# The Stereochemistry of cycloHexane Derivatives.

THE TILDEN LECTURE, DELIVERED AT BURLINGTON HOUSE, ON THURSDAY, OCTOBER 16TH, 1952, AND IN NEWCASTLE ON NOVEMBER 28TH, 1952.

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THE classical stereochemists were familiar with the concept of boat and chair conformations [1,2] for *cyclo*hexane. Only in the last decade has it become firmly established that the chair conformation is more stable [3,4] than the boat, although it is, of course, appreciated that the energy barrier separating the two forms is so low [5] as to prevent investigation of the phenomenon by the classical stereochemical methods at the disposal of the organic chemist.

The number of geometrically possible conformations becomes very much greater when the fusion of two *cyclo*hexane rings to give *trans*- and *cis*-decalin is considered. Fortunately, if chair conformations are accepted as being more stable than boat conformations, then there is a unique conformation for both *trans*- (I) and *cis*-decalin (II). (I) is the conformation of *trans*-decalin which has been accepted for many years, whereas (II) differs from the two-boat Sachse–Mohr *cis*-decalin conformation (III), which is usually depicted in the text books. Experimental evidence that (II) is the correct representation of *cis*-decalin has been obtained by the electron diffraction studies of Hassel and his colleagues [6] and is supported by chemical evidence.[7]

(I) (II) (III)
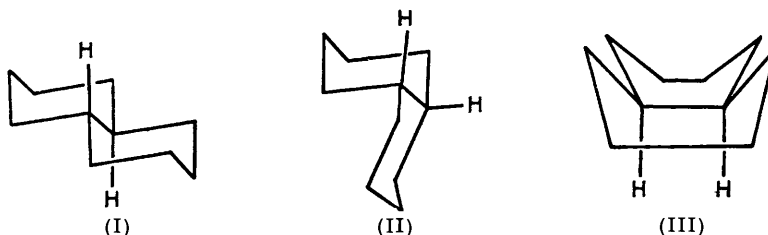
The energy differences between various conformational isomers can be calculated on a semi-empirical basis following the method introduced by Dostrovsky, Hughes, and Ingold [8] and by Westheimer and Mayer.[9] Table 1 summarises the results obtained and makes comparison with a more empirical, but more accurate, method proposed by R. B. Turner,[10] in extension of Pitzer's views.[11] This method is based, essentially, on the statistical mechanical evaluation of the barrier to free rotation about the single carbon–carbon bond of ethane. In both procedures there is qualitative agreement between the observed and the calculated stability order.

[1] The word " conformation " is used to denote those arrangements in space of the atoms of a molecule which are free from angle strain (other than that imposed by valency requirements) and yet are not superposable on each other. Clearly for many molecules, *e.g.*, ethane, an infinite number of conformations is possible. It is fortunate that the complexities which might arise from such considerations are minimised by the fact that, in general, only a few of the geometrically possible conformations are energetically favoured.

[2] In his fundamental work on large-ring molecules Prelog (see *J.*, 1950, 420) has used the word " constellation " with the same meaning.

[3] Infra-red evidence : Rasmussen, *J. Chem. Phys.*, 1943, **11**, 249, and papers there cited. Raman spectral evidence : Kohlrausch and Wittek, *Z. physikal. Chem.*, 1941, **48**, *B*, 177; Gerding, Smit, and Westrik, *Rec. Trav. chim.*, 1942, **61**, 561. Electron diffraction evidence : Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149, and papers there cited. Thermodynamic considerations : Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63**, 2029; Beckett, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2488.

[4] Most of the definitive information refers to the gaseous phase where intermolecular interactions are minimised and intramolecular interactions are dominant. It is fortunate that the latter are normally of greater importance than the former, so that the stability order established for the gaseous state seems also to hold for the liquid and even the crystalline state.

[5] Cf. Shoppee, *J.*, 1946, 1138.

[6] Bastiansen and Hassel, *Nature*, 1946, **157**, 765; Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149, and papers there cited.

[7] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Barton, *Experientia*, 1950, **6**, 316; Beyler and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1406.   [8] *J.*, 1946, 173.

[9] *J. Chem. Phys.*, 1946, **14**, 733; also Westheimer, *ibid.*, 1947, **15**, 252; Rieger and Westheimer, *J. Amer. Chem. Soc.*, 1950, **72**, 19, 28; Hill, *J. Chem. Phys.*, 1946, **14**, 465; 1948, **16**, 399, 938.

[10] *J. Amer. Chem. Soc.*, 1952, **74**, 2118.   [11] *Chem. Reviews*, 1940, **27**, 39.

On the basis of this evidence, and of correlations to be outlined in the sequel, it can be suggested that the most stable conformation of a fused *cyclo*hexane ring system will, in general, be that conformation with the maximum number of chairs. An interesting chemical

TABLE 1.

Compound	Energy differences, kcals.		Stability order
	Semi-empirical *	Empirical †	
*cyclo*Hexane	1·31 to 6·85	5·6	chair > boat
trans- and *cis*-Decalin (2-chair conformations)	0·52 to 8·23	2·4	*trans > cis*
2-Chair and 2-boat *cis*-decalins (2-boat Sachse–Mohr conformation)	2·87 to 7·28	8·8	2-chair > 2-boat

* Barton, *J.*, 1948, 340; see also Hazebroek and Oosterhoff, *Discuss. Faraday Soc.*, 1951, **10**, 87.
† Ref. 10.

confirmation of this view comes from the elegant experiments of Linstead and his colleagues [12] on perhydrophenanthrene derivatives, as further interpreted by W. S. Johnson.[13] Thus it has been shown that (IV) is *more* stable than the *trans*-isomer (V). Whereas (IV) may readily adopt a three-chair conformation, (V) can only be constructed as a conformation with at least one boat.

(IV)   (V)

In the chair conformation of *cyclo*hexane two types of geometrically distinct carbon–hydrogen bond can be distinguished.[14] Six of the bonds lie parallel to the threefold symmetry axis of the ring [as in (VI)] and have been designated " polar." The other six carbon–hydrogen bonds [as in (VII)], which are not so oriented, have been called " equatorial."

(VI)   (VII)
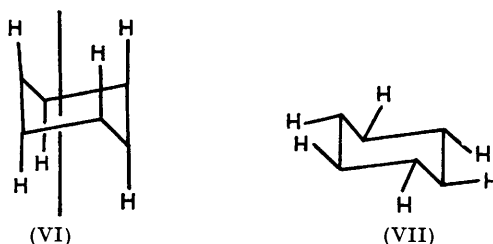
The admirable researches by O. Hassel and his colleagues at the University of Oslo on the electron diffraction of *cyclo*hexane compounds in the vapour phase have contributed greatly to our knowledge of these more subtle aspects of stereochemistry. Hassel [15] has shown that the conformation adopted by a substituted *cyclo*hexane is, in general, that with the maximum number of equatorial substituents. Such preferences in conformation undoubtedly arise from non-bonded interactions and it is logical, therefore, when a distinction has to be made between two alternatives, to make the larger substituent the equatorial one. On these bases mono-substituted *cyclo*hexanes are to be represented by (VIII) not (IX), *trans*-1 : 2- and *trans*-1 : 4-disubstituted *cyclo*hexanes by (X) and (XI) respectively, and *cis*-1 : 3-disubstituted *cyclo*-hexanes by (XII) not (XIII). The work of Bastiansen, Ellersen, and Hassel [16] on the conform-ations adopted by the stereoisomeric benzene hexachlorides is a particularly striking demonstration of these correlations. The general conclusions are supported by thermodynamic considerations.[17]

Based on this dichotomy of *cyclo*hexane bonds a number of chemically important generalis-ations can be made.[18] The application to simple *cyclo*hexane derivatives has been briefly

[12] *J.*, 1950, 1428, and papers there cited.   [13] *Experientia*, 1951, **7**, 315.
[14] Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488; Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929, and papers there cited.
[15] For summarising article see Hassel, *Research*, 1950, **3**, 504.
[16] *Acta Chem. Scand.*, 1949, **3**, 918.   [17] Beckett, Pitzer, and Spitzer, ref. 14.
[18] Barton, *Experientia*, 1950, **6**, 316; note also footnote 23.

outlined elsewhere.[19] The generalisations are, however, best illustrated by reference to the wealth of stereochemical data which has been accumulated in steroid and related fields of polyterpenoid chemistry, for in these compounds the locking together of several cyclohexane rings reduces the ambiguities of interpretation which are sometimes possible in simpler molecules containing only one cyclohexane ring.

