[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH AND THE UNIVERSITY OF WISCONSIN]

THE NOMENCLATURE OF THE CYCLOHEXITOLS AND THEIR DERIVATIVES

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In view of the present rapid progress in the elucidation of the chemistry of the cyclohexitols and their derivatives, there is need of a system of nomenclature for this unusual class of substances which will afford names unequivocally denoting specific structures and configurations. The present paper will describe some of the existing methods of naming the cyclohexitols and will show how these may be embodied in a rigorous system of nomenclature.

In 1900 Maquenne (1) applied to the cyclohexitols a system of nomenclature which Lespieau (2) had shortly before devised for naming the sugars. In this Lespieau-Maquenne system the configuration of the cyclitol was indicated by a "fraction"; the number denoting a particular carbon atom was placed in the "numerator" or "denominator" according to whether the hydroxyl group it bore lay above or below the plane of the ring.[2] Thus Maquenne stated, on purely stereochemical grounds, that *levo*-rotatory inositol is either $\frac{1.2.4}{3.5.6}$-cyclohexanehexol or $\frac{1.2.5}{3.4.6}$-cyclohexanehexol, there being, of course, only two optically active hexahydroxycyclohexanes possible. If it be assumed that the numbering is in a clockwise direction around the ring, these Lespieau-Maquenne names lead to unequivocal structures and configurations without further conventions. The reverse process, proceeding from a given structure to a name, is more difficult since additional conventions specifying the number and orientation of the cyclitol must be made. Here, then, is the stumbling block in the Lespieau-Maquenne system.

Two solutions to the problem present themselves. The first solution is the adoption of an arbitrary standard system of orientation and numbering for each of the inositols. Thus, one might always refer to the table of numbered structures published by Maquenne or to a similar standard in naming an inositol derivative. The second solution of the problem involves a search for rules which will lead to an unequivocal numbering for each of the nine isomeric inositols. While partial success in this latter direction has been achieved by Magasanik and Chargaff (3), attempts by the present authors to arrive at a solution embracing all the inositols and their derivatives and analogs have resulted in rules of unwieldly complexity. As a matter of practical convenience, then, a compromise solution is offered—

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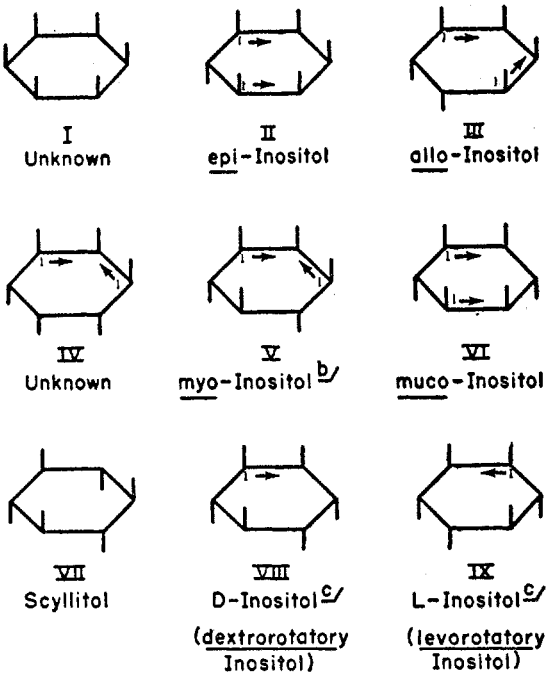
[2] For this discussion the cyclohexitols and their derivatives will be considered as having planar structures.

namely Table I, showing, in convenient form,[3] a *modified* Maquenne numbering for the nine inositol isomers; and three simple rules which constitute a system for the unequivocal application of the numbering presented in the table to derivatives and analogs of the inositols. The writers believe that the table and system together provide adequately for the nomenclature of the new types of cyclitol derivatives which may be discovered in the future. The origin of the numbering shown in Table I will now be discussed.

