THE INOSITOLS

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1. Introduction

Only two decades ago, the chemistry of the inositols (*cyclo*hexanehexols) was in the same state as that of the simple sugars at the advent of Emil Fischer: only a few naturally occurring isomers were known and their configurations had not been established. By now, thanks mainly to the excellent work of T. Posternak and of H. O. L. Fischer, and to recent advances made in Sydney, all the isomers predicted by theory are known, their configurations have been established, and methods have been developed for their interconversion.[1]

The study of the inositols is of interest and importance for two reasons. First, one of the isomers, *myo*inositol, is a compound of outstanding biological interest: it is of widespread occurrence in both plants and animals and it may have nutritional significance. Despite a large amount of work, however, there is still no definite knowledge of its biological function, or of its biosynthesis or its metabolism. This Review does not deal with the biochemistry of the inositols.[2]

Secondly, the inositols offer unique opportunities for stereochemical studies. They form the only set of hexasubstituted *cyclo*hexanes in which every possible isomer is known. (The all-*cis*-isomer is yet unknown amongst the hexachloro*cyclo*hexanes.) As derivatives of *cyclo*hexane, the inositols can be used to study the applications of conformational analysis.[3] As polyhydroxy-compounds, closely related to the sugars, they can serve as useful models for the study of some carbohydrate reactions; the behaviour of secondary hydroxyl groups can be examined without the disturbing effect—steric and electronic—of a ring-oxygen atom and without the possibility of ring-opening. The present Review discusses mainly the reactions of inositols and related compounds from the stereochemical point of view.

The first inositol was isolated by Scherer [4] in 1850 from muscle tissue (ἴς, ἰνός = sinew). The name inositol has since come to be used for the designation of all the isomers, which are differentiated by prefixes. The original inositol has been known for many years as *meso*- or *i*(inactive)-

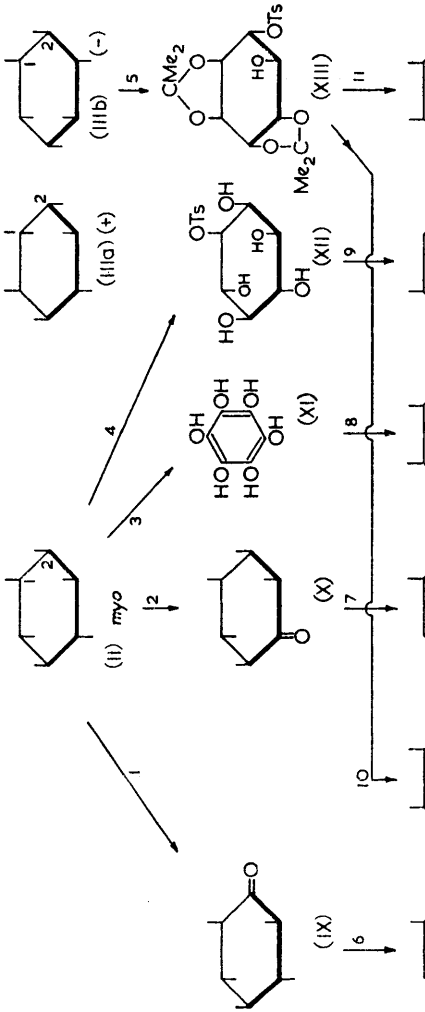
[1] For work up to 1947 see the review by Fletcher, *Adv. Carbohydrate Chem.*, 1948, **3,** 45. Other reviews: Dangschat in Paech and Tracey, "Moderne Methoden der Pflanzenanalyse", Springer, Berlin, 1955, p. 64 (analytical methods); Posternak, *Bull. Soc. Chim. biol.*, 1951, **33,** 1041 (naturally occurring cyclitols).

[2] For reviews of the biochemistry of *myo*inositol, see: Schopfer, *Bull. Soc. Chim. biol.*, 1951, **33,** 1113; Weidlein, "The Biochemistry of Inositol", Mellon Institute Bibliographic Series, Bulletin No. 6, 1951.

[3] Barton and Cookson, *Quart. Rev.*, 1956, **10,** 44.

[4] Scherer, *Annalen*, 1850, **73,** 322.

inositol; these unspecific prefixes have now been replaced [5] by *myo* ($\mu\tilde{\upsilon}\varsigma$ = muscle), but the compound is often referred to, particularly by biochemists, simply as inositol. The convenient term cyclitol is used to describe all polyhydroxy*cyclo*hexanes. Quercitol and inosose are the generic



Unsubstituted cyclitols are shown in schematic formulæ in which every "vertical" line represents a hydroxyl group and the hydrogen atoms attached to the *cyclo*hexane ring have been omitted. In substituted cyclitols every group is shown, except the hydrogen atoms. The inositols have been arranged in order of increasing number of axial hydroxyl groups.

Ts = p-$C_6H_4Me{\cdot}SO_2$.

Reagents: 1, *Acetobacter suboxydans* (5.2); 2, HNO_3 (2.2); 3, HNO_3 (3.1); 4, Five steps (5.2); 5, (*a*) Acetone–$ZnCl_2$ (5.2), (*b*) p-$C_6H_4Me{\cdot}SO_2Cl$; 6, Na–Hg (3.1); 7, H_2–Pt (3.1); 8, H_2–Pd-C (2.2); 9, Deacidite FF (5.7); 10, AcOH (5.6); 11, (*a*) OH^-, (*b*) H^+ (5.7).

Numbers in parentheses refer to the part of this Review in which the reaction is discussed.

names for *cyclo*hexanepentols and pentahydroxy*cyclo*hexanones, respectively; the individual isomers are distinguished by prefixes.*

[5] Fletcher, Anderson, and Lardy, *J. Org. Chem.*, 1951, **16**, 1238.

[6] Angyal and Macdonald, *J.*, 1952, 686.