(VIII) (IX) (X)

(XI) (XII) (XIII)
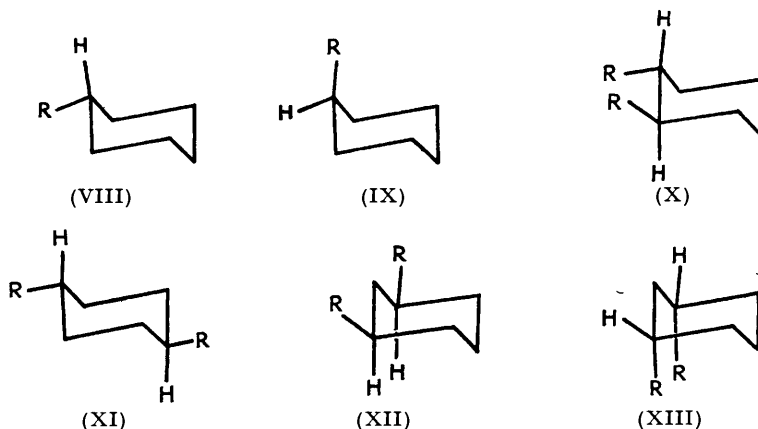
We commence by deducing conformations (XIV) and (XV) for *trans*-A/B- and *cis*-A/B-steroids respectively. These unique conformations are selected because they possess the maximum number of chairs—three in each case. The assumed conformations are supported by the X-ray data reported for cholesterol iodide.[20] The relation of equatorial and polar bonds in conformations (XIV) and (XV) to the Fieser and Fieser [21] α and β configurational nomenclature [22] is shown in Table 2.

(i) At a given carbon atom in a cyclohexane ring system an equatorial substituent is in general more stable than a polar substituent. The expressions (XVI) and (XVII) summarise [23] our present knowledge with regard to the more stable configurations of hydroxyl substituents in the steroid nucleus. In each case it is the equatorial substituent which is the more stable.

(ii) For relatively ready 1 : 2-elimination reactions of the ionic type the necessary geometric

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[19] Barton, *loc. cit.*, see also Birch, *Ann. Reports*, 1951, **48**, 192; Bose, *Experientia*, 1952, **8**, 458.

[20] Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64.

[21] Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corpn., 3rd Edn., 1949.

[22] α-Substituents lie on the opposite side of the molecule to the two methyl groups at $C_{(10)}$ and $C_{(13)}$, β-substituents lie on the same side.

[23] For references, see Barton, ref. 18; also Fieser and Fieser, *op. cit.*, p. 593; Barton and Rosenfelder, *J.*, 1951, 1048; Heusser, Anliker, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1537; Herzog, Oliveto, Jevnik, and Hershberg, *J. Amer. Chem. Soc.*, 1952, **74**, 4470. Most of the conclusions on relative stability are based on the nature of the preponderating isomer obtained on reduction of the corresponding ketone with sodium and an alcohol. It is well established (Vavon, *Bull. Soc. chim.*, 1931, **49**, 937; Hückel, *Annalen*, 1937, **533**, 1) that this procedure affords a mixture of alcohols of the same composition as is obtained by direct equilibration.

Reduction with sodium borohydride (cf. Elisberg, Vanderhaeghe, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 2814) and with lithium aluminium hydride (cf. Barton and Holness, *J.*, 1952, 78) 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 : see further below).

Some other useful generalisations are as follows : Catalytic hydrogenation of both hindered and unhindered ketone groups in strongly acid media (rapid hydrogenation) affords the polar alcohols. Similar reduction 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.

Another useful regularity is that treatment of equatorial amino-groups with nitrous acid affords stereospecifically the corresponding equatorial alcohol (Mills, *J.*, in the press; the author is much indebted to Mr. Mills for a copy of this paper before its publication).

condition is that the four centres of importance in the reaction should lie in one plane.[24]   This condition is satisfied in *cyclo*hexane systems by 1 : 2-*trans*-substituents, both being in the polar conformation (or being free to adopt this conformation).   It is not satisfied by 1 : 2-*trans*-

TABLE 2.

Position	*trans*-A/B α	*trans*-A/B β	*cis*-A/B α	*cis*-A/B β	Position	*trans*-A/B and *cis*-A/B α	*trans*-A/B and *cis*-A/B β
1	(p)	(e)	(e)	(p)	11	(e)	(p)
2	(e)	(p)	(p)	(e)	12	(p)	(e)
3	(p)	(e)	(e)	(p)	13	—	(p)
4	(e)	(p)	(p)	(e)	14	(p)	—
5	(p)	—	—	A(p); B(e)	15	(e *)	(p *)
6	(e)	(p)	(e)	(p)	16	—	—
7	(p)	(e)	(p)	(e)	17	(p *)	(e *)
8	—	(p)	—	(p)			
9	(p)	—	(p)	—			
10	—	(p)	—	A(e); B(p)			

* The asterisk here and elsewhere in this paper denotes that the term only has significance relative to the c-ring.

substituents when both are equatorial, or by 1 : 2-*cis*-related substituents, for one of these must necessarily be polar and one equatorial.   This reasoning is in line with the well-established preference of ionic-type 1 : 2-elimination reactions for the exhibition of *trans*-stereospecificity. It also predicts that this preference is based on a more fundamental geometrical relation than

(XIV) $\equiv$ (XVI)

(XV) $\equiv$ (XVII)
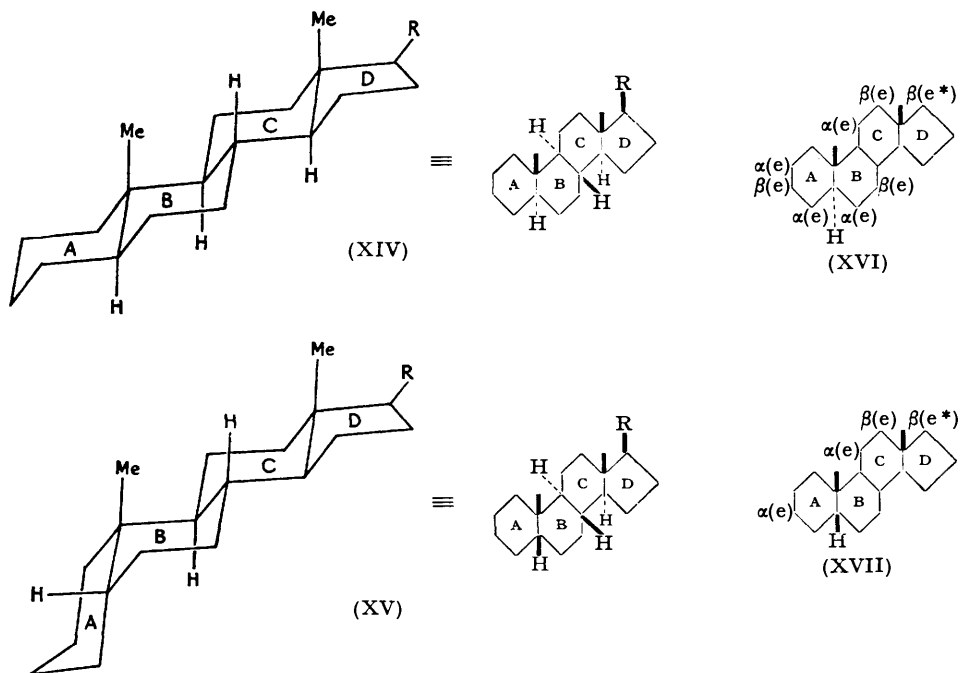
that indicated by a configurational prefix.   Thus there should be compounds where, although the substituents to be eliminated are *trans* relative to each other, yet, because they are both equatorial in conformation, the geometrical condition for easy elimination is not satisfied and therefore the reaction is relatively slow.   The data in Table 3 provide a striking demonstration

