Informations - Informationen - Informazioni - Notes

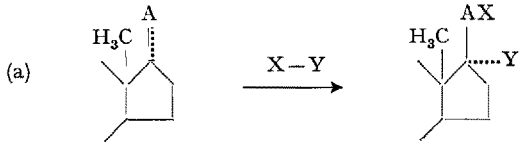
STUDIORUM PROGRESSUS

Steric Course of Reactions of Steroids

By LOUIS F. FIESER[1], Cambridge, Mass.

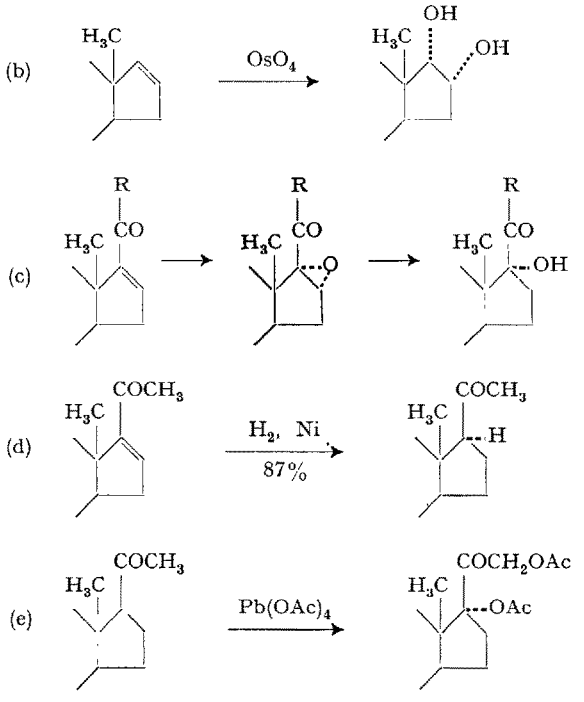
In previous reviews[2] attention was called to two types of hindrance effects that determine the steric course or rate of reactions involving functional groups at the 17-position of steroids. In this paper the concept will be defined more specifically and applied to other positions in the steroid structure.

Intra- and extraradial effects at C_{17}. One type of hindrance controls the direction of opening of a carbon-oxygen or carbon-carbon double bond extending from C_{17}; the relative disposition of atoms and groups in the immediate vicinity of the front and rear side of C_{17} appears to be such as to render C_{17} more accessible to attack from the rear than from the front, for the rear member of the double bond invariably opens preferentially or exclusively (a). Thus 17-ketones on hydro-

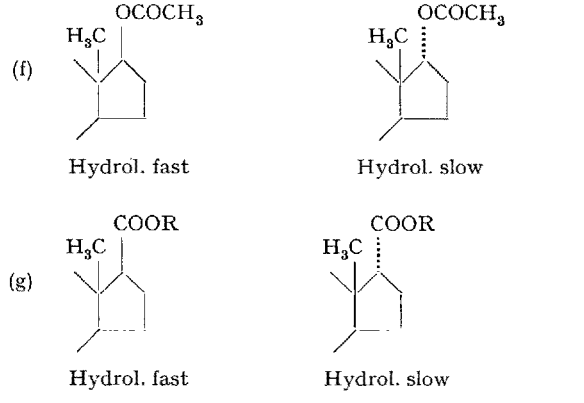


genation, reduction with lithium aluminum hydride, addition of Grignard reagents, or addition of potassium acetylide yield chiefly products in which the hydrogen atom attached to C_{17} is oriented to the rear (α-Y) and the hydroxyl group is oriented to the front (β-AX)[3]; 17,20-ethylenes add osmium tetroxide chiefly by rear-bond attack to give α-hydroxylated products with the normal β-side chain; 17,20-enol acetates react with perbenzoic acid in the same steric sense to give 17α-hydroxy-20-ketones of the normal series[4]. Other instances of preferential rear attack of C_{17} are: (b) formation of 17-epiestriol by osmium tetroxide hydroxylation of the Δ^{16}-ethylene; (c) reaction of a 16,17-ethylene with perbenzoic acid to give the 16,17-α-oxide convertible into a 17α-hydroxy compound[5]; (d) hydrogenation of a 16,17-unsaturated 20-ketone to a pregnanolone; (e) formation of a 17α,21-diacetoxy compound (rather than 17β,21-) as a by-product of acetoxylation of a 20-ketone.