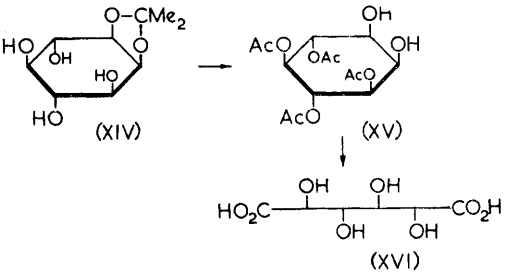
* The nomenclature of the cyclitols is in a confused state, several different systems being used by various authors (see refs. 5, 6, 49, 70). In this Review the cyclitols are named and numbered according to Angyal and Macdonald; more controversial features of nomenclature, such as the designation of enantiomorphs, have been avoided.

For the inositol structure theory predicts the existence of eight diastereoisomers, of which only one is racemic; the seven *meso*-forms and the two optically active isomers are shown, with their prefixes, by formulæ (I)—(VIII). The preparation of the rarer ones from the common isomers is also shown; the reactions involved are discussed below.

The inositols are—for polyhydroxy-compounds—surprisingly stable. They withstand the action of alkalis and acids, even of concentrated hydriodic acid, of reducing agents, and of heat up to about 250°. They are only slowly oxidised by concentrated nitric acid. They all melt above 200° and some above 300°.

2. Configuration and synthesis of the inositols

2.1. ***myo*Inositol.**—The structure of any inositol is easily established by its oxidation, with nitric acid, to a mixture of hydroxy-ketones which, in alkaline solution, isomerise and are oxidised to hexahydroxybenzene, tetrahydroxy-*p*-benzoquinone, and rhodizonic acid;[7] the last gives a characteristic red barium salt. Since every oxygen and carbon atom of the inositol is preserved, this transformation proves the *cyclo*hexanehexol structure; as a characteristic qualitative test for inositols, it is known as



the Scherer reaction.[8] Surprisingly, under the vigorous conditions of the oxidation, the *cyclo*hexane ring is not opened, whereas the quercitols (*cyclo*hexanepentols) are cleaved by nitric acid[9] at the methylene group under much milder conditions.

The configuration of *myo*inositol presented a more difficult problem because degradation by permanganate oxidation, designed to split the *cyclo*hexane ring, gave too many products owing to random fission. Little progress was made towards a solution, and indeed generally in the chemistry of inositols, until stereospecific reactions were developed for producing changes at one or two of the secondary hydroxyl groups only. Two such reactions were introduced in the thirties and both led, independently, to the configuration of *myo*inositol. Posternak[10] used enzymic dehydrogenation

[7] Gelormini and Artz, *J. Amer. Chem. Soc.*, 1930, **52**, 2483; Hoglan and Bartow, *ibid.*, 1940, **62**, 2397; Preisler and Berger, *ibid.*, 1942, **64**, 67.

[8] Scherer, *Annalen*, 1852, **81**, 375; Salkowski, *Z. physiol. Chem.*, 1910, **69**, 466 Fleury, Courtois, and Jouannet, *Bull. Soc. Chim. biol.*, 1951, **33**, 1889.

[9] Kiliani and Scheibler, *Ber.*, 1889, **22**, 517.

[10] Posternak, *Helv. Chim. Acta*, 1942, **25**, 746, and references there cited.

by *Acetobacter suboxydans* (5.1 ; this and similar designations refer to sections of this Review), first described by Kluyver,[11] to produce *scyllo*inosose (IX) ; this was oxidatively split at the keto-group to yield saccharic acids which were identified.

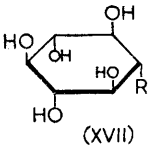
In 1942 Dangschat [12] described the preparation (5.2) of 1 : 2-*O*-*iso*propylidene*myo*inositol (XIV) ; acetylation of its free hydroxyl groups and removal of the *iso*propylidene group gave the tetra-acetate (XV) which was cleaved by lead tetra-acetate in one specific position. The production of (±)-idosaccharic acid (XVI) established the configuration of *myo*inositol as (II).

*myo*Inositol is produced commercially from maize steep liquors but it has also been synthesised by two methods, both of which are of considerable interest. In 1914, Wieland and Wishart [13] made the remarkable claim that hydrogenation of hexahydroxybenzene with a palladium catalyst gave the biologically important *myo*-isomer, alone amongst all the possible isomers, in high yield and purity. With the establishment of the configuration of *myo*inositol—many years later—the stereospecificity of the hydrogenation has become even more remarkable, and has still not been satisfactorily explained ; it has indeed often been doubted. A recent reinvestigation [14] has shown that the hydrogenation produces a complex mixture in which *myo*inositol, in a yield of about 20%, is indeed the predominant product ; several other inositols, as well as quercitols and *cyclo*hexane-tetrols and -triols have been isolated from the mixture by chromatography on cellulose powder, a method particularly useful in cyclitol chemistry.[15, 16] This method is suitable for the preparation of (uniformly) ^{14}C-labelled *myo*inositol.[17]

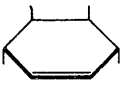
Many attempts have been made to cyclise hexose derivatives to inositols, thereby emulating Nature which, presumably, produces inositols in this way ; [18] but only one was successful. Grosheintz and Fischer [19] cyclised 6-deoxy-6-nitro-D-glucose (and its L-idose epimer) to a mixture of deoxynitroinositols from which the all-*trans*-isomer (XVII ; R = NO_2) was isolated. Presumably this isomer is readily formed because it is the most stable one, having all substituents in equatorial positions ; the stereochemistry of the other nitro-compounds, or the synthesis of isomeric ones by the use of different deoxynitrohexoses, has not been investigated. Reduction [19] of the nitro-group gave *scyllo*inosamine (aminodeoxy*scyllo*inositol) (XVII ; R = NH_2), which has been also prepared [20] from *scyllo*inosose (IX). The