[24] Although this concept has been inherent in the literature (*e.g.*, see Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61**, 1640; Winstein, Pressman, and Young, *ibid.*, p. 1645) for a number of years and was implied specifically in an important paper by Hughes, Ingold, and their collaborators (*J.*, 1948, 2117), it has only been developed in precise terms quite recently (Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Barton, ref. 18; Barton and Rosenfelder, *J.*, 1951, 1048).

of this thesis. It is of interest that this specificity is not restricted to E_2-type elimination reactions but holds equally well for E_1-eliminations.[25] Excellent examples of these geometrical requirements have also been given recently by Cristol and Hause [26a] and by Raphael and Scott,[26b] in both cases in non-steroid compounds.

TABLE 3.

Easy elimination of (p, p) configurations	relative to (e, e) configurations	Ref.
trans-A/B series.		
3α-OTs(p) and 2β- and/or 4β-H(p)	3β-OTs(e) and 3α- and/or 4α-H(e)	a
5α-Br(p) and 6β-Br(p)	5β-Br(e; relative to B-ring) and 6α-Br(e)	b
cis-A/B series.		
3β-OTs(p) and 2α-H(p)	3α-OTs(e) and 2β-H(e)	c
11β-Br(p) and 12α-Br(p)	11α-Br(e) and 12β-Br(e)	d
Δ⁴-3-*one* series.		
6β-H(p) and 7α-OH(p)	6α-H(e) and 7β-OH(e)	e

[a] W. Stoll, *Z. physiol. Chem.*, 1937, **246**, 1 : Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937. [b] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066. [c] Evans and Shoppee, *J.*, 1953, in the press. The author is much indebted to Professor Shoppee for a copy of this paper before its publication. [d] Barton and Rosenfelder, *J.*, 1951, 1048. [e] Greenhalgh, Henbest, and Jones, *J.*, 1952, 2375.

(iii) For rearrangement reactions of the Nametkin type, or related reactions in which the ring carbon atoms are not (formally) involved, reaction proceeds, in *cyclo*hexane ring systems, most readily if the groups which are eliminated or migrate are in polar conformations. Some good examples of the application of this generalisation in the D-homo-series of steroids have been discussed by Klyne and Shoppee.[27] The D-homosteroid represented by partial formula (XVIII), on treatment with nitrous acid, affords the rearranged product (XIX). The expression (XX) shows the view looking down the $C_{(17)}$–$C_{(17a)}$-axis and, as indicated, the four centres of importance for the ketonisation reaction lie in one plane. In the $C_{(17a)}$-stereoisomer of (XVIII), represented in (XXI), deamination furnishes an oxide (XXII). Clearly the conformation (XXIII) of the groups involved would lead to this result. Other examples relevant here are the formation of Westphalen's diol [28] and the ψ-androstene phenomena.[29]
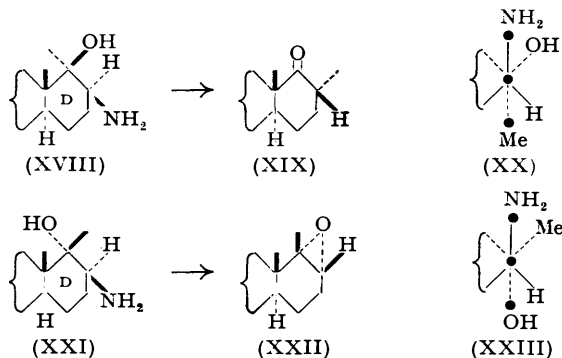
(iv) For rearrangement reactions in a *cyclo*hexane ring system in which a change in the number of ring carbon atoms is involved, the reaction proceeds with greater facility (and often exclusively) when the group eliminated possesses an equatorial orientation. Both this generalisation and that given under (iii) above are further examples of the necessary geometric condition of " four centres in a plane " (see above) for maximum ease of reaction.

The enhanced reactivity of *iso*bornyl compounds relative to bornyl compounds is illustrative.[30] Some excellent examples of the phenomenon have been discovered in the

[25] *E.g.*, see discussion by Barton and Rosenfelder, *J.*, 1951, 1048; also Mills, *J.*, in the press.
[26] (a) *J. Amer. Chem. Soc.*, 1952, **74**, 2193. (b) *J.*, 1953, in the press. The author is much indebted to Dr. Raphael for a copy of this paper before its publication.
[27] *Chem. and Ind.*, 1952, 470.
[28] See Ellis and Petrow, *J.*, 1952, 2246; Bladon, Henbest, and Wood, *ibid.*, p. 2737.
[29] See Miescher and Kägi, *Helv. Chim. Acta*, 1949, **32**, 761.
[30] Barton, *loc. cit.*; Brown, Hughes, Ingold, and Smith, *Nature*, 1951, **168**, 65; Winstein, Morse, Grunwald, Jones, Corse, Trifan, and Marshall, *J. Amer. Chem. Soc.*, 1952, **74**, 1127; Shoppee, *Chem. and Ind.*, 1952, 86.

triterpenoid and steroid series.   Thus if we consider rings A and B (XXIV) of the more common pentacyclic triterpenoids, we see that the four centres marked ● lie in one plane and are thus suitably disposed for the elimination of water (brought about by treatment with phosphorus pentachloride) in such a way as to lead to ring contraction (to XXV).   In contrast, when the hydroxyl group at $C_{(2)}$ is in the epimeric polar configuration (XXVI), then the geometrical requirement for rearrangement is no longer satisfied and the alternative elimination (to XXVII) without ring contraction takes place.[31]

(XXIV)   (XXV)

(XXVI)   (XXVII)
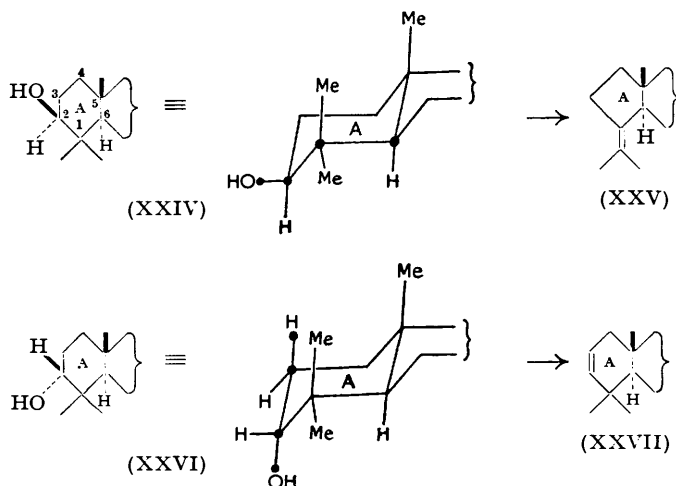
A somewhat similar situation pertains in the two terminal rings (D and E) of the pentacyclic triterpenoid lupeol (XXVIII).   The elegant investigations by Jones, Halsall, and their collaborators [32] have shown that (indirect) hydration of lupenyl acetate affords the 18-*iso*-β-amyranyl acetate derivative (XXIX), which in turn regenerates lupenyl acetate on dehydration. The stereochemistry of (XXIX) clearly satisfies the geometric requirement of coplanarity, giving back lupenyl acetate of the stereochemistry shown (XXX).   The epimer (XXXI) of (XXIX), with the hydroxyl group polar, is correspondingly dehydrated to germanicyl acetate (XXXII) without contraction of the ring system.   Again the reaction takes the course imposed upon it by the geometry (XXXI) of the molecule.


