STUDIORUM PROGRESSUS

The Conformation[1] of the Steroid Nucleus

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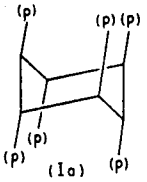
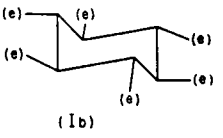
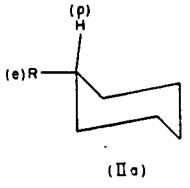
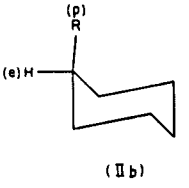
In recent years it has become generally accepted that the chair conformation of cyclohexane is appreciably more stable than the boat. In the chair conformation it is possible[3,4] to distinguish two types of carbon-hydrogen bonds; those which lie as in (Ia) perpendicular to a plane containing essentially the six carbon atoms and which are called[3] *polar* (p), and those which lie as in (Ib) approximately in this plane. The latter have been designated[3] *equatorial* (e).

The notable researches of HASSEL and his collaborators[5,6] on the electron diffraction of cyclohexane derivatives have thrown considerable light on these more subtle aspects of stereochemistry. Thus it has been shown[5] that monosubstituted cyclohexanes adopt the equatorial conformation (IIa) rather than the polar one (IIb). This is an observation of importance for it indicates that the equatorial conformations are thermodynamically more stable than the polar ones. It should perhaps be pointed out here that although one conformation of a molecule is more stable than other



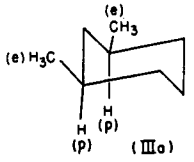


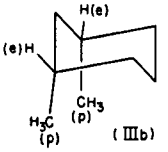


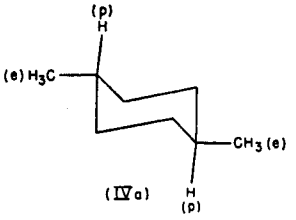


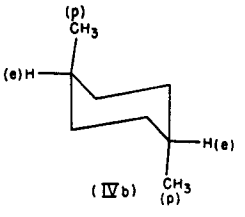
possible conformations, this does *not* mean that the molecule is *compelled* to react as if it were in this conformation or that it is rigidly fixed in any way. So long as the energy *barriers* between conformations are small, separate conformations cannot be distinguished by the classical methods of stereochemistry. On the other hand a small difference in free energy content (about one kilocal. at room temperature) between two possible conformations will ensure that the molecule appears by physical methods of examination and by thermodynamic considerations to be substantially in only *one* conformation.

The equatorial conformations are also the more stable in both cis-1:3- and trans-1:4- disubstituted cyclohexanes[1]. Thus cis-1:3-dimethylcyclohexane adopts the diequatorial conformation (IIIa) rather than the dipolar one (IIIb), whilst trans-1:4-dimethylcyclohexane exists as (IVa) rather than (IVb).









Thermodynamic calculations[1] show that trans-1:2-dimethylcyclohexane takes up the diequatorial conformation (V; R=CH_3) rather than the dipolar one (VI; R=CH_3). For cis-1:2-disubstituted cyclohexanes there are two possible conformations. In both of these one of the substituents forms an equatorial bond, the other a polar one. Since these differences in thermodynamic stability between equatorial and polar conformations are presumably of steric origin[1], it would appear logical to make the larger substituent form the equatorial bond.

Considerations of the same type can be extended to 2-substituted cyclohexanols. Thus[2,3] the cis-alcohols (VII; R= alkyl), on equilibration by heating with sodium, furnish almost entirely the trans-isomers (VIII; R= alkyl). In the former one substituent is polar, one equatorial; in the latter both are equatorial. The same conclusion on relative stability is reached from a consideration of thermochemical data[4]. Similarly[5] the 2:6-disubstituted cyclohexanol (IX), with two equatorial and one polar substituents, is isomerized to (X) on equilibration. The situation is the same[3] with the bicyclic trans-α-decalol. Here the isomer (XI) is isomerized to (XII) on equilibration.