TABLE I[a]

THE NUMBERING OF THE HEXAHYDROXYCYCLOHEXANES

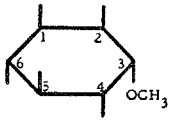


[a] Following common practice in this field, hydroxyl groups will be represented in formulas by "vertical" lines. [b] For the introduction of the prefix *myo* in place of *meso* for this compound, see comment under Rule 1. [c] The configurational designations will be discussed under Rule 2.

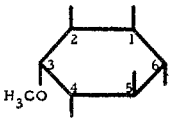
The original numbering system of Maquenne (1) has two marked disadvantages. The first of these lies in the assignment of different numbers to equivalent positions of the two optically active inositols—a decided departure from established practice. This difficulty was remedied by Fleury and Balatre (4) through

[3] That printed illustrations of numbering are in general more useful than rules is attested by the indispensable nature of *The Ring Index* by A. M. Patterson and L. T. Capell (Reinhold Pub. Corp., New York, 1940).

the renumbering of *dextro*rotatory inositol. For reasons which will appear later, in connection with the relationship of the optically active inositols with D- and L-glyceraldehyde, it is more convenient to renumber *levo*rotatory inositol. With this change, enantiomorphic derivatives of *dextro*- and *levo*-inositol are still designated by the same numbers. For example, 3-methyl-D-inositol (X) would be the enantiomorph of 3-methyl-L-inositol (XI)[4, 5] (5).

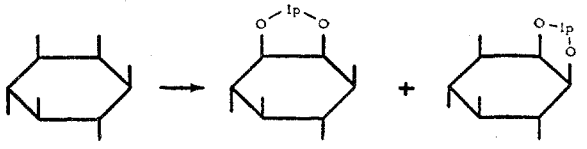


X
3-Methyl-D-inositol



XI
3-Methyl-L-inositol

The second marked disadvantage of Maquenne's system and, indeed, of all *single* systems of numbering the inositols, is that it is unsatisfactory for naming those symmetrical inositols which have become optically active through asymmetric substitution.[6] Thus, "acetonation" of the common inositol (m.p. 225°) gives an isopropylideneinositol which is a racemic mixture consisting of the two enantiomorphous structures portrayed below (XII, XIII) (6). Careful consider-



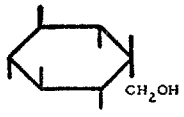
V
myo-Inositol

XII
D-1,2-Isopropylidene-*myo*-inositol

XIII
L-1,2-Isopropylidene-*myo*-inositol
(Ip = isopropylidene)

[4] These and some succeeding structures are cited only as examples and do not necessarily represent known substances. Pinitol and quebrachitol, naturally occurring monomethyl ethers of *dextro*rotatory and *levo*rotatory inositol, respectively, are evidently not enantiomorphs and therefore do not have their methyl groups in corresponding positions. See H. G. Fletcher, Jr., *Advances in Carbohydrate Chem.*, **3**, 45 (1948).

[5] As in the nomenclature of the carbohydrates (*cf.* Reference 5, Rule 7) substitution in the inositol series is normally considered to involve replacement of a hydrogen atom attached to an oxygen. Substitution of hydrogen attached to a carbon atom may be designated, as with the carbohydrates, with a prefixed, italic capital C (Reference 5, Rule 8). Thus hydroxymytilitol [Posternak, *Helv. Chim. Acta*, **27**, 457 (1944)] is *C*-hydroxymethylscyllitol.