(XXVIII)   (XXIX)   (XXX)

(XXXI)   (XXXII)
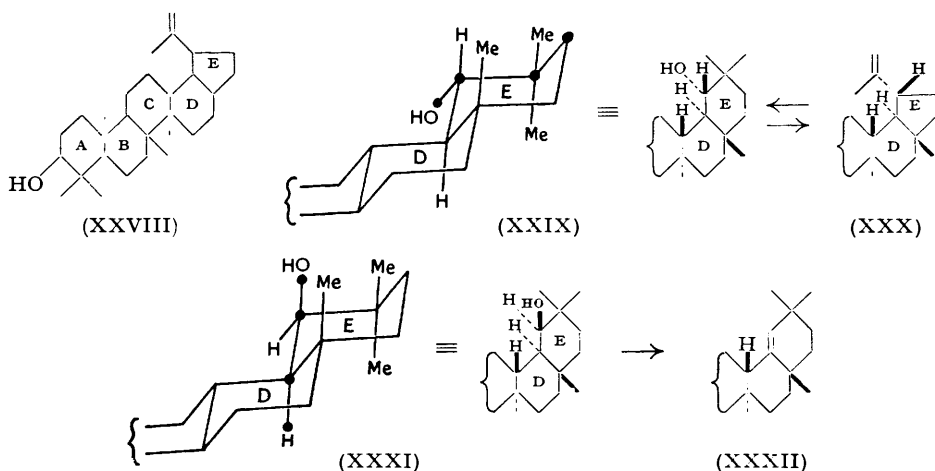
An excellent example of the same type of phenomenon has been discovered recently by Hirschmann, Snoddy, and Wendler.[33]   When the 12β-hydroxylated steroidal sapogenin

[31] For discussion and references see Barton, ref. 18.
[32] *J.*, 1952, 2862, 2868.   [33] *J. Amer. Chem. Soc.*, 1952, **74**, 2694.

(XXXIII) was converted into the 12-methanesulphonate and solvolysed, elimination was accompanied by rearrangement to the olefin (XXXIV). Clearly the geometry of (XXXIII) is suited to this reaction. In contrast when (say) the toluene-*p*-sulphonates of suitable 12α-hydroxylated compounds (XXXV) are heated with pyridine or collidine [34] the geometry of the molecule is not suited to rearrangement, but rather to elimination towards $C_{(11)}$ to give compounds as (XXXVI).

(XXXIII) ≡ → (XXXIV)

(XXXV) ≡ → (XXXVI)
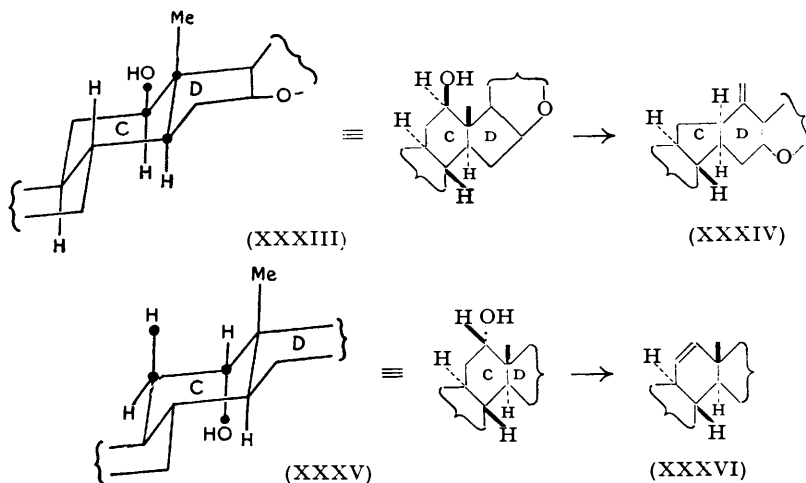
(v) When an oxide ring is opened, the product of ring opening has the carbon–hydroxyl bond and the newly formed carbon–addend bond both polar.[35] This useful generalisation, to which there are, as yet, no exceptions, is illustrated by data from the steroid series summarised in Table 4.

TABLE 4

Configuration of oxide	Ring-opened configurations (addition of HX)		Ref.
	trans-A/B-*Series.*		
2 : 3α	2β-X(p) : 3α-OH(p)	}	*a*
2 : 3β	2β-OH(p) : 3α-X(p)		
3 : 4α	3α-OH(p) : 4β-X(p)	}	*b*
3 : 4β	3α-X(p) : 4β-OH(p)		
5 : 6α	5α-OH(p) : 6β-X(p)	}	*c*
5 : 6β	5α-X(p) : 6β-OH(p)		
8 : 9α	8β-X(p) : 9α-OH (p)		*d*
17 : 17aα	17aα-OH(p) : 17β-X(p)		*e*
	cis-A/B *Series.*		
11 : 12α	11β-X(p) : 12α-OH(p)	}	*f*
11 : 12β	11β-OH(p) : 12α-X(p)		

a Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.   *b* Ref. 35.   *c* Fieser and Fieser, *op. cit.*, p. 222.   *d* Heusser, Anliker, Eichenberger, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 936.   *e* See ref. 27. *f* Fieser and Fieser, *op. cit.*, pp. 455, 460, 654, 656.

(vi) At a given carbon atom in a *cyclo*hexane ring system a polar is more hindered for acylation reactions than an equatorial hydroxyl group. Correspondingly the derived esters are respectively more and less easily hydrolysed. The extensive data available in the steroid series to test this concept are summarised (as less hindered configurations) in (XXXVII) and (XXXVIII).[36] In every case there is agreement with the generalisation propounded.

[34] *E.g.*, Meystre and Wettstein, *Helv. Chim. Acta*, 1948, **31**, 1890; Meystre, Tschopp, and Wettstein, *ibid.*, p. 1463; von Euw and Reichstein, *ibid.*, p. 2076.

[35] Fürst and Plattner, Abs. Papers, p. 409, 12th Internat. Congr. Pure & Appl. Chem., New York, 1951.