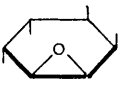
[11] Kluyver and Boezaardt, *Rec. Trav. chim.*, 1939, **58,** 956.
[12] Dangschat, *Naturwiss.*, 1942, **30,** 146.
[13] Wieland and Wishart, *Ber.*, 1914, **47,** 2082.
[14] Angyal and McHugh, *J.*, 1957, 3682.
[15] Anderson and Ballou, *J. Amer. Chem. Soc.*, 1953, **75,** 648.
[16] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[17] Weygand and Schulze, *Z. Naturforsch.*, 1956, **11**b, 370.
[18] Fischer, *Harvey Lectures*, 1945, **40,** 156.
[19] Grosheintz and Fischer, *J. Amer. Chem. Soc.*, 1948, **70,** 1479.
[20] Carter, Clark, Lytle, and McCasland, *J. Biol. Chem.*, 1948, **175,** 683 ; Anderson and Lardy, *J. Amer. Chem. Soc.*, 1950, **72,** 3141.

final step was carried out by Posternak [21] who obtained *myo*inositol by treatment with nitrous acid, in poor yield ; the yield is much improved if the penta-*O*-acetyl derivative of the inosamine is used.[22] In this case, as in all others [22, 23] known so far in cyclitol chemistry, the amino-group is replaced by a hydroxyl group mainly *with inversion* ; such behaviour is not in accordance with experience in other fields.[3]



(XVII)


(XVIII)



(XIX)

2.2. The Other Inositols.—Only two optically active inositols (IIIa and IIIb) can exist : both have long been known to occur in numerous plants as monomethyl ethers.[1] The most convenient source of quebrachitol, 2-*O*-methyl-(−)-inositol, is the latex of the rubber tree, *Hevea brasiliensis* ; [24] that of pinitol, 3-*O*-methyl-(+)-inositol, is the sugar pine, *Pinus lambertiana*.[25] [(+)-Pinitol has been found in nearly 300 plant species ; its enantiomer has recently been isolated from one plant.[26]] In each case the methyl group is readily removed by concentrated hydriodic acid. The configuration of (−)-inositol has been established [27] as (IIIb) by the isolation of D-glucosaccharic acid from its permanganate-oxidation products.

*scyllo*Inositol (scyllitol) (I) has been isolated from several plants and animals,[1] but it is more conveniently prepared [28] by reduction of *scyllo*inosose (IX) with sodium amalgam ; this reaction proves its configuration, since that of the inosose had already been established by Posternak.[10]

The other inositols have not been found in Nature and are prepared by synthesis from *myo*- or the optically active inositols. Oxidation of *myo*inositol by nitric acid, if interrupted at an early stage, gives *epi*inosose (X) in no more than 20% yield.[29] It is not known whether this dehydrogenation is stereospecific (which it may well be owing to the " 3-alkyl effect " [30]) or whether *epi*inosose is isolated because it is less soluble than its isomers. Its configuration was established by permanganate oxidation to DL-talomucic and DL-glucosaccharic acid ; hydrogenation gives *epi*inositol (V) whose configuration is thereby defined.[31]

[21] Posternak, *Helv. Chim. Acta*, 1950, **33**, 1597.

[22] L. Anderson, personal communication ; cf. Wintersteiner and Klingsberg, *J. Amer. Chem. Soc.*, 1951, **73**, 2917.

[23] Patrick, Williams, Waller, and Hutchings, *ibid.*, 1956, **78**, 2652 ; Mann and Woolf, *ibid.*, 1957, **79**, 120.

[24] van Alphen, *Ind. Eng. Chem.*, 1951, **43**, 141 ; for the structure of quebrachitol see Posternak, *Helv. Chim. Acta*, 1952, **35**, 50 and ref. 6.

[25] Anderson, *Ind. Eng. Chem.*, 1953, **45**, 593 ; for the structure of pinitol see Angyal, Macdonald, and Matheson, *J.*, 1953, 3321.

[26] Plouvier, *Compt. rend.*, 1956, **243**, 1913.

[27] Posternak, *Helv. Chim. Acta*, 1936, **19**, 1007.

[28] *Idem*, *ibid.*, 1941, **24**, 1045.

[29] *Idem*, *ibid.*, 1936, **19**, 1333.

[30] Klyne, *Experientia*, 1956, **12**, 119.

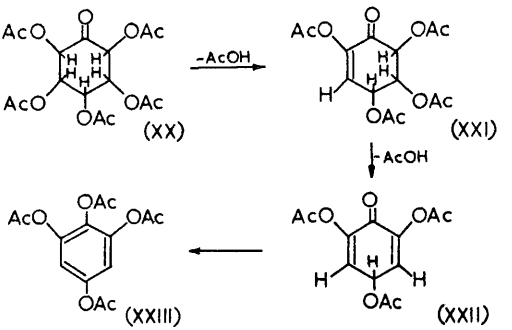
[31] Posternak, *Helv. Chim. Acta*, 1946, **29**, 1991.

allo- and *muco*-Inositol were first prepared by hydroxylation of conduritol (XVIII), a naturally occurring *cyclo*hexenetetrol,[32] the configuration of which was established by its oxidation to mucic acid. The two inositols were distinguished by oxidation of suitable derivatives to *allo*mucic and mucic acid, respectively. More recent preparations, from the naturally occurring inositols, are illustrated by the sequences (II → XII → VII) and (III → XIII → VIII).

*neo*Inositol (IV) has been made [33] by epoxide opening (5.7) of 1 : 2-anhydro*allo*inositol (XIX), a reaction which proves its configuration. *cis*Inositol (VI) was isolated,[14] in 4% yield, from the cyclitol mixture produced by hydrogenation of hexahydroxybenzene (2.1) with palladium ; the yield could be increased to about 20%, and *cis*inositol made the major product, by the use of a palladium–carbon catalyst. *cis*Inositol was the last of the possible isomers to be isolated ; hence its configuration can be deduced but has not been proved ; however, its chemical behaviour, particularly its reaction with boric acid (5.5) and periodic acid (5.4), is in accordance with the all-*cis*-configuration.