[6] A similar situation frequently arises in the sugar series. Thus allitol HOH_2C—H H H H
C—C—C—C—CH_2OH, a *meso* substance, gives two enantiomorphous 1-methyl derivatives,
OH OH OH OH

ation of these structures renders it apparent that no single direction of numbering will lead to the same names for the two isomers. It becomes evident, therefore, that in such cases one isomer must be numbered in a direction opposite to that employed for the other if they are to have the same name. In each of the formulas II–VI (Table I), therefore, two stereochemically equivalent carbons have been chosen as carbon 1 and an arrow beside each carbon 1 indicates the direction of numbering which must be followed when that carbon is considered as 1, the choice made between the two carbons being decided, in individual cases, according to which leads to the lower numbers for substituents.[7] The two cyclic acetals mentioned above are, therefore, 1,2-isopropylidene-*myo*-inositols. Scyllitol (VII) and the as yet unknown all-*cis* isomer (I) require no numbering system since all the positions in each of them are configurationally identical. Derivatives of these would be named to give the lowest possible number to substituents other than hydroxyl.[7]

With such an elective numbering system, any of a variety of types of names may be coined for the inositols and their derivatives. However, as in the sugar and other natural-product series, completely systematic names are more complex and of less practical value than those semi-systematic ones using the trivial name of the parent substance as a base. Three rules, leading to unequivocal names of the latter type and based upon the numbering system already discussed, will now be offered.

Rule 1. *In accordance with established practice in the carbohydrate field, the trivial names of the parent inositols will be used.*

It is proposed that one of the currently used trivial names be changed to a more suitable one. The common inositol of m. p. 225° has long been known by the name *meso*-inositol, a name which, as many authors have pointed out, is singularly inappropriate, inasmuch as six of its stereoisomers are also *meso* forms. Particularly confusing is the use of *meso* in names denoting optically active derivatives of this inositol, such as the *levo*rotatory *epi-meso*-inosose to be discussed later. It is suggested that, since the substance was first discovered in muscle (7) and was at one time called "muscle sugar," it is better called *myo*-inositol (Greek, μῦς, μυός, muscle) and this name will be used in the present paper.

It is to be expected that the two, as yet undiscovered inositols, corresponding to formulas I and IV, will eventually receive trivial names.

Rule 2. *The structures of the optically active cyclitols and of all optically active derivatives of the other cyclitols are designated as belonging to the* D *or* L *series, based upon the configuration of the highest numbered carbon atom.*

Some method is obviously needed to distinguish the name of a compound from that of its enantiomorph. When the rotation of one enantiomorph of a given pair

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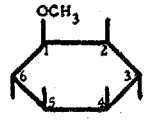
$H_3COH_2C-\underset{OH}{C}-\underset{OH}{C}-\underset{OH}{C}-\underset{OH}{C}-CH_2OH$ and $HOH_2C-\underset{OH}{C}-\underset{OH}{C}-\underset{OH}{C}-\underset{OH}{C}-CH_2OCH_3$. For such acyclic compounds Rosanoff's convention [*J. Am. Chem. Soc.*, **28**, 114 (1906)] affords a rigorous system of nomenclature.

[7] In numbering derivatives containing more than one type of substituent it is suggested that numbering preference be in the following order: C-substitutions, ketone, imine, amine, ester, ether, thio, desoxy.

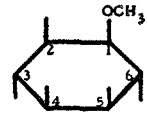
has been determined experimentally, the simple prefix *dextro* or *levo* will suffice for this purpose. However, a more general method, applicable where such experimental evidence is not available, is needed, and this is most readily provided by relating the configuration of a designated carbon atom in the compound with the primary standards of configuration of the sugar series, D- and L-glyceraldehyde. The configuration of the highest-numbered carbon atom (*i.e.*, number 6) is determined by projecting this carbon onto a plane in the usual manner with carbon 5 away from the viewer and the H and OH (or other substituent) above the plane. Following the precedent established by the Fischer-Rosanoff convention (8), if the hydroxyl now appears to the right of the carbon atom, when viewed from above the plane, this places the carbon atom and the compound in the D-series; a hydroxyl to the left places it in the L-series.[8]

The isomeric monomethyl-*muco*-inositols XIV, XVa, and XVb will serve as examples of the application of this rule. The latter two formulas are identical,