[36] For references: see Barton, ref. 18. Also Ruzicka, Fürter, and Goldberg, *Helv. Chim. Acta*, 1938, **21**, 498; Barton and Rosenfelder, *J.*, 1951, 1048; Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284; Hirschmann, Snoddy, and Wendler, *loc. cit.*; Romo, Stork, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 2918; Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892; Fieser, Herz, Klohs, Romero, and Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

It would appear instructive to consider in rather more detail the reason for the differing degree of steric hindrance shown by polar and equatorial hydroxyl groups. This is necessary in order that the relative degrees of hindrance of hydroxyl groups *not* attached to the same carbon atom may be evaluated. If we consider a substituent attached as R or R′ to a *cyclo*-hexane ring at $C_{(1)}$ of a chair conformation (XXXIX), then R is hindered by the four α- and β-hydrogen atoms attached at $C_{(2)}$ and $C_{(2')}$. All these are equidistant from R. We can call this hindering effect 4 (1 : 2-H) interactions. The substituent R′ is hindered by the two $C_{(2)}$-α- and $C_{(2')}$-α-hydrogen atoms which are the *same* distance from R′ as they are from R. R′ is also hindered by the two polar hydrogens, $C_{(3)}$-α and $C_{(3')}$-α, which hindrance can be denoted

(XXXVII)   (XXXVIII)   R′   (XXXIX)
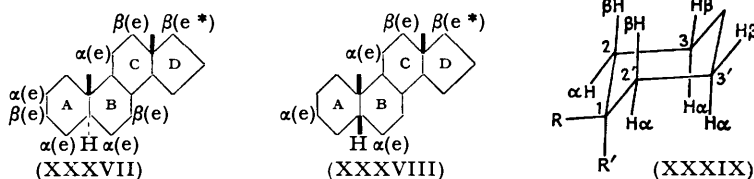
as 2(1 : 3-H) interactions. Now, if R and R′ are hydrogen, the (1 : 2) and (1 : 3) distances are almost equal, but if any substituent larger than hydrogen is introduced the 1 : 3 distances are *shorter* than the 1 : 2 distances. This follows from the simple   fact that the polar bonds are all parallel to each other and it is surely the fundament on which all the differential effects of equatorial and polar bonds are based. Accepting the fact that a methyl group is larger than hydrogen and therefore the (repulsive) interaction (1 : 3-Me) greater than (1 : 3-H) for a given substituent, we can analyse the relative degree of steric hindrance of (say) the four cholestan-2- and -3-ols. Clearly the steric hindrance order is cholestan-2β-ol (XL) > cholestan-3α-ol, (XLI) > cholestan-2α-ol (XLII) = cholestan-3β-ol (XLIII). The experimental percentage hydrolyses of the corresponding acetates under standard conditions are :[37] 11, 34, 87, and 92%, in excellent agreement with theory. No doubt this analysis can be extended to other positions in the steroid nucleus. One must conclude that, at least in the *trans*-A/B-series, all the remaining equatorial hydroxyl groups will be more hindered than those at $C_{(2)}$ and $C_{(3)}$ and that all the other polar hydroxyl groups must be more hindered than that at $C_{(3)}$. The potential application of these generalisations will be obvious.

1 (1 : 3-CH₃)   2 (1 : 3-H)   4 (1 : 2-H)   4 (1 : 2-H)
1 (1 : 3-H)   2 (1 : 2-H)
2 (1 : 2-H)
(XL)   (XLI)   (XLII)   (XLIII)
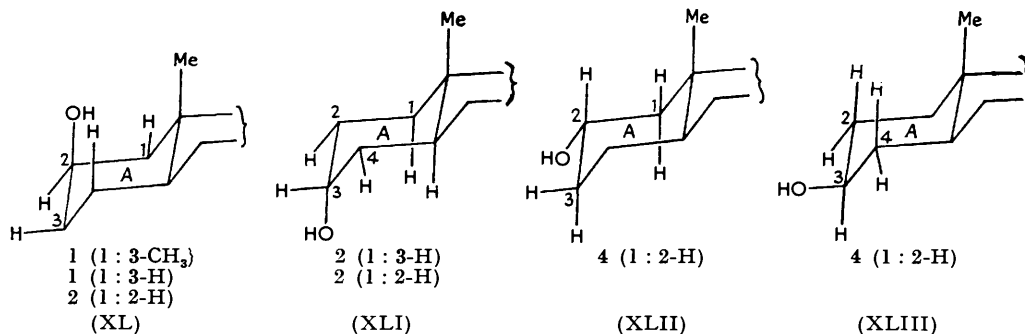
It seems that views of steric hindrance based on the concept of equatorial and polar bonds can be conveniently extended to a consideration of the relative degrees of hindrance shown by ketone groups in *cyclo*hexane systems. A ketone group is subject to steric hindrance when it does not react readily with reagents like semicarbazide, the phenylhydrazines, and so on. A necessary intermediate[38] in such reactions is of the type $\diagdown C \diagup \begin{smallmatrix} OH \\ NH \end{smallmatrix}$ which, on loss of water, affords the grouping $\diagdown C = N —$. In so far as the steric properties of (−NH−) must be similar to those of (−OH), it is submitted that the degree of hindrance of a ketone grouping can be measured approximately in terms of the summation of hindrance of the corresponding polar and equatorial hydroxyl groups. The following hindering effects seem to be of dominant importance : (*a*) the number of α-substituents, (*b*) the number of polar-type methyl groups

[37] Fürst and Plattner, *Helv. Chim. Acta,* 1949, **32**, 275.
[38] See, *e.g.,* Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co., 1940, p. 333.

attached at β-carbon atoms, and (c) an indeterminate addition for systems where the γ-carbon atom is bent round so as to hinder the ketone group. If we allow one (approximate and arbitrary) unit for effects (a) and (b) which seem to be of roughly equal significance, and indicate (c), which seems usually to be less than one unit in magnitude, by the + sign, then the degrees of steric hindrance of ketone groups in the *trans*-A/B-series of steroids is theoretically as indicated in (XLIV). So far as our knowledge goes [39] this is a good approximation to the correct order of hindrance if we accept that 3+ or more indicates a strongly hindered group (not giving functional derivatives even under vigorous conditions), 2+ or more a hindered group, and 2 or less a group showing non-significant hindrance to carbonyl reagents. In terms of the stereochemistry of the 18-*iso*oleanane (XLV) group of triterpenoids (see below) and lanostane (XLVI), the concept also predicts the correct relative degrees of steric hindrance. One must hasten to add that this is only an approach to a difficult problem, that effects (a), (b), and (c) are not the only foreseeable hindering influences, and that, in particular, systems having *cis*-fused rings may prove more complex.

(XLIV)   (XLV)   (XLVI)
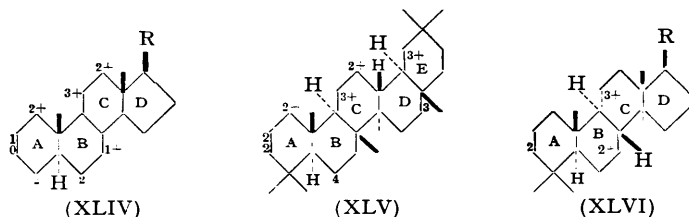
The foregoing discussion of the relative degree of hindrance of equatorial and polar hydroxyl groups has been confined to acylation and ester-hydrolysis reactions. When one turns to oxidation, either by chromic acid or by hypobromous acid, to the corresponding ketone the relative ease of reaction is inverted. This has been illustrated in the case of simple 2-substituted *cyclo*hexanols [40] and is shown, in the steroid series, by the greater ease of oxidation [41] of *epi*-cholestanol (XLVII) than of cholestanol (XLVIII). Such observations are adequately accommodated by the present theory if the rate-determining step in these reactions is not the formation of the corresponding esters, which is probably the first stage of reaction, but attack on the carbon–hydrogen bond. Westheimer and his colleagues [42] have provided excellent evidence that this is indeed the case, at least so far as *iso*propyl alcohol is concerned.

