THE STEREOISOMERISM OF CYCLOHEXANE DERIVATIVES

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I. Introduction

The postulations of Sachse (277, 278) and Mohr (201, 202), which elaborated on the van't Hoff–Le Bel concept of the tetrahedral valency angles of carbon and stated that alicyclic rings of more than five members do not possess a planar structure, have been confirmed by chemical and physical studies with numerous compounds, both mono- and polycyclic, particularly those containing partially or completely saturated six-membered rings. The construction of models, based on reliable data for atomic dimensions, has shown that the carbon atoms in such rings unite in a manner involving the minimum deviation from the tetrahedral angle and hence form "strainless" rings. Two forms of the latter are possible: (*1*) the "boat" or C-form; and (*2*) the "chair" or Z-form, also referred to as "puckered," "step-formed," or "staggered."

Despite these considerations, the stereochemistry of cyclohexane and its derivatives, of six-membered heterocycles such as pyranose compounds, and of fused-ring systems (viz., decalins, perhydroanthracenes, perhydrophenanthrenes, steroids, polyterpenoids, etc.) has been based largely upon the concept of the planar ring. Although no serious errors have been introduced thereby in accounting for the number of separable stereoisomers, recent investigations on the relative reactivity of such isomers, as related to the spatial orientation of substituent reacting groups, make it highly desirable to utilize the three-dimensional structure wherever possible. This approach constitutes the stereochemical basis of the modern theory of "conformational analysis," which not only contributes to a better understanding and interpretation of many types of reactions but very often permits the prediction of the course of a reaction. As pointed out by Birch (40), conformational analysis promises to have the same degree of importance in alicyclic studies as the use of resonance in aromatic systems.

II. Configuration and Geometrical Tautomerism

While both the boat and the chair forms of cyclohexane are equally strain-free in the classical sense (tetrahedral valency angles of carbon), the interaction of neutral non-bonded atoms is mainly repulsive. The most stable conformation of the molecule, therefore, is actually the chair form, in which the distances between the non-bonded atoms is at a maximum (10a).

Strong evidence for the chair-form cyclohexane ring was first provided by x-ray crystallographic investigations (82, 124) of the symmetrical compounds β-hexachlorocyclohexane (β-benzene hexachloride or β-BHC) and β-hexabromocyclohexane. Cyclohexane itself was examined (122) subsequently in the vapor phase by electron diffraction involving the rotating sector technique (313). In contrast to benzene, which has a planar hexagonal structure (shortest carbon–carbon distance, 1.40 Å.; carbon–hydrogen distance, 1.04 Å.), cyclohexane was found to exist in the chair form, in which all the valency angles are 109° 28′. The carbon–carbon distance is 1.54 Å., while the carbon–hydrogen distance is 1.10 Å. No derivative of cyclohexane which indicated the presence of the less symmetrical boat form of the carbon skeleton was detected by this procedure, presumably because of the fact that any form other than the chair form would make the

distances between atoms linked to different carbon atoms of the ring smaller than the sum of their van der Waals radii. The cyclohexane molecule must be more stable in the symmetrical chair form than in the boat form, in which four pairs of hydrogen atoms would be in a *cis* position and the distance between a fifth pair of hydrogen atoms would be only 1.83 Å., assuming normal valency angles (121). Nevertheless, the presence of a small amount of the less symmetrical boat form could not be rigidly excluded. As pointed out by Pitzer (230), if the puckered configuration is the potential minimum for rotation about single bonds, it should be expected to possess a lower energy, since it maintains the staggered position throughout, whereas the boat form twists two carbon–carbon bonds into an opposed configuration.

More recently, the spectroscopic and thermodynamic properties of cyclohexane have been investigated (37) with a view to assigning a molecular structure. The results of this study indicate that while cyclohexane has one predominantly stable configuration, the puckered form, a tautomeric equilibrium between the boat and chair forms is possible. The fraction in the boat form is small at room temperature but increases rapidly with increasing temperature. Since considerable heat is absorbed in the process, the heat capacity is higher. These considerations clarify the observed data for cyclohexane. The energy difference is assumed to be twice the internal rotational potential barrier in ethane, or 5.6 kcal., because the change from chair form to boat form twists two carbon–carbon bonds from their potential minima to their maxima. Also, since the symmetry number of the boat form is only 2 compared with 6 for the chair form, an entropy $R \ln 3$ greater has been assigned to the boat form. The potential energy of a planar ring was estimated to be 31 kcal. above the minimum for a puckered configuration.

By the use of bond bending and bond twisting (internal rotation) potential constants from related molecules, the potential or strain energy of cyclohexene has been calculated (36) for various configurations. The data show that cyclohexene may exist in two tautomeric forms, related to the chair or boat structures of cyclohexane, which differ in energy by about 2.7 kcal. per mole.

On the basis of mathematical analysis, Brodetsky (51) suggested that the chair form of methylcyclohexane could give rise to two isomeric monosubstituted derivatives (324, 325). Henriquez (125), however, was of the opinion that one fixed chair structure and an infinite number of mobile modifications, of which the boat form was one, were possible. Since the energy barrier encountered in "chair-boat-chair" conversion in cyclohexane is of the order of 5–10 kcal. (37, 172, 286, 287), a value which is small compared with the activation energies of most reactions and with energies which can be derived thermally, independent existence of such forms may be excluded in most cases. The existence of boat and chair isomers would be possible only if the substituents were of such a nature as to stabilize their spatial orientation. This stabilization has been realized among certain fused-ring systems. No comparable situation has been observed with monocyclic compounds.

The present general acceptance of "ring conversion" among cyclohexane de-

rivatives may be credited largely to the extensive investigations of Hassel and his associates at the University of Oslo. This process, which accounts adequately for the number of separable isomers actually observed among monocyclic compounds and is consistent with the results of chemical and physical investigations, may be described with reference to the chair-form rings illustrated in figure 1.

The diagrams in figure 1 show that the two bonds from each carbon to *other* substituents have directions differing in their geometrical relationship to the trigonal axis of the ring. In order to describe these bonds two systems of nomenclature have been used. The scheme most generally employed up to the present time (37) designates the vertical bonds, parallel to the trigonal axis, as p-bonds (polar, i.e., toward the poles). In the publications by Hassel (112) these bonds are designated as ϵ-bonds from the Greek word, ἐγιηκώζ, meaning "upright." There are six p-bonds per molecule (see figure 1).

The other bond from each carbon atom, denoted by e (equatorial), has a direction such that it makes an angle of 109° 28′ with the trigonal axis. In Hassel's (112) notation these are denoted as κ-bonds from the Greek κὲιμεγοζ, meaning "prostrate." There are six such bonds equatorially distributed about the periphery of the molecule. Groups or atoms attached to these e-bonds do *not* lie in one plane, but alternate above and below a horizontal plane (perpendicular to the axis) through the center of the molecule. Readers are urged to construct a three-dimensional model using tetrahedral carbon atoms in order to distinguish clearly the bond directions denoted by p and e.

A proposal (23a) to designate the p-bonds (Hassel's ϵ-bonds) as "axial" bonds, represented by the symbol *a*, has just recently appeared. However, since most of the publications on the stereochemistry of cyclohexane and its derivatives use the symbols p and e, they are used in the present review to facilitate the reader's examination of the literature up to December 1953.

Hassel has suggested that a conversion of the carbon ring can take place which does not involve the rupture of chemical bonds, but nevertheless transforms each e-bond into a p-bond, and *vice versa*. The carbon atoms constituting the

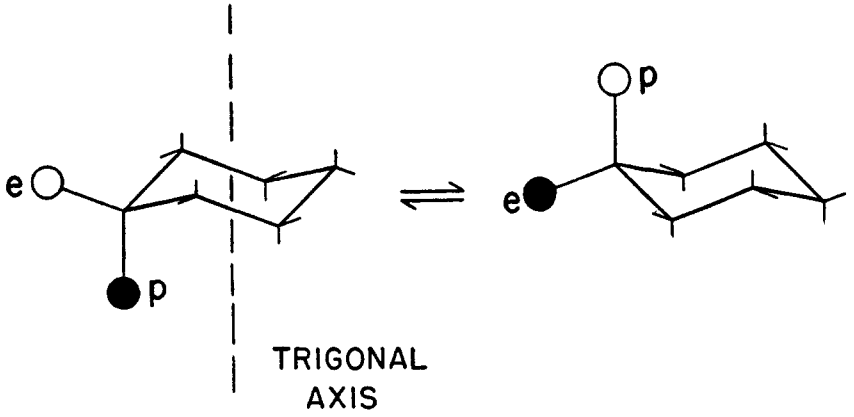


FIG. 1. Ring conversion in cyclohexane derivatives

cyclohexane ring form two planes, each containing three carbon atoms, the interplanar distance being approximately 0.5 Å. If the carbon atoms 1, 3, and 5 interchange planes simultaneously with the atoms 2, 4, and 6, a second chair form will result which may or may not be identical with the original configuration, depending on the nature of the substituents in the molecule. Thus cyclohexane itself will not undergo transformation as a result of this process of ring conversion. A substituted cyclohexane, such as monochlorocyclohexane, however, may exist in two distinct steric forms or "conformations"; the substituent may occupy either an equatorial or a polar position. Whether the compound, under a specific condition, exists exclusively in one form or the other, or as an equilibrium mixture, will depend on considerations of energy resulting from steric and electrostatic factors. Since the conversion process is considered to involve a comparatively small activation energy, it is not possible to separate one conformation from the other. Consequently, the number of separable steric isomers will be identical with that calculated on the basis of a planar ring.

The two forms of a compound constituting such an equilibrium mixture may show a difference in energy sufficiently large to make the concentration of one conformation many times greater than that of the other (31). In other cases, however, this energy difference may be small enough to make the concentrations nearly equal. It has been suggested (39) that, in the case of isomers of benzene hexachloride, "in the gaseous state or in solution, the conversion of the ring will give rise to a chemical equilibrium—more or less one-sided in position. In a crystalline modification, on the contrary, in general only one form will be present."

The term "inverted isomers" has been proposed (165, 204) for the two conformations of a compound which may be interconverted by the process described above.

III. Monocyclic Carbon Compounds

A. MONOSUBSTITUTED CYCLOHEXANES

In a monosubstituted cyclohexane such as monochlorocyclohexane or methylcyclohexane only two steric configurations are possible, one in which the substituent occupies an equatorial orientation and the other a polar disposition. Hassel and Viervoll (122, 123) have pointed out that the only atomic distances which are different in the two conformations of monochlorocyclohexane are those between the chlorine and carbon atoms. Differences of this type may be expected to contribute to the electron scattering of the molecule. Using the rotating sector technique, these investigators have determined experimental $\sigma(r)$ curves for cyclohexane and monochlorocyclohexane. A third curve representing the difference between the first two provided information concerning the position of the chlorine atom. Maxima corresponding to carbon–chlorine distances calculated for the p-form were not detected, but all carbon–chlorine maxima calculated for the e-isomer were found. These results indicated the predominance of the e-form, which therefore must be the more stable and hence the conformation of lower energy. This finding has been explained by analogy with isomeric chlorinated

ethanes. In polar monochlorocyclohexane, the distance between the chlorine atom and the two nearest hydrogen atoms, both of which are polar, would be nearly equal to the distance between a chlorine and a hydrogen atom linked to different carbon atoms in "*cis*" forms of chlorinated ethanes. This distance, 2.57 Å., no doubt is smaller than the sum of the van der Waals radii of the two atoms. On the other hand, the distance between an equatorial chlorine atom and the hydrogen atom linked to neighboring carbon atoms is nearly equal to the distance characteristic of the stable forms of chlorinated ethanes.

Evidence in support of the equatorial form as the predominant conformation of cyclohexyl mercaptan is based on similar experimental techniques and calculations (31, 123). The relatively small distance between a polar sulfhydryl group and the two nearest polar hydrogen atoms is believed to be responsible for the relative instability of the polar conformation.

Methylcyclohexane was found (37) to display steric interactions similar to those of *n*-paraffins. A strain energy (a = 0.8 kcal./mole) has been derived (229) in *n*-butane twisted 120° about the central carbon–carbon bond as compared with the stable planar configuration of that molecule. Polar methylcyclohexane has two similar interactions, whereas the equatorial conformation has no strain of this type. Hence, the energy of the p-form is greater than that of the e-isomer by twice the value for *n*-butane. The assigned value, 1.8 kcal./mole (or a = 0.9 kcal./mole), together with the frequency assignment and potential barrier for the methyl rotation, gives agreement between calculated and observed entropies.

Although the evidence for monosubstituted cyclohexanes supports the predominance of the thermodynamically more stable equatorial conformation, this preponderance may be reduced at elevated temperatures or during the course of chemical reactions. As pointed out by Barton (22), ". . . although one conformation of a molecule is more stable than other possible conformations, this does *not* mean that the molecule is *compelled* to react as if it were in this conformation or that it is rigidly fixed in any way. So long as the energy barriers between conformations are small, separate conformations cannot be distinguished by the classical methods of stereochemistry. On the other hand, a small difference in free energy content (about one kilocal. at room temperature) between two possible conformations will insure that the molecule appears by physical methods of examination and by thermodynamic considerations to be substantially in only one conformation."

On the basis of this hypothesis and of the demonstrated preference for *trans* elimination of adjacent polar hydrogen and chlorine atoms in base-catalyzed reactions (74, 76, 141, 143, 209), the dehydrohalogenation of monochlorocyclohexane, for example with alcoholic potassium hydroxide, may be visualized (figure 2) as involving the following steps: (*1*) a shift in the equilibrium of equatorial monochlorocyclohexane (I) to provide a trace of the higher-energy polar conformation (II) in which the p-chlorine atom is now *trans* and planar to the starred (*) vicinal polar hydrogens; (*2*) attack by the base (OH^-) in a typical concerted E_2 elimination, resulting in the formation of cyclohexene (III) and hydrogen chloride. Ring conversion, brought about as shown here, may be con-

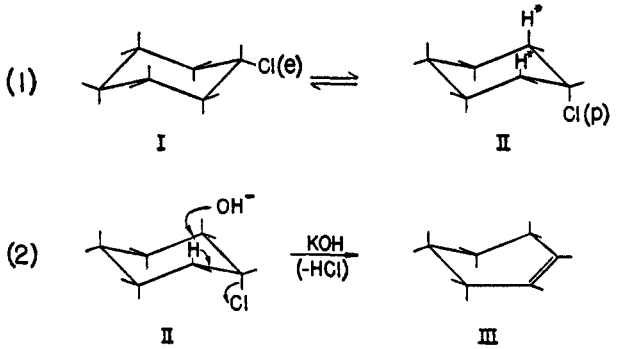


FIG. 2. Conformational interpretation of alkaline dehydrochlorination of monochlorocyclohexane.

sidered reasonable in accounting for the reactions of compounds the conformations of which differ in energy by moderate values. Wherever the energy differences are considerable, because of steric repulsions or rigidity of structure, as in steroids and polyterpenoids, lower rates of reaction may be expected together with possible differences in reaction mechanism or reaction products.

B. DISUBSTITUTED CYCLOHEXANES

1. Dihalocyclohexanes

In 1,1-disubstituted cyclohexane only one steric isomer is possible. The *gem*-dichloride of cyclohexane (61) may be designated therefore as (1e, 1p)-dichlorocyclohexane.

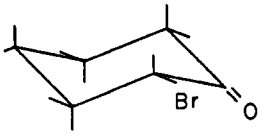
With other positional isomers, however, the number of separable steric forms increases. As shown in figure 2, successive carbon atoms around the puckered ring have their polar substituents directed alternatively up and down. In a disubstituted cyclohexane, $C_6H_{10}X_2$, the *cis*-1,2, *trans*-1,3, and *cis*-1,4 isomers have one polar and one equatorial X group, whereas in the *trans*-1,2, *cis*-1,3, and *trans*-1,4 isomers both substituents may be equatorial or both may be polar.

The three possible conformations of a 1,2-disubstituted cyclohexane may be designated as ep or pe (the *cis* form according to the older nomenclature), and as ee and pp (the *trans* forms). The preponderance of e-molecules, as in monochlorocyclohexane, has been explained by the strain associated with the small distance between a polar substituent and the nearest hydrogen atom. This suggests that the 1e, 2e conformation should be energetically more stable than the 1p, 2p form. In general, the more stable chair form, sterically, is that in which the substituents of high steric requirement occupy equatorial positions and those of low steric requirement occupy polar positions. In many cases, however, the distance between two vicinal equatorial substituents may be smaller than the sum of their van der Waals radii if normal valency angles are assumed. The interaction of the dipole moments of the two groups also may increase the energy of the 1e, 2e conformation. These factors appear to account for the equilibrium composition of *trans*-1,2-dibromocyclohexane in the vapor phase, 60 per cent of the diequatorial and 40 per cent of the dipolar conformation (31).

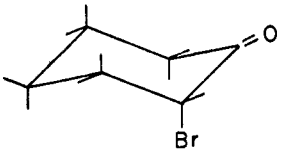
Dipole moment studies (307) of the isomeric 1,2-dichlorocyclohexanes provide additional confirmation for the stability relationships of disubstituted cyclohexanes. The calculated moment, $\mu = 3.1$ D, of the *cis* isomer (1e, 2p $\rightleftharpoons$ 1p, 2e) is identical with experimental values obtained in benzene solution at 40°C. and in the vapor phase at 236°C. For the *trans* isomer, the observed value in benzene is 2.66 D (40°C.) and in the vapor phase, 2.31 D at 239°C. Since the calculated moment of the 1p, 2p form is zero and that of the 1e, 2e conformation is 3.1 D, the mole fraction of the latter must be 0.56 in the vapor phase and 0.72 in benzene solution. The energy difference (pp − ee) has been calculated as 0.1 kcal./mole at 239°C. and 0.3 kcal./mole at 40°C. in benzene solution.

While 1,2-dichlorocyclohexane itself has not been investigated by means of x-ray or electron diffraction, such studies on other compounds with equatorial chlorines on adjacent carbon atoms show a deviation from normal valency angles as the result of repulsive forces acting between neighboring equatorial chlorine atoms (29, 30). Some deformation in the dipolar (1p, 2p) conformation involving a bending away of the polar carbon–chlorine bond from the principal axis of the ring has been demonstrated with 1e,2e,4p,5p-tetrachlorocyclohexane (116, 117) and is probably caused by the small distance between the 1p-chlorine and the 3p-hydrogen.

Corey (69) has pointed out that the occurrence of strong electrostatic interactions between groups might bring about some destabilization of the sterically less strained form and might even result in a stable form which is sterically more strained. Evidence for this observation has been obtained from a study of α-halocyclanones which contain two strong dipoles in close proximity, which are mutually repulsive when steric strains are at a minimum.



IV



V

The difference in energy between the chair forms IV (e-Br) and V (p-Br) of α-bromocyclohexanone has been formulated as

$$E_{IV} - E_V = (E^S_{IV} - E^S_V) + (E^E_{IV} - E^E_V)$$

where $(E^S_{IV} - E^S_V)$ is the difference in energy due to steric repulsions and $(E^E_{IV} - E^E_V)$ is that due to electrostatic (CO dipole − CBr dipole) repulsion. Using calculated values of −0.4 kcal./mole for the lower limit of $(E^S_{IV} - E^S_V)$ and 2.7 kcal./mole for the lower limit of $(E^E_{IV} - E^E_V)$, Corey has obtained a minimum value for $E_{IV} - E_V$ of 2.3 kcal./mole, which corresponds to over 97 per cent of the polar conformation V at room temperature. Similar calculations show that the energy

of the most stable of the six possible boat forms of α-bromocyclohexanone is at least 5 kcal./mole greater than that of V.

Confirmatory evidence for the predominance of V has been provided by infrared spectroscopy based on work with keto steroids (154) which indicates that the introduction of an α-bromo substituent shifts the carbonyl absorption (Δ = 13 to 25 cm.$^{-1}$) to higher frequencies if the carbon–bromine and carbon–oxygen bonds are approximately in the same plane (as in IV) but has little or no effect if these bonds are far from coplanar (as in V). With α-bromocyclohexanone a shift of only 4 cm.$^{-1}$ is observed, a result which indicates that the more stable chair form is that in which the carbonyl and bromine dipoles are not coplanar (V).

In 1,3-disubstituted cyclohexanes, the *trans* form corresponds to the 1e, 3p conformation and the *cis* form to the 1e, 3e $\rightleftharpoons$ 1p, 3p conformation (121). The results of electron diffraction and dipole moment investigations of the dihalocyclohexanes show that the 1e, 3e configuration is considerably more stable than that of the 1p, 3p form (100, 111).

The 1e, 4e $\rightleftharpoons$ 1p, 4p configuration in 1,4-disubstituted cyclohexanes corresponds to the *trans* isomer, while the 1e, 4p derivative corresponds to the *cis* form. Since there are no 1,2-interactions in compounds of this type, it is to be expected that the 1e, 4e conformation would predominate (100, 103–105, 111, 322). Indeed, by the use of electron and x-ray diffraction only the diequatorial configuration has been detected in the vapor and solid states of *trans*-1,4-dihalocyclohexane. From Raman spectral studies (166), however, both conformations appear to be in dynamic equilibrium (1p, 4p $\rightleftharpoons$ 1e, 4e) in solution, although only the diequatorial form is present in the solid state. By measuring the relative intensities of the Raman lines, the potential energies of both configurations in various solvents have been found. The 1p, 4p form is more stable in non-polar solvents (carbon tetrachloride, cyclohexane), with the exception of benzene, than in polar solvents (ethanol, diethyl ether). The 1e, 4e form, although predominant in the solid state, is generally less stable in the various solvents.

Ring conversion is important from the standpoint of optical isomerism in disubstituted cyclohexane derivatives (95, 114, 305). Among 1,2-disubstituted cyclohexanes in which both substituents are of the same kind, three steric conformations exist: ep, ee, and pp. One of the chemically separable forms, the ep or *cis* conformation, consists of a mixture of *d*- and *l*-molecules which are readily transformed into each other by conversion of the ring (figure 3). The separation of the *d*- and *l*-molecules is therefore impossible. The ee $\rightleftharpoons$ pp (or *trans*) form, on the other hand, also will consist of optically active molecules, but in this case the conversion process does not lead to isomerization and a separation of the optically active antipodes is theoretically possible. Indeed, optical resolution of *trans*-1,2-cyclohexanediol, which was shown (222) to exist predominantly as the diequatorial conformation, has been achieved (42). The crystals of the *cis*-1,2-diol contain both *d*- and *l*-molecules, but since ring conversion converts the 1e, 2p conformation into its optical antipode, 1p, 2e, it has not been possible to effect the resolution of the *cis* isomer.

In the *trans*-1,3-disubstituted cyclohexane, ep $\rightleftharpoons$ pe, in which both sub-

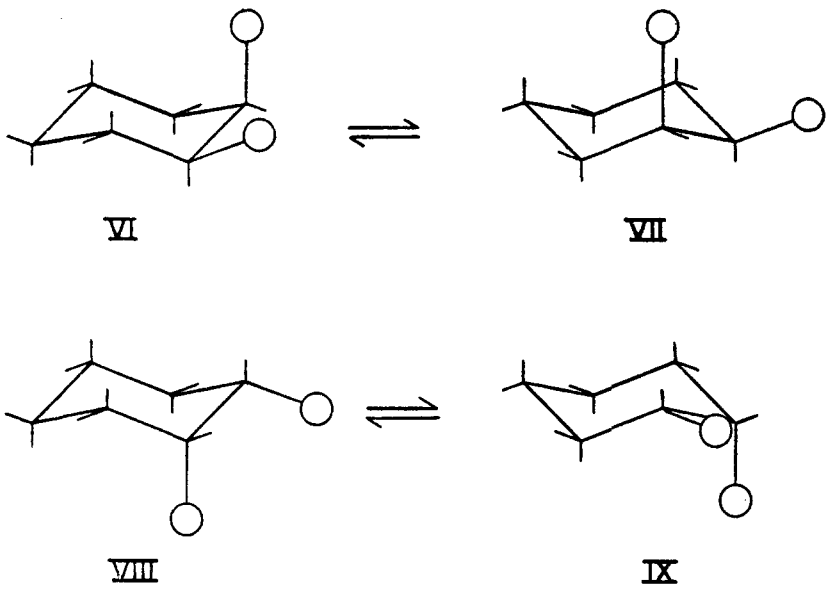


FIG. 3. Ring conversion of *cis*-1,2-disubstituted cyclohexanes containing identical substituents and corresponding to the configurations ep $\rightleftharpoons$ pe. VI and VIII, VII and IX are identical; VI and VII, VIII and IX are optical isomers.

stituents are of the same kind, ring conversion does not change the picture of the asymmetric molecule. It is to be expected, therefore, that optically active forms can be separated. This has been accomplished for *trans*-1,3-cyclohexanediol (265). The molecules of *cis*-1,3-cyclohexanediol (ee $\rightleftharpoons$ pp), the 1,4-cyclohexanediols, and the 1,3,5-triols all have a plane of symmetry and can therefore not be resolved.

In the case of *cis*(ep $\rightleftharpoons$ pe)-1,2 derivatives with two different substituents (or with a second, unsymmetrical ring attached to the cyclohexane ring in the 1,2-position), the two interconvertible configurations taken together represent one optically active species (114), each of which corresponds to a mirror image form of the other species (figure 4). The specific rotation of each of the two species will depend on the ratio of the two interconvertible conformations in the equilibrium mixture, assuming no interaction between solute and solvent.

2. Dimethylcyclohexanes

The 1,1, *cis*-1,2, *trans*-1,3, and *cis*-1,4 isomers have one polar and one equatorial methyl group. Since ring conversion gives the identical structure (ep $\rightleftharpoons$ pe), only one conformation is possible. The *cis*-1,2- and *trans*-1,3-dimethylcyclohexanes, however, have both *d*- and *l*-molecules, which accounts for their double probability, since *d*- and *l*-forms have the same energy (37). The *trans*-1,2 compound has *d*- and *l*-molecules with a symmetry number of 2 in each case, so that no net change in the relative probability of this substance arises. The optical

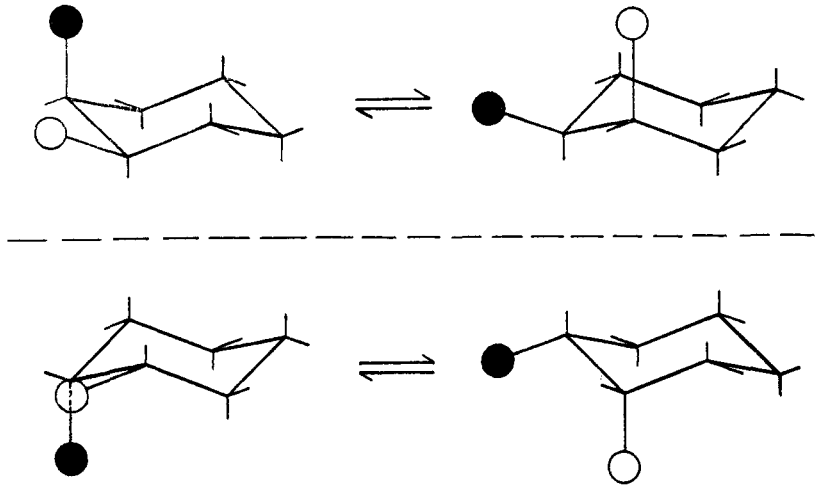


FIG. 4. Ring conversion of *cis*-1,2-disubstituted cyclohexanes containing different substituents and corresponding to the equilibrium ep $\rightleftharpoons$ pe.

isomers of *trans*-1,2-dimethylcyclohexane are theoretically capable of separation. In *cis*-1,2 compounds the enantiomorphs are in tautomeric equilibrium, while in *trans*-1,3 molecules they are true isomers interconvertible only by inversion of two carbon atoms.

The *trans*-1,2-, *cis*-1,3-, and *trans*-1,4-dimethylcyclohexanes have two tautomers (ee $\rightleftharpoons$ pp), one with only equatorial methyl groups, the other with only polar substituents. In each case the energy of the diequatorial conformation is lower. Beckett, Pitzer, and Spitzer (37) have calculated the energy difference in the *trans*-1,4 isomer to be twice that in methylcyclohexane, that is, 4*a* or 3.6 kcal./mole.[1] In the *trans*-1,2 compound, there is one *n*-butane-like interaction in the equatorial form and four in the polar conformation, giving an energy difference of 3*a* or 2.7 kcal./mole. In *cis*-1,3-dimethylcyclohexane, the presence of both methyl groups on the same side of the plane of the ring results in considerable steric strain. An energy difference of 6*a* or 5.4 kcal./mole has been arbitrarily assigned to the two conformations of the *cis*-1,3 isomer. This value is so high that the dipolar form can be ignored at lower temperatures. The energy difference (pp − ee), 3.6 kcal./mole, for the *trans*-1,4 isomer favors the diequatorial form.

While there is a possibility for chair–boat tautomerism, contributions from the latter structure may be neglected on the basis of conclusions derived for cyclohexane itself.

Equilibration experiments with the isomeric dimethylcyclohexanes, at 25°C. in 99.8 per cent sulfuric acid, yielded (269) equilibrium compositions which are in good agreement with thermochemical data (271) and with entropies and heats

[1] *a* = strain energy in *n*-butane, 0.9 kcal./mole.

of isomerization reported by Beckett *et al.* (37):

DIMETHYLCYCLOHEXANE	EQUILIBRIUM COMPOSITION	
	Observed	Thermochemical
	mole per cent	*mole per cent*
cis-1,2	5	7
trans-1,2	95	93
cis-1,3	95	94
trans-1,3	5	6
cis-1,4	7	10
trans-1,4	93	90

Besides interconversion of *cis* and *trans* isomers, considerable isomerization to yield the *cis*-1,3 form, the thermodynamically predominant conformation, has been reported.

While the assignment of configuration to disubstituted cyclohexanes is most readily determined by methods such as optical resolution of the *trans* isomer (only applicable to symmetrically substituted 1,2 and 1,3 compounds) or the preferential formation of an intramolecular reaction product (e.g., lactone) from the *cis* isomer (only applicable when there is no possibility of isomerization), in other cases the Auwers–Skita rule (12, 13, 292, 294–296) is often applied. According to this rule, one form (*cis*) of an epimeric pair has a higher density, refractive index, and boiling point than the other (*trans*). Usually, also, the *trans* form has a higher melting point and lower solubility and is the more stable of the two. In general, the differences are more marked with substituents on vicinal carbon atoms.

Hückel (134) has shown that the rule holds rigidly for 1,2 derivatives of cyclohexane, while Owen and Robins (223) have reported its application to 1,4 isomers. Exceptions to the Auwers–Skita rule, however, have been found in 1,3 derivatives. Thus, the resolvable (*trans*) 3,5-dimethylcyclohexanone has a higher refractive index than the *cis* isomer (48, 49), and optically active 1,3-dimethylcyclohexane has a higher boiling point and refractive index than does the inactive isomer (205, 206). Rossini and Pitzer (272) have established that the Auwers–Skita rule does not apply to isomeric 1,3-dimethylcyclohexanes; in fact, the reverse is true. In the latter compound the *cis* (ee $\rightleftharpoons$ pp) conformation is less strained; consequently it has the lower energy and therefore a lower density and refractive index than the *trans*-1,3 (ep) epimer. However, 1,2- and 1,4-cyclohexane derivatives follow the rule; hence assignments made on the basis of its validity are correct.

Chemical evidence that the Auwers–Skita rule should be reversed for the 1,3-dimethylcyclohexanes has recently been reported (102). The syntheses of the 1,2-, 1,3-, and 1,4-dimethyl isomers have been based on reactions involving the corresponding bishydroxymethylcyclohexanes, the configurations of which have been rigidly established by methods similar to those for the cyclohexanediols. The reactions employed do not give the possibility of a change of configuration and in each case the hydrocarbon or alcohol is known.

3. Cyclohexanediols

The conformations of the cyclohexanediol isomers have been investigated by the application of electron and x-ray diffraction, dipole moments, spectrophotometry, and optical resolution.