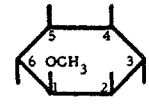


XIV

D-1-Methyl-*muco*-inositol



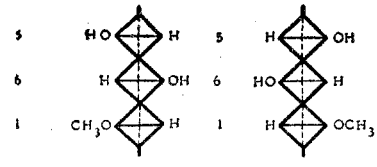
XVa



XVb

L-1-Methyl-*muco*-inositol

XVb being oriented like its enantiomorph XIV while XVa is juxtaposed in order to show more clearly its mirror image relationship to XIV. It will be seen that in formula XIV the upper left carbon in formula VI has been chosen as 1 and numbering done in a clockwise direction (with respect to formula VI). Projection of carbon 6 upon a plane in the prescribed manner may be illustrated by XVI.[9]



XVI XVII

Since the hydroxyl of carbon 6 lies to the right, the substance belongs to the D-series and is therefore named D-1-methyl-*muco*-inositol. In the case of XVb, the lower left carbon of formula VI has been taken as 1 and the numbering done in a counterclockwise direction. Projection of carbon 6 in this isomer (as illustrated by XVII) shows the compound to be a member of the L-series and it may be termed L-1-methyl-*muco*-inositol.

[8] The necessity of changing Maquenne's numbering of either *dextrorotatory* or *levorotatory* inositol in order to give stereochemically equivalent positions in the two enantiomorphs the same number was mentioned earlier. *Levorotatory* inositol was chosen for the change since, thereby, the substance, by rule 2, became L-inositol while its enantiomorph, *dextrorotatory* inositol, became D-inositol.

[9] The examination of mechanical models of the various cyclitol molecules discussed may prove of considerable assistance to the reader.

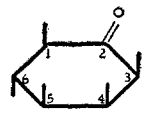
For those inositols of *meso* structure which have become asymmetric through substitution, the configurational designation is best placed at the beginning of the name, as in D-1-methyl-*muco*-inositol. On the other hand, derivatives of the two optically active inositols should be named with the D or L immediately before the word inositol (see, for example, the 3-methyl-D- and L-inositols X, and XI).

Rule 3. *When an inositol derivative contains less than six asymmetric carbon atoms, the compound will be named using the trivial name of one of the parent inositols to which it is related, the choice being that parent inositol which has the maximum number of* cis *hydroxyl groups.* Where this offers more than one possibility, as in the diketo-inositols, the following also apply. *Secondarily, the parent inositol chosen is that which has the lowest possible number for its substituents* cis *to the hydroxyl on carbon 1, or, finally which would confer the lowest possible numbering on substituents other than hydroxyl.*

This rule will be illustrated in the various sections below which deal with the application of the proposed system of nomenclature to derivatives other than those involving simple replacement of oxygen-attached hydrogens.

KETO-INOSITOLS

The term *inosose*, originally introduced by Posternak (9) has been widely used to designate cyclohexanepentolones. To distinguish the inosose made *via* nitric acid oxidation of *myo*-inositol from that obtained through the action of *Acetobacter suboxydans*, Posternak (10) coined the names *epi-meso*-inosose (*epi-myo*-inosose) and *scyllo-meso*-inosose (*scyllo-myo*-inosose), which refer in each case to the two inositols which could be obtained through the reduction of the ketose. While this nomenclature was convenient and logical at the time of its introduction, subsequent discoveries have rendered it less desirable. For instance, Posternak (11) resolved *epi-myo*-inosose into a *levo*rotatory form having structure XVIII

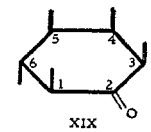


XVIII

D-2-Keto-epi-inositol

D-epi-Inosose-2

(l-epi-myo-Inosose)

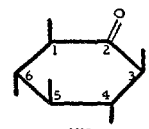


XIX

L-2-Keto-epi-inositol

L-epi-Inosose-2

(d-epi-myo-Inosose)

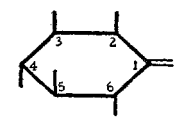


XX

2-Keto-myo-inositol

myo-Inosose-2

(scyllo-myo-Inosose)