3. Compounds related to inositols

3.1. The Inososes.—The inososes have not been found in Nature but they are important intermediates in the synthesis of inositols. They are formed in the dehydrogenation—catalytic or enzymic (5.1)—of inositols. Chemically, they resemble the sugars much more closely than the inositols, since they form phenylhydrazones and osazones, and reduce Fehling's solution and sodium hypoiodite in the cold. In the presence of bases, the inososes, and particularly their esters, aromatise very easily ; thus on treatment with sodium acetate and acetic anhydride, 1 : 2 : 3 : 5-tetra-acetoxybenzene (XXIII) is formed.[29] Isbell [34] proposed the mechanism (XX) → (XXIII) in which each step is thought to be preceded by enolisation :



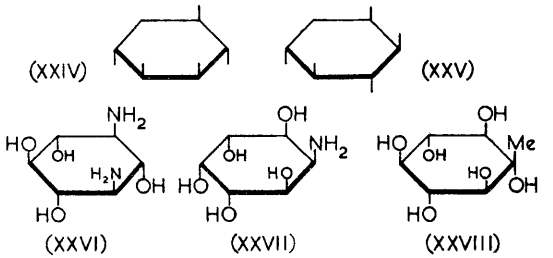
When a penta-ester of an inosose is heated to 150° in contact with soda-

[32] Dangschat and Fischer, *Naturwiss.*, 1939, **27**, 756.
[33] Angyal and Matheson, *J. Amer. Chem. Soc.*, 1955, **77**, 4343.
[34] Isbell, *Ann. Rev. Biochem.*, 1943, **12**, 213.

glass (but not with Pyrex glass), it loses one mol. of acid and is transformed [35] into an unsaturated ketone, presumably (XXI). Before this behaviour was discovered [36] the esters were believed to be dimorphous.

On reduction with sodium amalgam [29] the inososes give mixtures of epimeric inositols, the keto-group being reduced mainly to an equatorial hydroxyl group. Catalytic hydrogenation, on the other hand, gives mainly the axial epimer.[29] Sodium borohydride yields both epimers when the keto-group is unhindered but only the axial one when hindered by an axial hydroxyl group.[37]

3.2. The Quercitols.—Theory predicts the existence of ten diastereomeric quercitols of which four are symmetrical and the others represent six pairs of enantiomorphs. Only about half of these are known, but with our present knowledge it would be possible to prepare most of the unknown ones if required. Two have been found [1] in Nature : (+)-*proto*quercitol (XXIV), originally known as *d*-quercitol, which was discovered in acorns in 1849, and (−)-*vibo*quercitol (XXV), originally described as *l*-quercitol. The others were synthesised by the catalytic hydrogenolysis of the corresponding inososes in dilute sulphuric acid solution, an interesting method introduced by Posternak [28] for the complete reduction of the keto-group.



(XXVI) (XXVII) (XXVIII)

3.3. The Inosamines.—The discovery of streptamine,[38] 1 : 3-diamino-1 : 3-dideoxy*scyllo*inositol (XXVI), as a degradation product of streptomycin, has directed attention to the amino-derivatives of the inositols. Inosamines (aminodeoxyinositols) can be synthesised by hydrogenation of the oximes or phenylhydrazones of inososes,[20] by opening the epoxide ring of anhydroinositols with ammonia,[39] and by reaction of bromodeoxyinositols with ammonia.[40] Recently, 2-amino-2-deoxy*neo*inositol (XXVII) has been obtained as a fragment of the molecules of two new antibiotics.[23]

Amongst other compounds related to inositols mention may be made

[35] Mrs. E. Smith, Ph.D. Thesis, Sydney, 1956.

[36] Fleury, Lecocq, and Posternak, *Bull. Soc. chim. France*, 1954, 1107.

[37] Reymond, *Helv. Chim. Acta*, 1957, **40**, 492.

[38] Lemieux and Wolfrom, *Adv. Carbohydrate Chem.*, 1948, **3**, 337 ; for synthesis by ring-closure of a nitro-sugar (2.1) see Wolfrom, Olin, and Polglase, *J. Amer. Chem. Soc.*, 1950, **72**, 1724, and by catalytic dehydrogenation (5.1) see Heyns and Paulsen, *Chem. Ber.*, 1956, **89**, 1152.

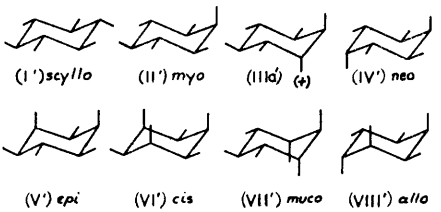
[39] Anderson, Abs. Papers, 129th Meeting, Amer. Chem. Soc., 1956, p. 27D ; Allen, *J. Amer. Chem. Soc.*, 1957, **79**, 1167.

[40] Wolfrom, Radell, Husband, and McCasland, *ibid.*, p. 160.

of the *C*-methylinositols of which two have been found in Nature : mytilitol,[41] which is *C*-methyl*scyllo*inositol (XXVIII), and laminitol,[42] of a configuration yet unknown.

4. The conformation of the inositols

It has generally been assumed that the inositols, in accordance with the tenets of conformational analysis,[3] exist predominantly in that chair conformation which has the smaller number of axial hydroxyl groups. These conformations—shown in formulæ (I′)—(VIII′)—have not been directly proved (as has been done for the pyranose sugars by Reeves [43]), but analogy with other polysubstituted *cyclo*hexanes and with the sugars leaves little doubt about them. The reactions discussed below are all in accordance with this assumption.* It is to be noted that the two possible chair forms are identical in the case of *cis*- and *muco*-inositol, each with three axial hydroxyl groups. And in the case of *allo*inositol the two chair forms are mirror-images of each other : *allo*inositol is therefore an inseparable racemic mixture of rotational isomers. Every hydroxyl group in *cis*-, *muco*-, and *allo*-inositol has an equal chance of being axial.