Electron diffraction studies (222) of the vapors of the chair-form *cis*- and *trans*-cyclohexanediols give all the theoretical maxima corresponding to e- and p-oriented oxygen atoms, although at different intensities. This indicates that the oxygen atoms in *both* the *cis*- and the *trans*-1,2-diol must be present in equatorial and polar positions. In view of the fact that the higher-melting diol (m.p. 104°C.) can be separated into optically active antipodes (42), it must be the ee $\rightleftharpoons$ pp form. The data indicate that, as in the 1,2-dibromide, the dipolar conformation predominates. The lower-melting (m.p. 99°C.) diol must be the ep isomer. Resolution of the latter, which contains both *d*- and *l*-molecules, has not been achieved because of ring conversion which transforms the 1e, 2p conformation into its optical antipode 1p, 2e.

Although the structures of the cyclohexanediols have been investigated by x-ray analysis (95), the conformations of the 1,2 and 1,3 isomers could not be deduced from x-ray data alone. Those of the 1,2-diols have been established with certainty by electron diffraction studies (222), while those of the 1,3 isomers have been proved by optical resolution (95) of the *trans* isomer, ep $\rightleftharpoons$ pe. As shown by x-ray investigation, two of the six molecules in the unit cell of the *trans*-1,4-diol possess a center of symmetry. This substance therefore has the structure ee or pp. The presence of an equal number of *d*- and *l*-molecules in the crystals of the *trans*-1,2- and -1,3-diols is consistent with the possibility of resolving these isomers. Ring conversion here does not give identity. Since the molecules of the *cis*-1,3-diol and the *cis*- and *trans*-1,4-diols all have a plane of symmetry, their optical resolution is impossible.

From a study of Fisher–Hirschfelder models of the cyclohexanediols, Svirbely and Lander (305) have concluded that internal hydrogen bonding may occur and that steric hindrance of two types may be encountered: (*1*) interference of hydroxyl hydrogens; (*2*) interference of polar hydroxyl hydrogens with polar hydrogens attached to carbons twice removed from the carbons bearing the hydroxyl hydrogens. Interaction energies calculated for the substituted groups are presented in the last column of their tabulated data (table 1).

TABLE 1

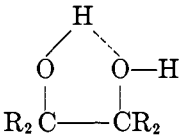
Hydrogen bonding, steric hindrance, and interaction energies of the cyclohexanediols

ISOMER	CONFIGURATION	IS INTERNAL HYDROGEN BONDING POSSIBLE?	TYPE OF STERIC HINDRANCE	$m_1m_2/d^6 \times 10^{54}$
cis-1,2	1e, 2p	Yes	(1), (2)	~13
trans-1,2	1e, 2e	Yes	(1)	~13
trans-1,2	1p, 2p	No	(2)	~9
cis-1,4	1e, 4p	No	(2)	~3
trans-1,4	1e, 4e	No	None	~1.8
trans-1,4	1p, 4p	No	(2)	~3

Qualitative considerations have shown (198) that if the interaction energy is of the order of magnitude of 4×10^{14} ergs per molecule, free rotation will be restricted and the measured dipole moment will differ from the moment calculated on the basis of free rotation. In the case of both 1,2-diols, the high values of the interaction energy and the existence of steric hindrance eliminate free rotation. Models indicate that hydrogen bonding is possible in both the ep and the ee conformations. A choice between the ee and the pp forms has not been possible on the basis of calculated moments alone. However, on the basis of generalizations previously proposed for the dimethylcyclohexanes (37), Svirbely and Lander have suggested that the diequatorial conformation is the more probable. This conclusion is at variance with that of Ottar (222), based on electron diffraction studies.

Only one configuration (ep) is possible for the *cis*-1,4-diol. The equatorial hydroxyl is free to rotate but the polar hydroxyl is hindered. The high interaction energy and steric hindrance eliminate free rotation. With respect to the *trans*-1,4-diol, no choice based on dipole moments has been possible between the ee and pp conformations. Svirbely and Lander's assignment of structure (ee) here, therefore, has also been based on energy considerations discussed by Beckett *et al.* (37).

Further knowledge of molecular structure and intramolecular hydrogen-bond formation has been provided by spectroscopic measurements (170) in the 3 μ region at such low concentration that intermolecular bonding would not be expected to take place. Some of the compounds studied were found to give two bands, while others had only one. Compounds having two bands exist in the internally bonded form:



The high-frequency band is due to the free hydroxyl and the low-frequency band to the bonded hydroxyl. Only those compounds in which the calculated length of the hydrogen bond is less than 3.3 Å. are reported to have two bands.

Table 2 lists the relationship between the hydrogen bond distance (H···O) and $\Delta\nu$, the difference in wave numbers ($cm.^{-1}$) between the free and bonded OH bands. The stronger the hydrogen bond (14), the greater is $\Delta\nu$, since it may be expected that the value of $\Delta\nu$ would vary with the length of the hydrogen bond. The symbol ϕ is the angle in 1,2-diols bounded by the two carbon–oxygen bonds. In the range of H···O values between 1.6 and 3.3 Å., a linear relationship between $\Delta\nu$ and the H···O distance was found to be given by the expression

$$\Delta\nu = \frac{250 \times 10^{-8}}{L} - 74$$

where L is the H···O distance in centimeters.

The data in table 2, which are based on the assumption that the orientation around the carbon–oxygen bond gives a minimum H···O distance, show that

TABLE 2

Relationship between H···O *distances and* $\Delta\nu$

COMPOUND	CONFORMATION	$\Delta\nu$	ϕ	H···O DISTANCE
				Å.
cis-1,2-Cyclopentanediol		61	0	1.84
trans-1,2-Cyclopentanediol		0	120	3.3
cis-1,2-Cyclohexanediol	ep	39	60	2.34
trans-1,2-Cyclohexanediol		32		
Equatorial	ee		60	2.34
Polar	pp		80	>3.3
cis-1,3-Cyclohexanediol		75		
Polar	pp			1.64
Equatorial	ee			>3.3
trans-1,3-Cyclohexanediol	ep	0		>3.3
cis- and *trans*-1,4-Cyclohexanediols	ep, ee, and pp	0		>3.3

in the *trans*-1,2-diol the hydroxyl groups are equatorial, while in the *cis*-1,3-diol they are polar. In other positions the hydroxyl groups would be farther apart than in *trans*-1,2-cyclopentanediol and hence would have no hydrogen bond. Kuhn (170) has suggested that the conformation which enables the hydroxyl groups to be as close together as possible is the one which is favored. As seen from the tabulated data, both *cis*- and *trans*-1,2-cyclohexanediols have the same calculated H···O distance, although the $\Delta\nu$ value is larger for the *cis* isomer. The attraction between the hydroxyl groups in forming a hydrogen bond tends to produce a rotation around the carbon–carbon bond and to reduce the angle ϕ. The result is to make the ring in the *cis* isomer more planar and in the *trans* isomer more puckered. The larger $\Delta\nu$ value for the *cis* as compared with the *trans* isomer is due to the fact that the hydroxyl groups in the former can take up closer positions than is possible in the *trans* diol.

4. Cyclohexanedicarboxylic acids

As in the case of the cyclohexanediols, three pairs of *cis–trans* isomers are possible. Assignment of configuration to the 1,2 and 1,3 derivatives has been based upon optical resolution of the *trans*-1,2 (320) and *trans*-1,3 (43) acids. Since the 1,4 acids can not be resolved because of the presence of a plane of symmetry, the structural assignments here have been made from a consideration of physical properties (15, 16, 246) such as the lower melting point and greater solubility of the *cis* acid.

An attempt to obtain a mathematical expression based on the inverse relationship between the intercarboxylic distance in a symmetrically dibasic acid and the ratio of its first to its second dissociation constants (41) has been refined (97, 321, 331) and applied to the stereochemistry of cyclohexanecarboxylic acids (171, 200, 301, 316). An important application of this relationship, involving the conformations of cyclohexanedi- and tricarboxylic acids, has been made recently by Barton and Schmeidler (27) in the elucidation of the A/C ring fusion in abietic and related resin acids. This approach is discussed in a later section.

TABLE 3

Conformations and rates of esterification of cyclohexanecarboxylic acids with methanol

ACID	PREDOMINANT CONFORMATION	$K \times 10^2$ AT 25°C.		
		K_1	K_2	K_2 (monoester)
		l./mole/sec.	*l./mole/sec.*	*l./mole/sec.*
Mono acid	e	1.18		
cis-1,2	ep	0.166	0.0287	0.0294
trans-1,2	pp	0.0778		0.0425
cis-1,3	ee	3.00	1.18	1.18
trans-1,3	ep	1.72	0.694	
cis-1,4	ep	1.62	0.676	
trans-1,4	ee	2.84	1.32	

Recently, Smith and Byrne (299) have shown that the relative rates of esterification of the cyclohexanedicarboxylic acids depend on the geometrical and positional arrangement of the carboxyl groups, particularly on the number of equatorial groups available for reaction. From the rate constants obtained for acid-catalyzed esterification, evidence for the favored conformation of each steric isomer has been obtained, as summarized in table 3.

Because of the proximity of the carboxyl groups in the 1,2 acids, esterification takes place more slowly than in the monocarboxylic acid. The rate for the latter, however, is close to the K_2 value for the *cis*-1,3 and *trans*-1,4 acids. Assuming the chair form, the *trans*-1,2 acid may have either the ee or the pp conformation, the latter being more probable because of the greater separation between the groups. Only one form (ep) is possible for the *cis*-1,2 compound. Since, in a polar carboxyl group, the carbonyl moiety is somewhat shielded, whereas in the equatorial position it is relatively open to attack, the first (e) acid group of the *cis* isomer may be expected to react more rapidly than either carboxyl (p) in the *trans* isomer. In confirmation of these conclusions, the data show that K_1 for the *cis* isomer is greater than K_2 (*cis*), K_1 (*trans*), and K_2 (*trans*). Once an equatorial carboxyl has been esterified, the presence of the ester group adds to the hindrance of the remaining polar carboxyl group (the ratio of K_1 to K_2 of the monoester is 5:1), although not appreciably (ratio 2:1) in the case of the *trans* isomer. This explains the slower rate of esterification of the second carboxyl group in the *cis* compared with the *trans* acid.

Only one *trans* form (ep) is possible for the 1,3 acid. Of the two *cis* possibilities, ee and pp, the diequatorial conformation may be expected to predominate because of the greater distance between the groups. In accordance with the considerations discussed above, the diequatorial *cis* isomer should have a K_1 value twice that for the *trans* isomer (only one equatorial carboxyl). This postulation is in accord with the rate data, which also demonstrate that K_2 for the remaining e-group in the *cis* isomer is greater than that of the unesterified polar hydroxyl in the *cis*-1,2 acid.

In the *cis*-1,4-dicarboxylic acid, the conformation is of the type ep. Although both ee and pp structures are possible for the *trans*-1,4 isomer, the ee form is

assumed to predominate. If, then, an equatorial carboxyl is more readily attacked than a polar group, the *trans* isomer may be expected to undergo esterification at twice the rate of the *cis* isomer; furthermore, the value for K_2 (*trans*) should exceed that for K_2 (*cis*). The data in table 3 are in full agreement with these interpretations.

Further confirmation for the assigned structures is provided by the fact that the *cis*-1,3 and *trans*-1,4 (both diequatorial) acids have almost identical rates, almost twice those for the *trans*-1,3 and *cis*-1,4 acids (both ep), which are similar to each other.

5. Monohydroxycyclohexanecarboxylic acids

The stereochemistry of the monohydroxycyclohexanecarboxylic acids is not only of interest *per se* but also because their structures have been applied (96, 212, 213, 288) to the conformational analysis of the methylcyclohexanecarboxylic acids and the methylcyclohexylamines, and to verify the reversal of the Auwers–Skita rule for 1,3-disubstituted cyclohexanes.

The steric structures of the 2-hydroxycyclohexanecarboxylic acids are currently based upon their mode of formation (by the reduction of 2-cyclohexanone-1-carboxylate ester) and the physical properties of their derivatives (224), which conform to the Auwers–Skita rule. Thus, the *cis* methyl ester (m.p. 81°C.) has a higher density, a higher refractive index, and a lower molecular refractivity than does the *trans* ester (m.p. 111°C.). The *cis* isomer exhibits a lower viscosity because internal hydrogen bonding between the hydrogen of the hydroxyl group and the carbonyl oxygen of the carboxyl group is possible. The *trans* isomer tends to favor intermolecular association and therefore shows a higher viscosity. The steric structures of the 3- and 4-hydroxycyclohexanecarboxylic acids have been assigned (45, 59) on the basis that only the *cis* isomers can form lactones and be re-formed by hydrolysis of the lactones.

Kilpatrick and Morse (160) have investigated the relative acid strengths and dissociation constants of the hydroxycyclohexanecarboxylic acids with a view to elucidating their spatial relationships. This approach was based on the premise that the dissociation constant of an acid depends upon the structure of the molecule and will be a function of the orientation and spatial interaction of dipolar groups and the distance of the dipolar center from the ionizable proton.

As in the case of other disubstituted cyclohexanes, the *cis*-1,2, *trans*-1,3, and *cis*-1,4 isomers may be assigned a single conformation, ep. Two possibilities (ee and pp) remain for the *trans*-1,2, *cis*-1,3, and *trans*-1,4 isomers.

The acid strengths (in water at 25°C.) of the monohydroxycyclohexanecarboxylic acids (160) and cyclohexanedicarboxylic acids (171), relative to cyclohexanecarboxylic acid as unity, show that in water all the substituted acids are stronger than the parent acid (table 4). For each *cis–trans* pair, the acid with the possibility of a diequatorial conformation is the stronger of the two. In all solvents studied, the *cis*-1,3 isomer has been found to be stronger than the *trans*-1,3 isomer and the *trans*-1,4 acid stronger than the *cis*-1,4 acid. The assignment of diequatorial conformations to the *cis*-1,3 and *trans*-1,4 isomers is in agree-

TABLE 4

Relative acid strengths of hydroxycyclohexanecarboxylic acids and cyclohexanedicarboxylic acids

DISUBSTITUTED ISOMER	RELATIVE ACID STRENGTHS*	
	$HOC_6H_{10}COOH$†	$C_6H_{10}(COOH)_2$‡
cis-1,2	1.28	2.5
trans-1,2	1.66	4.9
cis-1,3	2.00	4.3
trans-1,3	1.22	2.8
cis-1,4	1.17	2.4
trans-1,4	1.68	3.6

* Relative to cyclohexanecarboxylic acid. Solvent, water. Temperature, 25°C.

† Reference 160.

‡ Reference 171.

ment with those proposed for the cyclohexanedicarboxylic acids (299) and the dimethylcyclohexanes (37). The *trans*-1,2 acid has been found to be stronger in water than the *cis*-1,2 acid but weaker in solvents of lower dielectric constant. Since a decrease in dielectric constant is in the direction of intensification of repulsive forces, the more stable configuration will be the one with the greater distance between the hydroxyl and carboxyl groups. The dipolar form will then be favored over the diequatorial.[2] These results indicate that the *trans*-1,2 isomer may have the ee form in water and the pp form in non-aqueous solvents.

Pascual, Sistaré, and Régas (224) have reported that the *cis*-1,2 acid reacts readily with acetyl chloride in ether to form an acetyl derivative, whereas the *trans* acid requires the presence of pyridine. The *cis* acid and its methyl ester give the corresponding *p*-toluidides upon heating with *p*-toluidine, whilst the *trans* isomers react with difficulty. Similarly, the *cis* acetylated *p*-toluidide hydrolyzes more rapidly than the *trans* isomer. These differences may be ascribed to the relatively greater ease of esterification and hydrolysis of an equatorial as compared with a polar substituent. If the *trans* isomer exists primarily in the pp conformation, it would be expected to undergo esterification with greater difficulty than a *cis* isomer (ep) which has one equatorial substituent.

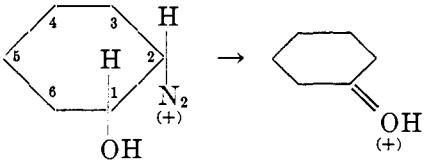
6. *Aminocyclohexanols*

The stereochemistry of the aminocyclohexanols involves the same general principles described for other disubstituted cyclohexanes. Consequently, a recent investigation (191) of 2-aminocyclohexanol provides a valuable illustration of the application of conformational analysis to the interpretation of chemical reactions. Owing to the presence of two dissimilar substituents, the *cis* and *trans* isomers lack a plane of symmetry; hence each is capable of resolution into optically active forms. Two racemates are known. Since one, melting at 68°C., has been formed by amination of cyclohexene oxide (57) and since the oxide ring is

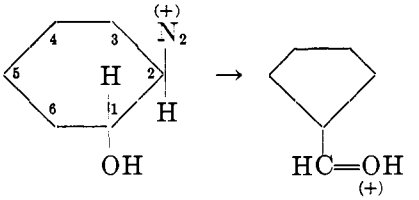
[2] The distances (Å.) between the center of the dipole and the ionizable proton have been calculated (160) as follows: *cis*-1,2 (ep), 3.96; *trans*-1,2 (ee), 3.96; *trans*-1,2 (pp), 5.42.

normally opened in the *trans* manner, this isomer must have the *trans* form. The latter assignment has been confirmed by an investigation of its tosylate derivatives (192). The other (*cis*) racemate melts at 72°C.

Decomposition with nitrous acid of the isomeric diazonium intermediates X and XII can result in the formation of the ketone XI or the aldehyde XIII,



X (*cis*) XI



XII (*trans*) XIII

respectively (191). The ketone results from migration of hydrogen from C_1, accompanied by displacment of N_2, whereas the aldehyde formation involves migration of R (i.e., ring contraction). Thus the ring at C_6 constitutes one migrating group and the hydrogen at C_1 the other. The displacement which will be favored will be that in which either H or R is *trans* and coplanar with respect to the diazonium group (231).

In the *trans* isomer (XII), H_1 is *cis* to the diazonium group. When the latter group is polar, H_1 is equatorial, and *vice versa*. When the diazonium group is equatorial, C_6 is in a favored position (*trans* and coplanar) for migration, but H_1 is not. When the diazonium group occupies a polar position, neither C_6 nor H_1 is favored for migration. In the *cis* isomer (X), H_1 is *trans* to the diazonium group. Hence, H_1 and $\overset{+}{N}_2$ are either both dipolar or diequatorial. A study of models indicates that the pp form favors hydrogen migration, and the ee conformation favors ring contraction. The relative extent of each migration then will depend on the ratio of ee and pp molecules.

On the basis of these considerations, McCasland (191) has predicted that *trans*-2-aminocyclohexanol should give ring contraction only and the *cis* isomer should give a mixture of both the aldehyde and the uncontracted ketone. Experimentally, these postulations have been confirmed.

7. Epoxycyclohexane

1,2-Epoxycyclohexane has an interesting structure (221) which displays certain similarities to that of cyclohexene and of the saturated ring in tetrahydronaphthalene. The epoxide consists of a six-membered carbon ring and a three-membered C—O—C ring, the two rings having a carbon–carbon bond in

common. The molecule may be considered to be disubstituted, the two substituents being directed from adjacent carbons to the same oxygen atom. From the standpoint of conformational chemistry, epoxycyclohexane is of interest because the six-membered ring theoretically can undergo ring conversion of the chair-boat-chair type without breaking of chemical bonds.

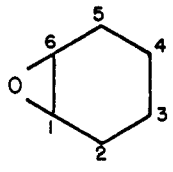
Starting with a normal cyclohexane ring, the oxygen atom may be attached to carbon in two ways:

(*1*) Two e-bonds may be engaged, bringing two carbon–oxygen bonds into the same plane. This will deform the six-membered ring, the C—C—C angles becoming smaller than the tetrahedral angle of the undeformed ring. The resulting ring will be asymmetrical and capable of existence in two optically active forms. Transformation of one to the other will break chemical bonds.

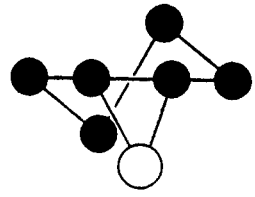
(*2*) By using one e- and one p-bond at C_1 and C_6 in the ring and bringing the two bonds into one plane, the six-membered ring may be transformed into one of two possible boat structures which may be interconverted without rupture of chemical bonds, or the six-membered ring (XIV) may be deformed in a manner such that the atoms C_1, C_2, C_5, and C_6 are coplanar, while one of C_3 and C_4 is above and one below the ring. The latter model involves the least deformation of the puckered ring.

Since two p-bonds point in opposite directions, any form of an epoxide based on a pp model would be impossible unless the six-membered ring were transposed, that is, all p-bonds converted into e-bonds.

On the basis of x-ray studies (221), the structure of the six-membered ring has been shown to be a deformed chair (XV) in which the four carbon atoms



XIV



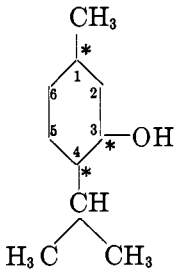
XV

nearest the oxygen atom are coplanar, and the two remaining carbons are placed one above and one below this plane.

C. TRISUBSTITUTED CYCLOHEXANES

1. Menthol

The chemistry of menthol, a subject of intensive investigation for more than a century (83, 84), has contributed considerably to the development of stereochemical knowledge. Examination of the formula for menthol (XVI) reveals the presence of three asymmetric carbon atoms (1, 3, 4). In accordance with classical theory, this compound can exist as 2^3 (or 8) optically active forms or as four externally compensated forms. The latter have been designated as (±)-menthol, (±)-isomenthol, (±)-neomenthol, and (±)-neoisomenthol (309). From a study of the methods of preparation, chemical reactions, and physical proper-



XVI

Menthol

ties of the isomeric menthols, and in the light of modern concepts concerning the structures of cyclohexane derivatives, their stereochemical relationships may be summarized as shown in table 5. On chemical grounds, the predominant conformations are believed to be those at the left of the arrows in the last column. Evidence based on physical techniques is not available. Figure 5 shows the structures in terms of the classical planar delineation and of the puckered ring. Hydrogen substituents have been omitted for purposes of simplification.

An inspection of table 5 and figure 5 indicates that the methyl and isopropyl groups in (±)-menthol and (±)-neomenthol bear a *trans* relationship, whereas in (±)-isomenthol and (±)-neoisomenthol these two groups are *cis*. Evidence (164, 247, 290) for this conclusion is derived from extensive investigations, notably by Read and his coworkers, dealing with the relationships between the

TABLE 5

Stereochemical relationships of the isomeric menthols

ISOMER	STERIC RELATION OF SUBSTITUENTS		CONFORMATION
	CH_3, OH	OH, i-C_3H_7	
(±)-Menthol	*cis*	*trans*	e-CH_3, e-OH, e-i-C_3H_7 ⇌ p-CH_3, p-OH, p-i-C_3H_7
(±)-Isomenthol	*trans*	*trans*	p-CH_3, e-OH, e-i-C_3H_7 ⇌ e-CH_3, p-OH, p-i-C_3H_7
(±)-Neomenthol	*trans*	*cis*	e-CH_3, p-OH, e-i-C_3H_7 ⇌ p-CH_3, e-OH, p-i-C_3H_7
(±)-Neoisomenthol	*cis*	*cis*	p-CH_3, p-OH, e-i-C_3H_7 ⇌ e-CH_3, e-OH, p-i-C_3H_7

TABLE 6

The relationship of optically active menthols to (−)-piperitone

		(−)-Piperitone			
		↙	↘		
(−)-Isomenthone	⇌	(+)-Menthone	(+)-Isomenthone	⇌	(−)-Menthone
↓		↓	↓		↓
(−)-Isomenthol		(+)-Menthol	(+)-Isomenthol		(−)-Menthol
+		+	+		+
(−)-Neoisomenthol		(−)-Neomenthol	(+)-Neoisomenthol		(+)-Neomenthol

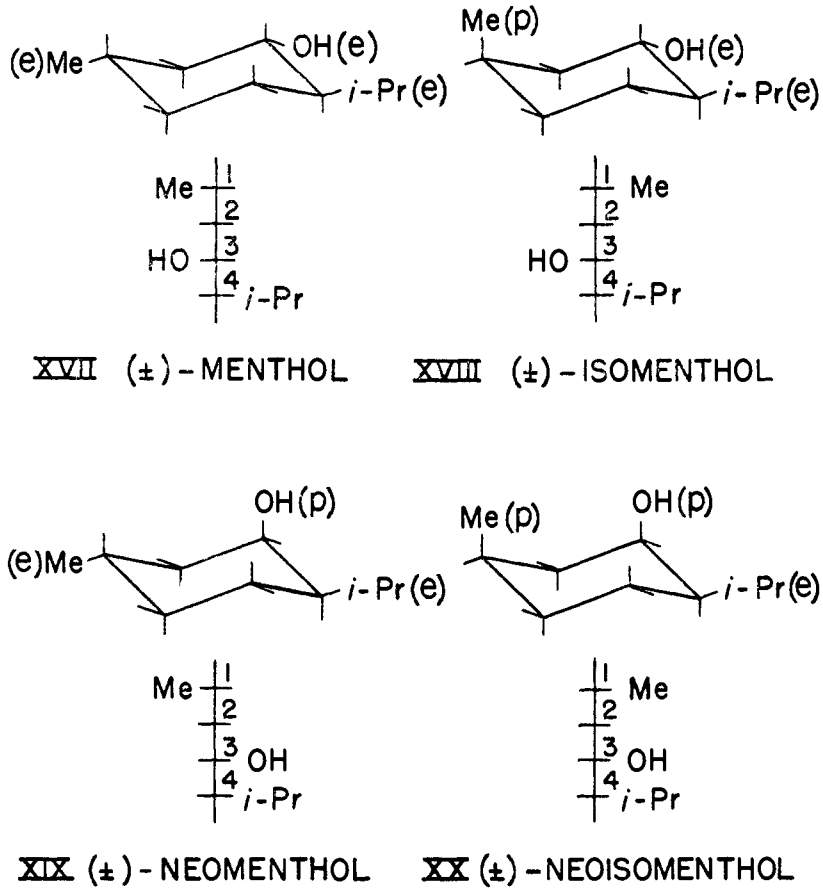
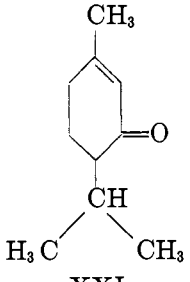


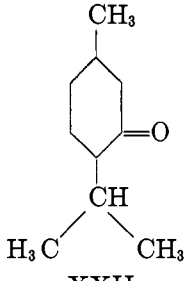
FIG. 5. Steric configurations of the isomeric menthols: *i*-Pr = isopropyl; Me = methyl

isomeric menthols, menthones, and piperitones, as summarized in table 6 (248), and from a study of the reactions of their derivatives, such as amines, esters, etc.

On catalytic hydrogenation (±)-piperitone (XXI) gives rise to a mixture of optically active menthone and isomenthone, in which the latter epimer predominates (140, 142, 249–251, 255, 300, 306).



XXI
Piperitone



XXII
Menthone

Menthone (XXII), containing two asymmetric carbon atoms, is capable of existing in two externally compensated *cis–trans* modifications, each of which is resolvable into optical enantiomorphs. Two geometrical isomers have been designated (±)-menthone and (±)-isomenthone. Their *cis–trans* relationship has been demonstrated conclusively (38, 255, 318, 319) by conversion via an intermediate enolic tautomer of (−)-menthone into mixtures of (−)-menthone and (+)-isomenthone by the use of heat or various alkaline and acidic reagents. Application (334) of the Auwers–Skita rule indicates that the methyl and isopropyl groups have the *trans* configuration in menthone; isomenthone is the *cis* isomer. The assignment of configuration for menthone and isomenthone has been confirmed by parachor determinations (62) and by electrolytic reduction (157) to *trans*- and *cis*-menthanes, respectively. The physical constants of the latter products indicate a *trans* configuration for the hydrocarbon derived from menthone.

(±)-Menthol and (±)-neomenthol, separated from the products of hydrogenation of thymol (52, 55, 56), have been shown (228) to be related structurally to (±)-menthone by oxidation with chromic acid to form the latter ketone. Chromic acid oxidation of (−)-menthol yields (−)-menthone, whereas reduction of the latter provides a mixture of (+)-neomenthol (70 per cent) and (−)-menthol (30 per cent) (99). The reduction of menthone to neomenthol by the Ponndorf method has been investigated recently (148). Using the aluminum alkoxides of sterically hindered secondary alcohols, such as methyl-*tert*-butylcarbinol, even higher yields of neomenthol have been realized than those (70 per cent) obtained with aluminum isopropoxide. Similarly, isomenthol and neoisomenthol have been related to isomenthone (252, 257).

TABLE 7

Elimination reactions of derivatives of menthol and neomenthol (141)

COMPOUND	PROCESS	RELATION OF OH TO BRIDGEHEAD H	ELIMINATION	
			Toward bridgehead*	Away from bridgehead†
			per cent	*per cent*
(−)-Menthyl chloride	Heating in alcohol	*cis*	70	30
(−)-Menthyl tosylate	Heating in alcohol	*cis*	70	30
(−)-Menthylamine	Nitrous acid	*cis*	No hydrocarbon	
(+)-Neomenthylamine	Nitrous acid	*trans*	70	30
(−)-Menthyl chloride	Sodium ethoxide	*cis*	0	100
(−)-Menthyl tosylate	Sodium ethoxide	*cis*	0	100
(+)-Neomenthyl chloride	Sodium ethoxide	*trans*	75	25
(−)-Menthylamine	Heating quaternary ion in water	*cis*	0	100
(+)-Neomenthylamine	Heating quaternary ion in water	*trans*	80‡	20‡
(−)-Menthyl methyl xanthate	Pyrolysis	*cis*	70	30
(+)-Neomenthyl methyl xanthate	Pyrolysis	*trans*	20	80

* Based on yield of 3-*p*-menthene.

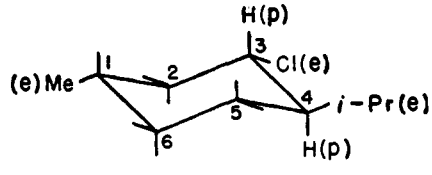
† Based on yield of 2-*p*-menthene.

‡ The original inverted values of Hückel *et al.* (141) are corrected here.

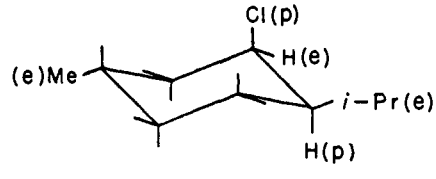
The assignment of a *trans* (ee or pp) configuration to the methyl and isopropyl groups in menthol and neomenthol (on the basis of the relationship of these alcohols to menthone) leaves the orientation of the hydroxyl group still to be clarified. The observation that menthol is more resistant than neomenthol to dehydration induced Zeitschel and Schmidt (334) to assume erroneously that the C_4-hydrogen and C_3-hydroxyl in neomenthol are in close proximity, that is, *cis*. This conclusion is at variance with that of Vavon and Couderc (311) based on the observation that (+)-neomenthol is esterified less readily than (−)-menthol.

The steric requirements of elimination reactions of menthol and neomenthol derivatives (141) have provided clean-cut evidence for clarification of the configurations of both alcohols (table 7). Whereas menthyl chloride is stable towards aniline or quinoline and gives 2-*p*-menthene with sodium ethoxide, neomenthyl chloride is dehydrochlorinated with ease to yield a mixture of 2-*p*-menthene and 3-*p*-menthene.

Clarification of these results may be simplified by reference to the chair-form conformations (XXIII and XXIV) of the isomeric chlorides:



XXIII Menthyl chloride



XXIV Neomenthyl chloride

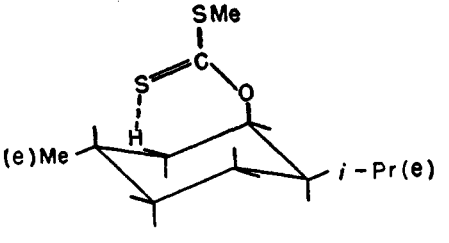
The formation of 3-*p*-menthene by heating (−)-menthyl chloride (or tosylate) in alcohol is an example of unimolecular elimination proceeding via an intermediate carbonium ion. Under polar control, reactions of this type are largely unrestricted by steric factors and follow the Saytzeff rule; this is indicated by the tendency for bridgehead elimination. The deamination of cyclohexylamines with nitrous acid has been reported to furnish different products depending upon the conformation of the amino group (47, 71): an equatorial amino substituent yields an alcohol of the same configuration, while a polar group gives elimination and inversion. The formation of (−)-menthol by treatment of (−)-menthylamine with nitrous acid is evidence for an equatorial orientation of the amino group (199). On the other hand, (+)-neomenthylamine (NH_2 polar) gives (+)-3-menthene (elimination) together with some 4-*p*-menthanol (rearrangement), products which suggest an intermediate carbonium ion (73).

