phenomenon will be referred to as " epoxide migration : "



Such a reaction was first postulated by Lake and Peat [13] to explain the formation of two epoxides, instead of the expected one, on treatment of methyl 2-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside with sodium methoxide. Buchanan [14] recorded another, similar case. Newth [15] recently assumed the occurrence of epoxide migration when he found that 1 : 6-anhydro-3-*O*-toluene-*p*-sulphonyl-β-D-altrose gave, not the expected 1 : 6-2 : 3-dianhydro-β-D-mannose, but 1 : 6-3 : 4-dianhydro-β-D-altrose; he gave a detailed discussion of the reaction. In these cases the epoxide migration was merely postulated; the actual conversion of one epoxide into another has, to our knowledge, not yet been described. The study of anhydroinositols has now enabled us to observe epoxide migration by converting one epoxide into another which was itself isolated, and by studying the position of the equilibrium.

On theoretical grounds the following predictions can be made concerning the occurrence of epoxide migration :

(i) Since the opening of an epoxide ring is a nucleophilic displacement on carbon,

[8] Schöpf and Arnold, *Annalen*, 1947, **558**, 123.
[9] Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756.
[10] Angyal and Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.
[11] Anderson, Abs. Papers, 130th Meeting, Amer. Chem. Soc., p. 27D; Allen, *J. Amer. Chem. Soc.*, 1957, **79**, 1167.
[12] Willstätter and Berner, *Ber.*, 1923, **56**, 1079.
[13] Lake and Peat, *J.*, 1939, 1069.
[14] Buchanan, *Chem. and Ind.*, 1954, 1484.
[15] Newth, *J.*, 1956, 441.

occurring with inversion,[16] the entering group must attack the carbon from the side opposite to that of the epoxide-oxygen atom. In a *cyclo*hexane system the hydroxyl group should be *trans* and capable of taking up an axial position.

(ii) The hydroxyl group must be present as an anion; therefore, epoxide migration can occur only in the presence of strong bases.

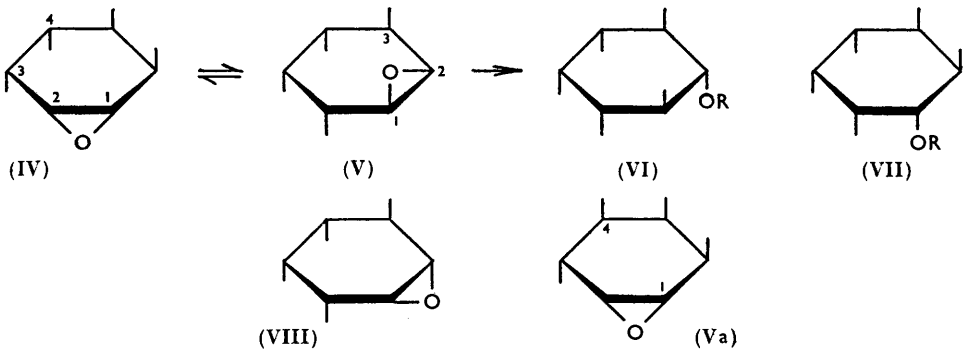
(iii) After migration, the new hydroxyl group will be *trans*-situated in respect of the new epoxide, in a suitable position for nucleophilic attack. Epoxide migration must therefore be a reversible reaction. The equivalence of starting and end product requires that the oxygen anion leaving the transition state, as well as the one entering it, be in an axial position; ring inversion thus occurs when the molecule passes through the transition state.

(iv) The position of the equilibrium will depend on the free energies of the two epoxides, the more stable one (as a rule, the isomer containing fewer axial substituents [17]) predominating.

The epoxide migrations observed amongst anhydroinositols, and also the cases described by Lake and Peat [13] and by Newth,[15] conform to the above rules.