XXI

L-1-Keto-myo-inositol

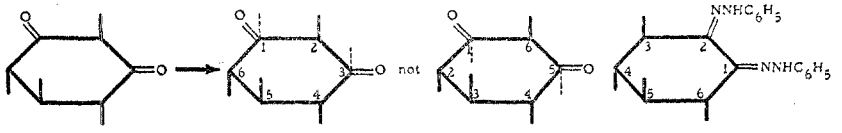
L-myo-Inosose-1

(d-Inosose)

This would be called *l-epi-myo*-inosose and its enantiomorph, XIX, *d-epi-myo*-inosose. On the other hand Magasanik and Chargaff (12) have oxidized *d*-inositol (now to be called D-inositol) with *A. suboxydans* and obtained an inosose, XXI, which could be reduced to either *d*-inositol or *myo*-inositol. In the Posternak system, this compound would be called *d-myo-d*-inosose, the first *d* denoting rotation and the second the relationship of the compound to *d*-inositol. This type of nomenclature is now patently unsatisfactory. Moreover, the name which Magasanik and Chargaff (12) chose for XXI, *viz. d*-inosose, is equivocal, since XIX is equally entitled to the name *d*-inosose, it being also a *dextro*rotatory inosose.

Much of this confusion may now be swept away by adopting our suggested numbering system and rules of nomenclature. Thus XVIII and XIX become D- and L-2-keto-*epi*-inositol (or D- and L-*epi*-inosose-2), respectively. The bacterial oxidation product of *myo*-inositol, XX, becomes 2-keto-*myo*-inositol (or *myo*-inosose-2), no configurational designation being made for this symmetrical compound. For XXI, which is related to both D-inositol and *myo*-inositol, Rule 3 confers the trivial prefix of *myo* while, with the numbering system of *myo*-inositol, Rule 2 places the compound in the L-series. It is thus L-1-keto-*myo*-inositol or L-*myo*-inosose-1.

The diketo-inositol shown in formula XXII is related to both *myo* and *muco* inositols (but not to either D- or L-inositol because these have fewer *cis* hydroxyl groups—see Rule 3). Since the substituents *cis* to the hydroxyl on carbon 1 in *myo*-inositol have a numbering sequence (1, 2, 3, 5) lower than that in *muco*-inositol (1, 2, 4, 5), the compound is correctly named 1,3-diketo-*myo*-inositol. By similar reasoning XXIV may be given the name L-1,2-diketo-*myo*-inositol bisphenylhydrazone.



XXII

XXIIIa
1,3-Diketo-*myo*-inositol

XXIIIb
1,5-Diketo-*muco*-inositol

XXIV
L-1,2-Diketo-*myo*-inositol bisphenylhydrazone

DESOXYINOSITOLS

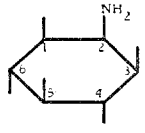
The nomenclature suggested for the desoxyinositols parallels that of the ketoinositols described above, each isomer being named through reference to a parent inositol. Formulas XXV and XXVI will serve for illustration. The well-established *trivial* names for the naturally occurring members of this class may, of course, be expected to continue in use.

XXV
2-Desoxy-*myo*-inositol
(Desoxyscyllitol)

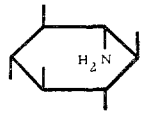
XXVI
D-1-Desoxy-*myo*-inositol
(*l*-viburnitol) (13)

AMINODESOXYINOSITOLS

Various workers have reduced nitrogenous derivatives of the inososes to obtain aminodesoxyinositols. Carter and his coworkers (14) have coined the term *inosamine* as a generic designation for this class of substance and other authors (15, 16) have continued the usage. The only monoaminodesoxyinositols for which complete configurational formulas can be written with reasonable assurance are XXVII and XXVIII, derived from 2-keto-*myo*-inositol (XX). Each of these *meso* structures may readily be named through reference to the corresponding inositol, the *myo*-inositol relative, XXVII, being called 2-amino-2-desoxy-*myo*-inositol (or *myo*-inosamine-2)[10] while XXVIII is simply aminodesoxyscyllitol (or *scyllo*-inosamine).