The predominance (70 per cent) of elimination toward the bridgehead therefore represents another case wherein the Saytzeff rule is controlling.

Bimolecular elimination from chlorides normally follows the Saytzeff rule. Providing steric conditions in the isomeric menthyl chlorides are such that the chlorine at C_3 and the hydrogen at C_4 are *trans* and coplanar, elimination will take place mainly toward the bridgehead. In the case of (−)-menthyl chloride (or tosylate), however, reaction with sodium ethoxide results exclusively in 2-*p*-menthene (away from the bridgehead). This reaction, involving abrogation of the Saytzeff rule, is rationalized by the fact that the C_4-hydrogen and C_3-chlorine are in a *cis* (p, e, respectively) relationship. Ring conversion, which places the C_3-chlorine in a polar disposition, and the presence of a polar hydrogen at C_2 permit the preferred *trans* (pp) elimination between C_2 and C_3. In (+)-neomenthyl chloride, where polar hydrogens are present on both C_2 and C_4, the predominant product is 3-*p*-menthene. The relative ease of dehydrochlorination of (+)-neomenthyl chloride, compared with the lesser reactivity of (−)-menthyl chloride, provides evidence for facile *trans* (pp) elimination.

On the basis of experimental data summarized by Hückel, Tappe, and Legutke (141), Ingold (144a) has attempted to apply the Hofmann rule to the bimolecular elimination of 'onium ions in the isomeric menthol series. In a private communication, Professor H. C. Brown has drawn the author's attention to an error in Hückel's summary table. The experimental data, as presented in the text of his paper, show the product from (+)-neomenthyltrimethylammonium hydroxide to be 80 per cent 2-*p*-menthene and 20 per cent 3-*p*-menthene instead of the inverse ratio listed in the table. Moreover, the recent data of McNiven and Read (193) show that this reaction yields 10.5 per cent (+)-*trans*-2-*p*-menthene and 89.5 per cent 3-*p*-menthene. From these results it follows that the Hofmann rule does not control eliminations in such ring systems. A discussion of the factors which control the direction of eliminations in these structures will shortly be published by Professor Brown. The corrected values for the products obtained from the neomenthyl 'onium compound are recorded in table 7.

Thermal decompositions, such as the Tschugaeff xanthate reaction, which result in olefin formation, require a cyclic transition state involving intramolecular hydrogen bonding (141). As shown in table 7, *cis* elimination, away from the bridgehead, is favored in the case of the neomenthyl compound. The cyclic intermediate formed by neomenthyl menthyl xanthate is illustrated by formula XXV.



XXV

Where conditions are sterically favorable, *cis* elimination takes place towards the bridgehead, as demonstrated by the predominance of 3-*p*-menthene in the product obtained by pyrolysis of the menthyl derivative. This tendency has been rationalized on the basis of a unimolecular reaction wherein the activation energy decreases in the series primary > secondary > tertiary, analogous to the direction of decreasing homolytic bond dissociation energies of C—X bonds (where X = H, OH, Cl, Br, etc.). By analogy, and in accordance with experimental results, pyrolytic deacylations, e.g., of acetates (144, 303) and benzoates (25, 26), and the dehydration of cyclic alcohols (1, 2, 11) also involve *cis* elimination.

Further evidence for the configuration of menthol has been provided by pyrolysis of (−)-menthyl acetate and of (−)-menthyl chloride (193). As in the case of the xanthate, the structure of (−)-menthyl acetate will permit *cis* elimination between C_2 and C_3 or C_3 and C_4, whereas *trans* elimination would involve C_2 and C_3. Pyrolysis yields (+)-3-*p*-menthene and (+)-*trans*-2-*p*-menthene in the ratio of 2:1. The major reaction, therefore, is *cis* elimination between C_3 and C_4 toward the tertiary or bridgehead carbon.

In the unimolecular mechanism encountered in the pyrolysis of chlorinated hydrocarbons, a four-center transition state has been postulated (20). For a minimization of activation energy, the four centers should lie in one plane. This implies that in cyclohexane derivatives *cis* should predominate over *trans* elimination. The homogeneous unimolecular thermal decomposition of (−)-menthyl chloride yields a mixture of 2-*p*-menthene and 3-*p*-menthene in the ratio of 1:3, thus confirming the structure shown in formula XXIII.[3]

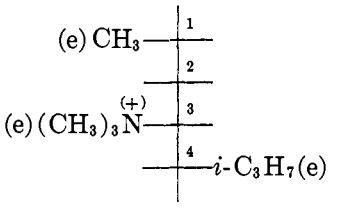
Another approach to the configurational characterization of the menthols has involved thermal decomposition of the optically active quaternary ammonium hydroxides to yield optically active menthenes (193):

QUATERNARY AMMONIUM HYDROXIDE	MENTHENE		
	(+)-trans-2-*p*-Menthene	(+)-*cis*-2-*p*-Menthene	(+)-3-*p*-Menthene
	per cent	*per cent*	*per cent*
(−)-Menthyl	96		4
(+)-Isomenthyl		99	1
(+)-Neomenthyl	10.5		89.5
(+)-Neoisomenthyl		Present	Mainly

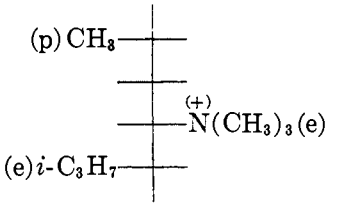
Since quaternary ammonium hydroxides yield olefins by a bimolecular ionic mechanism involving *trans* elimination (81), the experimental results may be

[3] Caution must be exercised in interpreting the steric course of pyrolytic eliminations. Although such reactions normally proceed *cis*, the pyrolytic elimination of strongly electron-attracting (or -repelling) substituents may constitute exceptions (25). Thus, pyrolysis of the potassium salt of the hydrogen sulfate of 3β-acetoxycholestan-6β-ol furnishes chiefly cholesteryl acetate with not more than 10 per cent of cholest-6-en-3β-yl acetate. This latter elimination presumably involves an ionic mechanism.

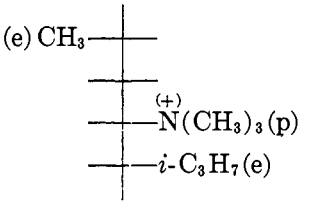
interpreted on the basis of the following configurations of the starting materials (*cf.* figure 5):



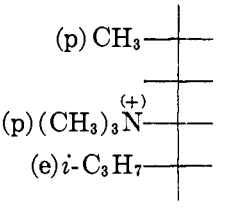
(−)-Menthyl



(+)-Isomenthyl



(+)-Neomenthyl



(+)-Neoisomenthyl

Trans elimination in the menthyl and isomenthyl derivatives can take place only between the C_3-$\overset{+}{N}(CH_3)_3$ and C_2-H substituents, presumably in the ring-conversion forms in which these substituents are polar. This is confirmed by the almost exclusive formation of 2-*p*-menthene. With the neo and neoiso compounds, *trans* elimination is possible between the C_2 and C_3 or the C_3 and C_4 substituents. The data show that the reactions of the two latter isomers proceed via both routes, although predominantly the latter, that is, involving the bridgehead polar hydrogen.

The kinetics of these reactions have not been investigated. It may be expected that the neo and neoiso derivatives would react more rapidly than the menthyl or isomenthyl compounds because the $\overset{+}{N}(CH_3)_3$ groups in the two latter hydroxides are equatorial and probably require conversion of the ring to place them in the more favored polar disposition for a concerted bimolecular (E_2) elimination. In the neomenthylammonium hydroxide the predominant conformation is undoubtedly the less populated 1e, 3p, 4e form; hence ring conversion is not necessary to facilitate pp elimination. Evidence to be presented below indicates that neoisomenthol and its derivatives react predominantly as the 1p, 3p, 4e conformation. Consequently, its quaternary hydroxide also may be expected to react relatively rapidly in bimolecular eliminations.

The existence of steric similarity between menthol and isomenthol, and between neomenthol and neoisomenthol, has been demonstrated by Hückel (135). Whereas the tosylates of (−)-menthol and (+)-isomenthol (equatorial tosylate group adjacent to equatorial isopropyl group) are stable, those of (+)-neomenthol and neoisomenthol (polar tosylate group adjacent to equatorial isopropyl group) are thermally unstable in ionizing solution.

The menthols and menthylamines differ in their relative velocities of esterification with acid chlorides. Neo- (1e, 3p, 4e) and neoiso- (1p, 3p, 4e) menthylamines react more rapidly with symmetric acid anhydrides, acid chlorides, and aldehydes than do menthyl- (1e, 3e, 4e) and isomenthyl- (1p, 3e, 4e) amines (257). Neomenthylamine reacts 1.16 times more rapidly with β-naphthoyl chloride and 1.46 times faster with *o*-nitrobenzoyl chloride than does menthylamine (253). On the other hand, (+)-neomenthol is esterified more slowly with acetic and butyric acids than is (−)-menthol, and the (+)-neomenthyl esters (acid phthalates, acetates) are correspondingly more difficult to saponify than those of (−)-menthol (311, 312, 334). In comparative reaction studies of the four series of alcohols with *p*-nitrobenzoyl chloride, the relative rates have been found to be: menthol, 16.5; isomenthol, 12.3; neoisomenthol, 3.1; neomenthol, 1.0 (253). Sterically, the C_3-hydroxyl and C_4-isopropyl groups must therefore be the same: ee in menthol and isomenthol, and pp in neo- and neoisomenthol.

Eliel (84a) has suggested that the rate of esterification of neoisomenthol (ppe) is greater than that of neomenthol (epe), because the former undergoes more facile ring conversion (to eep) than the latter (to pep); in these forms the hydroxyl groups are present in the reactive equatorial disposition. The lesser reactivity of isomenthol as compared with menthol has been explained on the basis of steric interference of the 3e-hydroxyl group in the former isomer by the 1p-methyl group. It is conceivable that the presence of a polar substituent (other than hydrogen) on one side of a molecule would reduce the statistical possibility of broadside attack from that direction.

Evidence for the conformations of the hydroxyl groups is provided by the fact that the free hydroxyl group of the monobenzoate of *trans*-1,2-cyclohexanediol (ee) is esterified more rapidly with *m*- and *p*-nitrobenzoyl chlorides and 3,5-dinitrobenzoyl chloride than is that of the monobenzoate of *cis*-1,2-cyclohexanediol (p-OH, e-$OCOC_6H_5$)(18). It may be concluded, therefore, that the hydroxyl groups are polar in the less reactive neomenthol and neoisomenthol, and equatorial in menthol and isomenthol.

A similar difference in reactivity between *cis* and *trans* hydroxyl groups has been reported in a number of alkylcyclohexanols. The *trans* (ee) isomer of 2-methylcyclohexanol reacts twice as rapidly with *o*-nitrobenzoyl chloride as does the *cis* (ep) isomer (147). The hydroxyl in the former is presumably equatorial and in the latter, polar.[4] In the case of 4-methylcyclohexanol, the ratio of reaction rates of the *trans* and *cis* forms is 2.5:1. The relative rates of hydrolysis of the *cis* and *trans* esters of 4-propylcyclohexanol give similar differences,

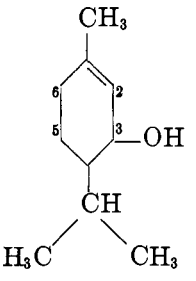
[4] A reverse relationship holds (310) for chromic acid oxidation of 2-substituted cyclohexanols. Here the *cis* alcohols are oxidized more rapidly than the *trans*. This observation is adequately accommodated by the present theory if the rate-determining step is attack upon the carbon-hydrogen bond rather than upon the equatorial carbon-hydroxyl linkage (22).

the *trans* form reacting more rapidly (68):

ESTER	$K \times 10^{-4}$ (55°C.)	
	cis	*trans*
Hydrogen phthalate	0.0954	0.248
Acetate	0.762	2.08

While the lesser reactivity of the *cis* isomer has been attributed to a steric effect by the neighboring alkyl group, it does not appear reasonable to employ the same explanation for 4-alkylcyclohexanols. The data are best interpreted in terms of an equatorial hydroxyl in the *trans* isomer and a polar hydroxyl in the *cis* isomer. In confirmation of these results, Fieser has reported that equatorial hydroxyl groups in steroid alcohols are selectively acylated by reaction with ethyl chloroformate (86).

Still another approach to the structural characterization of the menthols has been provided by hydrogenation of the *cis* and *trans* forms of piperitol (XXVI), which is formed by reduction of piperitone (18, 190).



XXVI

Piperitol

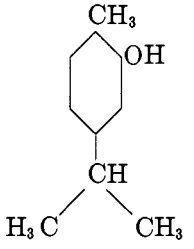
The products obtained, illustrated in figure 6 on page 377, confirm the *cis* (ep) relationship of the hydroxyl and isopropyl groups in neomenthol and neoisomenthol, and their *trans* (ee) relationship in menthol and isomenthol.

2. Carvomenthols

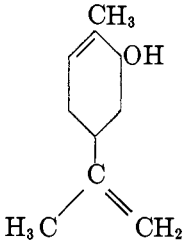
The stereochemical characterization of the terpene alcohols, the carvomenthols (XXVII), has involved an approach similar in many respects to that in the case of the menthols. At the same time the structures of the related alcohols, carveol (XXVIII) and dihydrocarveol (XXIX), and of the ketones, dihydrocarvone (XXX) and carvomenthone (XXXI), all derived from the parent compound carvone (XXXII), have been elucidated.

Because of the presence of two asymmetric carbon atoms, XXXI can exist in the form of *cis* and *trans* isomers, (−)-carvomenthone and (−)-isocarvomenthone, which may be readily interconverted (254) by chemical means. The preparation of the latter isomeric ketones has been achieved by catalytic reduction of (+)-carvone. On the basis of the Auwers–Skita rule, isocarvomen-

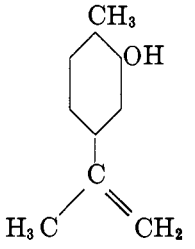
thone (higher density and refractive index) has been assigned the *cis* (ep) conformation, while the predominant carvomenthone is considered to be the *trans* (ee) form (152). Thus carvomenthone corresponds structurally to menthone, and isocarvomenthone to isomenthone.



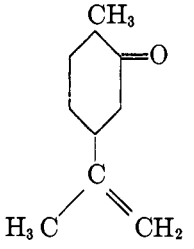
XXVII
Carvomenthol



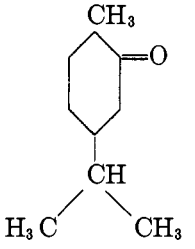
XXVIII
Carveol



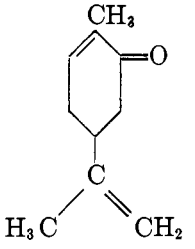
XXIX
Dihydrocarveol



XXX
Dihydrocarvone

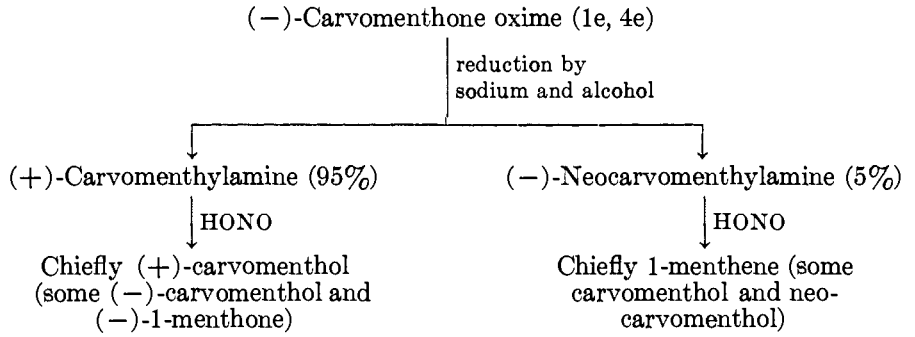


XXXI
Carvomenthone



XXXII
Carvone

Carvomenthol and neocarvomenthol have been prepared (254) by the reduction of carvomenthone oxime:



In view of the facile formation of olefin from (−)-neocarvomenthylamine, the amino group at C_2 must be *trans* to the hydrogen at C_1. Since the methyl group is equatorial, the C_1-hydrogen must be polar. Thus the orientation of the amino group is established as polar; hence the conformation of (−)-neocarvomenthylamine must be 1e, 2p, 4e. By analogous reasoning, (−)-carvomenthylamine (which gives only a trace of 1-menthene) must have the 1e, 2e, 4e conformation in which the amino group is *trans* (e) to the methyl (e) substituent. Both carvo-

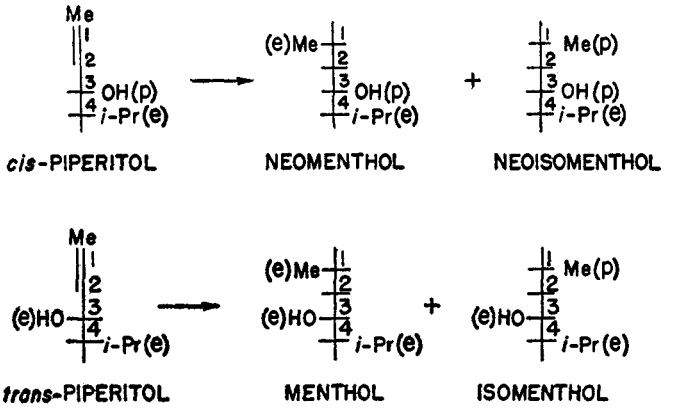
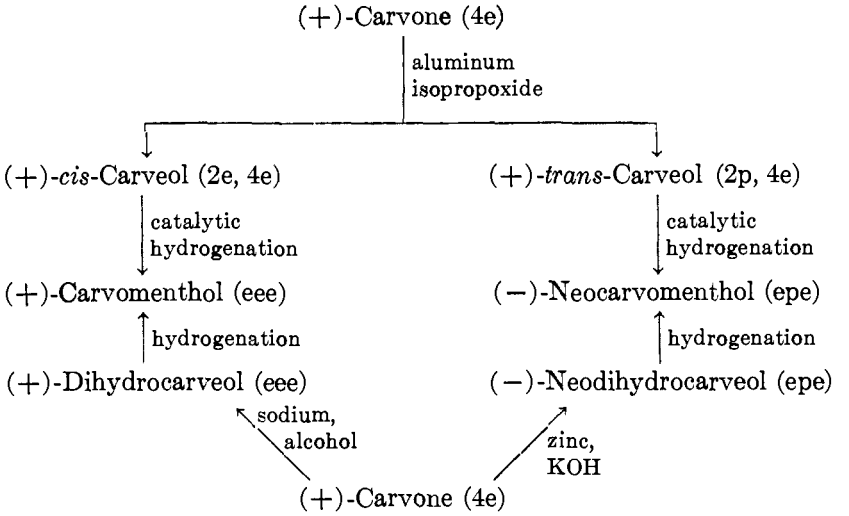


FIG. 6. Menthols derived from *cis*- and *trans*-piperitols

menthol and carvomenthylamine are structurally related to menthol and menthylamine, whereas neocarvomenthol and neocarvomenthylamine are related to neomenthol and neomenthylamine, respectively.

Additional evidence for the *trans* (ee) disposition of the methyl and isopropyl groups in (+)-carvomenthol (eee) and (−)-neocarvomenthol (epe) has been provided by oxidation of the alcohols with Beckmann's chromic acid reagent to yield (−)-carvomenthone (152). This reaction has been reported to proceed without inversion.

The syntheses of carvomenthol and neocarvomenthol from carvone by two alternate routes (151) are in accord with the proposed structures:

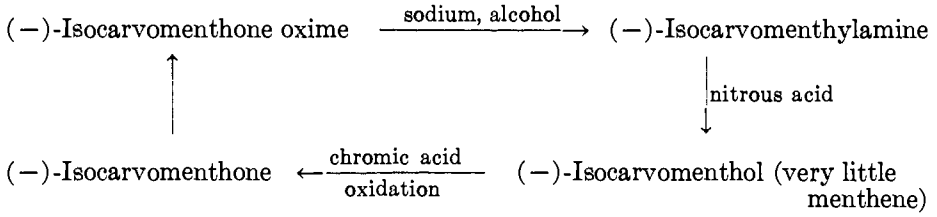


Despite the caution which must be exercised in applying the Auwers–Skita rule to 1,3-disubstituted cyclohexane derivatives, the evidence provided by the above sequence of reactions of (+)-carvone indicates that the application of the rule to the structures of the *cis*- and *trans*-carveols is valid. This may be

associated with the cycloölefinic bond and the resultant deformation of the carveol molecule. The solid carveol isomer, m.p. 24–25°C., having a higher density and refractive index ($d_4^{25°}$ = 0.9521, $n_D^{25°}$ = 1.4959) than the liquid isomer (b.p., 102°C./10 mm., $d_4^{25°}$ = 0.9484, $n_D^{25°}$ = 1.4942) has been designated *cis*, and the latter *trans* (151). In *cis*-carveol the hydroxyl and isopropenyl groups have the ee conformation; in *trans*-carveol, the hydroxyl group is polar and the isopropenyl group is equatorial. Considering these facts in conjunction with the data relating carvomenthol and neocarvomenthol with carvomenthone, the eee conformation of carvomenthol and the epe structure of neocarvomenthol appear to be assured. These assignments are identical with those proposed by Bose (46) on the basis of conformational analysis.

Steric structures may now be assigned to the dihydrocarveols: dihydrocarveol, eee; neodihydrocarveol, epe. The *trans* (1e, 4e) relationship of the C_1 and C_4 substituents has been confirmed by oxidizing the two latter "dihydrocarveols" to (−)-dihydrocarvone (280).

The structure of isocarvomenthol has been derived (152) in part from its relationship to isocarvomenthone:



Inasmuch as (−)-isocarvomenthone is the *cis* isomer (p-methyl, e-isopropyl), (−)-isocarvomenthol and (−)-isocarvomenthylamine can have one of two possible structures, pee or ppe.

Since reduction of ketones or oximes by sodium and alcohol normally leads to the formation of the thermodynamically more stable epimer (equatorial) of an alcohol or amine, Bose (46) has assigned the pee conformation to isocarvomenthylamine. This structure is supported by the fact that treatment with nitrous acid affords the corresponding alcohol with very little terpene. A polar disposition of the amino group, on the other hand, would make possible a four-centered planar transition state which would facilitate *trans* elimination and menthene formation. The reaction of neoisocarvomenthylamine, to which Bose has assigned the ppe conformation, with nitrous acid, has not been investigated however.

In contradiction of the assignments pee and ppe to isocarvomenthol and neoisocarvomenthol, respectively, are the results of the palladium-catalyzed hydrogenation of the *cis*- and *trans*-carveols, reported by Johnston and Read (152):

(+)-*cis*-Carveol (2e, 4e)	→	(+)-carvomenthol (eee)	+	(−)-neoisocarvomenthol (pee?)
(+)-*trans*-Carveol (2p, 4e)	→	(−)-neocarvomenthol (epe)	+	(−)-isocarvomenthol (ppe?)

Since the dispositions of the substituents at C_2 and C_4 would be expected to carry through the hydrogenation process, the neoiso structure should be pee while that of isocarvomenthol should be ppe. The discrepancy between Bose's conformational analysis and Johnston and Read's data has not been clarified.

In the menthol series, equatorial hydroxyl groups have been found to undergo more rapid esterification with acyl halides than do polar groups, and ester groups in an equatorial position are more readily saponified than are those in a polar disposition. Johnston and Read (152) have reported that (+)-carvomenthol (eee) reacts more rapidly with acyl halides than does (−)-neocarvomenthol (epe). This difference is consistent with the equatorial hydroxyl in the former and the polar hydroxyl in the latter alcohol. Similarly, in the dihydrocarveol series, a comparison of the rates of saponification of the acetates of (+)-dihydrocarveol and (−)-neodihydrocarveol shows that the former reacts four times faster than the latter (280). These observations confirm the structure eee for dihydrocarveol and epe for neodihydrocarveol.

trans-Carveol has been reported to react 1.57 times faster than *cis*-carveol with *p*-nitrobenzoyl chloride (151). The steric evidence presented above indicates a 2e, 4e conformation for *cis*-carveol, in which the hydroxyl group is equatorial. The apparent discrepancy in the lesser activity of this isomer, compared with saturated alcohols such as menthol and carvomenthol, both of which contain equatorial hydroxyl groups but are more reactive than the corresponding polar-oriented epimer, is not readily apparent, but may be associated with the distortion of the ring as the result of the presence of the cycloölefinic bond.

Further investigation of the stereochemistry and reaction kinetics of the carvomenthols and related substances would be desirable.

3. Cyclohexanetriols

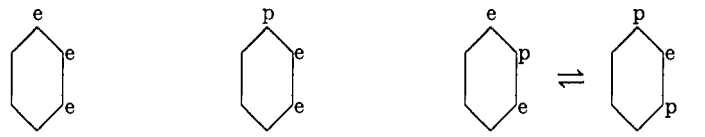
Symmetrical or 1,3,5-cyclohexanetriol exists in the form of two stereoisomers having the conformations eee and pee. On the basis of x-ray analysis (4), the structure of the α-isomer (α-phloroglucitol) has been established as eee, which is in agreement with the space group R3*c*. The β-isomer therefore must be the pee compound.

The 1,2,3-triol is capable of existence in three steric forms which have been designated α, β, and γ (176). From a conformational standpoint the orientation of the hydroxyl groups must be eee, pee, and epe. An attempt at elucidating their configurations by strictly chemical means has been unsuccessful. Thus, under conditions satisfactory for the condensation of *cis*-1,2-cyclohexanediol with acetone, all three isomers have failed to form an isopropylidene derivative (243).

Although the α-isomer is resistant to biochemical oxidation with *Acetobacter suboxydans*,[5] both the β- and γ-isomers are converted to keto derivatives (243). For oxidation, at least two vicinal hydroxyl groups must be *cis*. *cis*-1,2-Cyclohexanediol (ep), for example, yields (−)-hydroxycyclohexanone, whilst the

[5] For a detailed discussion of the nature of the oxidation effected by this organism see the section dealing with the hexahydroxycyclohexanes.

trans diol (ee $\rightleftharpoons$ pp) is resistant to this treatment. Owing to its lack of reactivity the α-isomer unquestionably has the all-*trans* structure eee (XXXIII). The products of oxidation of the β- and γ-forms have been precipitated as the phenylhydrazones. Whereas the unreacted triol from the γ-isomer is optically inactive and thus identical with the original material, the unreacted alcohol from the β-compound is optically levorotatory. These facts indicate that the β-triol is a racemic alcohol (XXXIV, pee), one antipode of which is oxidized more rapidly than the other. Hence the γ-isomer must have the meso structure (XXXVa (epe) $\rightleftharpoons$ XXXVb (pep)).



XXXIII(α) XXXIV(β) XXXVa XXXVb(γ)

The oxidation product of the meso alcohol (γ), (+)-*cis*-2,3-dihydroxycyclohexanone, has been reported to be readily reduced. With a platinum catalyst in neutral solution, only the original triol (γ) is formed. With sodium amalgam in acid solution, some dextrorotatory β-triol (pee) is obtained along with the γ-isomer (epe or pep). From a consideration of the results of biochemical oxidation of a number of polyhydroxycyclohexane derivatives (194), a polar hydroxyl group appears to be oxidized in preference to an equatorial group. Hence the formation of the 2,3-dihydroxyketone is consistent with structure XXXVb (pep) for the γ-triol; oxidation of the polar hydroxyl in XXXVa (epe) should have afforded the 2,6-dihydroxyketone instead. The conformation of the γ-triol, therefore, is XXXVb.

Writing the structure of the 2,3-dihydroxy ketone as pe(CO),[6] the results of reduction to the triol are more readily understood:

$$\text{pe(CO)} \xrightarrow[\text{neutral solution}]{\text{platinum}} \text{pep}(\gamma) \qquad (1)$$

$$\text{pe(CO)} \xrightarrow[\text{acid solution}]{\text{sodium amalgam}} \text{pee}(\beta) + \text{pep}(\gamma) \qquad (2)$$

Reaction 1 is consistent with the general tendency for a ketone, on catalytic hydrogenation, to yield a polar hydroxyl group, whereas reduction by sodium, particularly under alkaline conditions, gives the thermodynamically more stable equatorial epimer. Reduction of the ketone with a platinum oxide catalyst in 10 per cent sulfuric acid, however, results in the absorption of two molecules of hydrogen and formation of *cis*-1,2-cyclohexanediol.

Barton (23) has commented as follows:

> "Catalytic hydrogenation of both hindered and unhindered ketone groups in strongly acid media (rapid hydrogenation) affords the polar alcohols. Similar re-

[6] The symbols p and e represent the orientation of the hydroxyl groups; (CO) represents the keto group on the adjacent carbon atom.

duction in neutral media (slow hydrogenation) gives the equatorial alcohol if the ketone group is not hindered, the polar alcohol if it is strongly hindered. Reduction of oximes with sodium and alcohol affords the equatorial amines; catalytic hydrogenation of oximes follows the same course as catalytic hydrogenation of ketones, i.e., it is dependent on the acidity of the medium (and hence rate of hydrogenation) and the degree of hindrance of the ketone group from which the oxime is derived. These rules are a substitute for the corresponding von Auwers–Skita rule and, in many cases, are less ambiguous and more reliable. Reduction with sodium borohydride and with lithium aluminum hydride in general affords the equatorial epimer if the ketone group is not hindered, the polar epimer if it is hindered or very hindered. Ponndorf–Meerwein reduction, which is only applicable to relatively unhindered ketones, gives a higher proportion of the polar hydroxyl than do other methods (with the exception of catalytic hydrogenation in strongly acid media)."

The γ-triol (pep) contains three vicinal *cis* hydroxyl groups and thus should undergo oxidation with periodic acid or lead tetraacetate more rapidly than the β-isomer (pee), in which only one pair of hydroxyl groups is present in a *cis* relationship. The α-triol (eee), with no *cis* groupings, should react the most slowly. These expectations have been confirmed kinetically (243).

D. TETRASUBSTITUTED CYCLOHEXANES

Tetrahalocyclohexanes

Of the three positional isomers, 1,2,3,4-, 1,2,3,5-, and 1,2,4,5-tetrahalocyclohexane, stereochemical data are available only for the 1,2,3,4 and 1,2,4,5 compounds. Each positional isomer is capable of existence in ten theoretically possible conformations. However, on the basis of ring conversion, the number capable of chemical separation is reduced to six, as indicated in table 8. In agreement with the results of x-ray and electron diffraction studies, the bracketted forms are less probable thermodynamically, presumably owing to 1p, 3p chlorine–chlorine repulsions. The separable conformations of the 1,2,3,4-tetrahalo derivatives are illustrated in figure 7. The isomers eeee, peee, eepe, and peep may exist in independent mirror image forms; the enantiomorphic forms of eepp (and epep) are transformed into each other by ring conversion and hence may not be separated chemically.

TABLE 8

*Theoretical conformations of tetrachlorocyclohexane isomers**

eeee $\rightleftharpoons$ (pppp)
eeep $\rightleftharpoons$ (pppe)
eepe $\rightleftharpoons$ (ppep)
eppe $\rightleftharpoons$ peep
eepp ($\rightleftharpoons$ ppee, i.e., identity)
epep ($\rightleftharpoons$ pepe, i.e., identity)

* Since only the orientation of the chlorine substituents is given, the same descriptive symbols or nomenclature and the same equilibrium relationships may be applied to the isomeric tetrachlorocyclohexenes. The shape of the molecule of necessity will differ, depending on whether a double bond is or is not present.

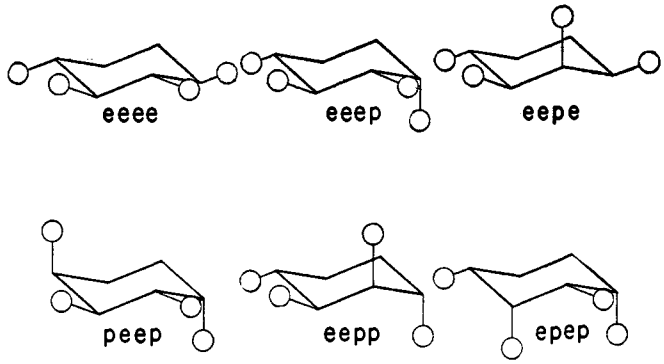


FIG. 7. Predominant conformations of the 1,2,3,4-tetrahalocyclohexane isomers. Only chlorine substituents are illustrated.