A consideration of the conformations[6] (XIII) and (XIV), assumed by the steroid nucleus when the A/B ring fusion is respectively trans- and cis-, provides a striking illustration of the usefulness of the concept of

[1] The word conformation is used to denote differing strainless arrangements in space of a set of bonded atoms. In accordance with the tenets of classical stereochemistry, these arrangements represent only one molecular species.

[2] Harvard University Visiting Lecturer, 1949–50, Harvard University, Cambridge 38, Mass.

[3] C. W. BECKETT, K. S. PITZER, and R. SPITZER, J. Amer. Chem. Soc. *69*, 2488 (1947).

[4] O. HASSEL's nomenclature[5] is different, but the distinction remains the same.

[5] O. HASSEL and H. VIERVOLL, Acta Chem. Scand. *1*, 149 (1947).

[6] See O. HASSEL and B. OTTAR, Acta chem. Scand. *1*, 929 (1947) for a summarizing paper and references to earlier work.

[1] C. W. BECKETT, K. S. PITZER, and R. SPITZER, J. Amer. Chem. Soc. *69*, 2488 (1947).

[2] G. VAVON, Bull. Soc. Chim. [4], *49*, 937 (1931).

[3] W. HÜCKEL, Ann. Chem. *533*, 1 (1937).

[4] A. SKITA and W. FAUST, Ber. Dtsch. Chem. Ges. *64*, 2878 (1931).

[5] G. VAVON and P. ANZIANI, Bull. Soc. Chim. [5], *4*, 1080 (1937). In connection with the conformations of poly-substituted cyclohexanes it should be mentioned that O. BASTIANSEN, O. ELLERSEN, and O. HASSEL, (Acta chem. Scand. *3*, 918 [1949]) have recently shown that the five stereoisomeric benzene hexachlorides assume, in agreement with our general argument, those conformations which have the maximum possible number of equatorial carbon-chlorine bonds.

[6] Conformations (XIII) and (XIV) are unambiguous representations of the steroid nucleus provided that rings A, B, and C are chairs. This is almost certainly true for a trans-A/B ring fusion (compare the X-ray evidence of C. H. CARLISLE and D. CROWFOOT (Proc. Roy. Soc. A *184*, 64 [1945]) on the conformation of cholesteryl iodide) and a similar situation, at least in solution, probably holds for a cis-A/B fusion. The justification for the latter has been more

Table I

Observation	Exptl. Method	References
Cholestane Series		
2α (e) more stable than 2β (p)	Reduction of 2-one	L. RUZICKA, P. A. PLATTNER, and M. FURRER, Helv. chim. acta *27*, 524 (1944).
3β (e) more stable than 3α (p)	Equilibration	pp. 98, 636*
4α (e) more stable than 4β (p)	Reduction of 4-one**	R. TSCHESCHE and A. HAGEDORN, Ber. *68*, 2247 (1935). – L. RUZICKA, P. A. PLATTNER, and M. FURRER, loc. cit.
6α (e) more stable than 6β (p)	Reduction of 6-one	pp. 223, 653.
7β (e) more stable than 7α (p)	Reduction of 7-one***	I. M. HEILBRON, W. SHAW, and F. S. SPRING, Rec. Trav. Chim. *57*, 529 (1938).
5β (e, p), 6α (e)-dibromide more stable than 5α (p), 6β (p)-dibromide	Equilibration	D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).
Coprostane Series		
3α (e) more stable than 3β (p)	Equilibration	pp. 99, 636.
11α (e) more stable than 11β (p)	Equilibration	L. F. FIESER, preceding paper.
12β (e) more stable than 12α (p)	Equilibration	pp. 461, 657.

* All references reported in this way are to L. F. FIESER and M. FIESER, *Natural Products Related to Phenanthrene* (3rd Edition, 1949, Reinhold Publishing Corp.).