*scyllo*Inositol (I) is the most stable isomer. The equilbrium constants of complex formation with boric acid (5.5) allow the approximate calculation [45] of the free-energy difference between the isomers ; thus *myo*inositol (one axial OH) is estimated to be less stable by 0·9 kcal./mole, *epi*inositol (two on the same side) by 2·8 kcal./mole and *cis*inositol (three axial groups on the same side) by 5·7 kcal./mole than *scyllo*inositol. Unfortunately no method is known whereby inositols can be equilibrated amongst themselves and therefore these figures have not been experimentally verified ; nor have the heats of combustion of the isomers been determined. At an elevated temperature hydrogen halides in acetic acid partially convert

[41] Posternak, *Helv. Chim. Acta*, 1944, **27**, 457.
[42] Lindberg and McPherson, *Acta Chem. Scand.*, 1954, **8**, 1875 ; 1955, **9**, 1097.
[43] Reeves, *Adv. Carbohydrate Chem.*, 1951, **6**, 107.
[44] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492 ; 1954, **76**, 4323.
[45] Angyal and McHugh, *Chem. and Ind.*, 1956, 1147.

* These conclusions are not incompatible with Kuhn's observation [44] that in dilute solution in a non-polar solvent *cis-cyclo*hexane-1 : 3-diol shows evidence (infrared spectrum) of internal hydrogen bonding, so that the diaxial conformation is present. The energy of the hydrogen bond is sufficient to compensate for the diaxial interaction. In hydroxylic solvents (the only ones in which inositols are soluble) intermolecular hydrogen bonding occurs and *cis-cyclo*hexane-1 : 3-diol would be expected to exist in the diequatorial conformation.

myo-, *scyllo*-, or (−)-inositol into (±)-inositol ; [46] but it is not known if this reaction is an equilibration (mono- and di-halogenated deoxyinositols are also formed in these reactions [47]).

An interesting correlation has been noted [48] between the natural occurrence of the cyclitols and their conformational stability. Inositols which have a high interaction energy owing to two axial hydroxyl groups on the same side (*epi*, *allo*, *muco*, *cis*) have not been found in Nature whereas all the other configurations occur in Nature either as inositols (*myo*, *scyllo*, active) or inosamine (*neo*). The two naturally occurring quercitols are also free from 1a : 3a-interactions.

An inositol methyl ether will be conformationally more stable if the methoxyl group is equatorial rather than axial. The axial 2-methyl ether of *myo*inositol has not been found in Nature but all the equatorial isomers occur,[16] at least in one enantiomorphous form : the inactive 5-methyl ether, sequoyitol ; the dextrorotatory 4-methyl isomer, ononitol ; and the 1-methyl ether, bornesitol, of which both enantiomers were found in plants. Similarly, the axial 1-methyl ether of the optically active inositols has not been found in Nature but quebrachitol and pinitol represent the 2- and the 3-isomer, respectively.* The two methoxyl groups in dambonitol, 1 : 3-di-*O*-methyl*myo*inositol, are also equatorial.[16] One is tempted to suggest that the final stage in the biosynthesis of inositols and their methyl ethers may be thermodynamically controlled.

5. Reactions of configurational or conformational interest

5.1. Dehydrogenation.—Much study has been devoted to the dehydrogenating action of *Acetobacter suboxydans* (the organism used for the production of L-sorbose from sorbitol) on cyclitols. The reaction is highly stereospecific : cyclitols are dehydrogenated to ketones according to the rule, first announced by Magasanik and Chargaff [49] and established by many examples, that only axial hydroxyl groups are dehydrogenated. No exception is known to this rule : it is valid also for *cyclo*hexanetetrols, but not for all the triols,[50] but it is possible that another enzyme is responsible for these dehydrogenations.[51] Thus, *scyllo*inositol and *scyllo*quercitol, devoid of axial hydroxyl groups, are unattacked ; *myo*inositol and *vibo*-quercitol are converted into monoketones ; the active inositols [49] and *neo*inositol,[52] each with two axial hydroxyl groups, give 1 : 2- and 1 : 4-

[46] Posternak, *Helv. Chim. Acta*, 1948, **31**, 2242 ; Fletcher, *J. Amer. Chem. Soc.*, 1948, **70**, 4050 ; Contardi and Ciocca, *Gazzetta*, 1949, **79**, 694.

[47] McCasland and Horswill, *J. Amer. Chem. Soc.*, 1953, **75**, 4020 ; 1954, **76**, 2373.

[48] Angyal and Mills, *Rev. Pure Appl. Chem.* (*Australia*), 1952, **2**, 185.

[49] Magasanik and Chargaff, *J. Biol. Chem.*, 1948, **174**, 173.

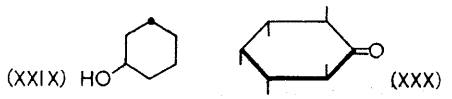
[50] Posternak and Ravenna, *Helv. Chim. Acta*, 1947, **30**, 441 ; Posternak and Friedli, *ibid.*, 1953, **36**, 251 ; Posternak and Reymond, *ibid.*, 1953, **36**, 260 ; 1955, **38**, 195.

[51] Anderson, Tomita, Kussi, and Kirkwood, *J. Biol. Chem.*, 1953, **204**, 769.

[52] Anderson, Angyal, McHugh, and Takeda, unpublished work.