The preparation (108, 335) of three of the six separable 1,2,3,4-tetrabromocyclohexanes has been confirmed, and structural studies have been carried out (119, 188). Two isomers, melting at 89–90° and 156°C., respectively, have been synthesized by the addition of bromine to 1,3-cyclohexadiene and to 3,5-dibromocyclohexene (m.p. 108°C.). A third isomer, melting at 142°C., has also been recovered from the bromination of the latter dibromocyclohexene (119).

The isomer melting at 142°C. has been shown by x-ray analysis to have the chair form (188). Since the molecular space group is *Fdd*, indicating a sixteenfold general position and point symmetry (a twofold axis associated with the eightfold special positions), the orientation of the bromine atoms is restricted to the following possibilities: eeee and eppe $\rightleftharpoons$ peep. Interpretation of Patterson projections has been difficult as a result of deviation of the molecule from an ideal structure and uncertainties as to the positions of the carbon atoms. Nevertheless, the data leave no doubt that the conformation is 1e, 2e, 3e, 4e. Chemical support of this structure has been provided by further bromination, which resulted in the formation of β-1,2,3,4,5,6-hexabromocyclohexane (eeeeee) (261).

By first adding two atoms of chlorine and then two of bromine to 1,3-cyclohexadiene, an isomer of 1,4-dibromo-2,3-dichlorocyclohexane (m.p. 128°C.), isomorphous with the tetrabromide melting at 156°C., has been synthesized (119). Although x-ray studies of these compounds and of the tetrabromo derivative, m.p. 89–90°C., have been carried out, the steric conformations have not yet been conclusively established.

Experimental data relating to the configurations of 1,2,3,4-tetrachlorocyclohexanes have not been reported.

Two of the six separable steric isomers of 1,2,4,5-tetrabromocyclohexane have been prepared by additive bromination of 1,4-cyclohexadiene. The structure of the lower-melting (187°C.) isomer has been shown by electron diffraction and x-ray studies to have the conformation 1e, 2e, 4p, 5p, whereas the tetrabromide melting at 218°C. has the 1e, 2e, 4e, 5e form (101, 106, 120). The correctness of the latter melting point has been questioned (5), because it is lower than the values found for the isomorphous tetrachloro (226°C.) and dibromodichloro (240°C.) isomers. A higher melting point of 255°C., obtained by rapid

heating of the compound melting at 218°C., has been attributed to almost complete transformation of the eeee to the eepp conformation.

Three tetrachlorocyclohexanes, melting at 110–111°, 123–125°, and 176°C., have been isolated (5) from the products of photochlorination of cyclohexane. On the basis of physical (116, 117, 120, 127) and chemical (120, 261, 262) studies, the latter has been established as the 1e, 2e, 4p, 5p form. This is consistent with the fact that the isomer melting at 176°C. is isomorphous with the 1,2,4,5-tetrabromo derivative melting at 187°C. Fourier analyses indicate, however, that the valency angles are not strictly tetrahedral. The two bonds are not parallel; each makes an angle of 7° with the principal axis of the ring. The 1e, 2e, 4p, 5p derivatives are optically active and, since their shape is not altered by conversion of the ring, a study of their antipodes should be possible. Whether the chlorine substituents in the two lower-melting isomers are 1,2,4,5-positional isomers, however, is not known. Chlorination of 1,4-cyclohexadiene or 4,5-dichlorocyclohexene not only yields the 1,2,4,5-tetrachloro (α) derivative, m.p. 176°C., thereby confirming the positions of the halogen substituents, but also furnishes a higher-melting isomer, the β form (m.p. 226°C.) (120). The presence of a —CCl_2— group in the latter is excluded by the formation of benzene on dehalogenation with zinc (261). Its structure, which has been confirmed as 1e, 2e, 4e, 5e (120), is not altered by heating.

Two dibromochlorocyclohexanes, isomorphous with the 1,2,4,5-tetrachloro and tetrabromo analogues, have been studied. Addition of bromine to 4,5-dichlorocyclohexene yields two 1,2-dibromo-4,5-dichlorocyclohexanes: α, m.p. 171°C. (120), (172–173°C.) (261); β, m.p. 240°C. (120), (242–243°C.) (260). As in the case of the 1,2,4,5-tetrachlorocyclohexane melting at 226°C., the latter is dimorphous. The dibromodichloro compound (m.p. 171°C.) is isomorphous with the tetrachloro derivative (m.p. 176°C.) and with the tetrabromo analogue (m.p. 187°C.) in which the conformations are 1e, 2e, 4p, 5p. By means of x-ray (118) and electron diffraction (34) studies of the dibromodichlorocyclohexane, it has been shown that the stable form both in the crystal and in the vapor phase is that in which the chlorine atoms are polar and the bromine equatorial. This conformation is probably due to the smaller repulsion between a polar chlorine and the nearest polar hydrogen compared with that between a polar bromine and the nearest polar hydrogen. Heating the isomer which melts at 240°C. (1e,2e-dibromo-4e,5e-dichlorocyclohexane) above the melting point transforms the compound into the form melting at 171°C. (1e,2e-dibromo-4p,5p-dichlorocyclohexane).

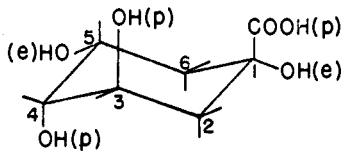
On the basis of similar isomorphic relationships with the tetrabromo and tetrachloro compounds, the higher-melting β-dibromodichlorocyclohexane must be in the form 1e, 2e, 4e, 5e (120). This structure is in agreement with dipole measurement data (260).

E. PENTASUBSTITUTED CYCLOHEXANES

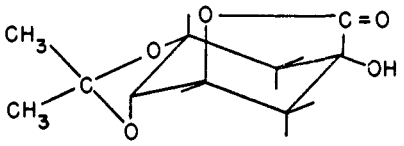
1. Tetrahydroxycyclohexanecarboxylic acids

The steric configuration of quinic acid (1,2,4,5-tetrahydroxycyclohexanecarboxylic acid) has been established along classical lines by formation of the

isopropylidene derivative of quinic lactone (89). From the standpoint of modern conformational theory the structures of these compounds may be represented as XXXVI and XXXVII, respectively.



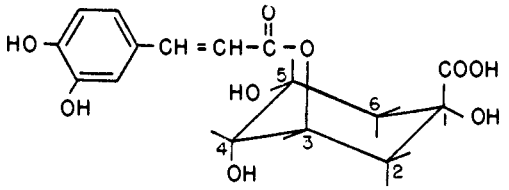
XXXVI



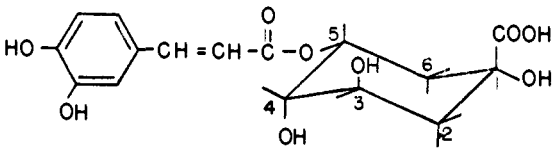
XXXVII

The participation of the carboxyl group at C_1 with the hydroxyl at C_3 in lactone formation proves these substituents to be in a *cis* (1p, 3p) relationship. The hydroxyl group at C_4 and C_5 must also be *cis* (ep) in order to give an isopropylidene derivative with acetone. 3-Methylquinic acid does not form a lactone. Hence the hydroxyl group at C_5 is *trans* with respect to the carboxyl function and must therefore be equatorial.

Two isomeric derivatives of quinic acid have been isolated from coffee (17). One of these, chlorogenic acid (XXXVIII) has been characterized (89, 94) structurally as the quinate ester of caffeic acid. The isomeric isochlorogenic acid (XXXIX) differs from it in that the equatorial hydroxyl at C_5 is involved in the ester linkage, whereas in chlorogenic acid the polar hydroxyl at C_3 is involved.



XXXVIII



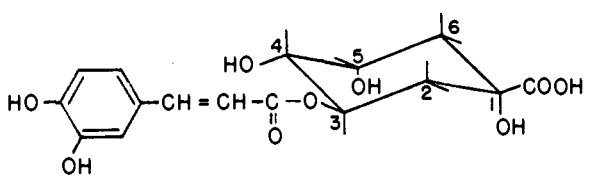
XXXIX

Both XXXVIII and XXXIX gave identical analyses, molecular weights, and saponification equivalents and yielded caffeic (3,4-dihydroxycinnamic acid) and quinic acids on hydrolysis. However, a difference in neutral equivalent was observed: *ca.* 580 for the iso compound and 354–359 for chlorogenic acid. This difference has been attributed to lactone formation between the polar hydroxyl group at C_3 and the polar carboxyl group at C_1 in the quinic acid portion of the molecule of isochlorogenic acid. Chlorogenic acid does not give a

lactone even on heating *in vacuo* over phosphorus pentoxide at 140°C.; under similar conditions isochlorogenic acid shows an increase in neutralization equivalent.

The hydroxyl groups at C_1, C_4, and C_5 have been considered as the possible location of the ester linkage. Since the electrical conductivity of boric acid is increased with both acids, a free pair of adjacent hydroxyl groups must be present. This observation establishes that the hydroxyl group in position 4 is free in both XXXVIII and XXXIX. The final choice of C_5 for the point of attachment in the isochlorogenic acid has been based upon the relative rates of oxidation of the two acids with periodic acid. Chlorogenic acid is oxidized more rapidly than is isochlorogenic acid, because a free vicinal pair of *cis* (ep) hydroxyls at C_4 and C_5 is available; in isochlorogenic acid the free hydroxyls at C_3 and C_4 are in a *trans* (pp) relationship. The oxidation rate of isochlorogenic acid is slowed down further by involvement of the hydroxyl at C_3 in lactone formation.

On the basis of conformational theory, chlorogenic acid probably exists predominantly as XXXVIIIa rather than XXXVIII, its ring conversion form.



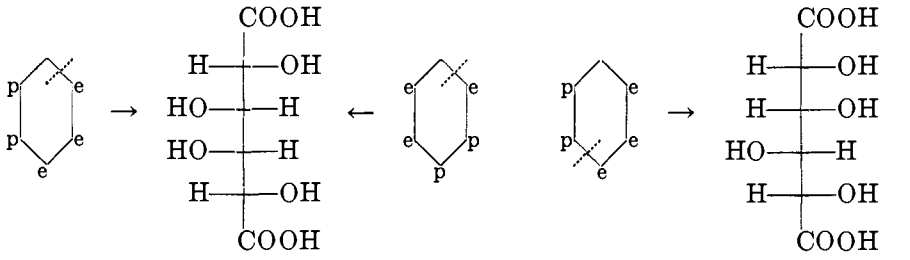
XXXVIIIa

2. Pentahydroxycyclohexanes

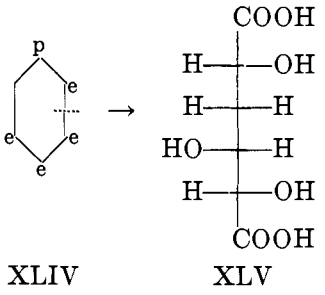
Although ten steric isomers of pentahydroxycyclohexane (pentol, quercitol, desoxyinositol) are theoretically capable of separation, only four have been described: desoxyscylloinositol or scylloquercitol (eeeee-),[7] desoxyepiinositol or epiquercitol (epeee-), desoxydextroinositol, dextroquercitol or protoquercitol (eeepp-), and desoxymesoinositol or desoxymyoinositol (eeeep-), which has also been named viburnitol or viboquercitol.

The first known pentol (232) to be characterized, desoxydextroinositol, is related structurally to dextroinositol (ppeeee). The optical activity of this compound excludes from consideration four steric structures which have a plane of symmetry and thus are optically inactive owing to internal compensation (eeeee-, eepee-, peeep-, and epepe-). The six remaining possibilities may exist as separable *dl*-pairs: eeeep-, eeepe-, eeepp-, eepep-, epeep-, and eeppe-. Oxidation with nitric acid yields mucic acid (XL), which can only come from the two pentols XLI and XLII. Permanganate oxidation, however, produces metasaccharinic acid (XLIII), which provides conclusive evidence that desoxydextroinositol has the structure XLI.

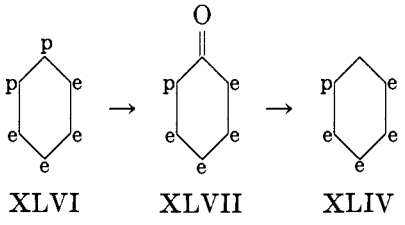
[7] The conformation eeeee- indicates the presence of five equatorial hydroxyl groups. The carbon from which a hydroxyl group is absent is designated by a hyphen. The name desoxyscylloinositol indicates a steric relationship with scylloinositol, eeeeee.



Another pentol found in *Gymnema sylvestre Br.* has been designated "*l*-quercitol" (245), although it is not an antipode of dextroquercitol. A levorotatory compound of the same composition, recovered from *Viburnum tinus L.*, has been named viburnitol (126). Upon rigorous purification, the latter material (m.p. 181–182°C.) was found to be identical with "*l*-quercitol" (244). Alkaline permanganate oxidation of viburnitol (XLIV) gives α-galactometasaccharonic acid (XLV), a result which demonstrates the presence of the group —CH₂— (239):



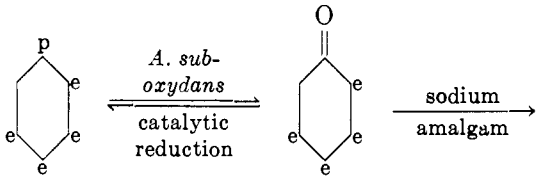
Biological oxidation of dextroinositol (XLVI) by means of *Acetobacter suboxydans* has been reported (195) to yield dextroinosose (XLVII), the term "inosose" indicating the keto form of the corresponding cyclitol. Catalytic reduction (240) of XLVII yields (+)-viburnitol (XLIV), the optical antipode of naturally occurring (−)-viburnitol.



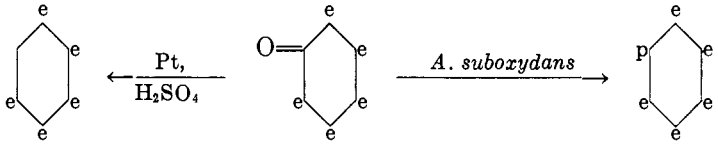
Biological oxidation with *A. suboxydans* of the polar hydroxyl group in XLIV

[8] The symbols p and e refer to the polar and equatorial orientations of the hydroxyl substituents.

furnishes an intermediate inosose (XLVIII) which, in effect, is desoxyscyllomyoinosose, whereas catalytic reduction of XLVIII results in the re-formation of the original pentol (polar hydroxyl group), (±)-viburnitol (241).



XLIV XLVIII



XLIX L LI

Reduction of XLVIII with sodium amalgam in acetic acid (which yields the *trans* or equatorial conformation) (22, 26) gives the optically inactive desoxyinositol (XLIX). The latter is identical with the pentol synthesized (236) by reduction with a platinum catalyst in sulfuric acid from scyllomyoinosose (L) which, in turn, is obtained from myoinositol (LI) by biological oxidation. This sequence of reactions confirms the equatorial conformation of the four hydroxyl groups in XLVIII and XLIX. Desoxyscylloinositol (XLIX) differs from viburnitol (XLIV) only in the configuration of a single hydroxyl group adjacent to the methylene group. The presence of a single polar hydroxyl group, and therefore of a single *cis*-α-glycol in XLIV, has been confirmed by formation of a monoisopropylidene derivative which has been isolated as the triacetate.

Reduction, with a platinum catalyst in hydrochloric acid, of the oxime of racemic epimyoinosose (LII) yields a desoxyinositol (LIII), m.p. 206–208°C., as the major product. The latter racemic pentol, which must have the same configuration as epimyoinosose (235), is epiquercitol (10, 90, 91).

LII LIII

An attempt to relate conformation with the dipole moments of the desoxyinositols has not yielded promising results (9), inasmuch as identical values (2.3 D) were obtained for the pentaacetates of desoxyscylloinositol (eeeee-) and viburnitol (eeeep-).

F. HEXASUBSTITUTED CYCLOHEXANES

1. Hexachlorocyclohexanes

Although eighteen positional isomers of hexachlorocyclohexane are theoretically possible, representatives of only two have been synthesized and their structures established. Of these by far the most important are the benzene hexachlorides (1,2,3,4,5,6-hexachlorocyclohexane), which are products of the additive chlorination of benzene. Only one isomer (α) has been detected as a product of the photocatalyzed substitution chlorination of cyclohexane, in addition to an isomer of 1,1,2,4,4,5-hexachlorocyclohexane (119, 275, 276).

Prior to 1947, only four isomers of benzene hexachloride had been identified although, on the basis of a planar six-membered ring, eight isomers were known to be possible. No rule had been proposed for correlating the structures of the known isomers with schematic planar models. One such attempt (298) subsequently has been shown to be largely without foundation. It was soon found necessary to discard the older planar concept in favor of a trigonal ring with tetrahedral valence angles. Primarily as a result of the fundamental and brilliant researches of Professor O. Hassel and his colleagues, the structures of the hexachlorides have been elucidated and a sound scientific basis for modern conformational theory has been established. The chair form of the benzene hexachloride molecule has been proven by x-ray analysis for each of the α- (115), β- (82, 87, 124), γ- (314, 315), δ- (44), and ϵ- (210) isomers.

Table 9 lists the various possibilities of e,p succession according to Hassel (121) and Bijvöet (39). Column a represents the less strained and hence the separable conversion forms. The first five structures listed in column b constitute ring conversion forms which are probably unstable (because of the steric strain

TABLE 9

Isomers of benzene hexachloride

ISOMER	META POLAR* NUMBER IN COLUMN a	NEW FORMULATION (TRIGONAL CARBON RING) a	b	META POLAR* NUMBER IN COLUMN b	OLD FORMULATION (PLANAR RING)	OPTICAL ACTIVITY
β.....	0	eeeeee $\rightleftharpoons$	pppppp	6	↑↓↑↓↑↓ or 135	0
δ.....	0	peeeee $\rightleftharpoons$	eppppp	4	↑↑↓↑↓↑ or 13	0
α†...	0	ppeeee $\rightleftharpoons$	eepppp	2	↑↓↓↑↓↑ or 124	±
θ.....	1	pepeee $\rightleftharpoons$	epeppp	3	↑↑↑↑↓↑ or 1	0
ϵ.....	0	peepee $\rightleftharpoons$	eppepp	2	↑↑↓↓↓↑ or 123	0
γ.....	1	pppeee ($\rightleftharpoons$ eeeppp, i.e., identity)		1	↑↓↑↑↓↑ or 14	0
η‡...	1	ppepee ($\rightleftharpoons$ eepepp, i.e., $d \rightleftharpoons l$ isomers)		1	↑↓↓↓↓↑ or 12	±
ι.....	3	pepepe ($\rightleftharpoons$ epepep, i.e., identity)		3	↑↑↑↑↑↑ or 123456	0

* Number of meta polar carbon–chlorine bonds.

† The conformation ppeeee represents a pair of separable *dl* isomers; ring conversion to eepppp gives rise to a different pair of *dl* isomers. There is no identity between the pairs of *dl* isomers.

‡ The conformation ppepee represents a *dl* pair. However, separation is impossible because ring conversion results in racemization.

resulting from the larger number of meta polar (1p, 3p) carbon–chlorine bonds) compared with the corresponding ring conversion forms in column a. As seen in the table, there are ten isomers for which conversion leads to a different form; when three e- and p-bonds are present, conversion results in identity (γ, ι) or a mirror image (η). The older formulation based on a planar ring does not differentiate between the two configurations (e.g., eeeeee, pppppp), which are of quite different shape.

If one were to assume that ring conversion does not take place readily, it would theoretically be possible to isolate thirteen steric isomers of benzene hexachloride, of which three would exist as optically active pairs, making a total of sixteen steric and optical isomers. If ring conversion is assumed to take place readily, then there are only eight separable steric isomers of which only one (α) has a separable pair of enantiomorphs. Chemical evidence for ring conversion (220) supports the smaller number.

Until recently considerable uncertainty existed as to the possible existence or stability of configurations containing two chlorine atoms in positions 1p, 3p (on the same side of the puckered ring). This was suggested by the short distance (2.52 Å.) between the substituents, compared with the van der Waals radius of the chlorine atom ($2\ \rho_{\text{Cl}} = 3.8$ Å.), if tetrahedral angles are conserved. The discovery of seven isomers of benzene hexachloride (156, 162) demonstrates that the existence of at least one pair of meta polar chlorine substituents does not impart sufficient steric strain to prevent formation of that isomer, although some distortion of the molecule may result. In the case of γ-benzene hexachloride (pppeee) the steric effect results in a bending out of the 1p, 3p carbon–chlorine bonds (315) (figure 8). The lines Cl_1—Cl_3, Cl_4—Cl_6, C_1—C_3, and C_4—C_6 are not parallel; in fact there are deviations from parallelism up to 4° in each coordinate. Most of the valency angles show but slight deviations from the tetrahedral value. The angle between C_1—C_2 and C_2—C_3, the carbons supporting the polar chlorines, amounts to 123°.[9]

The eighth theoretically separable benzene hexachloride, ι (pepepe), which has not yet been found, has an even more strained structure than do the γ (pppeee) η (peppee), and θ (pepeee) isomers, since three meta polar substituents (1p, 3p, 5p) project on the same side of the principal plane of the ring. For this reason,

[9] An example wherein the presence of a meta polar steric interaction actually results in ring conversion has been cited by Corey (69). Introduction of a *gem*-dimethyl group in the 4-position of polar 2-bromocyclohexanone (V) results in the formation of 2-bromo-4,4-dimethylcyclohexanone and conversion of the ring to give LIVa (bromine equatorial) rather than LIVb (bromine polar). This is an example wherein the meta polar bromine–bromine steric repulsion is more effective than the electrostatic bromine–carbonyl interaction which makes V the stable epimer of 2-bromocyclohexanone.

In *cis*-2,6-dibromocyclohexanone, the meta bromine–bromine steric repulsion overcomes the electrostatic effect and causes the equilibrium to favor the diequatorial conformation (70). The latter, however, is less stable than the *trans* (1e, 3p) isomer in which the meta polar steric effect is eliminated and, at the same time, the carbonyl electrostatic effect is relieved by one bromine substituent taking up a polar position.

These concepts have been extended recently as a means of predicting the stereochemistry of α-brominated ketosteroids (70a). When the product of bromination is thermodynami-

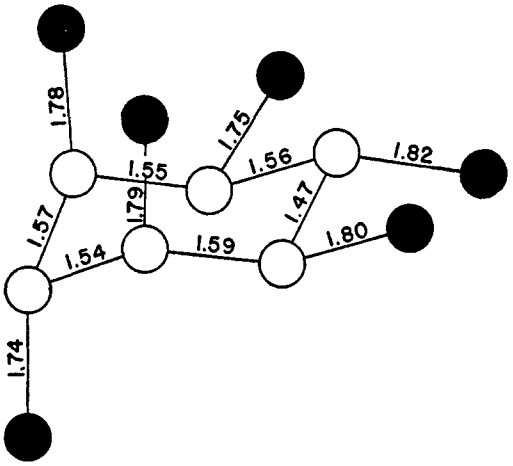


FIG. 8. Steric structure of γ-benzene hexachloride, indicating interatomic bond distances (Å.).

and because ι-benzene hexachloride represents an all-*cis* addition product, its formation and isolation appear improbable.

The conformations of the α-, β-, γ-, δ-, and ϵ-benzene hexachlorides have been established beyond doubt by physical and chemical techniques; those of the η- and θ-isomers have been derived on chemical grounds. Using the electron-

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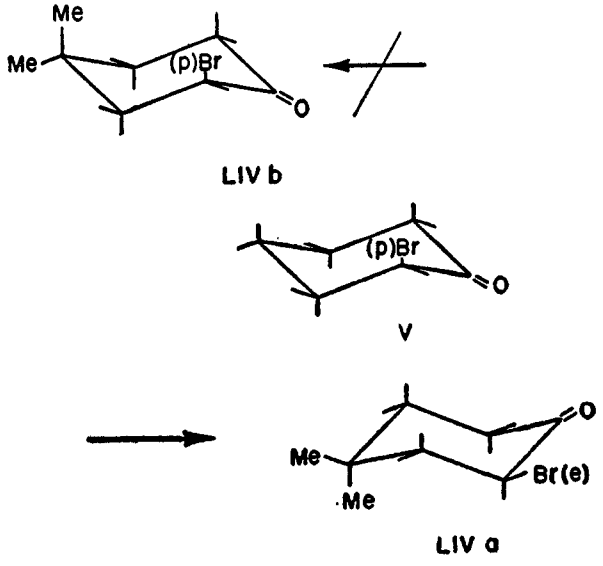
cally (equilibrium) controlled, the stable epimer will predominate. In kinetic(rate)-controlled bromination, the epimer which is formed faster is stated to be that in which the bromine is polar.

Ring conversion of the benzene hexachlorides, of course, would not relieve the meta polar strain.



diffraction sector method, Bastiansen, Ellefsen, and Hassel (29, 30) have investigated the structures of the α-, β-, γ-, δ-, and ϵ-isomers in the vapor phase. The interaction of atoms not directly linked together was considered sufficient to make the concentration of the less stable conformation (column b, table 9) in the vapor practically equal to zero. Examination of the $\sigma(r)/r$ curves showed seven pronounced peaks resulting from atomic interactions. The position of the sixth peak, due to the internuclear distance Cl_{1e}—Cl_{3e}, was the same in each case, but the heights observed decreased in the order $\beta > \delta > \alpha \approx \epsilon > \gamma$. This relationship coincided with the expected relative heights β (six meta equatorial chlorines), δ (four), α (two), ϵ (two), γ (one). Employing β-benzene hexachloride as a standard of reference, since its structure was known to be the all-*trans* form (82, 124), experimental and theoretical differential curves were compared for the isomer pairs: (β–δ), (β–α), (β–ϵ), and (β–γ). The (β–α) and (β–ϵ) curves were similar, requiring a consideration of the (ϵ–α) curve as well. The interpretation of these studies, which are in agreement with the results of x-ray investigations reported subsequently (44, 210, 314, 315), established the conformations of the isomers as α (ppeeee), β (eeeeee), γ (pppeee), δ (peeeee), and ϵ (peepee).

As shown in table 10, calculated dipole moments of the isomers are in agreement with reported experimental data.

Cristol (75) has provided chemical evidence for the structure of α-benzene hexachloride by demonstrating it to be capable of optical resolution. In accordance with theory, only the isomer pair ppeeee $\rightleftharpoons$ eepppp can exist separately as optically active isomers. The (−)-enantiomer (m.p. 128–132°C.) was separated by means of the reaction:

$$(\pm)\text{-}C_6H_6Cl_6 + \tfrac{3}{2}\text{brucine} \rightarrow \tfrac{1}{2}\text{-active } C_6H_6Cl_6 + \tfrac{3}{2}\text{ brucine}\cdot HCl + \tfrac{1}{2}C_6H_3Cl_3$$

X-ray investigation (115) of the purified product showed the crystal class to be orthorhombic sphenoidal, in conformity with the fact that the crystals contained levorotatory molecules only. The space group ($D_2^4 - P2_12_12_1$, four molecules per unit cell) does not require the molecule to possess a twofold axis of symmetry, which would have been compatible with the configuration revealed by electron diffraction analysis.

TABLE 10

Dipole moments of the benzene hexachlorides

ISOMER	EXPERIMENTAL MOMENT*			CALCULATED VALUE		
	(3, 127)†	(175)	(204)	(29, 30)	(175)	(204)
	D	*D*	*D*	*D*	*D*	*D*
α	2.20	2.16	2.22	3.4	3.2	2.25
β	0	0.34	0	0	0	0
γ	2.89	2.84	2.80	4.9	4.6	2.93–3.19
δ	2.17	2.24	2.22	3.4	3.2	2.25
ϵ		0.43	0	0	0	0

* Measured in benzene solution.

† Reference numbers are in parentheses.

From the relationships between the isomers of benzene hexachloride and those of the hepta- and octachlorocyclohexanes, Oiwa and coworkers (207, 214, 215) have provided chemical proof for the structures of the isomers of benzene hexachloride. Chlorination of β-benzene hexachloride yields α-heptachlorocyclohexane ($C_6H_5Cl_7$), m.p. 153–154°C. (196), and two isomers of octachlorocyclohexane ($C_6H_4Cl_8$). One of the latter, melting at 148–149°C., is also obtained by the additive photochlorination of *o*-dichlorobenzene, while the other (m.p. 262°C.) is obtained from *p*-dichlorobenzene (177, 178). The Japanese workers have designated these octachlorocyclohexanes as "*o*-octa" and "β-*p*-octa," respectively. Since β-benzene hexachloride has the conformation eeeeee, the structure of α-$C_6H_5Cl_7$ (which has also been prepared by the additive chlorination of monochlorobenzene) must be (pe)eeeee.[10] By the same reasoning, the structures of *o*-octa and β-*p*-octa must be (pe)(pe)eeee and (pe)ee(pe)ee, respectively. Both α- and δ-benzene hexachloride give rise to *o*-octa on further chlorination. Aside from β-benzene hexachloride, the only other structures which can form *o*-octa are peeeee and ppeeee. Since δ-benzene hexachloride, but not α-benzene hexachloride, may be chlorinated to α-$C_6H_5Cl_7$, (pe)eeeee, the configuration of the δ-isomer must be peeeee, whilst that of the α-isomer is ppeeee. β-*p*-Octa, on the other hand, may be obtained from only three hexachlorides, eeeeee (β), peeeee (δ), and peepee. Since ϵ-benzene hexachloride can form β-*p*-octa on chlorination, its structure must be peepee, which is in agreement with its zero dipole moment. The proof of structure of γ-benzene hexachloride (pppeee) is based on a valid though involved relationship between the theoretical and experimental chlorination and monodehydrochlorination products of the γ-isomer and the three remaining unassigned structures, peppee, pepeee, and pepepe.

Further chemical confirmation has been provided by the results of chlorination of the isomers of benzene tetrachloride (220).

A hexachlorocyclohexane melting at 145°C. and having a zero dipole moment was considered to be a new isomer (ζ) of benzene hexachloride and was erroneously assigned (33) the structure subsequently established for the ϵ-isomer. The compound melting at 145°C. has since been shown by x-ray and electron diffraction (85) and by chemical (58, 258, 261, 262, 264) investigation to have the structure 1(ep), 2e, 4(ep), 5e. Of the positional isomers of $C_6H_6Cl_6$, only two (1,1,3,3,5,5 and 1,1,2,4,4,5) in addition to β- and ϵ-benzene hexachloride can have a zero dipole moment. Dehydrochlorination of the substance melting at 145°C. yields only 1,2,4-trichlorobenzene (58), a result which is consistent with the 1,1,2,4,4,5 assignment; 1,1,3,3,5,5-benzene hexachloride would have yielded 1,3,5-trichlorobenzene. To establish the actual conformation, three steric isomers were considered (258, 261, 262, 264): 1(ep), 2e, 4(ep), 5e $\rightleftharpoons$ 1(ep), 2p, 4(ep), 5p, and 1(ep), 2e, 4(ep), 5p. The latter was excluded, since it would not possess a zero dipole moment. The second structure was excluded by the large repulsions of the meta polar chlorines in the 1,5- and 2,4-positions. Such repulsions would be

[10] The bracketted letters (pe) indicate the presence of a polar and an equatorial chlorine bonded to the same carbon atom.

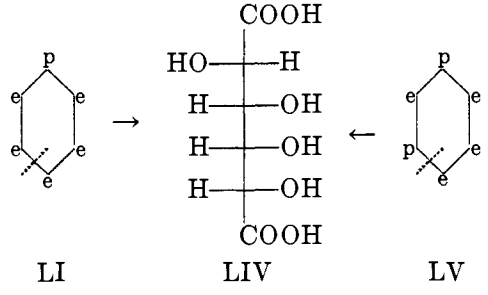
absent from the first of the three structures. Further evidence for the 1(ep), 2e, 4(ep), 5e assignment has been provided by chlorination of the isomer melting at 145°C., which yielded β-*p*-octa, 1(ep), 2e, 3e, 4(ep), 5e, 6e, and the so-called enneachlorocyclohexane, m.p. 95°C., 1(ep), 2(ep), 3e, 4(ep), 5e, 6e (119), the latter also obtained by the additive chlorination of 1,2,4-trichlorobenzene (326).