** The configurations are assigned (*vide infra*).

*** According to the standard tables of D. H. R. BARTON and W. KLYNE (Chem. and Ind. 755 [1948]) 7β-hydroxycholestane should have $[\alpha]_D$ *ca.* $+52^0$, whilst the 7α-isomer should exhibit $[\alpha]_D$ *ca.* $+8^0$. I. M. HEILBRON, W. SHAW, and F. S. SPRING, *loc. cit.*, observed $[\alpha]_D$ $+51^0$ and therefore the configuration of their alcohol must be 7β-.

polar and equatorial bonds. The relationship between the α- and β-nomenclature introduced by FIESER[1] and the occurrence of polar and equatorial bonds is also summarized in (XIII) and (XIV).

Thermodynamic Considerations. In a number of cases equilibration of hydroxyl groups at secondary positions in the steroid nucleus has been carried out. At other positions the corresponding ketones have been reduced by sodium and alcohol, a process which (in cyclohexane derivatives) is well established to give the thermodynamically more stable alcohols in approximately the same proportions as from equilibration experiments[2]. It is possible therefore to see how well the concept of more stable equatorial conformations is obeyed. As set out in Table I the expected relationships are observed. Also included in this Table is a reference to the equilibration of 5α:6β-dibromocholestane with the 5β:6α-isomer, for this is clearly relevant to the issue under discussion.

Elimination Evidence. Reactions whose mechanisms require concerted 1:2-elimination should proceed more readily when the four centres involved (the two carbon atoms and the two substituents) lie in one plane. For concerted ionic elimination reactions in cyclohexane derivatives the optimum arrangement of the substituents for the minimization of the activation energy is that in which both are polar[3,4]. There is much evidence in the literature which confirms this. Thus[1] cis-2-substituted cyclohexanols (VII) undergo acid catalysed dehydration [elimination of H(*p*) and OH(*p*)] more readily than the trans-isomers (VIII). In the menthol series[2] neomenthol (XV; R=CH_3, R'=H) loses water easily relative to menthol (XVI; R=CH_3, R'=H) and neoisomenthol (XV; R=H, R'=$CH)_3$ dehydrates easily relative to isomenthol (XVI; R=H, R'=CH_3)[3]. There are a number of interesting examples of this sort of phenomenon in steroid compounds. A summary is given in Table II.

Table II

Observation Easy elimination of	References
Cholestane Series	
6β-OH (p) and 5α-H (p)	D. H. R. BARTON and W. J. ROSENFELDER, J. Chem. Soc. 2459 (1949).
6β-H (p) and 5α-Cl (p)	D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).
6β-Br (p) and 5α-Br (p)	D. H. R. BARTON and E. MILLER, loc. cit.
7α-OH (p) and 8β-H (p)	pp. 241, 242, 631
Coprostane Series	
7α-OH (p) and 8β-H (p)	pp. 118, 631
11β-OH (p) and 9α-H (p)	pp. 408, 630
11β-Br (p) and 9α-H (p)	pp. 460, 631

extensively presented elsewhere[4,5]. See also the discussion by SOBOTKA[6].

[1] L. F. FIESER, *The Chemistry of Natural Products Related to Phenanthrene* (1st Ed. 1936, Reinhold Publishing Corporation).

[2] See footnotes 2 and 3 on p. 316, 2nd column.

[3] E. D. HUGHES and C. K. INGOLD *et al.*, J. Chem. Soc. 2117 (1948).

[4] D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).

[5] O. BASTIANSEN and O. HASSEL, Nature *157*, 765 (1946). – O. HASSEL and H. VIERVOLL, Acta chem. Scand. *1*, 149 (1947) and papers there cited. – D. H. R. BARTON, J. Chem. Soc. 340 (1948).

[6] H. SOBOTKA, *The Chemistry of the Steroids*, 1938, p. 48 *et seq.* (The Williams and Wilkins Co.).

[1] G. VAVON, Bull. Soc. Chim. [4], *49*, 937 (1931).

[2] For summary see J. L. SIMONSEN and L. N. OWEN, *The Terpenes*, Vol. I (Cambridge University Press, 1947).