The rule of rear attack at C_{17} thus seems to apply to a wide variety of structures and reagents. Whatever the source and nature of the spatial characteristics in the immediate vicinity of C_{17} that favor attack from the rear, the overall effect must be associated with atoms within the van der Waals radius of C_{17} and hence can be described as an intraradial effect.



That a hindrance effect of a second type determines the course of reactions involving functional groups attached to C_{17} can be recognized from the fact that attack from the front is favored over attack from the rear. Thus in the pairs of epimeric esters (f) and (g), the



17β-epimer is hydrolyzed more rapidly than the 17α-epimer. Here the attack is at carbonyl groups at some distance from C_{17}, and whatever hindrance effects determine the relative accessibility of groups oriented on the front and rear sides of the molecule these effects must operate outside the van der Waals radius of C_{17} and are therefore defined as extraradial with respect to the point of attachment to the nucleus. Other instances indicating greater availability of space on the front than on the rear side in the region extraradial to C_{17} are as

[1] Converse Memorial Laboratory, Harvard University, Cambridge 38, Massachusetts.

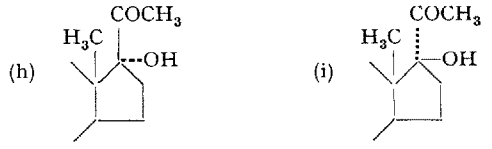
[2] L. F. FIESER and M. FIESER, Exper. *4*, 285 (1948); Natural Products Related to Phenanthrene, 3rd Ed., Reinhold, New York (1949).

[3] Unless otherwise indicated, references to the literature are to be found in the Monograph by FIESER and FIESER, loc. cit.

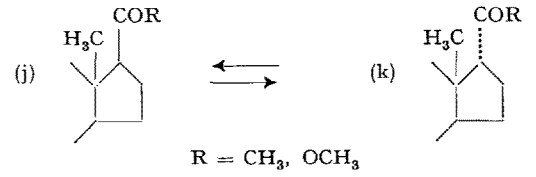
[4] B. A. KOECHLIN, D. L. GARMAISE, T. H. KRITCHEVSKY, and T. F. GALLAGHER, J. Amer. Chem. Soc. *71*, 2362 (1949).

[5] PL. A. PLATTNER, H. HEUSSER, and M. FEUSER, Helv. chim. acta *31*, 2210 (1948). – P. L. JULIAN, E. W. MEYER, and I. RYDEN, J. Amer. Chem. Soc. *71*, 756 (1949).

follows: in a 17α-hydroxy-20-ketone (h) the hydroxyl group is not acylable and the carbonyl group has normal additive power, whereas in a 17β-hydroxy-20-ketone of

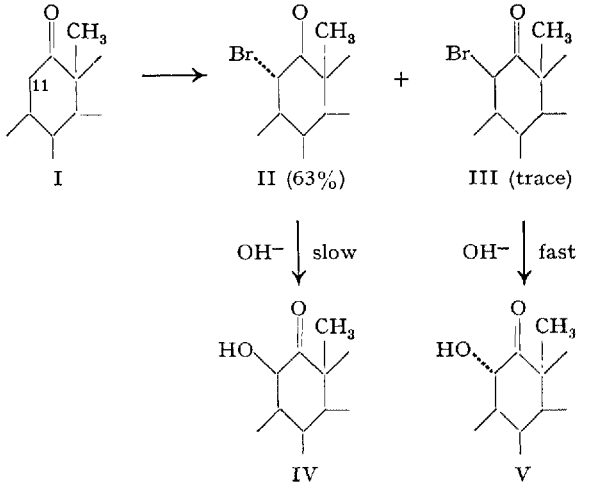


the 17-iso series (i) the hydroxyl group is acylable and the carbonyl group is unreactive; a 17-normal aceto compound or etio ester (j) is thermodynamically more



stable than the 17α-epimer (k) and predominates in the equilibrium mixture.