2. Hexahydroxycyclohexanes (inositols)

Because of their widespread occurrence in plant and animal tissues, the inositols represent the most important group of the so-called cyclitols (polyhydroxycyclohexanes). Despite considerable confusion in nomenclature based on the concept of the planar ring, as summarized in recent discussions on the subject (5, 10, 90, 91, 194), the classical stereochemistry of the cyclitols to a large extent has been clarified. It may be pointed out that structural assignments, based on the chair form of the cyclohexane molecule and the concept of equatorial and polar substituents, not only simplifies the steric picture of these compounds but also enables their relations to be more readily understood. As in the case of benzene hexachloride, eight separable steric isomers of inositol are possible, one of which can exist as optical enantiomorphs. Six of the steric isomers, including both of the separable optical isomers, have been characterized: scylloinositol (eeeeee), meso- or myoinositol (91) (peeeee), dextro- and levoinositol (ppeeee), epiinositol (pepeee), alloinositol (peppee), and mucoinositol (pppeee). Inositols having the structures peepee and pepepe are still unknown.

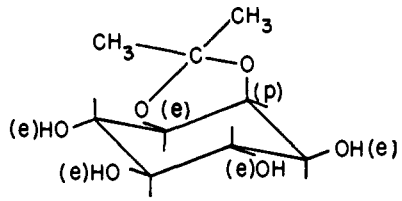
Myoinositol is the most widespread member of the cyclitol group in nature. It occurs in both plants and animals, *inter alia* as an optically active monomethyl ether, bornesitol(in rubber); as an inactive dimethyl ether, dambonitol (in latex); as lipositol, a phospholipid from the soybean; and as the calcium or magnesium salt of its hexaphosphoric acid ester, phytin. Its biochemical activity (92, 194, 211, 330) is presumably related to the presence of the single polar hydroxyl group.

Evidence for the steric structure peeeee has been provided largely by the following observations. Oxidation of myoinositol (LI) with alkaline permanganate yielded D,L-talomucic acid (LIV) (239). The only other inositol which can give the same acid is LV (pepeee). Formation of a monoisopropylidene derivative (LVI) of myoinositol by acetonation in acetic acid with zinc chloride as the

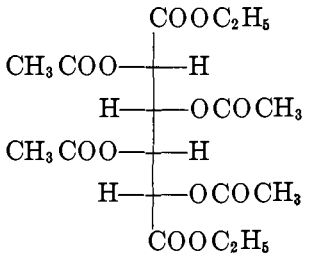


LI LIV LV

catalyst (77) strongly suggested the presence of at least one vicinal pair of *cis* hydroxyl groups. Acetylation of the four remaining free hydroxyl groups, followed by elimination of acetone to yield the tetraacetate, oxidation with lead tetra-



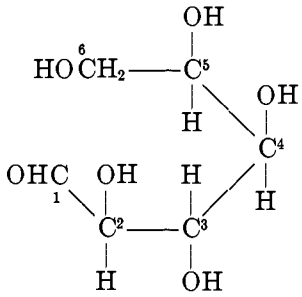
LVI



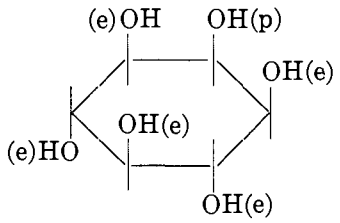
LVII

acetate and then with peracetic acid, and finally esterification, yielded diethyl tetraacetyl-D,L-idosaccharate (LVII). Since the latter is a derivative of the all-*trans* acid, the four free hydroxyl groups in LVI must be equatorial. Formula LI is thus unequivocally favored over LV.

Myoinositol (LIa) is configurationally related to D-glucose (LVIII). Ring closure of the latter by an aldol condensation involves the formation of two new asymmetric centers (1,6) in which the hydroxyl substituents are *trans*.

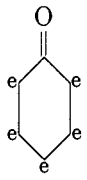


LVIII

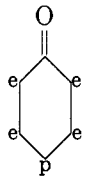


LIa

Scylloinositol (scyllitol) (10) is a naturally occurring inositol having the all-*trans* configuration, eeeeee. As in the case of β-benzene hexachloride, it is the symmetrical and therefore the highest-melting (m.p. 353–355°C.) (8) isomer. On biochemical oxidation with *A. suboxydans*, myoinositol furnishes an optically inactive inosose which must therefore be L or LIX (236). Reduction of the ketone with sodium amalgam in acetic acid yields a mixture of myoinositol and scyllo-



L

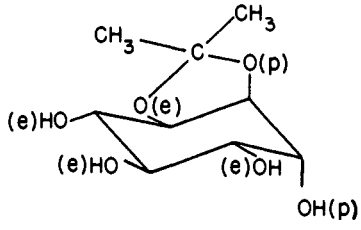


LIX

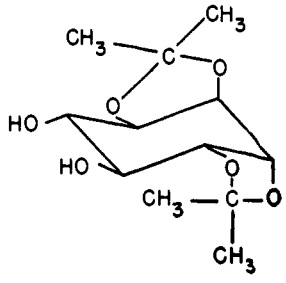
inositol. Since myoinositol has the form peeeee, the conformation of scylloinositol must be eeeeee and the ketone must be L. The latter is designated scyllomyo-inosose to denote generic relationship with scylloinositol and myoinositol (237). The all-*trans* configuration of scylloinositol has been confirmed by permanganate oxidation to D,L-idosaccharic acid (*cf.* LVII) and by its failure to yield an isopropylidene derivative (10).

Dextroinositol (D-inositol) occurs in plants *inter alia* as the monomethyl ether, pinitol. Its enantiomorph, levo- or L-inositol, is found in nature predominantly as a monomethyl ether, quebrachitol. As predicted by theory, the only hexa-substituted cyclohexane derivative which can exist as separable optical isomers must have the conformation ppeeee. The structure of D-inositol has been related to D-glucosaccharic acid by mild permanganate oxidation (234), whereas L-inositol is related to L-glucosaccharic acid.

In addition to a monoisopropylidene derivative (LX), L-inositol forms two other isopropylidene derivatives, LXI and LXII (10). The more soluble of the

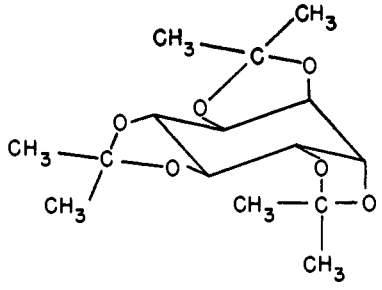


LX



LXI

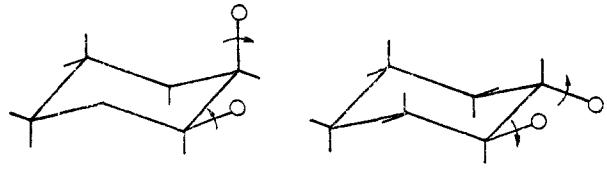
latter is 1,2,5,6-diisopropylidene-L-inositol (LXI); the higher-melting, less soluble derivative is the triisopropylidene compound (LXII), in which two *trans* (e) hydroxyl groups have reacted.



LXII

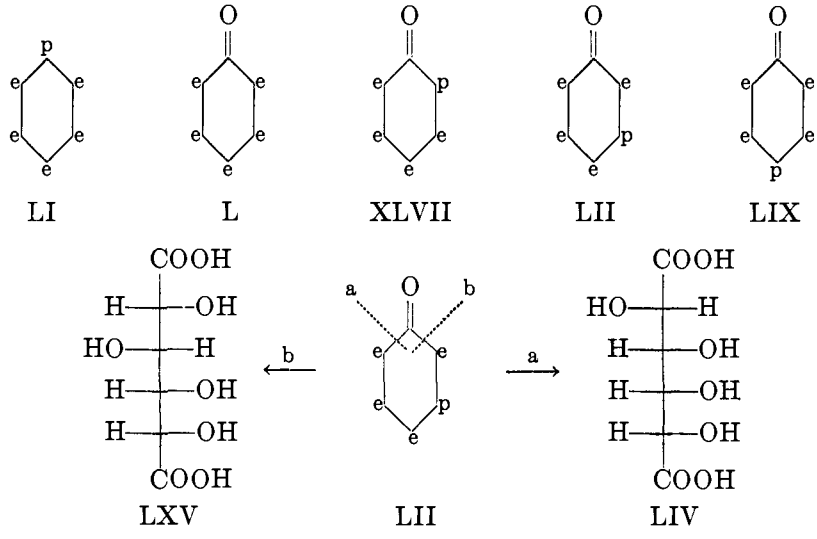
On the basis of the more stable chair form of the ring, the requirement of a *cis* relationship for cyclic acetal formation appears less obvious than from a planar ring formulation (10). For 1,2-substituents, the ee distance is the same as for ep groups. In the case of OH substituents, assuming tetrahedral angles, the

O–O distance (2.86 Å.) is too large to be bridged by one carbon atom (dipolar oxygen–oxygen distance is 3.66 Å.). In order to bring the two *cis* hydroxyls nearer to each other, the two carbon atoms to which they are attached must rotate about the carbon–oxygen bonds, as shown in formula LXIII. Comparatively little energy is involved here; the strain created is small and the inter-



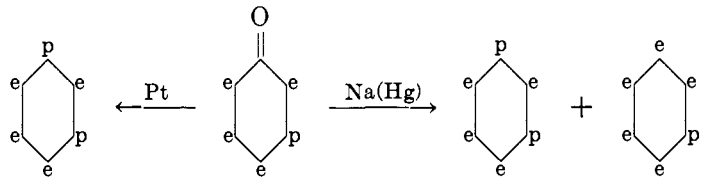
LXIII LXIV

atomic repulsions are not changed appreciably. This deformation makes the ring less puckered and increases the distance between the polar groups. When two equatorial *trans* groups are brought nearer by rotation of the carbon atoms (LXIV), the ring becomes more puckered and the two polar groups are moved nearer to the other polar substituents. Considerable energy is required because the distance between the polar groups (2.51 Å.) is not much larger than the sum of the van der Waals radii. If one of the polar groups is larger than the hydrogen, the van der Waals radii will touch or overlap. The energy is large and hence the rotation which brings the *trans* hydroxyl groups into a plane is sterically hindered. Formation of a diisopropylidene derivative from two pairs of *cis* hydroxyl groups has moved four of the polar groups nearer the equatorial belt and farther from the two remaining polar groups. Hindrance towards rotation (LXIV) is decreased and acetal formation is possible. Thus *trans* hydroxyl groups will react with acetone only if two *cis* pairs have already reacted.



The conformation of epiinositol is pepeee (235). Nitric acid oxidation of myo-inositol (LI) yields an optically inactive (racemic) inosose. Theoretically, four stereoisomeric inososes (XLVII, L, LII, and LIX) are possible. Of these, XLVII and LII can exist as optically active *dl*-pairs, whereas L and LIX are symmetrical and therefore inactive (meso). Since the configuration of L, related to scyllo-inositol, has been established (236), the choice of structure is restricted to XLVII, LII, and LIX. Oxidative cleavage of the inosose obtained from myoinositol furnishes D,L-talomucic acid (LIV) and D,L-glucosaccharic acid (LXV). These products are consistent only with formulation LII (238).

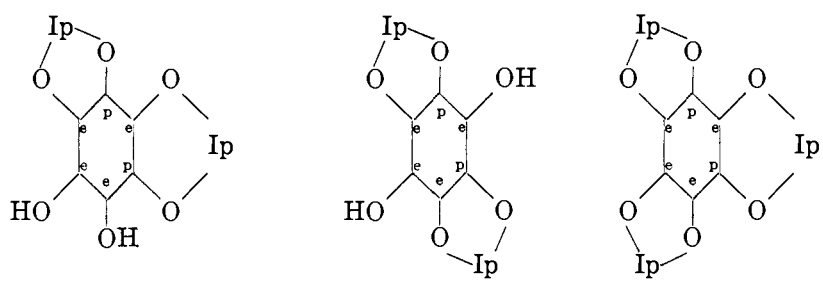
Catalytic reduction of the inosose LII yields epiinositol by introducing a polar hydroxyl group, whereas reduction with sodium amalgam in acid provides a mixture of myo- and epiinositols (235):



LV LII LV LI

These reactions unequivocally establish structure LV for epiinositol. In conformity with the accepted usage, the inosose LII has been designated epimyo-inosose.

Epiinositol, with two polar hydroxyl groups, gives two diisopropylidene derivatives (10). The one formed in larger amount (LXVI) consumes 1 mole of periodate. The other, which is resistant to oxidation, is the 1,2,4,5 derivative



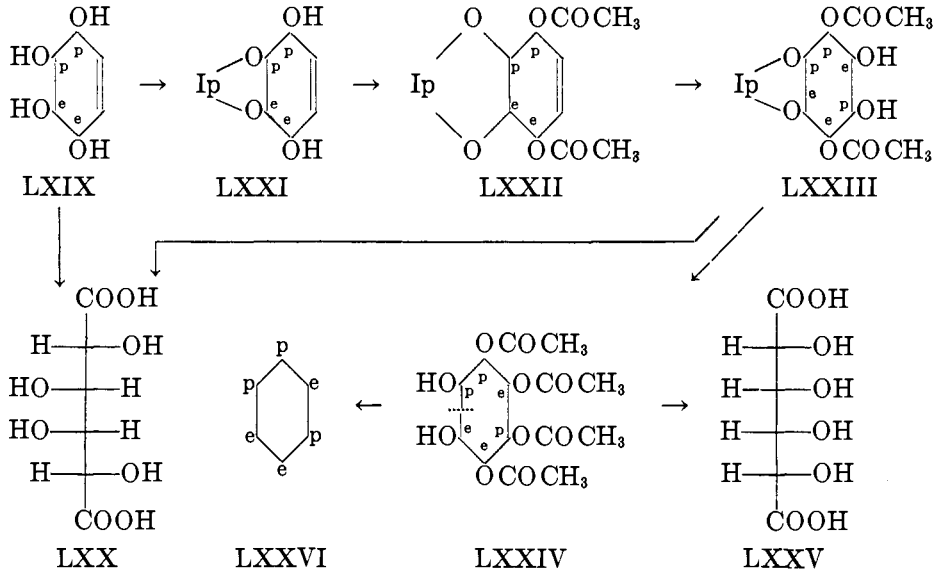
LXVI LXVII LXVIII

Ip = $C(CH_3)_2$.

(LXVII). A triisopropylidene product in which vicinal *trans* hydroxyl groups are involved in cyclic acetal formation also has been obtained. Since it yields LXVI on partial hydrolysis, the triisopropylidene compound must be LXVIII.

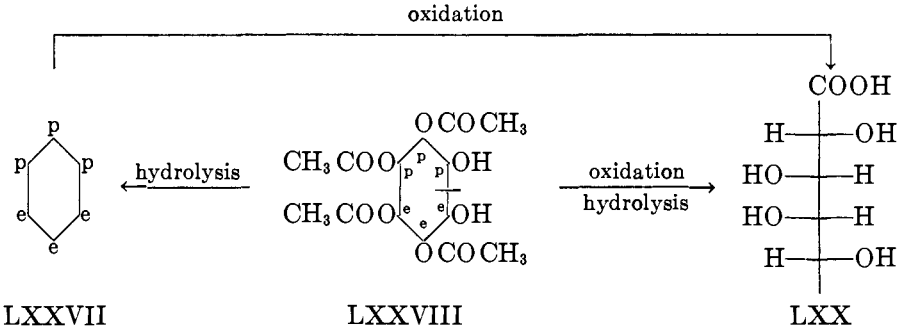
The structure of naturally occurring conduritol, a tetrahydroxycyclohexene

(LXIX), has been shown to be eepp by oxidative cleavage to mucic acid (LXX) (158).



Acetonation furnished an isopropylidene derivative (LXXI) which was stable toward lead tetraacetate (78). The diacetate ester (LXXII) of LXXI then was converted to the *cis* diol (LXXIII). Acetylation followed by deacetonation yielded the inositol tetraacetate (LXXIV), which on oxidation and hydrolysis produced allomucic acid (LXXV). Oxidation and hydrolysis of LXXIII gave mucic acid. These reactions establish the structure of alloinositol (LXXVI), the hydrolysis product of LXXIV, as ppeepe.

The structure of mucoinositol (LXXVII), the last of the known inositols (78), has been determined by hydroxylation of tetraacetylconduritol to a tetraacetylinositol (LXXVIII), which furnished mucoinositol on hydrolysis. Oxidation



of LXXVII and LXXVIII to mucic acid (LXX) confirms the configuration of mucoinositol to be pppeee, the same as that of γ-benzene hexachloride.

Although a rigorous assignment of configuration based on dipole moments has not been possible, largely because of deviations from tetrahedral angles

which make the actual moments smaller than the calculated values, the dipole moments of a number of inositol acetates were found to be in the expected sequence. To this extent, at least, the experimental data confirm the chemical proof of configuration (9).

An important relationship between the stereochemistry of the inositols and their chemical and biological activity has been investigated by Magasanik and Chargaff (194). Whereas oxidation of myoinositol (peeeee) (LI) with nitric acid yields epimyoinosose, eeepe(CO) (LII), biochemical oxidation with *Acetobacter suboxydans* (161, 236) provides scyllomyoinosose, eeeee(CO) (L). Epiinositol (pepeee) (LV) is converted by *A. suboxydans* to D,L-epimyoinosose (66). There is evidence (194) that the latter ketone, eeepe(CO), is resistant to further oxidation because the resulting product would be a 1,3-diketone, eee(CO)e(CO).

Biological oxidation with *A. suboxydans* of D-inositol (ppeeee) yields the corresponding D-inosose, eeeep(CO) (195). The structure of this inosose was proved by reduction with platinum oxide to a mixture of D-inositol and myoinositol. Absorption by the inosose of a second equivalent of oxygen yielded the 1,2-diketone, eeee(CO)(CO), which also has been obtained directly from D-inositol. Periodate oxidation of the bisphenylhydrazones from the enantiomeric diketo inositols (from D- and L-inositol) provided evidence that the carbonyl groups were vicinal (194). The unattacked hydroxyl groups were all *trans*. Hence only the polar hydroxyls had been oxidized to keto groups. The bisphenylhydrazones were found to be identical with a racemic product obtained from scyllomyoinosose (63).

Presumably owing to the absence of polar hydroxyls, scylloinositol (eeeeee) is not attacked by *A. suboxydans*.

On the basis of the data, only the polar hydroxyl groups of the inositols appear to be oxidized biologically. In epiinositol (pepeee), where two polar hydroxyl groups are present on one side of the principal plane of the ring, only one is converted to a carbonyl function. D-Inositol, however, may proceed to the diketo stage. From a study of aliphatic polyhydric alcohols, it has been shown that of two enantiomorphs, the isomer possessing the D configuration with respect to the secondary *cis* hydroxyls is oxidized more readily (107). This is confirmed by the fact that in L-inositol, which is oxidized more rapidly than the D-isomer, the hydroxyl groups that are oxidized and the neighboring *cis* hydroxyl groups have the D configuration.

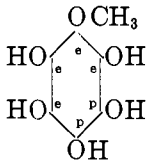
Posternak and Reymond (243a) recently have reported quantitative data on the extent of biological oxidation of a large number of polyhydroxycyclohexanes, including triols, tetrols, pentols, and inositols.

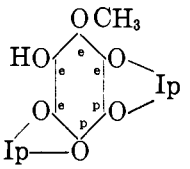
3. Inositol ethers and esters

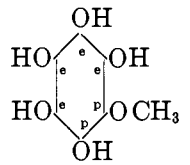
The optically active D- and L-inositols (eeeepp) occur in nature as monomethyl ethers. The more abundant of these, quebrachitol, is a derivative of L-inositol. The other, pinitol, is the ether of D-inositol. Since the ethers are not enantiomorphs, the methyl groups must be in a different position in each.

Pinitol has been condensed with two molecules of acetone (7). The methyl group, therefore, cannot be on either of the two pairs of *cis* hydroxyl groups.

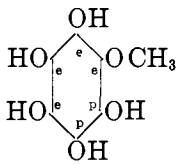
Since the two remaining hydroxyls are equivalent and equatorial, the structure of pinitol must be LXXIX and that of the diacetal, LXXX (10, 242). Quebrachitol, which may be LXXXI or LXXXII, yields a monoisopropylidene derivative

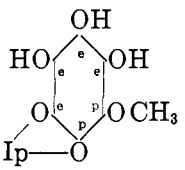

LXXIX

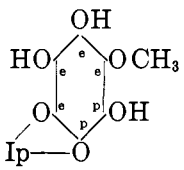

LXXX


LXXXI

(LXXXIII or LXXXIV, respectively). Posternak (242) has found that iso-

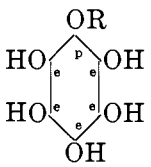

LXXXII

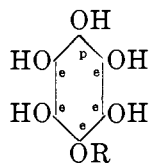

LXXXIII


LXXXIV

propylidene quebrachitol consumes 1 mole of periodate. This result is compatible only with LXXXIV, which has two free adjacent hydroxyl groups. On the other hand, LXXXIII has three adjacent hydroxyls and must therefore consume 3 moles of periodate. Quebrachitol, therefore, is LXXXII. Although both pinitol and quebrachitol have polar hydroxyl groups, neither compound is oxidized by *A. suboxydans* (194).

Sequoyital, an optically inactive (meso) monomethyl ether of myoinositol, can have either of two possible symmetrical structures, LXXXVa or LXXXVIa (189, 285). The former isomer contains only *trans*-α-glycol systems, whereas the

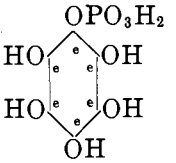

LXXXVa: R = CH_3
LXXXVb: R = PO_3H_2


LXXXVIa: R = CH_3
LXXXVIb: R = PO_3H_2

latter structure contains *cis*-α-glycol groupings which should react more rapidly than the *trans* arrangement. From a consideration of the results of oxidation by neutral sodium periodate, formula LXXXVa was favored (266). The course of oxidation was believed to be similar to that of myoinositol, in that the initial cleavage of the molecule took place at two points, giving three-carbon fragments (93). If *cis*-α-glycol groups had been present, such groupings would have been expected to react first and thus exclude the formation of tartronaldehyde. Stephen (302) observed identical behavior on oxidizing D-inositol and myo-inositol at 26°C. and noted that the oxidation of pinitol closely resembled that of sequoyital. Consequently, structures based on investigations of this kind should be treated with reserve. Further investigation of the configuration of sequoyital would be desirable.

The inositolmonophosphoric acids isolated from natural sources are optically inactive. Of the monosubstituted derivatives of myoinositol only the symmetrical structures LXXXVb and LXXXVIb should lack optical activity. The synthesis of one (LXXXVb), inositol-5-monophosphoric acid, has been accomplished from myoinositol in such a manner that the PO_3H_2 group was introduced in the molecule by phosphorylation of the polar hydroxyl group (145). The product acid is not attacked by *A. suboxydans*, presumably because the polar hydroxyl is blocked. Bioassay, involving the reaction of the polar hydroxyl group with *Saccharomyces cerevisiae*, is reduced to 4 per cent of that of free myoinositol, and with *Neurospora crassa*, to 10 per cent.

Scylloinositolmonophosphoric acid (LXXXVII) is an epimer of LXXXVb

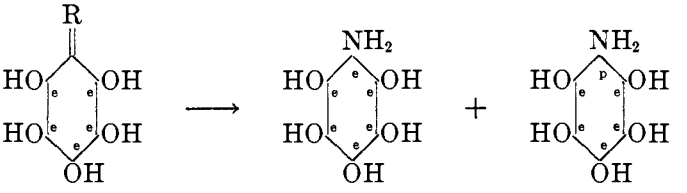


LXXXVII

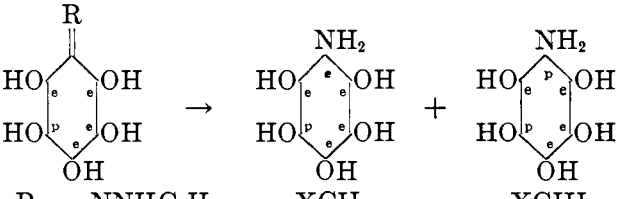
because the free hydroxyl groups are also equatorial, only the orientation of the esterified group being different.

4. Amino- and nitrodesoxyinositols

The generic name "inosamines" has been proposed for the 2,3,4,5,6-pentahydroxycyclohexylamines, which were first prepared by catalytic reduction of the phenylhydrazones or oximes of scyllomyoinosose and of racemic epimyoinosose (64). Unless carbon–oxygen bond inversions occur, the phenylhydrazone (LXXXVIIIa) or oxime (LXXXVIIIb) of scylloinosose should yield two theoretically possible inosamines (LXXXIX, XC) both of which would be meso forms. Racemic epimyoinosose phenylhydrazone (XCIa) likewise can give rise to two derivatives (XCII and XCIII), both racemic.



LXXXVIIIa: R = $NNHC_6H_5$ LXXXIX XC
LXXXVIIIb: R = NOH



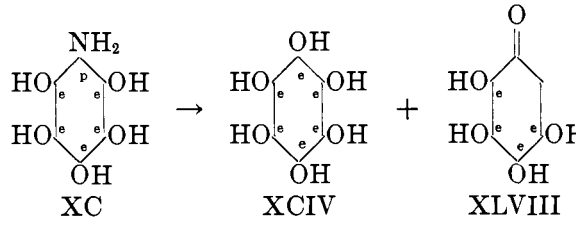
XCIa: R = $NNHC_6H_5$ XCII XCIII
XCIb: R = NOH

Carter, Clark, Lytle, and McCasland (64) obtained both LXXXIX and XC from LXXXVIII but were unable to make structural assignments. One isomer was designated "inosamine SA" and the other "inosamine SB." From XCIa, only one product, designated "*dl*-inosamine EA," was found.

Posternak (241) observed that catalytic hydrogenation (platinum oxide, acetic acid) of LXXXVIIIa and b gave primarily "inosamine SA", whereas reduction with sodium amalgam yielded chiefly the epimeric "inosamine SB." From a consideration of the reduction of cycloaliphatic ketones or oximes (134, 297, 317), the catalytic process should yield the *cis* derivative with respect to neighboring groups (NH_2 polar), while sodium reduction should give the *trans* isomer (NH_2 equatorial). Thus, the major product, "inosamine SA," from catalytic reduction of LXXXVIIIa and b must be XC, while "inosamine SB" obtained by the use of sodium amalgam must be LXXXIX. These assignments have been confirmed independently (6).

Further proof of the structures LXXXIX and XC has been provided by a study of the relative rates of oxidation of the two inosamines with periodic acid and lead tetraacetate (241). As in the case of polyhydroxy compounds, *cis* oxidation should proceed more rapidly than *trans* oxidation. XC has two hydroxyl groups and one amino group in a *cis* relationship, whereas all of the substituents of LXXXIX are *trans*. Since "inosamine SA" is oxidized more rapidly than its epimer, its configuration must be XC, as previously assigned.

Treatment of XC with nitrous acid at 0°C. yields chiefly scylloinositol (XCIV) together with a lesser amount of racemic desoxyscyllomyoinosose (XLVIII):



XC XCIV XLVIII

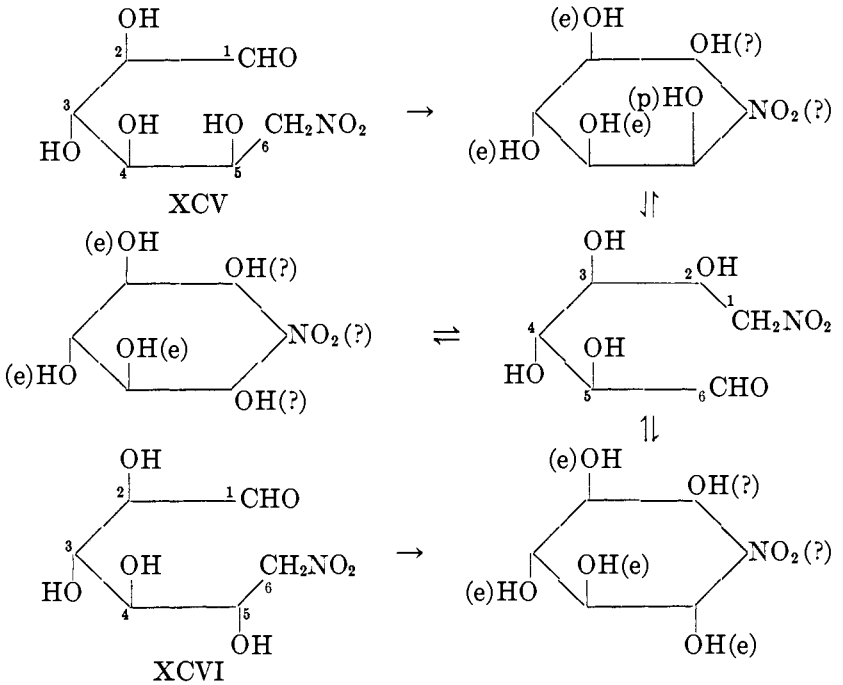
LXXXIX, subjected to similar treatment, yields myoinositol (eeeeep). The reactions of LXXXIX and XC with nitrous acid thus are accompanied by Walden inversion. While inversion is usually obtained on deamination of polar amino groups in cyclohexylamines, retention of configuration is normally the rule with equatorial NH_2 substituents (47, 71). Evidence of ring contraction to the cyclopentyl formaldehyde derivative has not been obtained.

The structure of "inosamine EA" also has been established (197, 304). The fact that it has been formed by catalytic reduction of the oxime XCIb indicates it to be XCIII. Sodium reduction of XCIb, on the other hand, furnishes the epimeric amine, XCII.

Using a mild alkaline catalyst, Grosheintz and Fischer (98) obtained a mixture of nitrodesoxyinositols (2,3,4,5,6-pentahydroxycyclohexanes) by ring closure, analogous to the aldol condensation, of 6-nitro-6-desoxy-D-glucose (XCV) and 6-nitro-6-desoxy-L-idose (XCVI). Theoretically, each of these nitrodesoxyaldehydes can yield four isomers. The asymmetric isomers from XCV, eeeepe

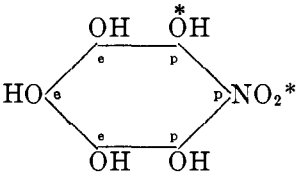
and eeeepṗ (where * indicates the location of the nitro group, and absence of * indicates a hydroxyl group) are enantiomorphic with the asymmetric derivatives of XCVI; the symmetric isomers (peeepė and peeepṗ) from XCV are different from the symmetric condensation products (eeeeeė and eeeeeṗ) from XCVI. Because of the possibility of racemic forms in the optically inactive products, Grosheintz and Fischer have been unable to exclude any of the theoretically possible conformations and thereby narrow the choice of possible structures.

The same products were obtained from both nitrodesoxyaldehydes. In the presence of dilute alkali, two derivatives resulted. One, "nitrodesoxyinositol I" (m.p. 147–148°C.; after partial purification, 172–173°C.), could not be acetonated; the other, "nitrodesoxyinositol II" (m.p. 185–186°C., dec.), yielded a diacetone derivative. In stronger alkali XCV yielded a third material ("nitrodesoxyinositol III") in 65 per cent yield. The latter product was not pure and did not react with acetone under the usual conditions for condensation. Inasmuch as the same nitrodesoxyinositols were obtained from both sugar derivatives, an equilibrium between the cyclic and open-chain forms of the nitrodesoxy sugars has been suggested:



Subsequent investigation (146) of "nitrodesoxyinositol I" yielded two pentaacetates, one of which is identical with an insoluble pentaacetate from "nitrodesoxyinositol III." The purification and characterization of the components of "nitrodesoxyinositol I" have not been reported. "Nitrodesoxyinositol II" yielded only one pentaacetate. Since its diacetone derivative is inert to oxidation with lead tetraacetate, the free hydroxyl group must be para to the nitro substituent. The structure which is in agreement with the experimental data must

therefore be XCVII (the starred substituents indicate the positions of the original CHO and CH_2NO_2 groups of the nitrodesoxyaldehyde). This assignment is consistent with a *trans* mechanism for the aldol ring closure (146), the nitro group assuming a *trans* position with respect to the neighboring hydroxyl group.