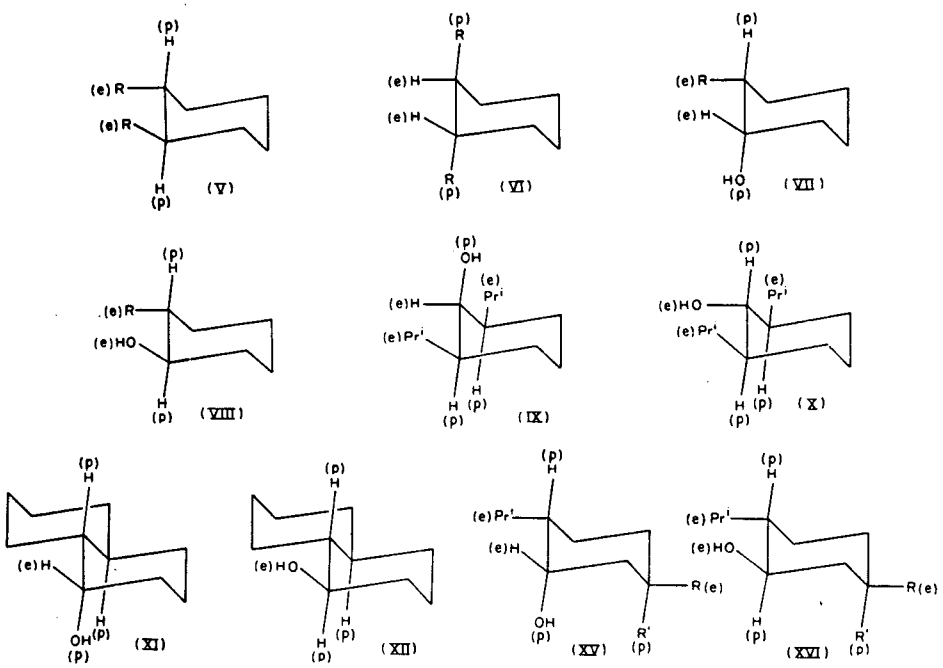
[3] Of course for pyrolytic elimination of substituents by "unimolecular" mechanisms (see D. H. R. BARTON, J. Chem. Soc. 2174 [1949]) cis-elimination is the rule and the discussion given here is no longer relevant.

Table III

Observation	References
Cholestane Series	
2β-OH (p) more hindered than 2α-OH (e)	A. FÜRST and P. A. PLATTNER, Helv. chim. acta *32*, 275 (1949).
3α-OH (p) more hindered than 3β-OH (e)	pp. 635, 636
6β-OH (p) more hindered than 6α-OH (e)	p. 223
6α-H (e) more easily oxidized than 3α-H (p)	L. F. FIESER and S. RAJAGOPALAN, J. Amer. Chem. Soc. *71*, 3938 (1949).
3β-H (e) more easily oxidized than 3α-H (p)	G. VAVON and B. JACUBOWICZ, Bull. Soc. Chim. [4], *53*, 581 (1933).
Coprostane Series	
3β-OH (p) more hindered than 3α-OH (e)	pp. 635, 636
6β-OH (p) more hindered than 6α-OH (e)	p. 652
11β-OH (p) more hindered than 11α-OH (e)	p. 408
12α-OH (p) more hindered than 12β-OH (e)	p. 658
7α-OH (p) and 12α-OH (p) more hindered than 3α-OH (e)	p. 125
7β-H (e) and 12β-H (e) more easily oxidized than 3β-H (p)	p. 126; L. F. FIESER and S. RAJAGOPALAN, J. Amer. Chem. Soc. *71*, 3935 (1949).

Steric Hindrance Evidence. The applicability of steric hindrance evidence in the assignment of configuration has long been recognised, although such assignments are not always reliable[1]. It seems possible to explain the relative magnitudes of many of the phenomena of steric hindrance in cyclohexane derivatives on the basis that polar bonds are more hindered than the corresponding equatorial bonds. An inspection of models makes this reasonable for a polar bond is always close in space to two other polar bonds each attached to the next but one carbon atom, whereas there is no similar relationship for equatorial bonds.