Anhydroinositols.—Epoxide migration was first studied in the case of (1*S*)-1 : 2-anhydro-*allo*inositol (IV), prepared by mild acid hydrolysis of its di*iso*propylidene derivative.[10] Cleavage of the epoxide ring by dilute sulphuric acid gave the expected mixture of nearly equal quantities of *neo*- and (−)-inositol. Cleavage with hot alkali, however, gave a mixture of *myo*- (VI; R = H) and *allo*-inositol (VII; R = H), suggesting that migration had occurred before opening of the epoxide ring. Proof of this rearrangement was obtained by treating the anhydride (IV) with dilute barium hydroxide solution at room temperature: from this reaction a new anhydroinositol was isolated. This anhydride was cleaved by both acid and alkali to a mixture of *myo*- and *allo*-inositol, a reaction which restricts the structure of the anhydride to either (V) or (VIII), or their enantiomers.

Opening of the epoxide ring of the new anhydride with sodium methoxide provided an unequivocal answer to its structure because in this reaction a methoxyl group labels the carbon on which ring-opening had occurred. Two methyl ethers were isolated from this reaction: one, which was optically active, gave *allo*inositol on demethylation, and the other, a *meso*-compound, was identified as sequoyitol, 5-*O*-methyl*myo*inositol [18] (VI; R = Me). The latter can be formed only from (V) or from its enantiomer (by attack of a

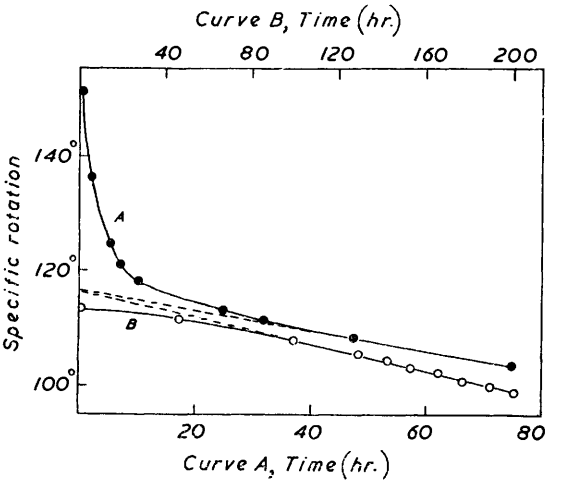


methoxide ion at $C_{(2)}$); structure (VIII), on the other hand, would give 4-*O*-methyl*myo*-inositol. The rearranged anhydride therefore has structure (V) or its enantiomer; the former, but not the latter, can be obtained from (IV) by epoxide migration. It is concluded

[16] Cf., *e.g.*, Winstein and Henderson in Elderfield's "Heterocyclic Compounds," J. Wiley and Sons, Inc., New York, 1950, Vol. I, p. 27.
[17] Cf., *e.g.*, Klyne, "Progress in Stereochemistry," Butterworths Ltd., London, 1954, Vol. I, p. 43.
[18] Anderson, Deluca, Bieder, and Post, *J. Amer. Chem. Soc.*, 1957, **79**, 1171.

therefore that (1*S*)-1 : 2-anhydro*allo*inositol (IV) underwent epoxide migration in alkaline medium to give (1*S*)-1 : 2-anhydro*neo*inositol (V), in accordance with the rules formulated above. The other methyl ether resulting from attack of methoxide ion on (V)—at $C_{(1)}$—must therefore be (1*S*)-1-*O*-methyl*allo*inositol (VII; R = Me); this conclusion has been confirmed by the synthesis of its enantiomer by an independent method.[19]

The epoxide migration can readily be followed polarimetrically since the anhydroinositols (IV) and (V) have specific rotations of +153° and +113°, respectively. The rotation does not come to a constant value, however, because of the simultaneous, though much slower, cleavage of the anhydrides; after a prolonged period in alkaline solution, only inositols were present. The rate of this hydrolysis is so slow that it can be considered as constant over the period of epoxide migration and extrapolation of the straight part of the curve (see Figure) to cut the *y* axis gives the final value for the epoxide migration, approx. +117°. This is higher than the rotation of anhydro*neo*inositol, suggesting an



Equilibration of anhydroinositols.