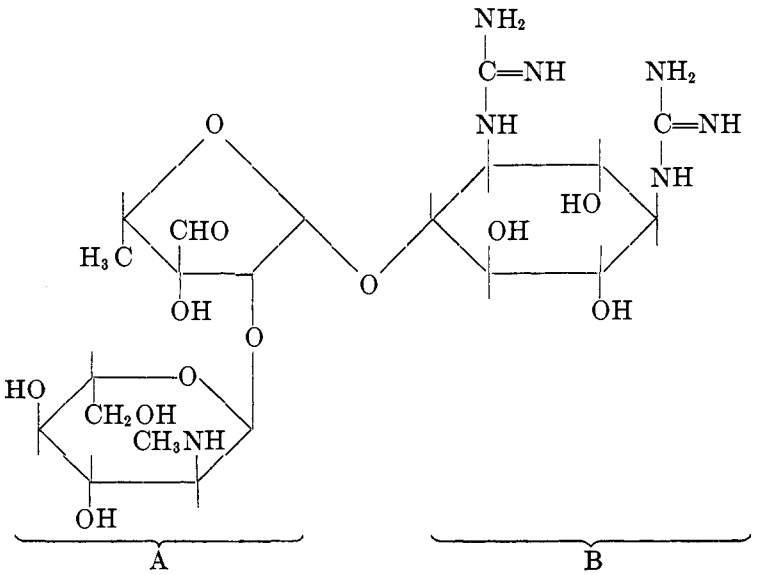


XCVII

Reduction of "nitrodesoxyinositol III" with Raney nickel (98) provides "aminodesoxyinositol III," m.p. 280–285°C. By comparison of its hexaacetate with that (m.p. 288°C.) of "inosamine SB" (LXXXIX), which gave no evidence of mixed-melting-point depression, Posternak (241) has concluded that both amino compounds are identical. This evidence suggests that "nitrodesoxyinositol III" is the all-*trans* isomer, eeeeeė, wherein the asterisk indicates the position of the nitro group.

5. Streptidine

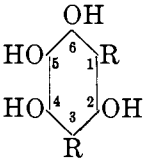
Streptomycin (XCVIII) has been established by stepwise degradation to be a compound of streptobiosamine (A) and streptidine (B), joined glycosidically in the order: *N*-methyl-L-glucosamine → L-streptose → streptidine (50, 174). On degradation of the streptidine moiety by permanganate oxidation, the presence of two guanido groups has been ascertained (226). Treatment of streptidine (XCIXa) with barium hydroxide results in the stepwise formation of a



XCVIII*

* Hydrogen atoms bonded to the ring carbon atoms are not shown.

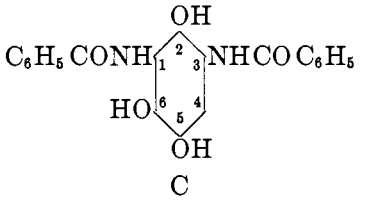
neutral substance, strepturea (XCIXb), and a basic substance (XCIXc). By periodate oxidation and other studies, streptidine was shown to be one of the meso forms[11] of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane. Strepturea and streptamine are the corresponding urea- and amine-like structures.



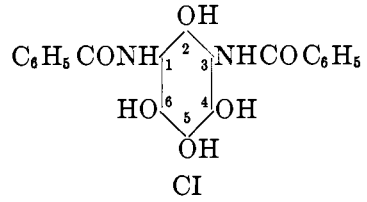
XCIXa: R = —NHC(=NH)NH_2
XCIXb: R = —NHCONH_2
XCIXc: R = —NH_2

From the results of attempted periodic acid oxidation of streptomycin, Carter, Loo, and Skell (65) have concluded that the streptobiosamine moiety may be attached to the streptidine ring in such a manner as to inhibit the oxidation, and have suggested that the streptidine portion of the molecule is attached at the C_5-position, although the possibility of attachment at C_4 or C_6 (equivalent) could not be excluded.

Reaction of streptomycin with benzoyl chloride and pyridine yielded undecabenzoylstreptomycin, from which heptabenzoylstreptidine was obtained (169). Treatment with periodate of *N*,*N*′-dibenzoyldesoxystreptamine and *N*,*N*′-dibenzoylstreptamine, products of further stepwise degradation, resulted in the consumption of 1 and 2 moles of periodate, respectively. The formation of α,γ-dibenzamido-β-hydroxyadipaldehyde from the oxidation of *N*,*N*′-dibenzoylstreptamine, as a result of cleavage between the C_5- and C_6-positions, is consistent with the presence of a free hydroxyl group at C_4 (or C_6) but not with one at C_2 or C_5 (168). These results indicate the structures of *N*,*N*′-dibenzoyldesoxystreptamine and *N*,*N*′-dibenzoylstreptamine to be C and CI, respectively, and



C



CI

provide evidence for attachment of the streptobiosamine moiety at the C_4-position of streptidine. Formation of more than one equivalent of dibenzoylguanidine upon chromic acid oxidation of heptabenzoylstreptidine shows that streptidine is linked to streptobiosamine through an oxygen atom (227).

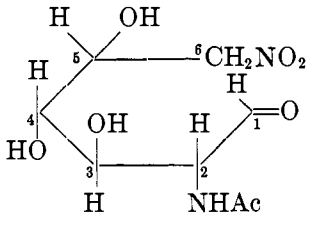
Although streptidine is optically inactive (meso) and has *cis* guanido (1e, 3e) groups, heptabenzoylstreptidine is optically active (168). This proves that the

[11] Eight meso forms of XCIX are possible: pep̊ep̊, pep̊ee̊, epe̊ep̊, epe̊ee̊, eep̊ep̊, ppe̊ee̊, eee̊pe̊, and eee̊ee̊, where * indicates the nitrogen-containing substituent. Since the compound is optically inactive, the two guanido (or amino) groups must lie on the same side of the ring.

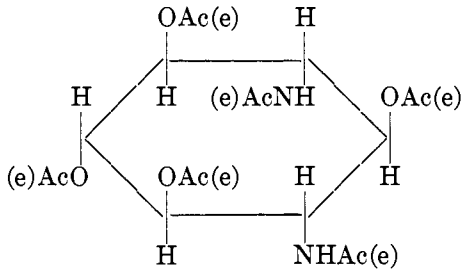
unbenzoylated hydroxyl group (the hydroxyl involved in the glycosidic linkage) cannot be at the C_2 or C_5 of streptidine, since such an arrangement would result in a plane of symmetry and optical inactivity. These considerations place the unbenzoylated hydroxyl group in heptabenzoylstreptidine at C_4 (or C_6).

Upon hydrolysis with hydrochloric acid, the *O*-tetramethyl derivative of *N*,*N'*-diacetylstreptamine yields *O*-tetramethylstreptamine dihydrochloride (226, 328). Oxidation of the latter furnished an acidic product which was converted to a mixture of methyl esters, distilled, and converted to the diamides by reaction with ammonia or methylamine in methanol. From the lower-boiling fractions D,L-dimethoxysuccinic acid diamide and D,L-dimethoxysuccinic acid di-*N*-methylamide were isolated. If streptamine and streptidine are meso compounds, the results would indicate that the hydroxyl group at C_5 is *trans* to those at C_4 and C_6; only such an arrangement could yield a racemic dimethoxysuccinic acid. The eight theoretically possible meso forms of streptamine are thus narrowed down to four: eeeėėė, eeeėpė, eeepėp, and pppėėė.

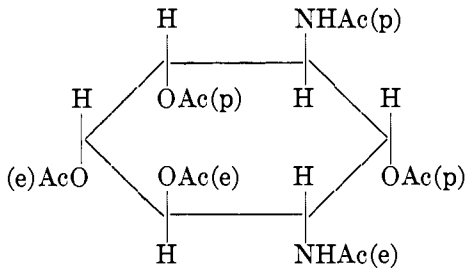
Unequivocal evidence which established the conformation of streptidine as eeeėėė has been provided by the synthesis of streptamine from active D-glucosamine via the intermediate nitroaldehyde CII (329). Intramolecular ring closure of the latter yielded two stereoisomeric products which were isolated as the hexaacetyl derivatives (CIII and CIV) of 1,3-diaminotetrahydroxycyclohexane. By conversion of the major product (CIII) to streptidine sulfate monohydrate (CV), identical with the product obtained by hydrolysis of streptomycin, the all-*trans* structure (eeeėėė) of CIII has definitely been established as identical with that of the substituent groups in streptidine. CIV represents the only other



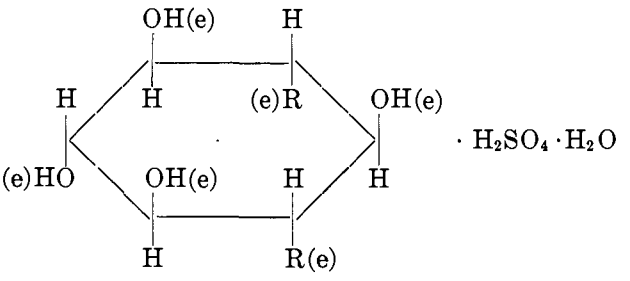
CII



CIII



CIV



CV

Ac = $COCH_3$; R = $NHC(=NH)NH_2$.

possible substance derivable from D-glucosamine and possessing the all-*trans* configuration on the centers C_1, C_5, and C_6, which were involved in the carbonyl condensation reaction.

G. HEPTASUBSTITUTED CYCLOHEXANES

Heptachlorocyclohexanes

On the basis of ring conversion, the twenty theoretically possible isomers of heptachlorocyclohexane are reduced to ten separable forms (column a, table 11). The correlation between isomers which reportedly have been isolated and the tabulated theoretical conformations has been complicated by conflicting interpretations based in part upon inadequate experimental data. Owing largely to the intensive investigations of Oiwa, Nakazima, and their associates (204, 207, 209, 214–218), it has been possible to assign with certainty the configurations of the α-, γ-, δ-, and ϵ-isomers. Evidence for the structures of additional heptachlorocyclohexanes has been presented (72, 263).

The structure of α-$C_6H_5Cl_7$ (i), (pe)eeeee, appears to be certain, since it is

TABLE 11

The isomers of heptachlorocyclohexane

NO.	CONFORMATION		BENZENE HEXACHLORIDE PRECURSOR	DIPOLE MOMENT (204)		SYMBOL	MELTING POINT
	a	b		Calculated	Found		
							°C.
i	(pe)eeeee	⇌ (ep)ppppp	β, δ	1.02	1.19	α	153–154
ii	p(pe)eeee	⇌ e(ep)pppp	α, δ	1.25	1.35	γ	85–86
iii	pe(pe)eee	⇌ ep(ep)ppp	δ, θ	2.67			
iv	pee(pe)ee	⇌ epp(ep)pp	δ, ϵ	1.45		ζ	154
v	ppee(pe)e	⇌ eepp(ep)p	α, η	2.20	2.20	δ	139–140
vi	ppeee(pe)	⇌ eeppp(ep)	α, γ	2.22	2.20	ϵ	55–55.5
vii	peepe(pe)	⇌ eppep(ep)	ϵ, η	0.85		η	101*
viii	pee(pe)ep	⇌ epp(ep)pe	η, θ	2.37			
ix	p(pe)peee	⇌ e(ep)eppp	γ, θ	1.97			
x	epepe(pe)	⇌ pepep(ep)	ι	3.44			

* Private communication from R. Riemschneider.

formed only from β- and δ-benzene hexachlorides and by additive chlorination of monochlorobenzene (196). Upon chlorination, α-$C_6H_5Cl_7$ forms two octachlorocyclohexanes, "*o*-octa", (pe)(pe)eeee, and "β-*p*-octa", (pe)ee(pe)ee. Isomer ii can give rise to "*o*-octa" but not to "β-*p*-octa. Coutier (72) obtained "β-heptachlorocyclohexane," m.p. 240°C., from the chlorination of β- and δ-benzene hexachlorides and assigned the structure (pe)eeeee to it. However, Oiwa *et al.* have indicated that Coutier's compound is undoubtedly "β-*p*-octa", m.p. 260°C. (218). This conclusion has been confirmed by the formation of penta- rather than tetrachlorobenzene by dehydrohalogenation of the so-called "β-heptachlorocyclohexane" (259).

The only heptachlorocyclohexane other than i which can yield "*o*-octa" is ii, p(pe)eee. Since γ-$C_6H_5Cl_7$, m.p. 85–86°C., obtained from both α- and δ-benzene hexachloride (214, 215), does indeed yield "*o*-octa" (216), its structure is without doubt p(pe)eeee.

In addition to γ-heptachlorocyclohexane, α-benzene hexachloride can form v and vi. The latter isomer, which also may be obtained by the chlorination of γ-benzene hexachloride, is capable of resolution into optically active forms. From the product of chlorination of γ-benzene hexachloride, Oiwa, Yamada, and Ohno (217) have isolated a heptachlorocyclohexane, m.p. 55–55.5°C., and succeeded in separating a levorotatory enantiometer from it by means of (−)-brucine. This reaction characterizes the compound melting at 55°C. as vi, i.e., ε-heptachlorocyclohexane. δ-Heptachlorocyclohexane, m.p. 139–140°C., the other product obtained from α-benzene hexachloride, must therefore be v. Coutier's "ζ-heptachlorocyclohexane," m.p. 39°C., is probably the ε-isomer, m.p. 55–55.5°C.

Coutier also has described the synthesis of three additional heptachlorocyclohexanes: "α", m.p. 143°C., "ε", m.p. 96°C., and "η", m.p. 148°C. The isomer melting at 143°C. was obtained from δ-benzene hexachloride, and those melting at 96° and 148°C. from ε-benzene hexachloride. Owing to the absence of experimental data and structural corroboration, the assignments for his isomers melting at 143°C. and 96°C. are presumed to be tentative.

Riemschneider (263) has reported the chlorination of the α-, β-, γ-, δ-, and ε-benzene hexachlorides to yield $C_6H_5Cl_7$, separation of the constituent isomers by partition chromatography, and further chlorination of the latter (except ε-$C_6H_5Cl_7$) to octa- and enneachlorocyclohexanes. From the chlorination products of δ- and ε-benzene hexachlorides, ζ-$C_6H_5Cl_7$ (m.p.154°C.) has been isolated. The structure of its precursor hexachlorides and that of the octachlorocyclohexane, (ep)ee(ep)ee, formed on further chlorination, establish the conformation of the ζ-isomer as iv, pee(pe)ee. The latter appears to be identical with Coutier's η-$C_6H_5Cl_7$, m.p. 148°C. Riemschneider also has reported the synthesis from ε-benzene hexachloride of a heptachlorocyclohexane, peepe(pe), which he has designated as η. Further chlorination of the latter yields enneachlorocyclohexane, (ep)(ep)e(ep)ee, the structure of which is known in view of its synthesis by additive chlorination of 1,2,4-trichlorobenzene. The relationships between the isomers of benzene hexachloride and their more highly chlorinated derivatives are illustrated in figure 9.

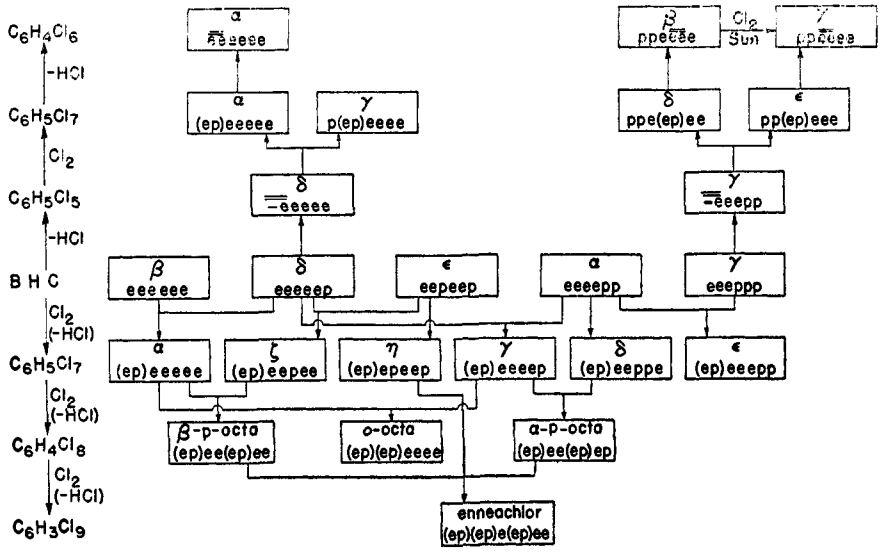


FIG. 9. Steric relationships of chlorinated cyclohexane derivatives of benzene hexachloride. Hexachlorocyclohexene, $C_6H_4Cl_6$; heptachlorocyclohexane, $C_6H_5Cl_7$; pentachlorocyclohexene, $C_6H_5Cl_5$; benzene hexachloride, BHC; octachlorocyclohexane, $C_6H_4Cl_8$; enneachlorocyclohexane, $C_6H_3Cl_9$.

H. CYCLOHEXENE DERIVATIVES

Whereas the carbon skeleton in unbridged saturated cyclohexane derivatives has been established by physical means as essentially of the chair form, that of cyclohexene derivatives is presumably a deformed chair undoubtedly similar in all important respects to δ-pentachlorocyclohexene (225) and the partially saturated ring of α-naphthalene tetrachloride (173). In the former compound, the allylic (C_3, C_6) and the unsaturated (C_1, C_2) carbon atoms lie approximately in one plane, the largest deviation from planarity being 0.04 Å. The two remaining carbon atoms (C_4, C_5) are situated one above and one below the plane; the distances have been reported to be 0.34–0.40 Å. above and below with respect to the mean plane of the molecule. The cyclohexene portion of the molecule of α-naphthalene tetrachloride is of the same general shape.

A nomenclature (220) which appears to be ideally suited to characterizing the various possible isomers and relating them readily to the corresponding saturated cyclohexane compounds is based on the equatorial-polar system of Beckett, Pitzer, and Spitzer (37). In a model of the cycloölefin, benzene tetrachloride (3,4,5,6-tetrachloro-1-cyclohexene), normal e- and p-orientations of the substituents are recognized at C_4 and C_5, the carbon atoms opposite to the double bond. Substituents at the allylic carbons, although not strictly equatorial or polar because of the distortion of the chair by the double bond, may be designated as e or p on the basis of the orientation which they will assume as a result of the formation of the undistorted chair, for example, after addition of chlorine to yield benzene hexachloride.

In penta- and hexachlorocyclohexene, respectively, one or both of the hydrogen

atoms at the olefinic carbons have been replaced by chlorine. As in benzene tetrachloride, chlorine substituents at the saturated carbons are designated e or p on the basis of the configuration present in the corresponding saturated parent substance, hexa- or heptachlorocyclohexane (163). To indicate the position of the double bond with reference to the structure of the saturated precursor, a double horizontal line is employed. A short dash under the double line indicates the absence of chlorine from that position. Thus, δ-pentachlorocyclohexene (-̿eeeee) is structurally related to two possible precursors of benzene hexachloride, peeeee and eeeeee. β-Hexachlorocyclohexene (ppe̿e̿e̿e) bears an analogous relationship to two heptachlorocyclohexanes, pp(ep)eee and ppe(ep)ee. A chlorine substituent remaining on a carbon attached to the double bond, indicated in pentachlorocyclohexene as the single letter e and in hexachlorocyclohexene as the double letter e under the double horizontal line (-̿eeeee and ppe̿e̿e̿e, respectively), actually

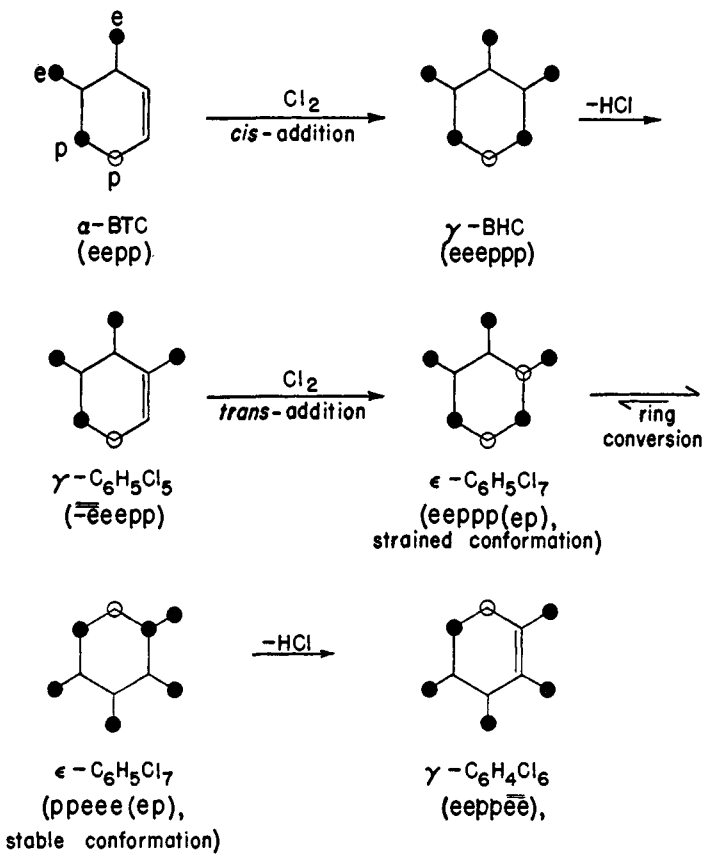


FIG. 10. Nomenclature of cyclohexane and cyclohexene derivatives. ●, chlorine atom at the equatorial position or in polar position above plane of ring; ○, chlorine atom below plane of ring.

has no steric significance in the cycloölefin itself. The conformation of a pentachlorocyclohexene, -ēeeee, is undistinguishable from that described as -p̄eeee. When the molecule becomes saturated, for example by addition of a chlorine molecule to the double bond, the chlorine originally present on the unsaturated carbon atom or atoms may become either equatorial or polar. The orientations of the remaining substituents, however, do not change with respect to each other. The convention of indicating the presence of a chlorine substituent at the double bond by the letter e placed under the double horizontal line has therefore been adopted.

This system of nomenclature is compared with the symbols employed by Nakazima, Okubo, and Katumura (209) in figure 10. In both systems only the chlorine substituents are indicated, inasmuch as their positions automatically fix the orientations of the hydrogen atoms. Since all carbon atoms are equivalent, the designations based on the abbreviated e, p system may be written in a number of ways, all of which refer to the same isomer:

ISOMER	EQUIVALENT DESIGNATION
γ-Benzene hexachloride	eeeppp, pppeee, eepppe, peeepp, etc.
ε-Heptachlorocyclohexane	p̄peee(pe), (ep)p̄peee, etc.
γ-Pentachlorocyclohexene	-ēeepp, pp-ēee, etc.
γ-Hexachlorocyclohexene	p̄p̄ēeee, eepp̄ē̄e, etc.

In the case of the isomers of benzene tetrachloride the position of the double bond is not indicated. Care must be taken here to employ the correct designation. For example, α-benzene tetrachloride may be referred to by the conformational abbreviations eepp or ppee, but not by eppe or peep, which designate the β-isomer.

1. Benzene tetrachloride

In accordance with the concept of ring conversion, the ten theoretically possible steric isomers of benzene tetrachloride are reduced to six forms, representing different equilibrium mixtures or identities. The relationships of the chlorine substituents of all possible forms are given in table 8. On theoretical grounds, the predominant conformations are considered to be those shown in the first column (220).

The steric structures of the five known isomers of benzene tetrachloride, the first five listed in table 8, have been established by photochlorinating the isomers individually and ascertaining the benzene hexachloride isomers formed (220). Utilizing the conformations reported (30) for five known benzene hexachlorides and postulating straightforward *cis* (ep or pe) and *trans* (ee or pp) addition of chlorine to the double bond of benzene tetrachloride, and no isomerization, the theoretical relationships given in table 12 have been postulated. Upon chlorination, each of the five tetrachlorides yielded a different set of product hexa-

TABLE 12

Theoretical relationships between the benzene tetra- and hexachlorides

BENZENE TETRACHLORIDE		BENZENE HEXACHLORIDE ISOMERS EXPECTED		
		cis addition	*trans* addition	
Conformation	Symbol	(ep or pe)	ee	pp
eeee	δ	δ	β	α
eeep	γ	α, θ	δ	γ
eepe	ϵ	ϵ, θ	δ	η
peep (or eppe)	β	η	ϵ (or α)	$1/\alpha$ (or $1/\epsilon$)*
eepp	α	γ, η	α	$1/\alpha$*
epep†	ζ†	ι†, η	θ	η

* $1/\alpha$ and $1/\epsilon$ designate the strained ring conversion forms of α and ϵ, respectively.
† These isomers have not been found.

chlorides, corresponding to the tabulated relationships. This agreement made possible the assignment of structures to the benzene tetrachlorides (as shown in the first two columns of table 12), which subsequently have been confirmed by dipole moment (35) and electron diffraction (28) investigations.

The theoretical basis for ring conversion (51, 112, 125) has been substantiated largely by physical evidence and by the fact that the number of steric isomers of cyclohexane derivatives actually observed may be accounted for adequately by this mechanism. The chlorination of β-benzene tetrachloride, which has been shown by dipole moment measurements to be an equilibrium mixture eppe $\rightleftharpoons$ peep predominant in the latter conformation (17:87 ratio), has provided direct chemical evidence for ring conversion (220). If conversion were assumed *not* to take place, chlorination of β-benzene tetrachloride should yield the hexachlorides tabulated below:

β-BENZENE TETRACHLORIDE CONFORMATION	POSSIBLE BENZENE HEXACHLORIDE PRODUCTS
eppe	η, α (eeeepp), $1/\epsilon$ (eppepp)
peep	η, ϵ (eepeep), $1/\alpha$ (eepppp)

Actually, both α- and ϵ-benzene hexachloride were formed with no evidence of the presence of the strained conformations, $1/\alpha$ or $1/\epsilon$. Despite the predominance of the form peep in the initial material, 80 per cent of the product was α-benzene hexachloride. Unless ring conversion were possible, either in the original tetrachloride or in the resultant hexachloride, it should not have been possible to obtain both α- and ϵ-benzene hexachloride.

The effect of structure upon reactivity has been demonstrated in a study of the base-catalyzed eliminations of the benzene tetrachlorides from a kinetic and stereochemical standpoint (219), in which the following preference for elimina-

tion has been observed: *trans*-1,2 (involving p-Cl and p-H) > *trans*-1,4 (p-Cl, p-H) > *cis*-1,2 (p-H, e-Cl or e-H, p-Cl) > *cis*-1,4 (p-H, e-Cl or e-H, p-Cl). In all cases the reactions are bimolecular, with the initial attack of base on a proton attached to an allylic carbon atom. In 1,2 elimination, an allylic polar hydrogen and the adjacent polar chlorine react more rapidly than do an allylic equatorial hydrogen and the adjacent equatorial chlorine, presumably because pp elimination involves a planar four-center transition state and can thus proceed by a one-step concerted mechanism. On the other hand, ee elimination requires ring conversion to the pp form or, if ring conversion is hindered sterically, proceeds via a multiple-step carbanion intermediate process similar to that of *cis* or ep elimination in β-benzene hexachloride.

2. Penta- and hexachlorocyclohexenes

Four isomers of 1,3,4,5,6-pentachloro-1-cyclohexene ($C_6H_5Cl_5$) and of 1,2,3,4,5,6-hexachloro-1-cyclohexene ($C_6H_4Cl_6$) have been synthesized by the partial additive chlorination of mono- and *o*-dichlorobenzene, respectively (163). Two isomers of the former and three of the latter compound also have been obtained by monodehydrochlorination of individual isomers of benzene hexachloride and heptachlorocyclohexane, respectively (208, 209, 217). Since the structures of the parent hexa- and heptachlorocyclohexanes are known, assignment of configuration to the products of monodehydrochlorination has been possible.

The preference for *trans* elimination of the elements of hydrogen chloride from adjacent carbon atoms under base-catalyzed conditions has been reliably established (141, 143). In bimolecular (E_2) reactions, a concerted mechanism involving vicinal polar hydrogen and chlorine has been confirmed by kinetic studies with the isomers of benzene hexachloride (74, 76). Using evidence from x-ray analysis, Pasternak (225) has shown that the monodehydrohalogenation of δ-benzene hexachloride (peeeee) involves the removal of the only polar chlorine atom in the molecule together with an adjacent proton (which must be the polar hydrogen). All other chlorocyclohexanes having at least one pair of vicinal polar chlorine and hydrogen substituents react in the same manner. β-Benzene hexachloride, in which all the chlorine atoms are equatorial, is dehydrohalogenated with difficulty by a multiple-step process involving inversion of a carbanion intermediate. In the case of a hepta- or octachlorocyclohexane containing one or two —CCl_2— groups, respectively, monodehydrochlorination involves preferentially the polar chlorine of the latter group, rather than a polar chlorine from a —CHCl— group.

Employing these concepts, the monodehydrochlorination reactions of the hexa- and heptachlorocyclohexanes have been interpreted and the structures of the product penta- and hexachlorocyclohexenes elucidated (163, 208, 209, 217). The results of these investigations, summarized in figure 9, indicate the known conformations to be as follows: γ-$C_6H_5Cl_5$ ($\bar{\bar{e}}$eepp), δ-$C_6H_5Cl_5$ ($\bar{\bar{e}}$eeee), α-$C_6H_4Cl_6$ ($\bar{\bar{e}}$eeee), β-$C_6H_4Cl_6$ (ppe$\bar{\bar{e}}$e), and γ-$C_6H_4Cl_6$ (ppe$\bar{\bar{e}}$e).

3. *Naphthalene tetrachloride*

Naphthalene tetrachloride may be considered a hexasubstituted cyclohexene derivative in which a benzene ring is attached to the olefinic carbon atoms. As shown by x-ray analysis (173), the shape of the tetrahydro ring is essentially identical with that described in the preceding section for δ-pentachlorocyclohexene: the unsaturated and allylic carbons are coplanar; the two remaining carbons are situated one above and one below the plane of the ring. As in the case of benzene tetrachloride, six steric isomers are possible: eeee, eeep, eepe, eepp, peep (or eppe), and epep. Three have been separated (281) and an attempt has been made to assign structures on the basis of kinetic dehydrochlorination data.

Assuming vicinal elimination of hydrogen and chlorine, the rate must parallel the ratio of possibilities of *trans* elimination. From a consideration of the experimental data, the configurations have been narrowed down as follows:

ISOMER	NUMBER OF POSSIBLE *trans*-1,2 ELIMINATIONS	POSSIBLE ORIENTATION OF CHLORINE ATOMS
α	2	epep, peep
δ	1	epee, eeep
γ	0	eeee, eepp

One of the conformations (peep) suggested for the α-isomer has been confirmed by x-ray analysis (173). From the rates of dehydrohalogenation alone, however, without detailed and reliable analyses of the reaction products, further assignments have not been possible.

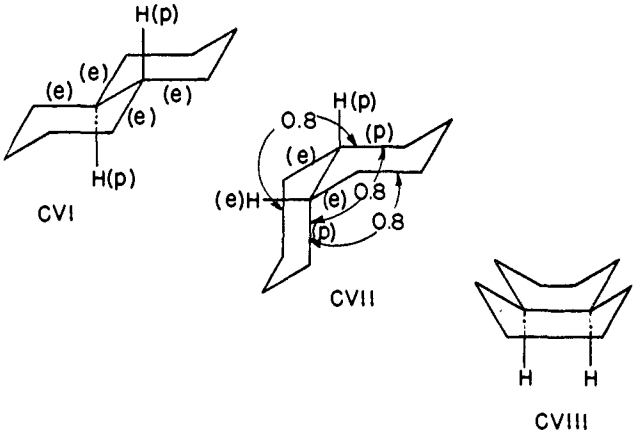
IV. Bicyclic Carbon Compounds

A. *Cis-* and *trans*-decahydronaphthalene

Fusion of two cyclohexane rings to form *cis-* and *trans*-decalin (decahydronaphthalene) gives a number of steric possibilities. Although Sachse (277) and Mohr (203) had postulated the existence of two stable geometrical isomers of decalin, Wightman (323) demonstrated by means of models that four *cis* and three *trans* forms could be constructed. The presently accepted (113) structure (CVI) of *trans*-decalin involves two chair conformations of cyclohexane linked by equatorial bonds. By means of electron diffraction studies, Bastiansen and Hassel (32) have established conclusively that *cis*-decalin has the structure CVII, consisting of two chair-form cyclohexane rings joined by e,p bonds, rather than the two-boat Sachse–Mohr conformation CVIII. This conclusion is in agreement with the greater stability of the chair form as compared with the boat form of cyclohexane and of monocyclic cyclohexane derivatives.