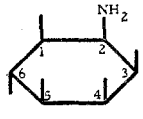


XXVII
2-Amino-2-desoxy-*myo*-inositol
myo-Inosamine-2

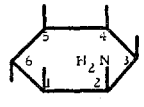


XXVIII
Aminodesoxyscyllitol
scyllo-Inosamine

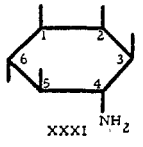
The reduction of nitrogenous derivatives of D,L-2-keto-*epi*-inositol (XVIII–XIX) may give two enantiomorphous pairs of inosamines: D,L-2-amino-2-desoxy-*epi*-inositol (D,L-*epi*-inosamine-2, XXIX–XXX) and D,L-4-amino-4-des-



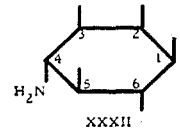
XXIX
D-2-Amino-2-desoxy-epi-inositol
D-epi-Inosamine-2



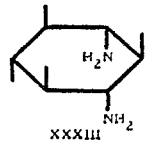
XXX
L-2-Amino-2-desoxy-epi-inositol
L-epi-Inosamine-2



XXXI
D-4-Amino-4-desoxy-myo-inositol
D-myo-Inosamine-4



XXXII
L-4-Amino-4-desoxy-myo-inositol
L-myo-Inosamine-4



XXXIII
1, 3-Diamino-1, 3-dideoxyscyllitol

[10] This compound was originally termed *meso*-inosamine-2 by Anderson and Lardy (16).

oxy-*myo*-inositol (D,L-*myo*-inosamine-4, XXXI–XXXII). One of these compounds was made by Carter and his coworkers (14); identification of the racemic amine as XXIX–XXX or XXXI–XXXII has not yet been made.

While proof of the entire configuration of the biologically important streptamine is still lacking, the available evidence points to structure XXXIII (17) which may be called 1,3-diamino-1,3-didesoxyscyllitol.

SUMMARY

Previous efforts toward a rational nomenclature for the cyclohexitols (inositols) are discussed briefly and are incorporated into a new, rigorous system of nomenclature. The application of this system to the inositols and their derivatives is discussed and illustrated.

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REFERENCES

(1) MAQUENNE, *Les sucres et leurs principaux dérivés*, Carré et Naud, Paris, 1900, p. 190.
(2) LESPIEAU, *Bull. soc. chim. France*, [3] **13**, 105 (1895).
(3) MAGASANIK AND CHARGAFF, *J. Biol. Chem.*, **174**, 173 (1948).
(4) FLEURY AND BALATRE, *Les Inositols*, Masson, Paris, 1947, Table I.
(5) *Chem. Eng. News*, **26**, 1623 (1948).
(6) DANGSCHAT, *Naturwissenschaften*, **31**, 146 (1942).
(7) SCHERER, *Ann.*, **73**, 322 (1850).
(8) HUDSON, *Advances in Carbohydrate Chem.*, **3**, 1 (1948).
(9) POSTERNAK, *Helv. Chim. Acta*, **19**, 1333 (1936).
(10) POSTERNAK, *Helv. Chim. Acta*, **25**, 746 (1942).
(11) POSTERNAK, *Helv. Chim. Acta*, **29**, 1991 (1946).
(12) MAGASANIK AND CHARGAFF, *J. Biol. Chem.*, **175**, 929 (1948).
(13) POSTERNAK, *Helv. Chim. Acta*, **33**, 350 (1950).
(14) CARTER, CLARK, JR., LYTLE, AND MCCASLAND, *J. Biol. Chem.*, **175**, 683 (1948).
(15) MAY AND MOSETTIG, *J. Org. Chem.*, **14**, 1137 (1949).
(16) ANDERSON AND LARDY, *J. Am. Chem. Soc.*, **72**, 3141 (1950).
(17) WOLFROM, OLIN, AND POLGLASE, *J. Am. Chem. Soc.*, **72**, 1724 (1950).