A, (1*S*)-1 : 2-Anhydro*allo*inositol (0·2583 g.) in 0·05N-barium hydroxide (10 ml.) at 20°. *B*, (1*S*)-1 : 2-Anhydro*neo*inositol (0·0925 g.) in 0·05N-barium hydroxide (10 ml.) at 20°.

equilibrium of the two anhydrides. The equilibrium was approached also from the other side (see Figure) and extrapolation * agrees with the value of approx. +117°. (The two curves are shown on the same Figure though the time-scales are different.) The value +117° shows that there are approximately 90% of anhydro*neo*- and 10% of anhydro*allo*-inositol in equilibrium at 20°. The equilibrium constant, *K*, is ~9 and calculation by the equation $\Delta F = -RT \ln K$ shows that anhydro*neo*inositol is more stable than its isomer by 1·3 kcal./mole.

Writing the anhydro*neo*inositol as (V*a*) shows that it is an epimer of anhydro*allo*inositol (IV), differing only in the configuration at $C_{(4)}$. The latter compound has two, the former only one, axial hydroxyl group in its preferred conformation; hence the former is more stable. Winstein and Holness [20] gave the energy difference between an equatorial and an axial hydroxyl group, when isolated from other groups, as 0·8 kcal./mole; in our case the energy difference is greater because the axial hydroxyl group which is present in (IV), but not in (V), would suffer steric interaction from the oxygen atom of the epoxide ring.

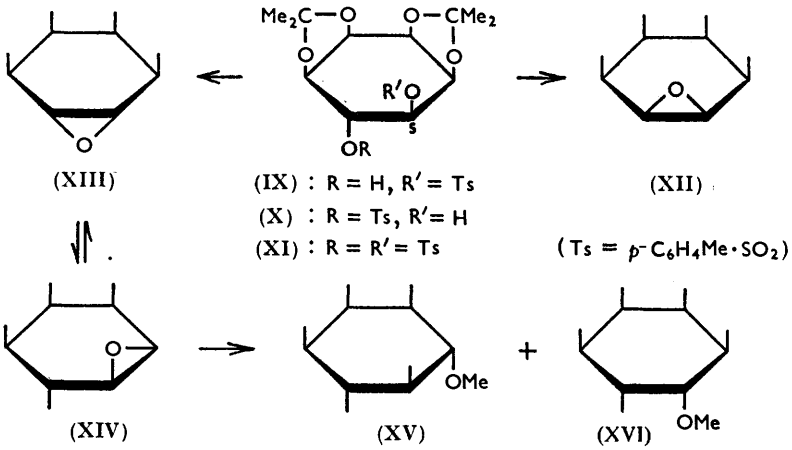
It is seen that epoxide migration occurs under surprisingly mild conditions, namely, in dilute aqueous alkali solution at room temperature; these conditions are milder than those used for the cleavage of epoxides by bases. The rearrangement of scopine to scopoline (1 : 2-anhydride to 1 : 4-anhydride) is slower.[12] Since the usual conditions for preparing

* Although extrapolation of curve *A* is from two experimental points only, that of curve B is accurate and it is satisfactory that curve *A* fits this more precise determination.

[19] Angyal and Gilham, unpublished work.

[20] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.

epoxides from bromohydrins or toluene-*p*-sulphonyl compounds are more vigorous than those required for migration, the initially formed (but less stable) epoxide is not usually obtained in those cases where epoxide migration can occur. In our example the less stable isomer was obtained because epoxide formation was carried out while the neighbouring hydroxyl groups were blocked by *iso*propylidene groups, and these were eventually removed under acidic conditions.



Two new anhydroinositols were prepared from 1 : 2-3 : 4-di-*O*-*iso*propylidene*epi*-inositol.[2] Toluene-*p*-sulphonylation, under appropriate conditions, readily gave either the 5 : 6-di-*O*-toluene-*p*-sulphonyl compound (XI) or a mono-*O*-toluene-*p*-sulphonyl derivative which may have structure (IX) or (X). On treatment with sodium methoxide each ester gave an anhydride, these not being identical; removal of the *iso*propylidene groups then yielded two anhydroinositols of which one must have structure (XII) and the other (XIII). Respective structures were allocated as a result of the study of the epoxide migration.