Using the parameters (37) of 3.6 kcal. for the eclipsed and 0.8 kcal. for the skew conformation of the *n*-butane portion of a hydrocarbon chain, Turner (308)

has calculated the difference in energy between the *cis* and *trans* forms of decalin to be 2.4 kcal., a value which, after correction for the heats of vaporization, is in excellent agreement with the experimental data. As further elucidated by Johnson (150), *cis*-decalin differs from the *trans* isomer (which has been arbitrarily assigned the value zero) only in the three skew interactions involving the two polar bonds linking the individual cyclohexane rings of the decalin molecule. The energy difference, hence, is $3 \times 0.8 = 2.4$ kcal.



Barton (23) has compared (table 13) the energy differences between the various conformational isomers calculated by Turner with his own earlier semiempirical values (19) and has found qualitative agreement by both procedures between the observed and the calculated orders of stability. In general, the most stable conformation of a fused cyclohexane ring system will be that with the maximum number of chairs.

Although his calculations favor structure CVII rather than CVIII for *cis*-decalin, at least in the vapor phase or in solution, Barton has indicated that

TABLE 13

Energy differences and order of stability of cyclohexane and decalin

COMPOUND	ENERGY DIFFERENCES		ORDER OF STABILITY
	Semiempirical (19)	Empirical (308)	
	kcal.	*kcal.*	
Cyclohexane	1.31 to 6.85	5.6	Chair > boat
cis- and *trans*-Decalins (two-chair conformation)	0.52 to 8.23	2.4	*trans* > *cis*
Two-chair and two-boat *cis*-decalins (two-boat Sachse-Mohr conformation)	2.87 to 7.28	8.8	Two-chair > two-boat

CVII may not necessarily be packed more conveniently than CVIII into a crystal lattice, for in the lattice non-bonded interactions of atoms with those in the neighboring molecules may play a dominant part. In a study of the heat capacity of *cis*- and *trans*-decalins, Seyer (282) has observed a discontinuity in the data for the *cis* isomer between 50.1° and 50.5°C. Evidence for an intermolecular or intramolecular change at this temperature also has been encountered for the *cis* but not for the *trans* isomer in the course of other physical measurements, such as surface tension (284) and dielectric constant (283). Seyer has suggested that the properties of the *cis* isomer below this critical temperature may be attributed to the two-boat conformation and above this temperature to the two-chair structure of the molecule. In view of the energy differences between the various forms (table 13) and the steric factors involved, any "two-boat" contribution to the properties of *cis*-decalin must be treated with caution, pending direct substantiation, for example, by x-ray investigation.

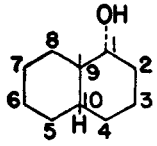
B. MONOSUBSTITUTED DECAHYDRONAPHTHALENES

1. Decalol

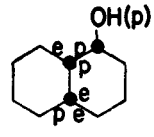
Two 1-decalones, corresponding to the *cis* and *trans* forms of decalin, are the parent substances of four theoretically possible 1-decalols, the structures and reactions of which permit interesting extensions of the theory of conformational analysis. The configurations of these compounds (as well as those of the 2-decalol series) have been elucidated largely by W. Hückel and his colleagues along classical stereochemical lines (179) and have been reëvaluated by more recent investigations based on considerations relating to the predominant chair structure of the decalin nucleus.

Reduction of α-naphthol over a nickel catalyst yields two *trans*-1-decalols (m.p. 63° and 49°C.) which give the same *trans*-1-decalone (m.p. 33°C.) on oxidation. Reduction of *ac*- or *ar*-1-tetralol with platinum in acetic acid gives *cis*-1-decalol (m.p. 93°C.), which in turn is oxidized by chromic acid to *cis*-1-decalone (m.p. 2°C.). Distillation of the latter ketone at atmospheric pressure results in an irreversible isomerization to form *trans*-1-decalone. The other *cis*-1-decalol (m.p. 55°C.) is obtained by the action of nitrous acid on the corresponding *cis*-1-decalylamine (m.p. −2°C.). *trans*-1-Decalol (m.p. 63°C.) also has been prepared by reduction of *trans*-1-decalone and by isomerization and reduction of *cis*-1-decalone with sodium and alcohol. Platinum-catalyzed hydrogenation of *trans*-1-decalone, on the other hand, furnishes the *trans*-1-decalol (m.p. 49°C.) (130, 131, 136).

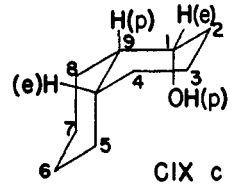
The structures of the isomeric 1-decalols (figure 11) were assigned originally from considerations involving the method employed in their formation and on the basis of their physical properties (130, 136, 293). In lieu of the classical structures at the left, an alternate planar formulation has been suggested (180) wherein a dot is used to show a hydrogen substituent above the general plane of the molecule. By convention a dot is always placed at C_9. The structures at



CIX a

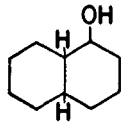


CIX b

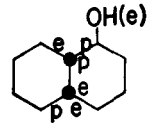


CIX c

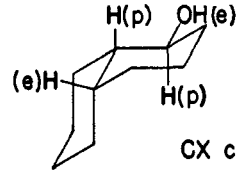
cis-1-decalol (m.p. 93°)
(Series I, *cis-cis*)



CX a

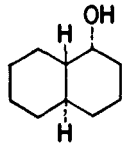


CX b

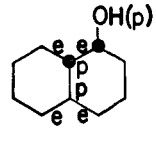


CX c

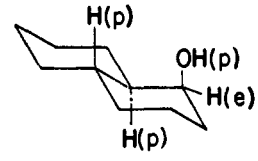
cis-1-decalol (m.p. 55°)
(Series II, *cis-trans*)



CXI a

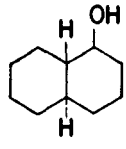


CXI b

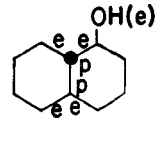


CXI c

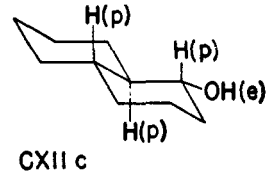
trans-1-decalol (m.p. 49°)
(Series I, *trans-cis*)



CXII a



CXII b



CXII c

trans-1-decalol (m.p. 63°)
(Series II, *trans-trans*)

FIG. 11. Structural representation of the isomeric *cis*- and *trans*-1-decalols

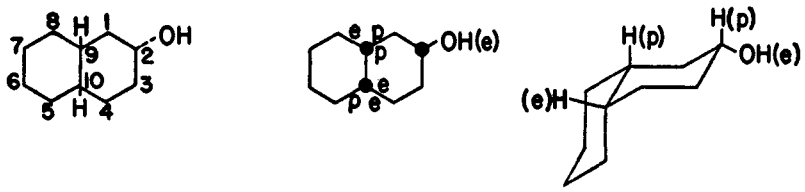
the right are based on modern conformational theory, which permits of ring conversion depending on steric and energy factors and the nature of the reaction involved. The equatorial and polar orientations of hydrogen and hydroxyl, indicated as e and p, respectively, in figure 11 are those of the ring containing the hydroxyl group, since it is the reactions of the substituents in this ring which provide chemical evidence for the structural assignments.

In the *cis*-1-decalols, Hückel (136) has designated the isomer melting at 93°C. (*cis–cis* relation of hydrogen at C_9, C_{10}, and C_1) as Series I and the isomer melting at 55°C. (*cis–trans*) as Series II, while in the *trans*-1-decalols the isomer melting at 49°C. (*trans–cis*) has been termed Series I and the isomer melting at 63°C. (*trans–trans*), Series II.

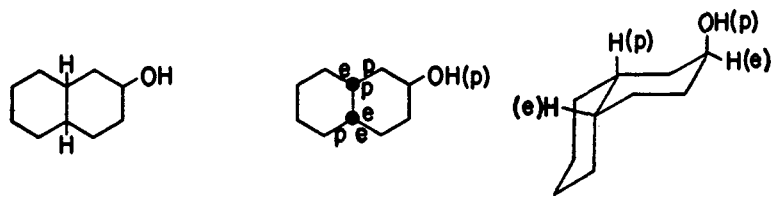
In 2-decalol (as in 1-decalol) the presence of three asymmetric carbon atoms allows a maximum of eight optically active forms or four racemic mixtures and, hence, four theoretically separable steric isomers. Catalytic reduction of *cis*-2-decalone (m.p. −14°C.) yields only *cis*-2-decalol (m.p. 105°C.) (130, 132), whereas alkaline reduction furnishes a second *cis*-2-decalol (m.p. 18°C.) as well as the isomer melting at 105°C. Similarly, *trans*-2-decalone (m.p. 6°C.) has been converted to *trans*-2-decalol (m.p. 75°C.) by reduction with sodium and alcohol, and to a mixture of both theoretically possible *trans*-2-decalols (m.p. 53° and 75°C.) by hydrogenation with a platinum catalyst. Mild oxidation of the two *cis*- and two *trans*-2-decalols provides the original *cis*- and *trans*-2-decalones, respectively. The *cis* ring-juncture in *cis*-2-decalone has been established by Clemmensen reduction to *cis*-decalin and by alkaline permanganate oxidation to a mixture of *cis*-cyclohexane-1-carboxylic-2-propionic acid and *cis*-cyclohexane-1,2-diacetic acid. Similar treatment of *trans*-2-decalone furnishes *trans*-decalin on Clemmensen reduction and a mixture of *trans*-cyclohexane-1-carboxylic-2-propionic acid and *trans*-cyclohexane-1,2-diacetic acid on permanganate oxidation. Whereas *cis*-1-decalone is easily transposed to the *trans* form, isomerization of *cis*-2-decalone does not occur (130).

The original assignment (132) of configuration to the isomeric 2-decalols, based on the Auwers–Skita rule and the method of synthesis, has been confirmed subsequently by a variety of methods. Figure 12 records the various structures in terms of the classical and conformational methods of representation.

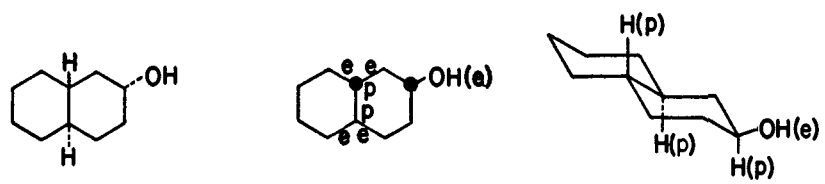
The principle that catalytic reduction, for example of ketones, normally yields the *cis* derivative whereas alkaline reduction gives the *trans* epimer as the major product was recognized by Skita (291, 292) and Hückel (135, 137) and utilized in assigning structures to the isomeric decalols. In the light of modern theory, a hydroxyl group resulting from catalytic reduction of a ketone is polar, while that from alkaline reduction is in the thermodynamically more stable equatorial form. Table 14 correlates the orientations of the C_9-H and of the C_1-OH and the C_2-OH in the 1- and 2-decalols, respectively, with the method of synthesis involved and summarizes data obtained by thermal treatment of the *p*-toluenesulfonate (tosylate) and methyl xanthate esters on the basis of which the structural configurations have been deduced (20, 135, 137, 139, 141).



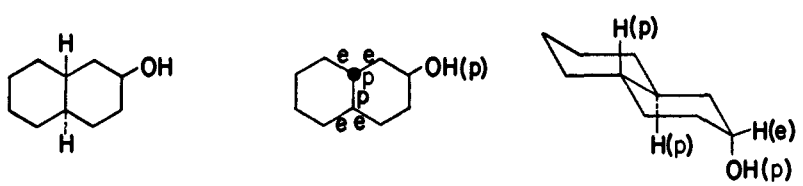
cis-2-decalol (m.p.105°C)
(Series I, *cis-cis*)



cis-2-decalol (m.p. 18°C)
(Series II, *cis-trans*)



trans-2-decalol (m.p. 75°C)
(Series II, *trans-cis*)



trans-2-decalol (m.p. 53°)
(Series I, *trans-trans*)

FIG. 12. Structural representation of the isomeric *cis*- and *trans*-2-decalols

A marked difference in thermal stability of the tosylate esters of the 1- and 2-decalols has been noted. In general, the esters of both the *cis*- and the *trans*-2-decalols are stable when refluxed in methanol. Because of this observation and the fact that both equatorial and polar hydrogens are available at C_1 and C_3 for participation with the C_2 ester group in the stereospecific Tschugaeff elimination, it is not possible to confirm by these thermal reactions the configurations of the 2-decalols. In the 1-decalol series, however, a distinct parallel between the conditions of formation of the cyclanols and the stability of the corresponding tosylates is evident. The esters of alcohols formed by catalytic hydrogenation of ketones are less stable than those obtained by alkaline reduction. Consequently the stability of the esters can serve for determination of configuration. The esters of the *cis*- and *trans*-1-decalols (m.p. 93° and 49°C., respectively), with a polar hydroxyl group at C_1 (which is *trans* to the polar hydrogen at C_9), are unstable and yield 75 per cent $\Delta^{1,9}$-octalin and 25 per cent $\Delta^{1,2}$-octalin; those of the *cis*- and *trans*-1-decalols (m.p. 55° and 63°C., respectively), with an equatorial hydroxyl at C_1 (*cis* to the polar hydrogen at C_9), are relatively stable.

The stereospecificity of Tschugaeff's xanthate reaction, normally proceeding through a cyclic transition state involving *cis* (ep) reacting groups, provides additional evidence for the conformations of the 1-decalols. In the case of the *cis*-1 and *trans*-1 isomers (m.p. 93° and 49°C., respectively), elimination takes place predominantly away from the bridgehead to give $\Delta^{1,2}$-octalin as the major product; elimination towards the bridgehead would require a *trans* mechanism. In *trans*-1-decalol (m.p. 63°C.), however, the relation of the C_9-H(p) with the C_1-OH(e) is *cis*; this is consistent with the preference for elimination toward the bridgehead.

TABLE 14

Method of formation, structure, and stability of the isomeric 1- and 2-decalols and their ester derivatives

DECALOL	MELTING POINT	CONFIGURATION			METHOD OF SYNTHESIS	STABILITY OF TOSYLATE*	OCTALIN FROM PYROLYSIS OF METHYL XANTHATE	
		C_1-OH	C_9-H	C_2-OH			$\Delta^{1,9}$	$\Delta^{1,2}$
	°C.						*per cent*	*per cent*
cis-1	93	p	p		Catalytic reduction	Unstable	10	90
cis-1	55	e	p		HNO_2, amine	Stable	Not investigated	
trans-1 . .	49	p	p		Catalytic reduction	Unstable	20	80
trans-1 . .	63	e	p		Alkaline reduction	Stable	80	20
cis-2	105		p	e	Catalytic reduction	Stable		
cis-2	18		p	p	Alkaline, catalytic reduction	Stable		
trans-2 . .	53		p	p	Alkaline, catalytic reduction	Stable		
trans-2 . .	75		p	e	Alkaline reduction	Stable		

* As determined by refluxing in methanol.

The bimolecular (E_2) elimination reactions of several decalyl tosylates with sodium alcoholate (141) provide further evidence for the 1-decalol structures. In reactions of this type, the presence of adjacent polar hydrogen and ester groups provides steric conditions for facile reaction. As shown below, *cis*-1-decalol (m.p. 93°C.), with *trans*-related C_9-H and C_1-OH, undergoes elimination

TOSYLATE ESTER OF 1-DECALOL		CONFIGURATION		OCTALIN	
Isomer	Melting point	C_1-OH	C_9-H	$\Delta^{1,9}$	$\Delta^{1,2}$
	°C.			*per cent*	*per cent*
cis	93	p	p	100	0
cis	55	e	p	Not investigated	
trans	49	p	p	10	90
trans	63	e	p	0	100

exclusively toward the bridgehead. Although both *trans*-1-decalyl tosylates give $\Delta^{1,2}$-octalin (away from the bridgehead) as the major product, a slight amount of $\Delta^{1,9}$-octalin is formed when the C_1-OH and C_9-H groups are dipolar and *trans*, whereas no $\Delta^{1,9}$-octalin can be detected from the reaction of the ester of *trans*-1-decalol (m.p. 63°C.) with an equatorial hydroxyl at C_1 and a polar hydrogen at C_9.

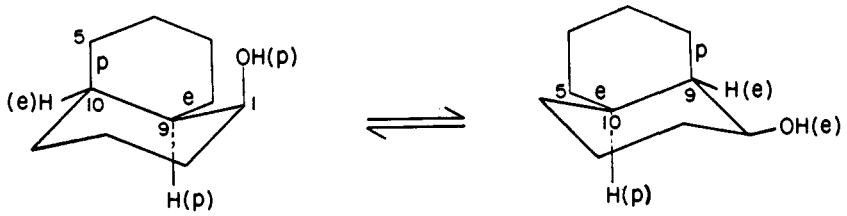
The generalization that cyclohexanols with polar hydroxyl groups are more difficult to esterify and their esters more difficult to hydrolyze than the epimeric alcohols and their esters with equatorial hydroxyl groups has been extended to the *cis*- and *trans*-2-decalols and the *trans*-1-decalols (table 15) (133, 138). The reverse order of reactivity, however, may be noted in the case of the *cis*-1-decalols. The explanation for this discrepancy can best be explained on the basis of ring conversion. The conformation CXIII (identical with CIXc) for *cis*-1-

TABLE 15

Relation between steric conformation and rates of hydrolysis of decalyl esters

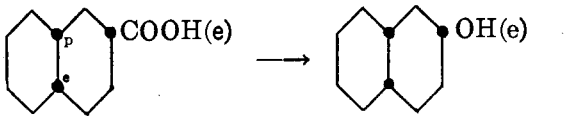
DECALOL		CONFIGURATION			HYDROLYSIS RATE CONSTANT (K)	
Isomer	Melting point	C_1-OH	C_9-H	C_2-OH	Acid succinate (40°C.)	Acid phthalate (60°C.)
	°C.					
cis-1	93	p	p		0.452	0.0635
cis-1	55	e	p		0.130	0.0209
trans-1	49	p	p		0.01162	
trans-1	63	e	p		0.244	0.0341
cis-2	105		p	e	1.16	0.0779
cis-2	18		p	p	0.704	
trans-2	53		p	p	0.154	0.0224
trans-2	75		p	e	1.22	0.134

decalol (m.p. 93°C.), which is consistent with the results of thermal treatment of the tosylate and methyl xanthate and with the catalytic method of synthesis, may be under steric strain associated with the meta polar repulsion (1p, 3p) of the C_1–OH bond and the C_{10}–C_5 bond. The conformation CXIV (in which the polar hydroxyl group in CXIII has been transformed to an equatorial disposition) resulting from ring conversion presumably accounts for the appreciable rate of hydrolysis of the acid succinate and acid phthalate. Similarly, *cis*-1-decalol, m.p. 55°C., must be regarded as an equilibrium mixture of ring-conversion isomers possessing both equatorial and polar hydroxylic character.

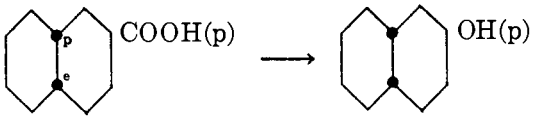


CXIII CXIV

A reinvestigation of the *cis*-2-substituted decalols and their derivatives has been undertaken (79) to clarify discrepancies as to the structural relationship between the decalols and the corresponding amines. One *cis*-decahydro-2-naphthoic acid (m.p. 80–81°C.) was obtained by hydrogenation with a platinum catalyst of 2-naphthoic acid in acetic acid at low pressure and room temperature. The amide (m.p. 179–180°C.) was prepared via the acid chloride under conditions not involving inversion, as seen by careful hydrolysis with nitrous acid to re-form the original acid. The second *cis* acid (m.p. 92–94°C.) was obtained from *cis*-2-decalol (m.p. 105°C.) via the bromide and Grignard reagent, converted to the amide (m.p. 186–187°C.), and the latter again hydrolyzed with nitrous acid without affecting the steric asymmetry of the molecule. In view of its method of preparation, the acid melting at 80–81°C. should have a *cis–cis* structure (CXV) (184), while the isomer melting at 92–94°C. should be the *cis–trans* epimer (CXVI). To confirm these configurations and to correlate them with previously prepared isomeric *cis*-2-decalols and *cis*-2-decalylamines, the



CXV *cis*-2-Decalol (m.p. 105°C.)



CXVI *cis*-2-Decalol (m.p. 18°C.)

acids have been converted to the latter compounds by reactions involving retention of configuration: namely, the peracid oxidation of methyl ketones and the Schmidt reaction. These reactions and the products thus obtained constitute indirect proof of the structures (figure 12) of the *cis*-2-decalols.

A suggestion (153) that the infrared spectrum in the 1200–1600 cm.$^{-1}$ region might be employed to elucidate the stereochemical relationship between the C_3-hydroxyl group and the C_5(bridgehead)-hydrogen atom in steroid derivatives has been utilized (80) to clarify further the configurations of the *cis*-2-decalols. If the structures of the four 2-decalols in figure 12 are correct and the suggested method of spectral analysis is applicable, only a single band in the 1200–1600 cm.$^{-1}$ region would be expected when the acetoxy group (of the 2-decalyl acetate) at C_2 and the bridgehead hydrogen at C_9 are *trans* (that is, polar C_9-H, equatorial C_2-$OCOCH_3$). With a *cis* relationship (both substituents polar), however, two or three spectral bands would be expected. Hence the acetates of *cis*-2-decalol (m.p. 105°C.) and *trans*-2-decalol (m.p. 75°C.), with equatorial acetoxy groups, should show one strong band and those of the two remaining 2-decalols (polar function) should exhibit multiple bands.

In a study of the infrared spectra of these substances Dauben, Hoerger, and Freeman (80) have found that the acetates of *cis*-2-decalol (m.p. 18°C.) and *trans*-2-decalol (m.p. 53°C.) show a multiplicity of bands, as expected. The acetate of the isomer melting at 105°C. possesses a single strong band but, under high resolution, the apparent single band of the ester of *trans*-2-decalol (m.p. 75°C.) is found to consist actually of two bands. The clear distinction between *cis* and *trans* configurations of the 2-acetoxy, 9-hydrogen substituents in the 2-decalols, therefore, is similar to that in the steroids. Rosenkrantz, Milhorat, and Farber (270) have found that in steroids in which the C_3-OH and C_5-H are *cis* the absorption bands are in the region 1042–1000 cm.$^{-1}$, whereas in steroids with *trans*-related substituents the bands have shifted to the 1075–1042 cm.$^{-1}$ region. A similar shift, but less clearly defined, is observed with the 2-decalols (80).

Unsaturated steroids, such as the acetates of cholesterol, ergosterol, or lumisterol, which lack a hydrogen at C_5 fit into this pattern if they are classified according to the e, p orientation of the ester group at C_3 (67, 128). In general, multiple peaks are observed if the 3-acetoxy group is polar in a molecule in which ring A occupies the chair form.

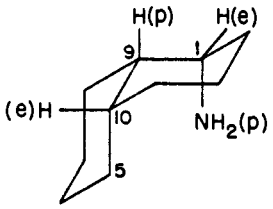
These results, applied to the isomeric 2-decalol series, confirm the presence of an equatorial hydroxyl group in the isomers melting at 105° and 75°C., and of a polar hydroxyl group in those melting at 18° and 53°C.

2. Decalylamine

As in the case of the decalols, the method of synthesis of the isomeric decalylamines was utilized by Hückel and his coworkers as the main basis for assignment of configuration. In agreement with observations made concerning

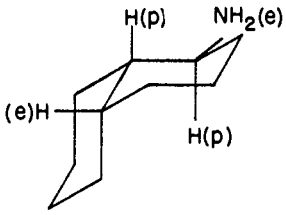
the reduction of the *cis*- and *trans*-decalones, the amino group in the major decalylamine obtained by catalytic hydrogenation of the corresponding decalone oxime was assigned a *cis* (polar) orientation, while that formed on alkaline reduction was believed to be *trans* (equatorial). The classical structures proposed by Hückel for the 1-decalylamines and the *trans*-2-decalylamines are considered to be valid, but those of the *cis*-2-decalylamines have recently been shown to be in error because of the formation of appreciable amounts of the epimeric amine, which complicated the picture and led to incorrect structural interpretation.

cis-1-Decalylamine (m.p. 8°C.), formed as the major product of catalytic reduction of 1-tetralone oxime, has been assigned the *cis–cis* configuration (Series I), whereas the epimeric *cis* amine (m.p. −2°C.), obtained by alkaline reduction of *cis*-1-decalone oxime (m.p. 103°C.), has been designated as the *cis–trans* isomer (Series II). Alkaline reduction of *trans*-1-decalone oxime (m.p. 168°C.) yields *trans*-1-decalylamine (m.p. −1°C.) while, in addition to the latter, catalytic hydrogenation of the oxime melting at 168°C. also gives *trans*-1-decalylamine (m.p. −18°C.) (130, 136). The conformations of the four 1-decalylamines, therefore, are as shown in formulas CXVII–CXX:



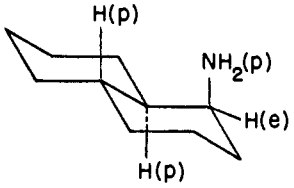
CXVII

cis−1−decalylamine
m.p. 8°C.
(*cis*−*cis*, Series I)



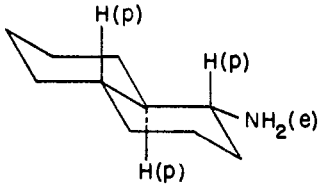
CXVIII

cis−1−decalylamine
m.p. −2°C.
(*cis*−*trans*, Series II)



CXIX

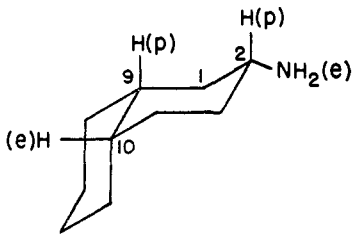
trans−1−decalylamine
m.p. −18°C.
(*trans*−*cis*, Series I)



CXX

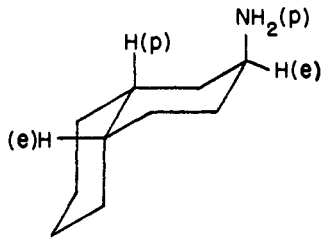
trans−1−decalylamine
m.p. −1°C.
(*trans*−*trans*, Series II)

The conformations of the four 2-decalylamines are represented by formulas CXXI–CXIV:



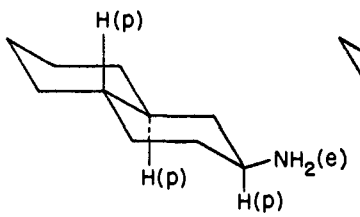
CXXI

cis–2–decalylamine
m.p. ≥20° C.
(cis–cis)



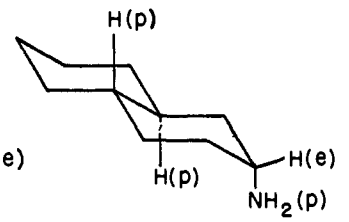
CXXII

cis–2–decalylamine
m.p. 14°C.
(cis–trans)



CXXIII

trans–2–decalylamine
m.p. 15° C.
(trans–cis)



CXXIV

trans–2–decalylamine
m.p.–47°C.
(trans–trans)

By alkaline reduction of *trans*-2-decalone oxime, Hückel (132) obtained *trans*-2-decalylamine (m.p. 15°C.) (CXXIII), which has a *trans–cis* relationship between the C_9, C_{10} hydrogens (*trans*, p, p) and the C_9, C_2 hydrogens (*cis*, p, e). In addition to the amine melting at 15°C., a second *trans*-2-decalylamine (m.p. −47°C.) has been obtained by catalytic hydrogenation of *trans*-2-decalone oxime. The latter amine (CXXIV) has a *trans–trans* configuration. In the case of the *cis*-2-decalylamines, Hückel obtained one isomer (m.p. 14°C.; m.p. of benzamide derivative, 202°C.) by catalytic reduction, and a mixture of the isomer melting at 14°C. with a second epimer (m.p. ≥ 20°C.; m.p. of benzamide, 127°C.) by alkaline reduction. To the product obtained by platinum-catalyzed hydrogenation Hückel assigned the *cis–cis* structure, and to the amine having a benzamide melting at 127°C., the *cis–trans* configuration.

In a reinvestigation of the structures of the *cis*-2-decalylamines, Dauben and Hoerger (79) have found that catalytic hydrogenation of *cis*-2-decalone oxime,

under the conditions employed by Hückel, gives both isomeric amines in about equal but small yield (*ca.* 9 per cent). Hückel's assignment of configuration is thus questionable. By the Schmidt reaction with *cis*-decahydro-2-naphthoic acid (CXV) and *cis*-decahydro-2-naphthoic acid (CXVI), Dauben and Hoerger obtained two isomeric decalylamines (CXXI and CXXII, respectively). The decalylamine obtained by the Schmidt reaction from the *cis–cis* acid (CXV) had been assigned a *cis–trans* structure by Hückel, while the amine from CXVI (*cis–trans*) had been erroneously considered the *cis–cis* epimer. Since no inversion was found to occur, the steric relationships postulated by Hückel between the *cis*-2-decalols and the *cis*-2-decalylamines must be incorrect. The correct data for the *cis*-2-decalin derivatives follow:

CONFIGURATION		MELTING POINTS			
C_9, C_{10} hydrogen	C_9, C_2 hydrogen	Acid	Amine	Decalol	Decalylbenzamide
		°C.	°C.	°C.	°C.
cis	*cis*	81	≥20	105	128
cis	*trans*	98	14	18	204

Deamination by means of nitrous acid of cyclohexylamines with simple alkyl substituents in the ring is conformationally specific: if the amino group is equatorial in the most stable conformation of the molecule, deamination affords an alcohol of the same configuration; if it is polar, elimination and inversion occur (47, 71). This general relationship between the conformation and products of deamination may also be applied (199) to the *trans*-1-decalylamines and both the *cis*- and the *trans*-2-decalylamines, but not to the *cis*-1-decalylamines. Table

TABLE 16

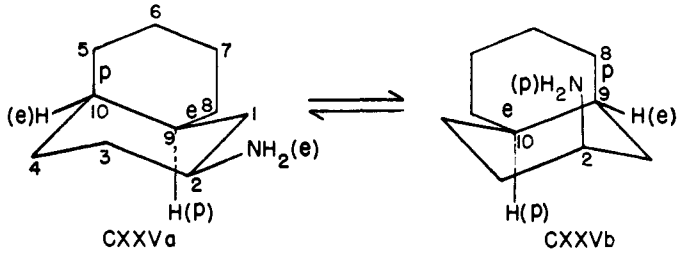
Deamination reactions of the isomeric decalylamines

AMINE			CONFIGURATION			PRODUCTS OF DEAMINATION			
Isomer	Melting point	Melting point of corresponding decalol	C_1-NH_2	C_9-H	C_2-NH_2	Decalol			Octalin
						Total	Not inverted	Inverted	
	°C.	°C.				*per cent*	*per cent*	*per cent*	*per cent*
cis-1	8	93	p	p		100	100	0	0
cis-1	−2	55	e	p		75	90	10	25
trans-1	−18	49	p	p		30	10	90	70*
trans-1	−1	63	e	p		100	100	0	0
cis-2	≥20	105		p	e	100	100	0	0
cis-2	14	18		p	p	70	90	10	30
trans-2	−47	53		p	p	30	10	90	70
trans-2	15	75		p	e	100	100	0	0

* Ratio of $\Delta^{1,2}$- to $\Delta^{1,9}$-octalin, 1:1.