Positions 11 and 12. GALLAGHER and KRITCHEVSKY[1] have noted that the concept of preferential rear attack in reactions involving intraradial steric effects can be extended to positions 11 and 12. Reduction of an 11-ketone by hydrogenation or with lithium aluminum hydride proceeds exclusively by opening of the rear member of the double bond. Bromination of a 12-ketone (I) proceeds chiefly by attack from the rear to give the 11α-bromo derivative II. This substance and the isomer III, isolated as a by-product, undergo hydrolysis with

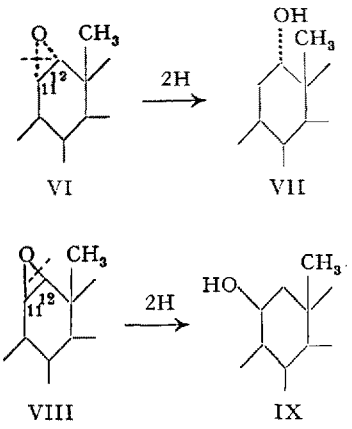


inversion to give IV and V and hence the attack by hydroxide ion probably occurs by the S_N2 mechanism. That the 11α-bromoketone II is hydrolyzed much more slowly than β-epimer presumably is because the required frontal approach of the nucleophilic agent is subject to the same screening that prevents front-bond opening of an 11-carbonyl group.

Position 12 also seems to be more accessible to attack from the rear than from the front, since an 11-ketone on bromination gives chiefly the 12α-bromo-11-ketone. The reaction of an 11,12-unsaturated steroid with perbenzoic acid involves attack of both positions from the rear to give the 11α,12α-oxide.

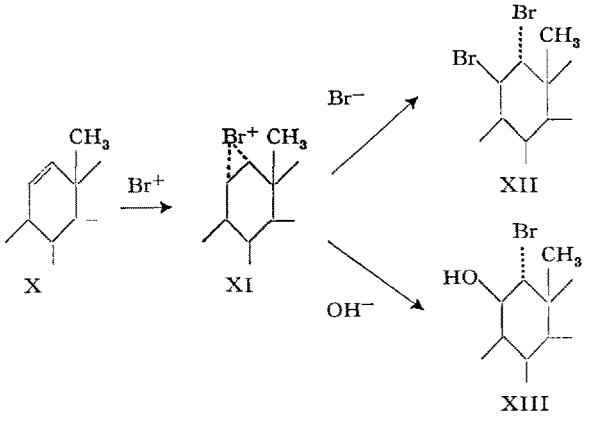
Hindrance effects beyond the limit of van der Waals forces at C_{11} and C_{12} can be inferred from the results of acylation and hydrolysis experiments. An 11β-hydroxyl group is strongly hindered, since it is not acylable by any known method; an 11α-hydroxyl group is readily acylable. Thus of the two epimeric 11-hydroxy derivatives IV and V above, the first resists acetylation and the second forms an acetate without difficulty. These facts, together with comparative rates of hydrolysis of a series of acetates, establish the order of relative hindrance of the extraradial type as follows: 11β>12α>12β>11α. At position 11 both the extra- and intraradial effects operate to make the rear side (α) the more accessible to attack. At position 12, as at position 17, the two effects operate in opposite directions.