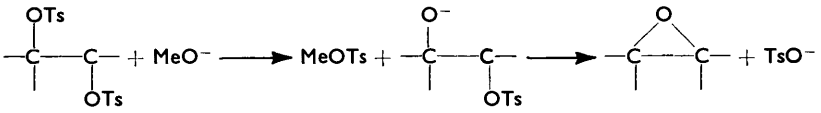
The anhydride made from the monotoluene-*p*-sulphonyl compound gave *epi*inositol on acid hydrolysis but *myo*- and *allo*-inositol on treatment with alkali; epoxide migration had therefore occurred. The rearranged anhydride was not isolated but its structure was established by cleavage with sodium methoxide which gave methyl ethers of *myo*inositol and of *allo*inositol. The former was shown to be (±)-4-*O*-methyl*myo*inositol (XV); although this racemic compound was previously unknown, its structural identity with ononitol,[21] the naturally occurring (+)-4-*O*-methyl*myo*inositol, was shown by the identity of the infrared spectra of their penta-acetates.[22] Formation of the ether (XV) and of a methyl ether of *allo*inositol proves that the rearranged anhydride is 1 : 2-anhydro*epi*inositol (XIV), and the methyl ether of *allo*inositol is consequently (±)-5-*O*-methyl*allo*inositol (XVI). (All the compounds formed from *epi*inositol are, of course, racemic and the formulæ show only one, arbitrarily chosen, enantiomer.) It follows that the original anhydride is (±)-5 : 6-anhydro*allo*inositol (XIII) and the parent monotoluene-*p*-sulphonyl ester is (±)-1 : 2-3 : 4-di-*O*-*iso*propylidene-5-*O*-toluene-*p*-sulphonyl*epi*inositol (IX).

The anhydride formed from the ditoluenesulphonyl derivative (XI) must therefore be 1 : 2-anhydro*cis*inositol (XII). It is hydrolysed by both acid and alkali to *epi*inositol; thus epoxide migration does not occur in this compound in which the hydroxyl groups are *cis* to the epoxide ring, although it contains two axial hydroxyl groups.

In the toluenesulphonylation of 1 : 2-3 : 4-di*iso*propylidene*epi*inositol the sulphonyl group would, of course, react preferentially with the less hindered oxygen atom. The

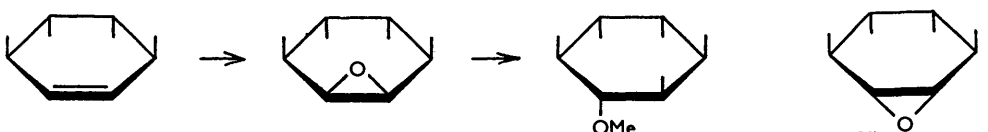
[21] Plouvier, *Compt. rend.*, 1955, **241**, 983.
[22] Angyal, Gilham, and Macdonald, *J.*, 1956, 1417.

planar formula may suggest that $O_{(5)}$—*cis* to the two *iso*propylidene groups—is hindered but inspection of an atomic model (Courtauld's) shows that both free hydroxyl groups are unhindered. The experimental evidence now indicates that, in fact, $O_{(5)}$ is more accessible than $O_{(6)}$. The direction of epoxide formation from disulphonyl compounds [10] such as (XI) has not been discussed previously. It appears probable that the first sulphonyl group is removed by O–S fission,[23] facilitated by the inductive effect of the other sulphonyloxy-group :



The more accessible sulphonyl group would be removed first, in our case the one on $O_{(5)}$, explaining the formation of the *cis*-anhydride (XII).

The reaction of the naturally occurring *cyclo*hexenetetrol, conduritol [9] (XVII), with perbenzoic acid gives only one epoxide,[8] which may be 2 : 3-anhydro*allo*inositol (XVIII) or 1 : 2-anhydro*muco*inositol (XIX). Opening with sodium methoxide can be used to distinguish between these possibilities : the former (XVIII) would be converted into 3-*O*-methyl-(±)-inositol (XX), whereas structure (XIX) would give 2-*O*-methyl-(±)-inositol without epoxide migration, or 1-*O*-methyl-(±)-inositol and *O*-methyl*scyllo*inositol



(XVII) (XVIII) (XX) (XIX)

if migration occurred. Only 3-*O*-methyl-(±)-inositol (XX) was obtained; it was identified by comparison with a sample made by mixing natural pinitol and its synthetic enantiomer.[24] Conduritol oxide is therefore 2 : 3-anhydro*allo*inositol (XVIII). The direction of epoxidation is in accordance with Henbest and Wilson's recent conclusion [25] that peracids will add oxygen to the double bond of allylic *cyclo*hexenols so as to produce an epoxide in *cis*-relation to the adjacent free hydroxyl group.