* One may note that the active inositols, though dissymmetrical, have a two-fold axis of symmetry ; positions 1 and 6, 2 and 5, 3 and 4 are therefore equivalent, and only three different monosubstitution products are possible.

diketones, respectively. *epi*Inositol, with its two axial hydroxyl groups in 1 : 3-position, however, gives only a monoketone.[49] This instance, and some other cases, led to postulation of a second rule,[53] namely, that an equatorial hydroxyl group is required in the "*meta*"-position to the carbon atom carrying the axial hydroxyl group, in counterclockwise direction when viewed from the axial hydroxyl group (XXIX). However, *cis*inositol and *cis*quercitol, which do not conform to this rule, are dehydrogenated, albeit only slowly.[52] The group in "*para*"-position to the axial hydroxyl group also has some effect, the reaction rate decreasing as the group



is varied according to the sequence : e-OH > = O > H > a-OH > e-OMe. A methoxyl group in nearly every position inhibits the dehydrogenation, (+)-bornesitol and (−)-pinitol being the only known exceptions.[52]

Similar stereospecificity is shown in the platinum-catalysed dehydrogenation of inositols in aqueous solution, a reaction introduced by Heyns and Paulsen.[54] Inososes are produced, albeit in a yield somewhat lower than in the bacterial reaction, and again only axial hydroxyl groups are affected ;[55] *scyllo*inositol remains unchanged, *myo*inositol gives *scyllo*-inosose, etc. In two respects, however, this method differs from *Acetobacter* dehydrogenations : the reaction usually stops at the monoketone stage, enabling the preparation,[56] for example, of *neo*inosose (XXX), not obtainable by the use of *Acetobacter* ; and methyl ethers are also dehydrogenated [55, 57] if they have a free axial hydroxyl group.

The stereospecificity of these two reactions is probably due to the direction of adsorption on the (catalyst or enzyme) surface. It is worth noting that the catalytic dehydrogenation is reversible : whereas only axial hydroxyl groups are converted into keto-groups, the latter are hydrogenated, over the same catalyst, to axial hydroxyl groups.

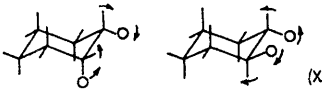
5.2. *iso*Propylidene Derivatives. — Cyclitols which possess adjacent hydroxyl groups in *cis*-relation react with acetone in the presence of acidic catalysts to form *iso*propylidene derivatives.[6] This is in accordance with general experience in carbohydrate chemistry and with the case of the *cyclo*hexane-1 : 2-diols of which only the *cis*-isomer reacts with acetone.* Accordingly, *scyllo*inositol and *scyllo*quercitol remain unchanged, *myo*inositol, *vibo*- and *proto*-quercitol, sequoyitol,[57] and quebrachitol give mono*iso*propylidene compounds, and the optically active inositols and

[53] Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2618.
[54] Heyns and Paulsen, *Chem. Ber.*, 1953, **86**, 833 ; 1956, **89**, 1152.
[55] Angyal and Pitman, unpublished work.
[56] Allen, *J. Amer. Chem. Soc.*, 1956, **78**, 5691.
[57] Anderson, Deluca, Bieder, and Post, *ibid.*, 1957, **79**, 1171.
[58] Fenton, Salcedo, and Franz, Abs. Papers, 130th Meeting, Amer. Chem. Soc., 1956, p. 7-o.

* Both isomers give *iso*propylidene derivatives on reaction with acetone diethyl acetal.[58] This reaction has not yet been applied to cyclitols.

*epi*inositol form di*iso*propylidene derivatives.[6] The reaction with the other inositols has not yet been described.

In an ideal chair form, the distance between 1 : 2-*cis*-substituents is the same as between *trans*-substituents when these are equatorial. One might therefore expect cyclisations involving these substituents to take place with equal ease. However, attachment of a five-membered ring involves some distortion of the *cyclo*hexane molecule in order to bring the 1 : 2-substituents into a more nearly coplanar position.[59] In case of *cis*(e,a)-groups, the distortion flattens the ring somewhat and moves the axial groups further apart (XXXI) : little resistance is offered to such distortion. On the other hand, when *trans*(e,e)-groups are forced nearer to each other (XXXII), the axial groups are compressed and the ring is more strongly puckered, and therefore more energy is required. This explanation is supported by the interesting observation that (+)- or (−)- and *epi*-inositol form tri*iso*propylidene derivatives, as well as the di*iso*propylidene compounds ; [6] a *trans*-pair of hydroxyl groups has also reacted. The formation of each *cis-iso*propylidene ring has moved two axial groups away from their axial neighbours and thus the way has been opened for the remaining axial groups to undergo the distortion indicated in (XXXII).



(XXXI) (XXXII)

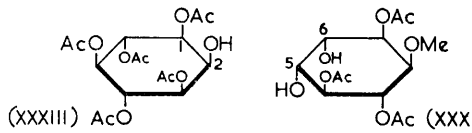
*myo*Inositol is more resistant than the other cyclitols to the action of acetone, and conditions for a reproducible reaction have only recently been worked out.[16] The difficulty is probably due to the resistance of the axial hydroxyl group to the movement indicated in (XXXI) since it is forced to approach *two* neighbouring equatorial hydroxyl groups.

*iso*Propylidene derivatives, being partially substituted, are useful intermediates. Thus, toluenesulphonylation [33] of the 1 : 2-5 : 6-di-*O-iso*propylidene derivative of (−)-inositol—in which the two free hydroxyl groups are equivalent—gives the monotoluenesulphonyl derivative (XIII), the intermediate in the synthesis of *neo*- and *allo*-inositol. Acetylation of 1 : 2-*O-iso*propylidene*myo*inositol (XIV), followed by removal of acetone by mild acid hydrolysis, gives a tetra-acetate (XV) from which the 1-*O*-monotoluenesulphonyl compound (XII), the intermediate in the synthesis of *muco*inositol, is prepared.

5.3. Steric Hindrance.—The presence of six oxygen atoms attached to a *cyclo*hexane ring results in congestion which is particularly accentuated if some of the hydroxyl groups are acetylated. Under these conditions the usual reluctance of axial hydroxyl groups to take part in reactions involving replacement of the hydrogen atom becomes very marked. Thus, it was found impossible to methylate the free axial hydroxyl group of 1 : 3 : 4 : 5 : 6-penta-*O*-acetyl*myo*inositol (XXXIII) ; under vigorous conditions acetyl migration occurred and the equatorial 1-hydroxyl group thus uncovered

[59] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929.

was methylated.[60] Only the equatorial 5-hydroxyl group, but not the 6-axial group, could be toluenesulphonylated[55] in 1 : 3 : 4-tri-*O*-acetylquebrachitol (XXXIV).