In support[2] of this generalization it has been observed that cis-2-substituted cyclohexanols (VII) with polar hydroxyls are more difficult to esterify, and their esters more difficult to hydrolyse, than the corresponding trans-alcohols and their esters. The same effects are observed with trans-α-decalol[1]. The esters of the alcohol (XI) (polar hydroxyl) are more difficult to hydrolyse than those of the alcohol (XII) (equatorial hydroxyl). In the menthol series[2] menthol (XVI; R=CH_3, R′=H) is more easily esterified than neomenthol (XV; R=CH_3, R′=H) and a similar relationship holds for isomenthol (XVI; R=H, R′=CH_3) and neoisomenthol (XV; R=H, R′=CH_3).



However, a reverse relationship holds[3] for chromic acid oxidation of 2-substituted cyclohexanols. Here the cis-alcohols are oxidized more rapidly than the trans-.

[1] W. HÜCKEL, Ann. Chem. *533*, 1 (1937). – Compare the preceding paper in which L. F. FIESER has discussed steric effects under the headings intraradial and extraradial.

[2] G. VAVON, Bull. Soc. Chim. [4], *49*, 937 (1931).

[1] W. HÜCKEL *et al.*, Ann. Chem. *533*, 128 (1937).

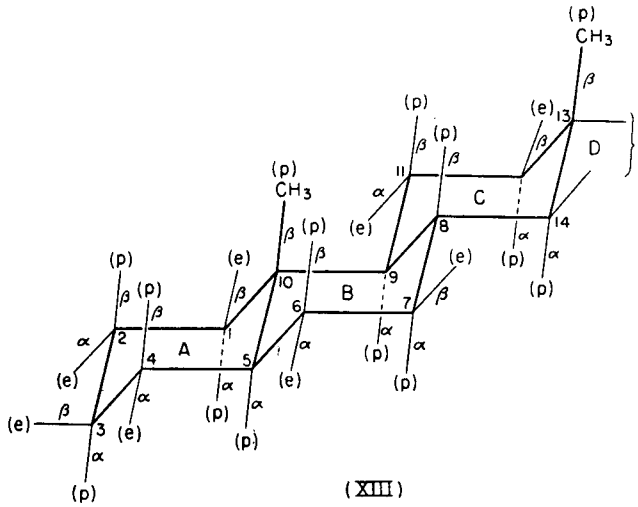
[2] For summary see: J. L. SIMONSEN and L. N. OWEN, *The Terpenes*, Vol. I (Cambridge University Press, 1947).

[3] G. VAVON, Bull. Soc. Chim. [4], *49*, 937 (1931).

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 carbon-hydroxyl linkage.

The situation in the steroid field is summarized in Table III. In every case the expected order of hindrance holds good. Also included are data for oxidations of alcohols by Br^+ to give the corresponding ketones. If such oxidations are assumed to involve attack upon the carbon-hydrogen bond then the results are in agreement with the other observations summarized in the Table.

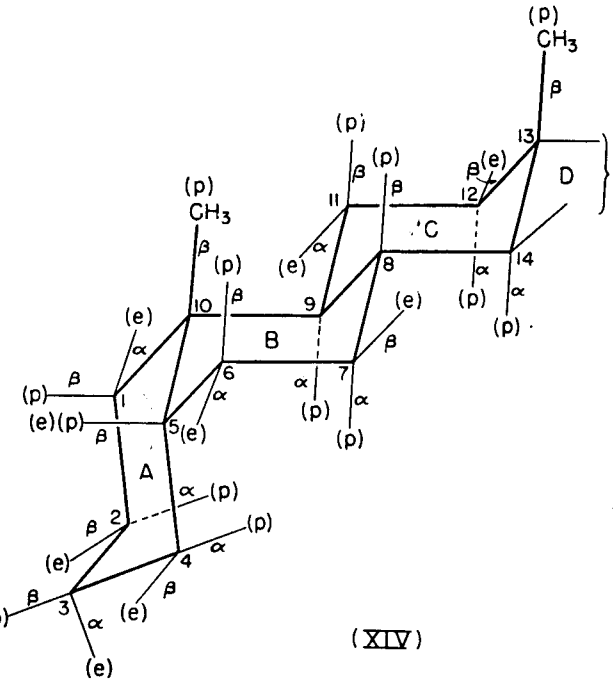
Although the concept of polar and equatorial bonds is not, of course, applicable to cyclopentane, it is of interest to note that the 17α-bond in the steroid nucleus has, because of the ring fusion to a six-membered ring, the character of a polar bond with respect to that ring. Also the 17β-bond has in its relationship to ring C the aspect of an equatorial bond. These facts are in agreement with the greater thermodynamic stability of 17β-substituents and the greater degree of steric hindrance shown by 17α-substituents[1].