Schöpf and Schmetterling [26] prepared 2 : 3-epoxysuccindialdehyde from conduritol oxide by glycol fission with lead tetra-acetate. Any of the other 1 : 2-anhydroinositols would serve as a starting material, and the ready availability of 1 : 2-anhydro*allo*inositol will make this interesting dialdehyde more accessible.

Experimental

M. p.s are corrected.

(1S)-1 : 2-*Anhydro*allo*inositol* (IV).—(1*S*)-1 : 2-Anhydro-3 : 4-5 : 6-di-*O*-*iso*propylidene*allo*-inositol [10] (10 g.) was heated in acetic acid (20 ml.) and water (20 ml.) for ½ hr. on a steam-bath. After cooling, the product which crystallised was filtered off and washed with ethanol. Recrystallisation from aqueous ethanol gave the *anhydride* (4·05 g., 60%) as plates, $[\alpha]_D^{25}$ +153° (*c* 0·5 in H_2O) (Found : C, 44·15; H, 6·15. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). When heated to *ca.* 200°, the compound melts and sets to a hard glass, probably owing to polymerisation. Acid hydrolysis, as shown by paper chromatography,[27] yields (−)- and *neo*-inositol.

[23] Honeyman and Morgan, *J.*, 1955, 3664; for discussion and references see Cope and Shen, *J. Amer. Chem. Soc.*, 1956, **78**, 5912.
[24] Angyal, Macdonald, and Matheson, *J.*, 1953, 3321.
[25] Henbest and Wilson, *Chem. and Ind.*, 1956, 659.
[26] Schöpf and Schmetterling, *Angew. Chem.*, 1952, **64**, 591.
[27] Angyal, Gilham, and McHugh, *J.*, 1956, 1432.

Alkaline Hydrolysis of (1S)-1 : 2-*Anhydro*allo*inositol*.—The anhydride (0·2 g.), dissolved in 0·5N-barium hydroxide (10 ml.), was set aside overnight and then heated on the steam-bath for 3 hr. After removal of the barium as carbonate, the solution was evaporated to dryness *in vacuo* and the residue was chromatographed on a cellulose-powder column [22] with acetone–water (4 : 1 v/v); 5 ml. fractions were collected. Fractions 10—18, which showed the presence of *allo*inositol by paper chromatography, were combined and evaporated to dryness; the gummy residue was acetylated by hot acetic anhydride–pyridine (1 : 1). Evaporation to dryness *in vacuo* and crystallisation from water gave *hexa*-O-*acetyl*allo*inositol* (101 mg.), m. p. 144°, undepressed by a sample prepared by the acetylation of *allo*inositol (Found: C, 50·05; H, 5·45. $C_{18}H_{24}O_{12}$ requires C, 50·0; H, 5·6%). In the preliminary publication on *allo*inositol [9] the hexa-acetate is not described but Dr. H. O. L. Fischer kindly informed us that Dr. Dangschat recorded its m. p. as 141—142°.

Fractions 30—44, on evaporation and acetylation, gave hexa-*O*-acetyl*myo*inositol (45 mg.), m. p. and mixed m. p. 210° (Found: C, 49·85; H, 5·55. Calc. for $C_{18}H_{24}O_{12}$: C, 50·0; H, 5·6%).

(1S)-1 : 2-*Anhydro*neo*inositol* (V).—(1*S*)-1 : 2-Anhydro*allo*inositol (1 g.) was dissolved in 0·5N-barium hydroxide solution (20 ml.) and set aside for 5 hr. After removal of the barium as carbonate, the solution was evaporated to dryness *in vacuo* and the residue was extracted several times with cold anhydrous ethanol. The extracts were concentrated *in vacuo* and the resulting crystals were recrystallised several times from anhydrous ethanol to yield the *anhydride* (0·3 g., 30%), m. p. 154°, $[\alpha]_D^{25}$ +113° (*c* 1·0 in H_2O) (Found: C, 44·65; H, 6·25. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). It is difficult to obtain this anhydride pure because the starting material, present in equilibrium, is less soluble.