5.4. Oxidation with Periodate.—Oxidation of inositols with periodate is anomalous ; more than the expected 6 mol. of reagent are consumed and less than 6 mol. of formic acid are formed. Over a mol. of carbon dioxide is also produced and glyoxylic acid has been identified as an intermediate.[61,62]

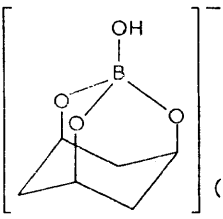
The initial reaction presumably consists in the splitting of a 1 : 2-glycol group to give a dialdehyde. The rate of the initial reaction depends on the relative positions of the hydroxyl groups,[63] and considerations similar to those concerning the formation of *iso*propylidene derivatives will apply. A *cis*-diol is split faster than a *trans*-diol ; the reaction of *scyllo*inositol (relative rate, *R*, 1) is slower than that of any other isomer ; *myo*inositol, which has three contiguous *cis*-hydroxyl groups, is oxidised more slowly (*R*, 2·2) than cyclitols with only two adjacent *cis*-hydroxyl groups, such as *vibo*quercitol (*R*, 3·8) and *proto*quercitol (*R*, 5·3), owing to the unfavourable effect of an axial group flanked by two equatorial ones (p. 222). The reaction rates of *allo*- (*R*, 120), *epi*- (*R*, *ca.* 200), and *cis*-inositol (*R*, *ca.* 200), which all have two axial hydroxyl groups on the same side, are particularly high ;[63] this may be due either to release of compression energy in the transition state of the reaction, or to mutual repulsion of the axial hydroxyl groups which brings them nearer to their neighbours than they would otherwise be.

Once past the initial fission, the reaction with periodate becomes complex. The dialdehyde probably forms cyclic tautomers (cf. the reaction of glucose[64]), and their further cleavage, coupled with hydroxylation (" over-oxidation "[65]), may account for the observed results. The reaction has been discussed by Fleury *et al.*[61] and by Schwarz.[62]

5.5. Borate Complexes.—Another reaction of glycols which depends on the steric arrangement of the hydroxyl groups is the formation of complexes with boric acid. The behaviour of the cyclitols on ionophoresis in borate buffers has been studied[63,66] and has led to the discovery of a new type of complex. In many cases the ionophoretic mobility showed no direct relation to the number of *cis*-1 : 2-diol groups ; however, the 1 : 3 : 5-*cis*-triol arrangement usually caused high mobility, and it was postulated[63]

[60] Anderson and Landel, *J. Amer. Chem. Soc.*, 1954, **76**, 6130.
[61] Fleury, Poirot, and Fiévet, *Compt. rend.*, 1945, **220**, 664 ; *Ann. Pharm. franç.*, 1947, **5**, 209 ; Fleury and Dizet, *Bull. Soc. Chim. biol.*, 1955, **37**, 1099.
[62] Schwarz, *Chem. and Ind.*, 1955, 1388.
[63] Angyal and McHugh, *J.*, 1957, 1423.
[64] Schöpf and Wild, *Chem. Ber.*, 1954, **87**, 1571.
[65] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621.
[66] Foster and Stacey, *Chem. and Ind.*, 1953, 279 ; Foster, *ibid.*, p. 591.

that "tridentate" complexes of type (XXXV) were formed. Thus, the mobility of *myo*inositol (II) was not substantially changed by methylation in the 2- and the 4-position, though the former left no free *cis*-1 : 2-diol group; but it was much reduced by methylation at position 1 or 5, though adjacent *cis*-hydroxyl groups were left intact.



(XXXV)

More information on complex formation was obtained by studying the pH changes caused by addition of cyclitols to a borax solution (the complexes being strong acids). It was found that, when a *cis*-1 : 3 : 5-triol grouping was present, the complex was formed from the cyclitol and boric acid in a 1 : 1 ratio, and the equilibrium constant, $K = [\text{Complex}^-]/[\text{Cyclitol}][\text{Borate}^-]$, could be determined. *cis*Inositol, with three axial 1 : 3 : 5-hydroxyl groups in either chair conformation, has a remarkably high equilibrium constant; the other cyclitols have to change into the less stable of the chair forms to achieve the requisite arrangement of three axial hydroxyl groups; their equilibrium constants are smaller and fall into the order predicted by conformational analysis.[63] From the equilibrium constants values of the various steric interactions in cyclitols have been calculated.[45]

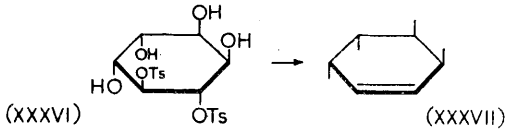
Tridentate borate complexes are also formed by appropriate acyclic polyhydroxy-compounds, *e.g.*, by pentaerythritol, and probably by some sugar derivatives.

5.6. Reactions of Toluenesulphonyl Derivatives.—Solvolysis of toluene-*p*-sulphonyl esters in the absence of bases, a common reaction of simpler compounds, has never been observed with carbohydrates. Some *O*-monotoluene-*p*-sulphonylinositols, however, are solvolysed smoothly in boiling 95% acetic acid.[67] Thus, 3-*O*-toluene-*p*-sulphonyl-(−)-inositol [formed from (XIII) by removal of the two *iso*propylidene groups] gives *allo*inositol (VIII) in good yield, the reaction occurring with complete inversion. In other cases, *e.g.*, 1- or 6-*O*-toluene-*p*-sulphonyl*epi*inositol, inversion is accompanied by considerable retention. Some toluenesulphonyl compounds, like (XII), react very slowly under the same conditions. Insufficient examples are yet known to allow conclusions about the stereochemistry of the reaction.