(XLVII)   (XLVIII)   (XLIX)
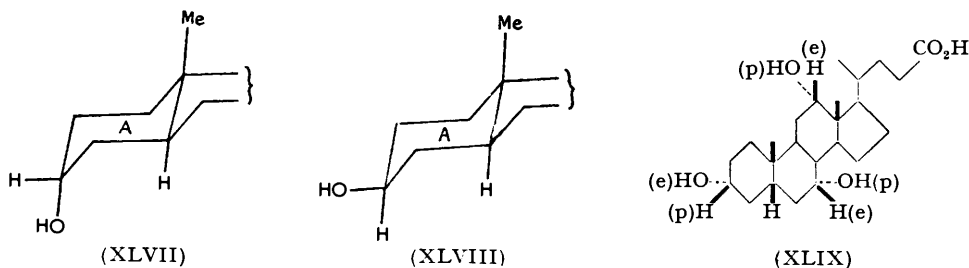
This approach to steric hindrance of oxidation furnishes some rationalisation of the other-wise curious fact that, whilst the order of relative hindrance to acylation of the hydroxyl groups in cholic acid (XLIX) is $C_{(12)} > C_{(7)} > C_{(3)}$, the order of hindrance for oxidations is $C_{(3)} > C_{(12)} > C_{(7)}$.[43]

Applications in Infra-red Spectroscopy.—The extensive arguments outlined above in favour of particular (more stable) conformations for *cyclo*hexane and its congeners naturally raise the question whether the chemical regularities find a reflection in any physical property. Recent progress in the study of infra-red spectra has provided a decisive answer in favour of the

[39] Cf. Fieser and Fieser, *op. cit.*; Hauptmann, *J. Amer. Chem. Soc.*, 1947, **69**, 562; Hauptmann and Campos, *ibid.*, 1952, **74**, 3179.
[40] Vavon, *Bull. Soc. chim.*, 1931, **49**, 937.   [41] Vavon and Jacubowicz, *ibid.*, 1933, **53**, 581.
[42] Westheimer and Nicolaides, *J. Amer. Chem. Soc.*, 1949, **71**, 25; Holloway, Cohen, and Westheimer, *ibid.*, 1951, **73**, 65; Leo and Westheimer, *ibid.*, 1952, **74**, 4383; Cohen and Westheimer, *ibid.*, p. 4387; see also Westheimer, *Chem. Reviews*, 1949, **45**, 419.
[43] Fieser and Fieser, *op. cit.*, p. 126; Fieser *et al.*, ref. 36.

existence of such a correlation.[44]   Tables 5 and 6 show [45] that, for alcohols, the band at 1000 cm.$^{-1}$ is dependent on whether the hydroxyl group is equatorial or polar and that for acetates the complexity of the acetoxy-band at 1240 cm.$^{-1}$ is also dependent on the equatorial or polar character of the acetoxy-group.   In the latter case the difference is intelligible in

TABLE 5.

| | | δ(OH), cm.$^{-1}$ | |
Compound type		equatorial	polar
trans-A/B-Series. Cholestan-2-ol	....	α; 1030	β; 1010
Cholestan-3-ol	....	β; 1040	α; 1000
Cholestan-4-ol	....	α; 1040	β; 1000
Lumistan-3-ol	....	α; 1034	β; 1010

TABLE 6.

| | | Acetoxy-band at 1240 cm.$^{-1}$ | |
Derivatives of		equatorial	polar
Cholestan-2-ol	....	α; simple	β; complex
Cholestan-3-ol	....	β; ,,	α; ,,
Cholestan-4-ol	....	α; complex	β; ,,
Coprostan-3-ol	....	α; simple	β; ,,
Lumistan-3-ol	....	α; ,,	β; ,,

terms of enhanced steric hindrance to freedom of rotation in the polar-type acetates.   Data for lumistane derivatives have also been included in Tables 5 and 6.   At first, lumistanyl acetate was regarded as exceptional,[46] but recent work by Cole [47] has shown that all the infra-red (and chemical) facts are explained if lumistanol has the conformation (and configuration) shown in (L).

It has also been established [48] that there is a well-defined relation between the carbonyl frequencies of α-brominated ketones and the existence of the carbon–bromine bond in the equatorial or polar conformation.   The exact significance of this finding in configurational terms remains to be defined.

Applications to Adsorption Phenomena.—Some recent work by Savard [49] on the paper chromatography of steroids has provided an excellent illustration of the generalisation that, at a given carbon atom in a *cyclo*hexane ring system, the polar type epimer is *less* strongly

TABLE 7.   *Relative ease of elution of steroidal alcohols.*

3α(p) > 3β(e)	(*trans*-A/B-Series)	7 α(p) > 7β(e)
3β(p) > 3α(e)	(*cis*-A/B-Series)	11β(p) > 11α(e)
6β(p) > 6α(e)		17α(p *) > 17β(e *)

adsorbed than the corresponding equatorial epimer.   Some of the data are summarised in Table 7.   The relatively strong adsorption of the equatorial alcohols corresponds to their relative ease of esterification and is intelligible on the basis of the same sort of argument as has been advanced above.

A critical test of any theory is its application to the solution of a problem which can also be solved by a different method of accepted unambiguity.   The successful use of conformational analysis in steroid chemistry and in other simpler *cyclo*hexane systems prompted its extension to the more difficult problem of the stereochemistry of the pentacyclic triterpenoids of the β-amyranol group (LI) [and, as it subsequently devolved, of the lupeol group (LII)].   It is not possible within the allotted time to discuss at length the evidence available; a full treatment has been given elsewhere.[50]   The basic assumption was made that, provided the bridge carbon atoms bearing hydrogen had been equilibrated, or had been shown to be present in the more stable configurations, then all five rings would adopt chair conformations.

Rings A and B had been shown to be *trans*-fused from the known relation [51] to the diterpenoid

[44] Cf. also Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2618.
[45] R. N. Jones, Humphries, Herling, and Dobriner, *ibid.*, 1951, **73**, 3215; Cole, R. N. Jones, and Dobriner, *ibid.*, 1952, **74**, 5571; Fürst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 951; Cole, *J.*, in the press (the author is much indebted to Dr. Cole for a copy of this paper before its publication).
[46] R. N. Jones *et al.*, ref. 45.   [47] Cole, ref. 45.
[48] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[49] *J. Biol. Chem.*, in the press.   The author is much indebted to Dr. Savard for a copy of this paper before its publication.   [50] Barton and Holness, *J.*, 1952, 78.
[51] Barton and Schmeidler, *J.*, 1948, 1197; 1949, S 232; Barton, *Quart. Reviews*, 1949, **3**, 36.

abietic acid. Rings D and E were shown to be *cis*-fused with the less stable orientation at $C_{(18)}$. Nevertheless, since ring E is a terminal ring there is no difficulty in giving it a chair conformation based on the two-chair *cis*-decalin (II). The configuration at $C_{(13)}$ in β-amyranol derivatives was shown to be the more stable one and to have the hydrogen on the same side of the molecule as the $C_{(17)}$-methyl group.[52] Correlation with the perhydrophenanthrene

(L)   (LI)   (LII)
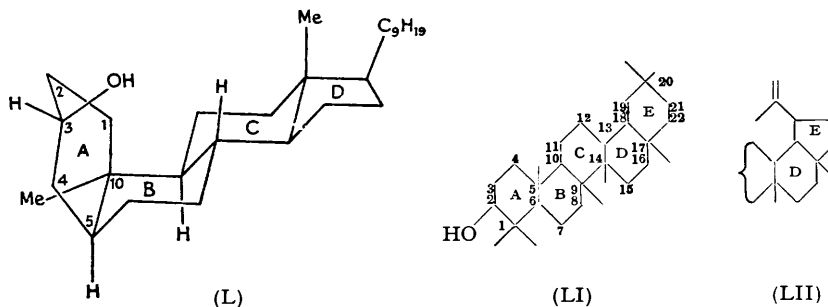
stereochemistry mentioned above showed that rings C and D must be *trans*-fused. Conclusive evidence has been forthcoming [53] that $C_{(10)}$ is also fused in the more stable orientation. If both $C_{(10)}$ and $C_{(13)}$ in β-amyranol are to represent the more stable configurations, then, by analogy again with perhydrophenanthrene stereochemistry, this requires either (B/C-*trans*)($C_{(9)}$: $C_{(14)}$-*anti*)(C/D-*trans*) or (B/C-*cis*)($C_{(9)}$: $C_{(14)}$-*syn*)(C/D-*trans*), as in formulæ (LIII) and (LIV) respectively.