Reaction of (1S)-1 : 2-*Anhydro*allo*inositol with Sodium Methoxide*.—The anhydride (0·4 g.) was added to a solution of sodium methoxide made from sodium (0·2 g.) and anhydrous methanol (10 ml.). After 24 hr. most of the material had dissolved and paper chromatography showed that the anhydro*allo*inositol had rearranged to anhydro*neo*inositol. The solution was then heated under reflux for 5 hr., after which paper chromatography indicated that all the epoxide had reacted. After the addition of a few drops of water, carbon dioxide was passed through the solution which was then evaporated to dryness *in vacuo*. The residue was dissolved in water (1 ml.), and the solution diluted with acetone (4 ml.), filtered, and chromatographed through a cellulose-powder column with acetone–water (4 : 1 v/v). Paper chromatography of the fractions showed two compounds with slight over-lapping.

Fractions containing the first compound (R_F 0·41) were combined and evaporated. The gummy residue (179 mg.) was acetylated with acetic anhydride–pyridine (1 : 1) on the steam-bath for 1 hr. Evaporation *in vacuo*, followed by crystallisation from water, gave (1S)-*penta*-O-*acetyl*-1-O-*methyl*allo*inositol*, m. p. 145—146°, $[\alpha]_D^{19}$ +9° (*c* 0·7 in $CHCl_3$) (Found: C, 50·8; H, 5·9. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0%). Deacetylation gave the methyl ether of *allo*inositol as a gum. Demethylation with hydriodic acid, followed by acetylation, gave hexa-*O*-acetyl*allo*inositol, m. p. 144°.

The fractions containing the second methyl ether (R_F 0·33) were combined and evaporated. The residue (150 mg.) on crystallisation from ethanol gave sequoyitol, m. p. and mixed m. p. 241—242° (Found: C, 43·25; H, 7·35. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·25%).

(±)-1 : 2-3 : 4-*Di*-O-iso*propylidene*-5 : 6-*ditoluene*-p-*sulphonyl*epi*inositol* (XI).—1 : 2-3 : 4-Di-*O*-*iso*propylidene*epi*inositol [2] (2·9 g.) and toluene-*p*-sulphonyl chloride (8·5 g.) were dissolved in anhydrous pyridine (30 ml.). After one week the mixture was diluted with water and the precipitated product was filtered off and washed with water. Crystallisation from ethanol gave the *ditoluene*-p-*sulphonyl derivative* (5·64 g., 89%), m. p. 208—209° (Found: C, 55·05; H, 5·7. $C_{26}H_{32}O_{10}S_2$ requires C, 54·95; H, 5·65%).

1 : 2-*Anhydro*-3 : 4-5 : 6-*di*-O-iso*propylidene*cis*inositol*.—The ditoluene-*p*-sulphonyl compound (XI) (2·0 g.) was added to anhydrous methanol (20 ml.) in which sodium (0·5 g.) had been dissolved. The mixture was heated under reflux for 5 hr., then chloroform (40 ml.) was added to the dark mixture. After being washed with water and dried (Na_2SO_4), the solution was evaporated to dryness. The crystalline residue was sublimed at 110°/1 mm. and the sublimate recrystallised from light petroleum to yield the *anhydride* (447 mg., 54%), m. p. 142—143° (Found: C, 59·7; H, 7·45. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

1 : 2-*Anhydro*cis*inositol* (XII).—The above compound lost its *iso*propylidene groups when heated in 50% acetic acid at 100° for 30 min. Evaporation *in vacuo* and crystallisation from

ethanol gave the *anhydride* as plates, m. p. 59—60° (Found : C, 44·5; H, 6·3. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). Hydrolysis by sulphuric acid or sodium hydroxide gave *epi*inositol as the sole product shown by paper chromatography.