(XIII)

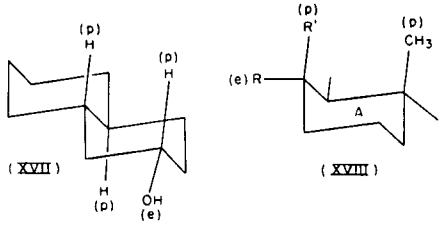
Use of the Concept. It will be clear that it is possible to assign configurations on the basis of the concept of polar and equatorial bonds. One such example has already been given in Table I. An additional illustration is provided by trans-β-decalol[2]. The more stable epimer m.p. 75° must have the hydroxyl in the equatorial conformation as in (XVII); this is in agreement with the fact that its esters are more rapidly hydrolysed than those of the epimeric (polar hydroxyl) alcohol. Other examples are mentioned below.

Extension to di- and tri-terpenoids. It would seem reasonable to extend the concept of equatorial and polar bonds to the correlation of the stereochemistry of other ring systems built up from fused cyclohexane units. Thus ring A of the diterpenoid abietic acid may be represented[3] by (XVIII; $R=CO_2H$, $R'=CH_3$) with the carboxyl occupying an equatorial conformation. It is understandable then that the esters of this acid should be more easily hydrolysed than those of (say) podocarpic acid where ring A is as shown in (XVIII; $R—CH_3$, $R'=CO_2H$), for in the latter the carboxyl occupies the more hindered polar conformation.

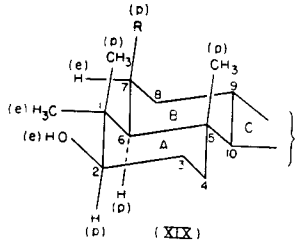


(XIV)

Now that it is recognised[1] that rings A and B of the α- and β-amyrin groups of triterpenoids and also[2] those of the lupeol group are trans-fused, it is possible to make a tentative representation of their stereochemistry



(XVII) (XVIII)



(XIX)

as shown in (XIX; R=H). Placing the hydroxyl in the equatorial conformation explains the more facile hydrolysis of β-amyrin acetate relative to epi-β-amyrin

[1] L.F. Fieser, Exper. *6*, 312 (1950).
[2] W. Hückel, Ann. Chem. *533*, 1 (1937). – W. Hückel *et al.*, Ann. Chem. *533*, 128 (1937).
[3] D.H.R. Barton, Quart. Rev. *3*, 36 (1949).

[1] D.H.R. Barton, Quart. Rev. *3*, 36 (1949).
[2] T.R. Ames and E.R.H. Jones, Nature *164*, 1090 (1949).

acetate[1] and of lupanol relative to epi-lupanol[2]. It also accounts for the easy elimination of water accompanied by molecular rearrangement, which is induced in these compounds or their derivatives by treatment with phosphorus pentachloride[3]. Such a reaction then becomes comparable to the very easy dehydration of isoborneol to give camphene, in that all the four atomic centers of importance in the reaction lie in one plane. The marked hindrance of the 7-hydroxyl group in sumaresinolic acid and its easy elimination under acid dehydrating conditions[4] are best explained if it has the polar conformation as in the part expression (XIX; R=OH).

In connection with the nomenclature of triterpenoids it would appear desirable to extend FIESER's α-, β-convention for steroids to cover triterpenoid stereochemistry also. A convenient reference point is the C_5 methyl group. Substituents on the same side of the main- ring plane as this methyl group should be regarded as having the β-configuration, those on the opposite side as having the α-configuration. Thus sumaresinolic acid would be designated 2β:7β-dihydroxyolean-12-ene-17-carboxylic acid.