(LIII)   (LIV)
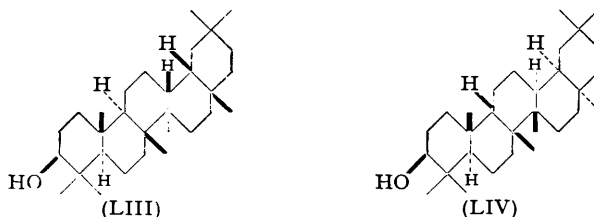
The configurations at $C_{(2)}$ and $C_{(9)}$ remain for discussion. That at $C_{(2)}$ is regarded as β,[54] on elimination evidence mentioned above and the steric properties which are those of an equatorial hydroxyl group.[55]

Our attention has been directed to an alternative interpretation (LV) of the stereochemistry at $C_{(2)}$, which becomes logically acceptable if ring A is assumed to adopt the boat conformation. A possible factor in determining the latter would be the repulsive interaction between polar-type methyl groups at $C_{(1)}$ and $C_{(5)}$ which is avoided by the change to (LV). On the other hand, (LV) suffers from the disadvantage of having opposed interactions at $C_{(3)}$: $C_{(4)}$ and $C_{(1)}$: $C_{(6)}$ and from the strong repulsive interaction between the $C_{(2)}$-β-hydrogen atom and the $C_{(5)}$-methyl group. Evidence against (LV) and in favour of (XXIV) comes from the following considerations.

It is known [56] that rings A and B correspond to the first two rings in abietic acid (LVI). It is also known that abietic acid has the carboxyl group in the less hindered equatorial configuration.[57] On the basis of (XXIV), abietic acid must be (LVII); on the basis of (LV) it must be (LVIII). Oxidation of abietic acid by nitric acid affords a C_{11}-tricarboxylic acid which has been proved [51] to have the stereochemistry illustrated in (LIX). Oxidation of (LVIII) would afford (LX) with the wrong stereochemistry. Formula (LV) is, therefore, to be discounted.

The assignment of configuration at $C_{(9)}$ is on a less certain basis. If one considers the fusion of ring C to ring B, both being in chair conformation, then, since only equatorial + equatorial

[52] Barton and Brooks, *J.*, 1951, 257; Barton, Brooks, and Holness, *ibid.*, p. 277.
[53] Barton and Holness, ref. 50; Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019.
[54] The symbols α and β are used with the same significance as in steroid chemistry (see footnotes 21 and 22).
[55] Barton, *Experientia*, 1950, **6**, 316; Barton and Holness, ref. 50.
[56] For summary see Jeger, " Fortschritte der Chemie organischer Naturstoffe," 1950, Vol. VII.
[57] See Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III.

or equatorial + polar bonds can be employed, only three different fusions are possible, *viz.* : (LXI), (LXII), and (LXIII). Of these, (LXIII) does not explain the observed ready elimination of water from polar 11-hydroxy-compounds to give Δ^{10}-olefins,[58] for the centres concerned in the reaction would not satisfy the necessary geometrical requirement of coplanarity (see above). This leaves (LXI) and (LXII) for consideration, the corresponding complete

(XXIV)   (LV)   (LVI)

(LVII)   (LVIII)

(LIX)   (LX)
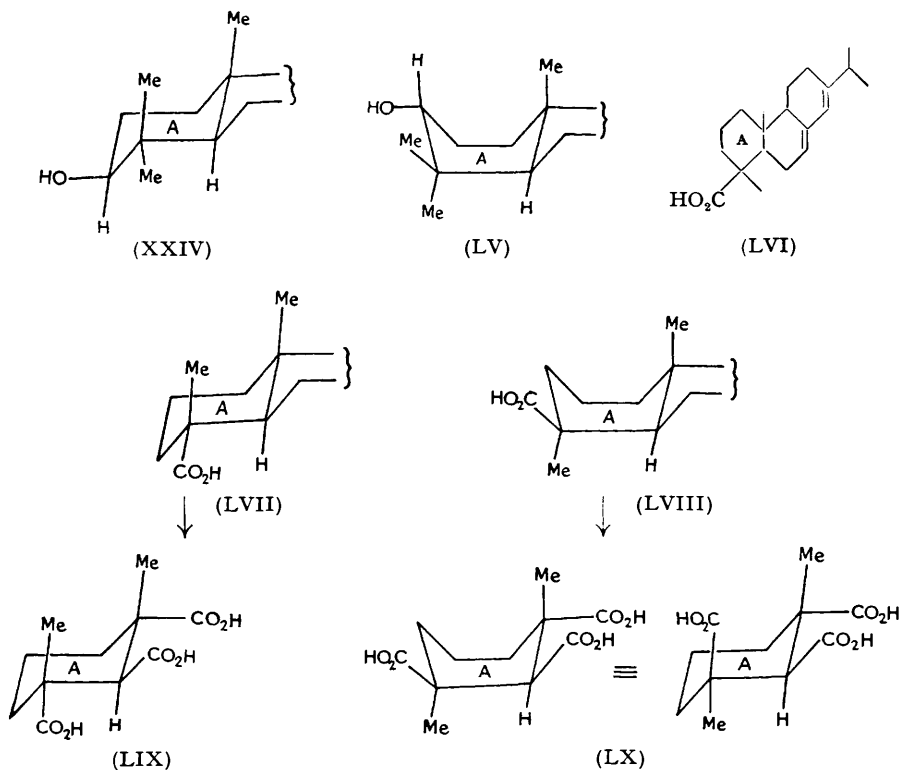
stereochemical representation being (LIII) and (LIV). A distinction between these has not, so far, been attainable on chemical grounds but, on the basis of generalised molecular rotation arguments, Klyne [59] has been able to decide in favour of (LIII). Carlisle and (Miss) Abd El Rehim [60] have recently conducted an *X*-ray investigation of methyl oleanolate iodoacetate (LXIV), a member of the β-amyrin group of triterpenoids, from which they conclude that the stereochemistry of the molecule is correctly represented by (LXV) in agreement with the

(LXI)   (LXII)   (LXIII)
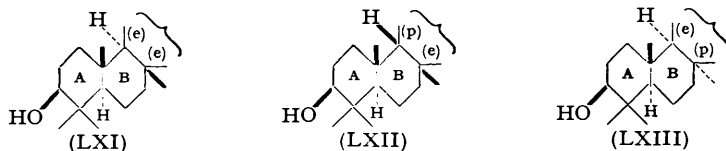
expression (LIII). It is gratifying that the two very different methods of approach lead to the same conclusion.

As will be seen from the discussion above, there is a weighty body of experimental evidence in support of the correctness of the concept of equatorial and polar bonds. It must be realised, however, that the agreement is based, fundamentally, on the summation of bonded and non-bonded interactions and that it refers, in the main part, to compounds where the interactions of dipoles are not of major importance. Some exceptions which have been noted are the following :

(i) *trans-cyclo*Hexene dibromide appears to exist more in the di-polar than in the di-

[58] Barton and Holness, ref. 50.   [59] *J.,* 1952, 2916.   [60] Personal communication.

equatorial conformation;[61] in the light of more recent work by Hassel and his school on the polyhalogeno*cyclo*hexanes this observation may require re-investigation.