(±)-6-O-*Acetyl*-1 : 2-3 : 4-*di*-O-iso*propylidene*-5-O-*toluene*-p-*sulphonyl*epi*inositol*.—1 : 2-3 : 4-Di-*O*-*iso*propylidene*epi*inositol [2] (1·0 g.) and toluene-*p*-sulphonyl chloride (0·72 g.) were dissolved in anhydrous pyridine (5 ml.). After one week, acetic anhydride (3 ml.) was added and the mixture kept for a further day. The solution was then poured on ice, and the precipitated gum (1·6 g.), which slowly solidified, was crystallised from methanol to give the *compound* as plates (1·0 g., 56%), m. p. 182° (Found : C, 54·9; H, 6·0. $C_{21}H_{28}O_9S$ requires C, 55·25; H, 6·2%).

Heating on the steam-bath with 2N-hydrochloric acid for 1 hr. and crystallisation from water gave (±)-5-O-*toluene*-p-*sulphonyl*epi*inositol*, m. p. 227° (decomp.) (Found : C, 46·6; H, 5·4. $C_{13}H_{18}O_8S$ requires C, 46·7; H, 5·45%).

5 : 6-*Anhydro*-1 : 2-3 : 4-*di*-O-iso*propylidene*allo*inositol*.—The above acetyl toluene-*p*-sulphonyl compound (1·0 g.) was added to anhydrous methanol (20 ml.) in which sodium (0·25 g.) had been dissolved. The mixture was warmed until the compound dissolved and then set aside for 24 hr. Chloroform was added, and the solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was extracted with light petroleum which, on concentration, deposited needles; crystallisation from light petroleum gave the *anhydride* (0·41 g., 78%), m. p. 97—98° (Found : C, 59·65; H, 7·4. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%).

5 : 6-*Anhydro*allo*inositol* (XIII).—The above compound (1·0 g.) was heated on the steam-bath in 50% acetic acid (4 ml.) for 1 hr. Evaporation *in vacuo* left a crystalline residue; it was extracted twice with ethyl acetate from which the *anhydride* (0·3 g., 45%), m. p. 120—122°, crystallised (Found : C, 44·45; H, 6·2. $C_6H_{10}O_5$ requires C, 44·45; H, 6·2%). Another preparation gave a product melting at 148—150° which had the same R_F values. Paper chromatography after acid hydrolysis showed *epi*inositol and after alkaline hydrolysis *allo*- and *myo*-inositol.

Reaction of 5 : 6-*Anhydro*allo*inositol with Sodium Methoxide*.—The anhydride (0·2 g.) was added to a solution of sodium methoxide made from sodium (0·2 g.) and anhydrous methanol (15 ml.), and the solution was heated under reflux for 10 hr. After neutralisation with hydrochloric acid and evaporation, the residue was extracted with anhydrous methanol, and the contents of this solution were chromatographed through a cellulose-powder column with acetone–water (4 : 1 v/v).

The faster-moving material (210 mg.), which did not crystallise, was acetylated and crystallised from water to give (±)-5-O-*methyl*allo*inositol penta-acetate*, m. p. 124° (Found : C, 50·5; H, 5·95. $C_{17}H_{24}O_{11}$ requires C, 50·5; H, 6·0%).

The slower-moving material was acetylated and crystallised from ethanol–water to yield (±)-4-O-*methyl*myo*inositol penta-acetate* (8 mg.), m. p. 129—130° (Found : C, 50·6; H, 5·9%).

Reaction of Conduritol Oxide with Sodium Methoxide.—The oxide was prepared by Schöpf and Arnold's method [8] and melted, as described by them, at 112°. A later report [26] gives m. p. 130°. Crude oxide (made from 135 mg. of conduritol) was heated for 8 hr. with methanol (10 ml.) in which sodium (0·1 g.) had been dissolved. After treatment with carbon dioxide and evaporation, the residue was acetylated and crystallised from water to give the 3-O-*methyl*-(±)-*inositol penta-acetate* (40 mg.), m. p. 125° (Found : C, 50·65; H, 5·85%). For comparison, a sample was prepared by hydrolysing (1*R*)-3-*O*-methyl-1 : 2-5 : 6-di-*O*-*iso*propylideneinositol [24] with dilute acid, mixing the resulting (1*R*)-3-*O*-methylinositol with an equal amount of pinitol and acetylating the mixture. The penta-acetate (Found : C, 50·65; H, 6·0%) melted at 125° and did not depress the m. p. of the previous sample.

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