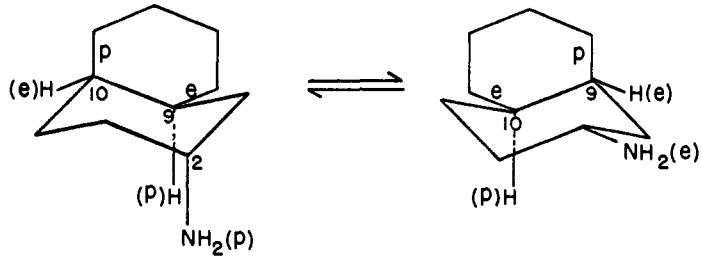
16 records the experimental results obtained by Hückel on treating the *trans*-1- and -2-decalylamines with nitrous acid (134, 141). His data for the *cis*-2-decalylamines are revised here in accordance with the corrected structures established by Dauben and Hoerger.

Deamination of *trans*-1- and *cis*- and *trans*-2-decalylamines with equatorial amino groups affords quantitative yields of *trans*-decalols of the same configuration, whereas their epimers with polar amino groups react by elimination plus inversion. Mills (199) has suggested that the reason why all the *cis* amines are deaminated with retention of configuration is that a single substituent at positions other than ring junctions in *cis*-decalin tends to occupy an equatorial position. This gives the maximum number of e substituents and is brought about by ring conversion. For example, each of the two *cis*-2-decalylamines can exist in two conformations. The latter can be transformed into different conformations without rupturing chemical bonds, but involving the transformation of each e-bond into a p-bond, and *vice versa*.



CXXVa CXXVb

cis-2-decalylamine (m.p. ≧ 20° C.)



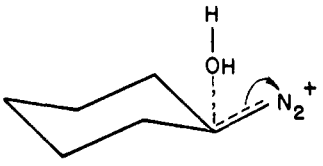
CXXVIa CXXVIb

cis-2-decalylamine (m.p. 14° C.)

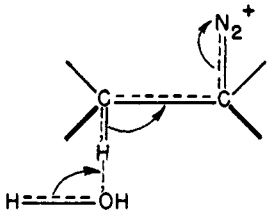
Inversion of the more probable conformation (CXXVa) produces a form (CXXVb) in which a meta polar repulsion between the polar amino and the C_8 group imparts considerable conformational instability to the molecule. This effect presumably accounts for the total absence of polar character on deamination (100 per cent retention, no elimination). Inversion of CXXVIa (2e, 3p), however, results in a molecule with three e and only two p substituents in the ring containing the amino group. The difference in energy between both con-

formations may be small. Indeed, the resulting equilibrium mixture exhibits both equatorial and polar character when subjected to deamination. The formation of octalin in 30 per cent yield suggests a polar configuration for the amino group, whilst decalol formation (70 per cent yield) with 90 per cent retention of configuration is evidence for the equatorial disposition of the amino group.

The stereospecific process resulting in retention of configuration may involve a broadside displacement of the diazonium group, proceeding through a pyramidal transition state (CXXVII) (199). The geometry of the puckered ring favors this type of displacement when the reacting group is equatorial. The retention of configuration by molecules with equatorial amino groups seems to exclude a carbonium-ion intermediate.[12] Displacement of the amino group in decalylamine with inversion or elimination may be rationalized in terms of an S_N2 or an E_2 mechanism, respectively, proceeding through a four-centered planar transition state CXXVIII, which would be favored when the amino group and an adjacent hydrogen are polar.



CXXVII



CXXVIII

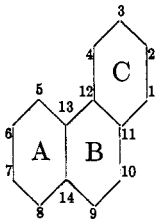
The results of deamination of the *cis*-1-decalylamines do not conform to those for the other isomeric amines. The epimer possessing the polar amino group, as shown, for example, by the Tschugaeff reaction, affords an alcohol with retention of configuration, whereas the one with the equatorial amino group reacts by elimination and inversion. These data may be explained on the basis of ring conversion, which in each case would give a certain number of molecules of inverted configuration. The functional group in the *cis*-1-decalylamine (CXVII) corresponding to the decalol melting at 93°C. may have a substantial proportion of equatorial character because of steric interference from the C_5-substituent. Additional evidence for the partial equatorial character of this decalol has been noted in table 15: namely, the greater rate of hydrolysis of its esters compared with those of the epimeric decalol melting at 55°C. At first glance, these seeming discrepancies constitute chemical evidence for ring conversion in decalin derivatives.

[12] On the other hand, whilst (−)-menthylamine (NH_2 equatorial) is deaminated to (−)-menthol with retention of configuration and so presumably without intervention of a carbonium ion, (+)-neomenthylamine (NH_2 polar) gives (+)-3-*p*-menthene (elimination) accompanied by 4-*p*-menthanol (rearrangement), products which suggest the formation of a carbonium ion (73).

V. Tricyclic Carbon Compounds

A. Perhydrophenanthrenes and Perhydroanthracenes

Because of the presence of four asymmetric carbon atoms (11, 12, 13, and 14), perhydrophenanthrene (CXXIX) can exist in six steric forms of which four are



CXXIX

racemic (*cis-syn-trans*, *cis-anti-cis*, *cis-anti-trans*, and *trans-anti-trans*)[13] and two are meso (*cis-syn-cis* and *trans-syn-trans*).[14] The configurations of ring fusion A/B or B/C are designated *cis* or *trans* depending on whether the C_{13} and C_{14} (or C_{11} and C_{12}) hydrogens are on the same side of the molecule. The configuration of the backbone, C_{12}-C_{13}, is *syn* if the hydrogens on C_{12} and C_{13} are on the same side of the molecule and *anti* if on opposite sides. In terms of the convention proposed by Linstead (180), hydrogen substituents at the asymmetric centers are shown in the planar representation of the isomers as black dots if they project above the molecule; a dot is always placed on C_{13}. The maximum number of dots is employed; otherwise the *cis-syn-cis* isomer would be unmarked.

Table 17 records the structures of the perhydrophenanthrenes and the related tricyclic perhydroanthracenes along classical lines, as modified by Linstead (185) and as depicted on the basis of boat or chair conformations. The structures of all six isomers, in terms of classical stereochemistry, have been elucidated in a brilliant series of papers by Linstead and coworkers (181–185). The data reported there have been utilized by Johnson (149) as a basis for deriving conformational stability rules for polycyclic compounds.

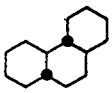
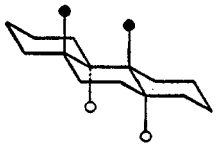
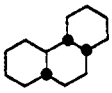
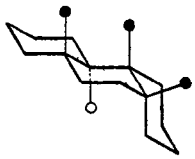
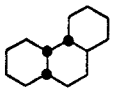
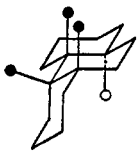
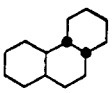
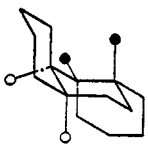
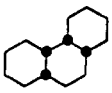
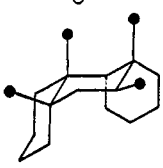
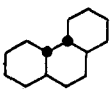
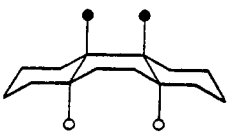
In the case of the 9-ketoperhydrophenanthrenes, Linstead *et al.* have shown that the *c-s-c* form (CXXXIV) may be isomerized to the *c-s-t* isomer (CXXXII), and a similar transformation (*t-a-c* → *t-a-t*) can be effected for CXXXI and CXXX. In a study of the 10-keto derivatives, the *c-s-t* (CXXXII) isomer could not be isomerized to *t-s-t* (CXXXV). In the latter, the central ring B cannot exist in the chair form; it is impossible on steric grounds to have a ring fused in the *trans* configuration through two vicinal p-bonds, since they lie perpendicularly on opposite sides of the ring. The *t-s-t* form must exist in the chair-boat-chair arrangement, in which rings A and C are fused to B by four equatorial-boat bonds (e-b) and must be less stable than the *c-s-t* isomer.

[13] Abbreviated as *c-s-t*, *c-a-c*, *c-a-t*, and *t-a-t*, respectively.

[14] *c-s-c* and *t-s-t*, respectively.

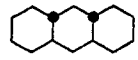
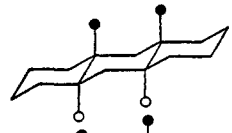
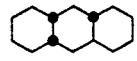
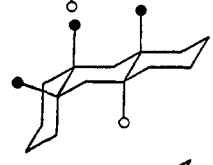
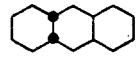
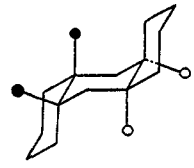
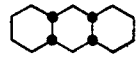
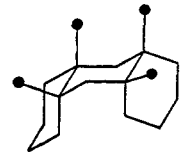
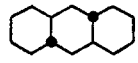
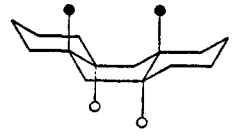
TABLE 17

Stereochemical relationships and energy differences between the isomeric perhydrophenanthrenes and perhydroanthracenes

NUMBER	ISOMER	NUMBER OF e, p CARBON–CARBON BONDS	*E*	PLANAR FORMULATION	CHAIR-BOAT CONFORMATION*
				Perhydrophenanthrenes	
			kcal.		
CXXX	*t-a-t*	4e	0.8		
CXXXI	*t-a-c*	3e,1p	3.2		
CXXXII	*c-s-t*	3e,1p	3.2		
CXXXIII	*c-a-c*	2e,2p	4.8		
CXXXIV	*c-s-c*	2e,2m-p	7.2		
CXXXV	*t-s-t*	4(e-b)	>5.6		

* The ring-junction hydrogen substituents above the plane of the molecule are represented as ●, equivalent to the dots in the planar formulation; those represented as ○ are below the plane of the molecule.

TABLE 17—(*Continued*)

NUMBER	ISOMER	NUMBER OF e, p CARBON-CARBON BONDS	*E*	PLANAR FORMULATION	CHAIR-BOAT CONFORMATION*
		Perhydroanthracenes			
			kcal.		
CXXXVI	*t-s-t*	4e	0		
CXXXVII	*c-s-t* (*t-a-c*)	3e,1p	2.4		
CXXXVIII	*c-a-c*	2e,2p	4.8		
CXXXIX	*c-s-c*	2e,2m-p	6.4		
CXL	*t-a-t*	4(e-b)	>5.6		

Johnson has proposed three rules for saturated systems containing six-membered or larger (medium-sized) rings:

"1. In saturated fused six-membered ring systems with all rings assumed to have the chair conformation, those configurations with the larger number of e-bonds at the point of ring fusion will be the more stable, the number of e- and p-bonds being determined as substituents of the most highly substituted rings, and that alternative assignment being chosen which gives the greater number of e-conformations.

"2. Since two meta p-substituents [as in CXXXIV (*c-s-c*)] show steric interfer-

ence, such a form is less stable than one with two para p-substituents [as in CXXXIII, *c-a-c*].

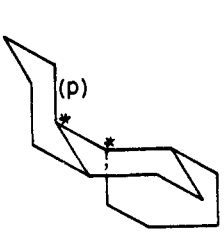
"3. In configurations [such as CXXXV, *t-s-t*] where both alternative assignments lead to attachment of a single ring by two ortho p-bonds, the ring involved may be forced into the boat conformation."

From a consideration of these rules, the following order of stability has been deduced: *t-a-t* (4e) > *t-a-c* and *c-s-t* (3e, 1p) > *c-a-c* (2e, 2p) > *c-s-c* (2e, 2 meta-p); *t-s-t* (4(e-b)) < *t-a-c* and *c-s-t*.

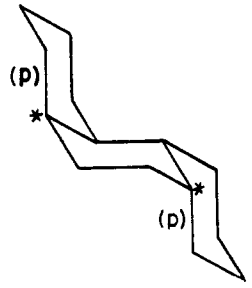
These rules do not apply to five-membered and smaller rings which, because of internal steric factors, tend toward coplanarity and hence favor *cis*-locking of the rings. Thus *cis*-hydrindane is more stable than *trans*-hydrindane and, as the size of one ring is reduced further, the *cis* configuration may be expected to become increasingly more stable, with the cyclohexane ring tending toward the boat conformation.[15] In the extreme case of a three-fused to a six-membered ring, the *trans* isomer would be so unstable that it might not be expected to exist.

Similarly, conformational analysis of the perhydroanthracenes (CXXXVI–CXL) leads to the following order of stability: *t-s-t* (4e) > *c-s-t* (=*t-a-c*, 3e, 1p) > *c-a-c* (2e, 2p) > *c-s-c* (2e, 2 meta-p); and *c-s-t* (3e, 1p) > *c-a-c* (4(e-b)).

Using the method previously described for calculating the energy difference (vapor phase, 25°C.) between the *cis*- and *trans*-decalins, Johnson (150) has estimated quantitatively the order of stability of the perhydrophenanthrenes and perhydroanthracenes (table 17). In both compounds the most stable isomer is that with the greatest number of e-bonds, *t-s-t* perhydroanthracene and *t-a-t* perhydrophenanthrene. Since the *t-s-t* perhydroanthracene is the isomer of lowest energy, it has been assigned an arbitrary energy value of zero. The most stable perhydrophenanthrene (*t-a-t*) differs from it by one skew interaction between the bonds forming the angle of the three rings, or by 0.8 kcal. The most highly strained isomers are those (*c-s-c* perhydrophenanthrene and *c-s-c* perhydroanthracene) in which two of the polar carbon–carbon bonds on the central



CXLIa



CXLIb

cyclohexane ring are in a meta relationship, and those (*t-s-t* perhydrophenanthrene and *t-a-t* perhydroanthracene) in which the central ring is boat-formed.

The *c-a-c* isomer of perhydrophenanthrene may exist in two possible con-

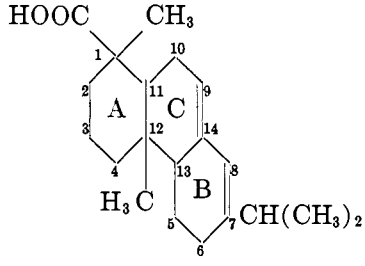
[15] This is by no means a proven generalization, as shown by the chair form of the six-membered ring in epoxycyclohexane.

formations (CXLIa and b), the former with 1,2-dipolar substituents on the central ring and the latter with 1,4-dipolar substituents. The energy value calculated for the former (4.8 kcal.) has been defined by two *cis*-decalin interactions. In the latter, an angular skew interaction is operative, producing an increment of 0.8 kcal. or a total value of 5.6 kcal. The former conformation therefore is the more stable.

B. THE RESIN ACIDS

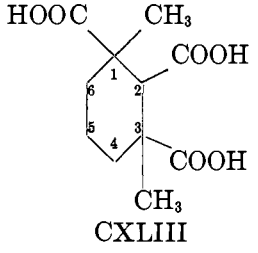
1. Abietic acid

In view of evidence for both *cis* (186) and *trans* (53, 60, 129, 332, 333) fusion, the nature of the A/C ring fusion in abietic acid (CXLII) has been the subject of some uncertainty. The problem has been solved by investigation of two homologous carboxylic acids, $C_{11}H_{16}O_6$, m.p. 219°C. (CXLIII), and $C_{12}H_{18}O_6$, m.p. 212–213°C. (CXLIV), obtained by the oxidation of abietic and also of dextropimaric (CXLV) acid.

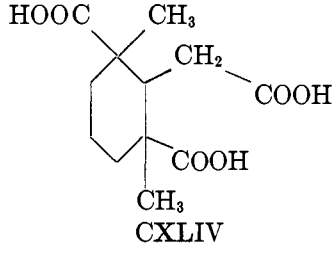


CXLII

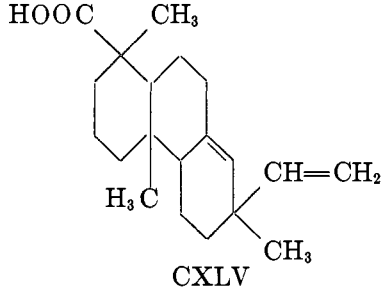
Treatment (273) of CXLIII with acetyl chloride gives two anhydrides (CXLVI, melting at 100°C., and CXLVII, melting at 170–172°C.), whereas CXLIV yields a monomer (CXLVIII, m.p. 182–183°C.) and a dimer (CXLIX, m.p. 230°C.)



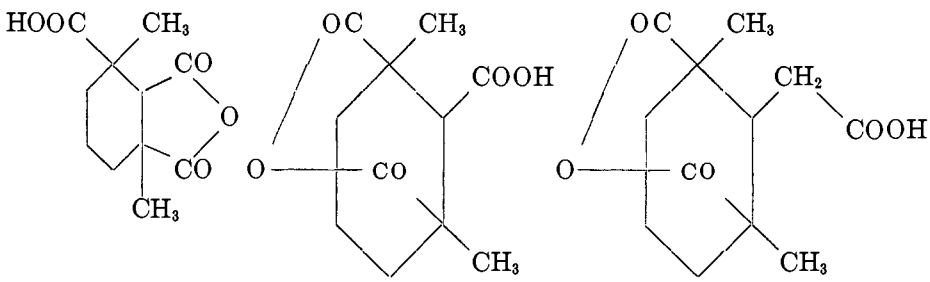
CXLIII



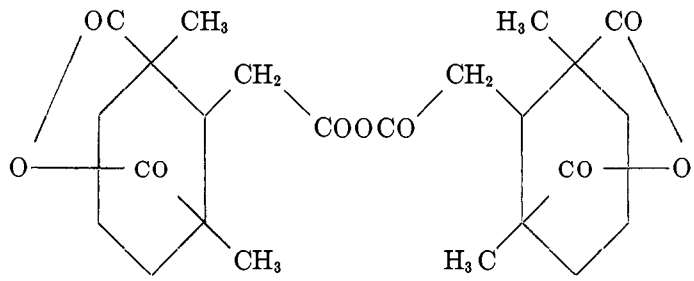
CXLIV



CXLV



CXLVI CXLVII CXLVIII

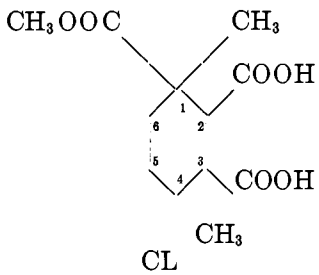


CXLIX

The acids CXLIII and CXLIV, being optically inactive, must possess the meso structure, wherein the 1,3-carboxyl groups (at C_1 and C_3) are in a *cis* (ee or pp) relationship to each other. This is indicated by the formation of CXLVII by heat alone. Since *trans*-1,3-carboxylic acids do not yield anhydrides readily and then only after rearrangement to the *cis* form, a possible *trans*-1,3 structure is excluded by the re-formation of the original acids from CXLVI, CXLVII, and CXLVIII by the action of boiling water; the reconversion of CXLIX requires boiling aqueous hydrochloric acid. The experimental evidence indicates that the carboxyl group at C_2 is sterically hindered in CXLIII and CXLIV.

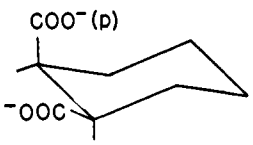
The configuration of the substituents at C_1, C_{11}, and C_{12} in abietic and pimaric acids has been solved by a consideration of the thermodynamic dissociation constants of CXLIII (27). *Cis*- and *trans*-1,2-dicarboxylic acids particularly show a marked difference in p_ω, the difference in the logarithms of the first and second measured dissociation constants, or ΔpK_a:

ACID	p_ω	
	cis	*trans*
1,2-Cyclohexanedicarboxylic acid	1.80	1.15
1,2,3,4-Tetrahydronaphthalene-2,3-dicarboxylic acid	1.89	1.10
1,3-Cyclohexanedicarboxylic acid	0.76	0.82

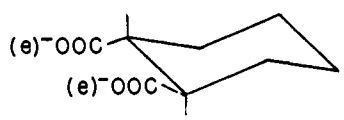


CL

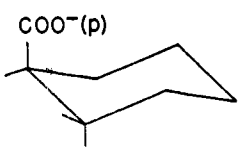
The asymmetric 1-carbomethoxy ester (CL) of CXLIII gives a p_ω (1,2-dicarboxylic acid) value of 1.11, indicating that the carboxyl group at C_2 is *trans* with respect to the carboxyl groups at C_1 and C_3. Assuming the chair configuration of 1,2-cyclohexanedicarboxylic acid, three conformations are possible: CLI (*cis*, ep), CLII (*trans*, ee), and CLIII (*trans*, pp). On electrostatic grounds, CLIII rather than CLII may be considered the probable structure of



CLI



CLII

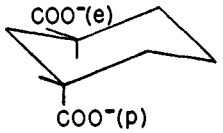


CLIII

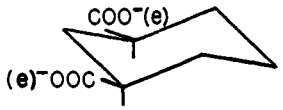
the *trans* anion. The larger value (1.8) for p_ω (1,2-dicarboxylic acid) in the *cis*, as compared with that (1.1) for *trans* acids, is mainly due to the smaller COO^-–COO^- distance in the former (CLI).

Three conformations of 1,3-cyclohexanedicarboxylic acids are possible: CLIV (*trans*, ep), CLV (*cis*, ee), and CLVI (*cis*, pp). Since the charges in CLV are separated by a greater distance (6.66 Å.) than in CLVI (2.51 Å.), on electrostatic reasoning CLV is more stable than CLVI.

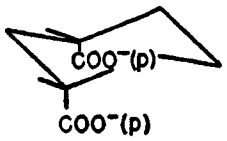
Also, inasmuch as the acid $C_{11}H_{16}O_6$ (CXLIII) is internally compensated, the 1,3-dicarboxyl groups are of the type shown by CLV or CLVI. Three possible conformations must be considered, therefore, to account for the carboxyl function at C_2. CLVII represents the *cis* (epe) ion, whereas CLVIII (ppp) and CLIX (eee) represent the *trans* tervalent ions. By evaluation of the electrostatic



CLIV

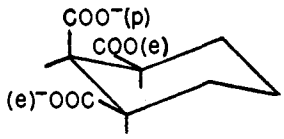


CLV

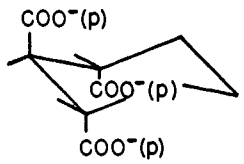


CLVI

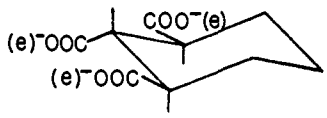
energy differences, Barton and Schmeidler (27) have shown that CLIX is more stable than CLVIII by about 1 kcal. The experimental data favor the *trans*



CLVII



CLVIII

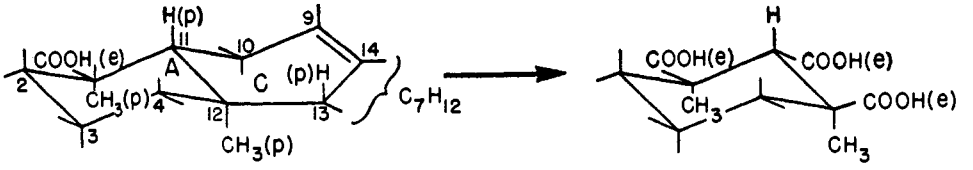


CLIX

configuration eee for the tricarboxylic acid (CXLIII) and consequently establish the A/C ring fusion in abietic (and pimaric) acid as *trans*.

It has been suggested (289) that the remaining asymmetric center in abietic acid (CXLII) at C_{13} also may be in a *trans* relationship to the C_{12}-methyl group because of the fact that treatment of colophony or rosin with acidic reagents (the procedure involved in the preparation of abietic acid) would provide conditions for the assumption of the more stable configuration at this center. The rearrangement of isoabietic acid (in which the spatial configuration at C_{13} is different from that in abietic acid) to abietic acid under acidic conditions supports this argument.

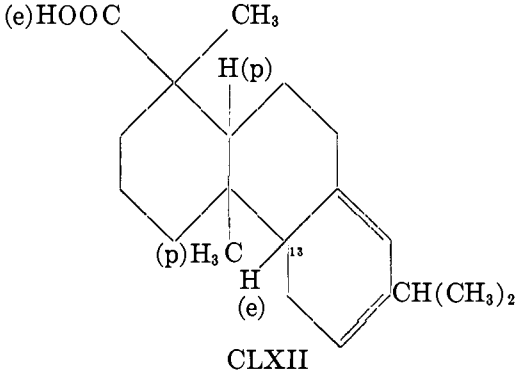
CLX represents the conformation of rings A and C in abietic acid, based on the evidence presented above, while CLXI illustrates the tricarboxylic acid, $C_{11}H_{16}O_6$, obtained by oxidative degradation of abietic acid. Owing to the presence of the C_9–C_{14} double bond, ring C is pictured as a deformed chair.



CLX CLXI

2. Other resin acids

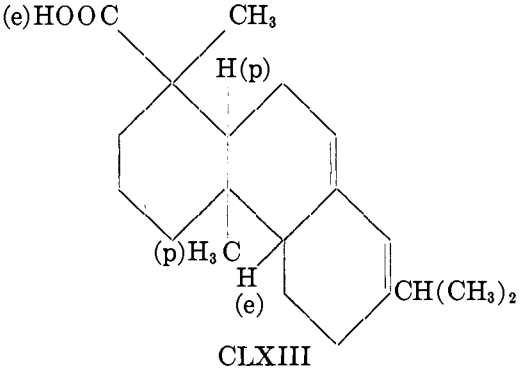
Abietic acid is considered to be a "secondary" resin acid because it is formed from levopimaric acid (CLXII), a precursor found in colophony, by isomerization with heat or acidic reagents (109, 187, 267). This preparation establishes that the A/C fusion in CLXII is *trans* and that the conformation at C_1 and C_{13} is identical with that in abietic acid. The presence of the conjugated double



CLXII

bonds in ring B has been confirmed *inter alia* by the ultraviolet absorption spectrum of levopimaric acid (109, 167). Barton (21) has suggested that both abietic and levopimaric acids have the same configuration (p-H) at C_{13} because of the strong levorotation displayed by these isomers. More recently, on the basis of molecular rotation studies, Klyne (161a) has concluded that the C_{13}-hydrogen is *cis* to the polar C_{12}-methyl group and therefore is oriented equatorially.

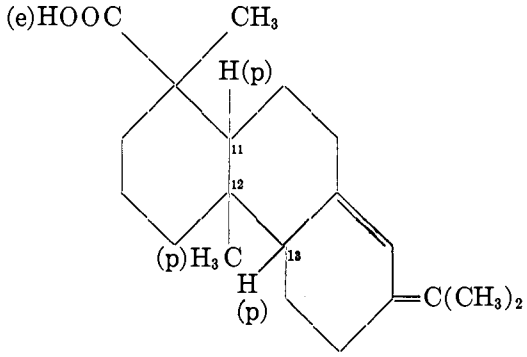
Isoabietic acid (CLXIII), prepared by the action of potassium hydroxide on abietic acid dihydrobromide, gives an absorption spectrum identical with



CLXIII

that of abietic acid. Sandermann (279) has suggested that the only difference between the two compounds is the orientation of the hydrogen at C_{13}.

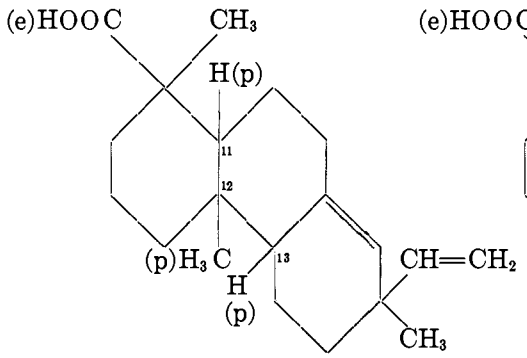
The structure of neoabietic acid (CLXIV) has been established (109) as a simple double-bond isomer of abietic acid. Like levopimaric acid it is almost



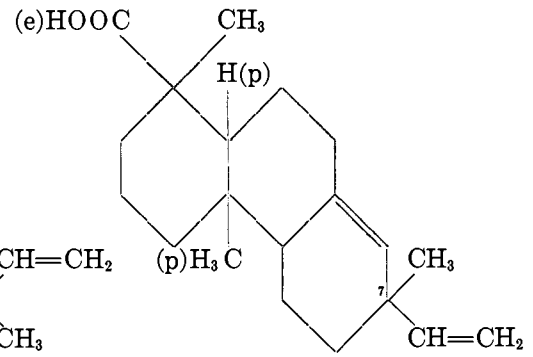
CLXIV

quantitatively isomerized to abietic acid by mineral acids (268). Consequently its configuration at C_1, C_{11}, and C_{12} must be identical with that of abietic acid. Although the strong dextrorotation of neoabietic acid was interpreted as indicating that the configuration at C_{13} may be opposite (e) to that in abietic acid (289), Klyne (161a) considers the polar conformation to be correct.

Like levopimaric acid, dextropimaric acid (CLXV) is a primary resin acid but, unlike other primary resin acids, it is relatively stable to heat and to treatment with mineral acids. Although oxidation with nitric acid to yield the same tri-



CLXV



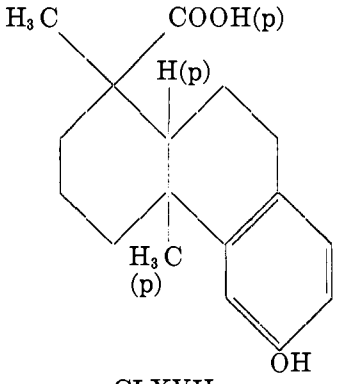
CLXVI

carboxylic acids CXLIII and CXLIV, previously obtained from abietic acid, establishes an identical relationship at C_1, C_{11}, and C_{12} (274), the stereochemistry at C_{13} has not been determined with certainty. Klyne (161a) believes the C_{13}-hydrogen to be *trans* to the C_{12}-methyl substituent.

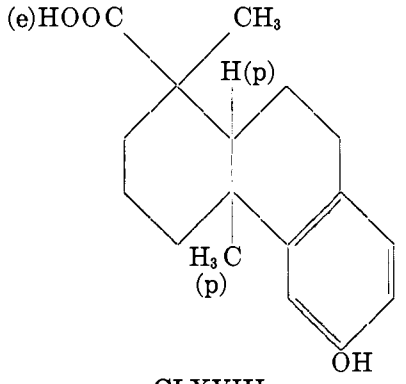
Isodextropimaric acid (CLXVI) is reported to be epimeric at C_7 with dextropimaric acid (110). This structure has been confirmed by infrared absorption studies (54).

Although podocarpic acid (CLXVII) is not a diterpenoid resin acid, it is a

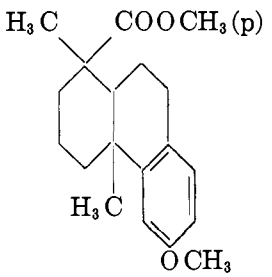
stereoisomer of 6-hydroxydehydroabietic acid (CLXVIII). Campbell and Todd (60) have converted methyl podocarpate methyl ether (CLXIX) to the 7-isopropyl derivative (CLXX), which was not identical with the isomeric methyl-6-



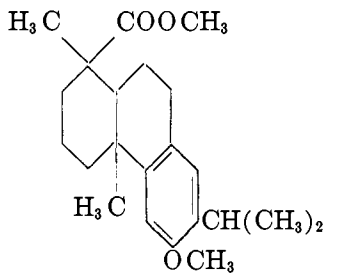
CLXVII



CLXVIII



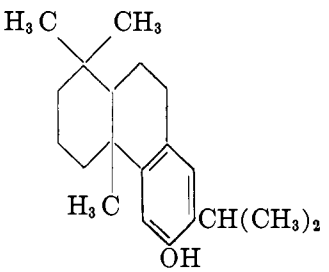
CLXIX



CLXX

methoxydehydroabietate obtained from 6-hydroxyabietic acid. The suggestion that the carboxyl group in podocarpic acid (polar) is epimeric with that (equatorial) in abietic acid is supported by the greater difficulty of hydrolyzing podocarpate as compared with abietate esters. This difference in reactivity of equatorial and polar carboxyl groups is in agreement with the conclusions of Smith and Byrne (299) on cyclohexanedicarboxylic acids. The C_{12}-methyl group in podocarpic acid is pictured as *cis* (and therefore polar) to the carboxyl group (161a).

Investigation of the phenolic diterpenoid ferruginol (CLXXI) provides additional evidence in support of the structure of podocarpic acid. Its formation



CLXXI

by partial synthesis (60) from podocarpic and dehydroabietic acids demonstrates conclusively that the carboxyl groups in the two acids are epimeric. The conformation of podocarpic acid, therefore, is that given by formula CLXVII.

VI. References

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