(ii) Dimethyl and diethyl *trans-cyclo*hexane-1 : 3-dicarboxylate (one polar, one equatorial substituent) are said to be more stable [62] than the *cis*-isomers (two equatorial substituents).
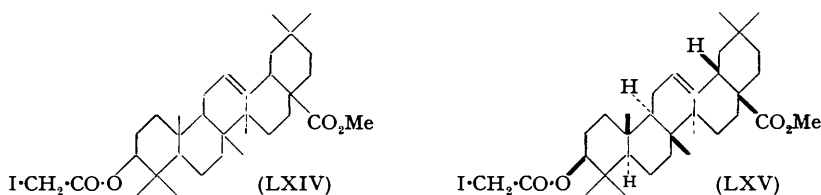
(iii) The *cyclo*hexanetricarboxylic acid anhydride (LXVI) is more stable with the carboxyl group polar, as in (LXVII), than if it is equatorial.[63, 64] This result corresponds to the preferred orientation [65] of the carbomethoxyl group at $C_{(10)}$ in triterpenes in which ring c has been opened as in (LXVIII). The preferred orientation is further illustrated in (LXIX).

A further apparent exception was provided by *trans*-3-methyl*cyclo*hexanol which had been reported to be more stable than the *cis*-isomer. Recent significant work by Noyce and Denney and by Goering and Senes [67] has shown that the relative stability order is correct, but that the configurational prefixes have been wrongly assigned.
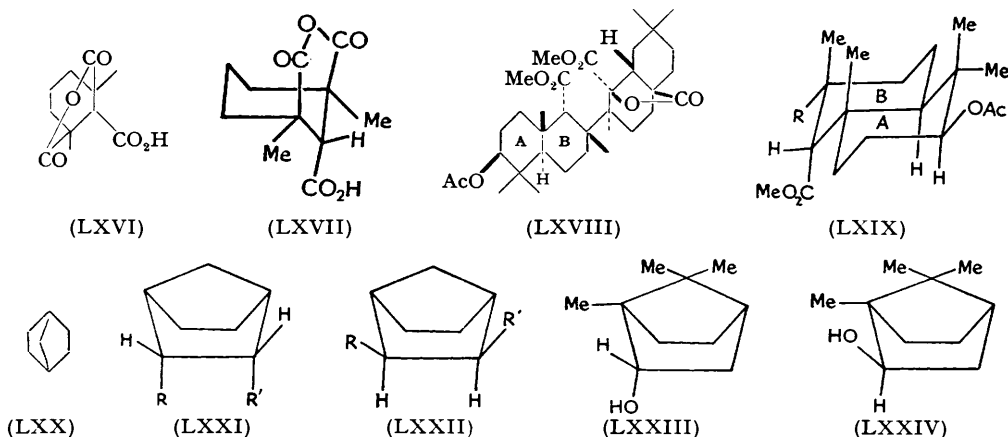
The concept of equatorial and polar bonds can be extended to include bridged *cyclo*hexane rings; the extension must, however, be made with caution as shown by the following examples. In general, Diels–Alder adducts which can be regarded as derivatives of norcamphane (LXX) are formed under kinetic control of reaction products and are *endo* (LXXI) in configuration. Isomerisation affords the more stable *exo*-derivatives (LXXII).[68] Thus, *exo*-norborneol (LXXII; R = OH, R' = H) is more stable than *endo*-norborneol (LXXI; R = OH, R' = H). The former has an equatorial, the latter a polar hydroxyl group. The relative degrees of steric

[61] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929.
[62] Skita and Rossler, *Ber.*, 1939, **72**, 265.
[63] Barton and Schmeidler, *J.*, 1949, S 232.
[64] It appears probable that this is not an isolated example and that αα'α'-tetrasubstituted *cyclo*hexanes (or their equivalents) may prove exceptional. If one analyses non-bonded interactions in the two conformations of 2 : 2 : 6 : 6-tetramethyl*cyclo*hexanol according to the principles outlined on p. 1034, and compares the results with a similar analysis of the two 2 : 2-dimethyl*cyclo*hexanol conformations, where it is known that the equatorial conformation is the more stable, then it is readily shown that an inversion of stability order for the tetramethyl compound is possible provided that (1 : 2-Me) > (1 : 2-H), a condition which is known to be satisfied.
[65] Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1154.
[66] Skita and Faust, *Ber.*, 1939, **72**, 1127.
[67] *J. Amer. Chem. Soc.*, in the press : the author is much indebted to Drs. Goering and Noyce for copies of these papers before their publication.
[68] For example : Alder and Stein, *Annalen*, 1934, **514**, 211; 1936, **525**, 183. For reviews : Kloetzel, "Organic Reactions," Vol. IV, p. 1; Holmes, *op. cit.*, p. 60.

hindrance and ease of rearrangement [69] are also in consonance with these assignments. However, in the case of the corresponding derivatives of camphane, borneol (LXXIII), and *iso*-borneol (LXXIV), the stability order [70] and steric hindrance order [71] are the reverse, but the ease of rearrangement [30] remains greatly in favour of the equatorial hydroxyl group. The reversed effects must be attributed to the hindrance exerted by the *gem*-dimethyl bridge.[72] Extension of the discussion to fenchyl alcohols and related compounds, and to other types of bridged *cyclo*hexane derivatives, provides interesting possibilities but, owing to limitation of time, the subject cannot be pursued further at this juncture.

The concept of equatorial and polar bonds is clearly applicable to sugar chemistry and to the cyclitols. The excellent work of Reeves [73] may be cited as illustrative in the former field, whilst in the latter a number of interesting investigations have been reported.[74] An elegant correlation between cyclitol stereochemistry and specificity of oxidation by *Acetobacter suboxydans* has been propounded.[75] Applications in alkaloid chemistry have been discussed.[76]

The above summary of the applicability of the concept of conformational analysis to *cyclo*-hexane compounds must surely demonstrate the utility of this approach. Similar analysis of preferred conformation in other ring systems has already been undertaken by Prelog [77] with marked success and is, no doubt, capable of considerable extension.[78] An analogous treatment of acyclic compounds must surely be possible. The applicability of conformational analysis with its emphasis on the geometrical aspects of structure and reactivity must not, however, lead us to neglect the significance of electronic factors in organic chemistry. Both these approaches to the solution of the problems that beset the organic chemist are fundamental.

Finally I must express my heartfelt thanks to those under whose inspiring direction I have worked; I must also make grateful acknowledgment to all my present and former colleagues, who have taught me more of chemistry than I have taught them, and to my friends at Harvard in the fires of whose constructive criticism the ideas presented here were first tempered.

[69] See Winstein and Trifan, *J. Amer. Chem. Soc.*, 1952, **74**, 1147, 1154; cf. Roberts, Bennett, and Armstrong, *ibid.*, 1950, **72**, 3329.

[70] Asahina, Ishidate, and Sano, *Ber.*, 1936, **69**, 343.

[71] Vavon, *Bull. Soc. chim.*, 1931, **49**, 937; Lipp and Bund, *Ber.*, 1935, **68**, 249; Bode, *Ber.*, 1937, **70**, 1167.

[72] Shoppee, *Chem. and Ind.*, 1952, 86.

[73] For summary see *Adv. in Carbohydrate Chem.*, 1951, **6**, 107.

[74] Chargaff and Magasanik, *J. Biol. Chem.*, 1946, **165**, 379; 1948, **174**, 173; 1948, **175**, 929, 939; Angyal and MacDonald, *J.*, 1952, 686.

[75] Magasanik, Franzl, and Chargaff, *J. Amer. Chem. Soc.*, 1952, **74**, 2618.

[76] Fodor and Nador, *Nature*, 1952, **169**, 762; *J.*, 1953, 721; Fodor, *Nature*, 1952, **170**, 278; Cookson, *Chem. and Ind.*, 1953, in the press.

[77] See *J.*, 1950, 420; see also Wilson Baker, McOmie, and Ollis, *J.*, 1951, 200, and later papers.

[78] For example, in terms of the excellent work of H. C. Brown and his colleagues (*inter al., J. Amer. Chem. Soc.*, 1951, **73**, 212).