It is well established in carbohydrate chemistry that two adjacent toluenesulphonyloxy-groups are removed by iodide ion, with the formation of a double bond, but only if one of the groups is primary.[68] However, two

[67] Angyal, Gilham, and Pitman, unpublished work.
[68] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 108.

secondary groups have been eliminated from inositols,[69] *e.g.*, the 3 : 4-di-*O*-toluene-*p*-sulphonyl derivative (XXXVI) of (—)-inositol yields the *cyclo*hexenetetrol (XXXVII). By following a suggestion by Tipson,[68] it was

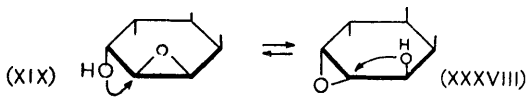


(XXXVI) (XXXVII)

found that *p*-nitrobenzenesulphonyl groups react faster and give a better yield. In the examples so far studied the two sulphonyl groups are in *trans*-relation, but this is not believed to be an essential requirement for the reaction.

5.7. Anhydroinositols.—Inositols cannot be dehydrated directly but 1 : 2-anhydroinositols are readily prepared by the action of bases on toluenesulphonyl derivatives in which an adjacent hydroxyl group is free and *trans*-situated.[70] Thus the 1 : 2-5 : 6-di-*O*-*iso*propylidene-3-*O*-toluene-*p*-sulphonyl derivative (XIII) of (—)-inositol gives, after the subsequent removal of the *iso*propylidene groups, 1 : 2-anhydro*allo*inositol (XIX). These epoxides are useful intermediates because they yield inositols by acid- or base-catalysed hydration, inositol methyl ethers with sodium methoxide, inosamines with ammonia,[39] etc. Hydration of 1 : 2-anhydro-*allo*inositol (XIX) provides the synthesis [33] of *neo*inositol (IV).

The anhydroinositols have provided an opportunity for study [70] of the " epoxide migration ", *i.e.*, opening of an epoxide ring by rear attack of an adjacent *trans*-situated hydroxyl group, with formation of another epoxide ring. This rearrangement has often been postulated in carbohydrate chemistry [71] but no clear-cut example has previously been described. All the anhydroinositols in which there is an adjacent *trans*-hydroxyl group undergo epoxide migration in alkaline solution at room temperature. 1 : 2-Anhydro*allo*inositol (XIX) gives 1 : 2-anhydro*neo*inositol (XXXVIII) ; the reaction is reversible. The position of the equilibrium is in accordance with conformational considerations, the isomer with fewer axial hydroxyl groups (for the half-chair conformation of *cyclo*hexene oxide [72]) being the more stable. The anhydride (XIX) has two axial (or quasi-axial) hydroxyl groups but (XXXVIII) only one ; in the equilibrium mixture they were found in a ratio of 1 : 9.

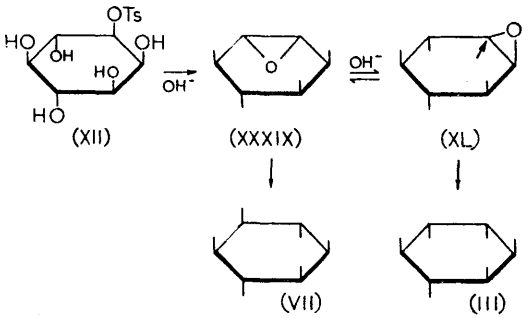


(XIX) (XXXVIII)

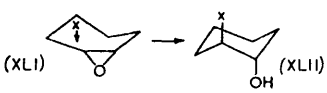
Because of epoxide migration, the reaction of sulphonyl compounds with strong bases often yields a rearranged, instead of the expected, anhydride. For example 1-*O*-toluene-*p*-sulphonyl*myo*inositol (XII) gives

[69] Angyal and Gilham, *J.*, 1957, in the press.
[70] Angyal and Gilham, *J.*, 1957, 3691.
[71] For a discussion see Newth, *J.*, 1956, 441.
[72] Cf. ref. 3.

1 : 2-anhydro*myo*inositol (XL) *via* the less stable (±)-1 : 2-anhydroinositol (XXXIX) in the cold, and (±)-inositol (III) in hot alkali.[73] (All the compounds in this sequence are racemic, the formulæ showing only one enantiomer.) Epoxide migration can be minimised by the use of weaker bases; thus *muco*inositol (VII) can be prepared from the sulphonyl compound (XII) by heating it with a strong-base ion-exchange resin (Deacidite FF) in the carbonate form.



The direction of ring-opening of epoxides in the carbohydrate field is not clearly understood, despite considerable discussion;[74, 75] inductive effects, particularly that of the ring-oxygen atom, complicate the picture. With the anhydroinositols only conformational effects need to be considered and the prevalent direction of ring-opening can be predicted.[75] Electrophilic or nucleophilic opening occurs in such a way as to place the new groups—at least initially—into axial positions according to the Fürst–Plattner rule[76] (XLI → XLII); subsequently the molecule may invert into the other chair form. Each half-chair form of the epoxide can undergo diaxial opening; the proportion of the products will depend on the proportion of, and that, in turn, on the relative energies of, the two half-chair forms. In 1 : 2-anhydro*allo*inositol (XIX) both half-chair forms have two axial (or quasi-axial) hydroxyl groups and are therefore of similar



stability: the two possible products, *neo*- and (−)-inositol, are formed in approximately equal amounts. In the other anhydroinositols mentioned here, one half-chair form has fewer axial hydroxyl groups than the other and the inositol derived from this form (by diaxial opening) predominates. 1 : 2-Anhydro*neo*inositol (XXXVIII) gives mainly *allo*inositol; the main products of the hydration of the other anhydrides have already been indicated.

[73] Angyal and Curtin, unpublished work.
[74] Cookson, *Chem. and Ind.*, 1954, 223, 1512; Overend, *ibid.*, 1955, 995.
[75] Angyal, *ibid.*, 1954, 1230.
[76] Fürst and Plattner, Abs. Papers 12th Internat. Congr. Pure Appl. Chem., New York, 1951, p. 405; see also Barton, *J.*, 1953, 1027.