The extraradial effect seems to control the direction of fission of the two 11,12-oxides, as though the initial attack were at the oxygen atom, rather than at a carbon center. Thus the fission of the α-oxide VI at the bond

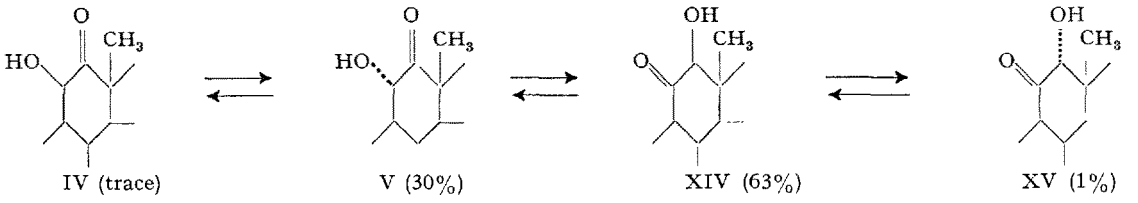


extending to C_{11} is in line with the greater hindrance of a 12α- than of an 11α-ester group. An 11β-group is more hindered than a 12β-group, and hence the β-oxide VIII is cleaved at the less hindered C_{12}-linkage.

The reactions of Δ^{11}-cholenic acids with bromine and with hypobromous acid may actually be highly complicated, but a useful empirical interpretation is that the key process is a rear attack to give the bromonium ion XI, followed by fission in a manner analogous to fission of the α-oxide. The products, XII and XIII, have the expected 11β,12α-orientation.



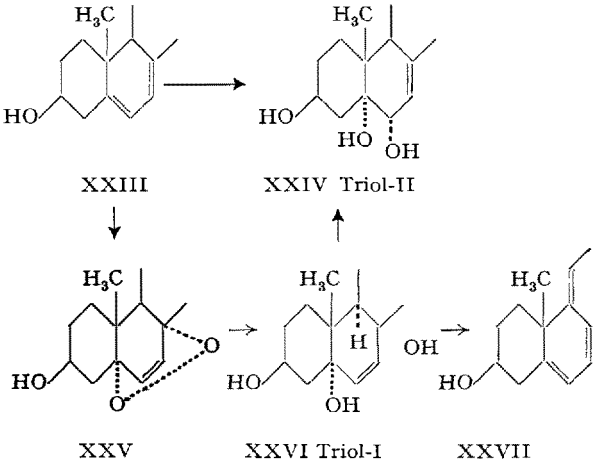
[1] T. F. GALLAGHER and T. H. KRITCHEVSKY, J. Amer. Chem. Soc. *72*, 882 (1950).



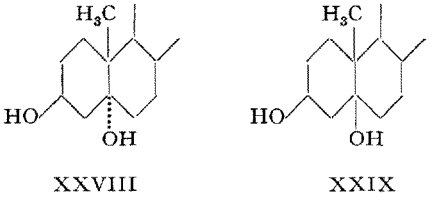
When either of the epimeric 11-hydroxy-12-keto acids IV or V or their bromo precursors is refluxed with alcoholic alkali an equilibrium mixture of isomers results in which the Marker-Lawson acid XIV predominates; the yields of components obtained after equilibration of pure XIV (GALLAGHER) are indicated under the formulas. GALLAGHER and KRITCHEVSKY have suggested an interpretation of the predominance of XIV based on the concept of a rear-attack by a proton of a common enediol ion, but this explanation seems inadmissible because the relative rates of enolization reactions cannot influence the final position of equilibrium. The phenomenon seems rather to be related to the isomerization of 17-ketones and etio esters discussed above; the position of equilibrium should be dependent upon the relative availability of space in the front and rear extraradial regions surrounding position 11 and 12. If accommodation of the hydroxyl group alone were involved, the relative abundance of the isomers expected from relative hindrance in the hydrolysis of esters would be: V>XIV>XV>IV; this corresponds to the actual order except for the reversal of V and XIV.

Positions 5 and 6. Many reactions involving the 5,6-double bond bear evidence that attack is predominately from the rear. Thus hydrogenation of cholesterol gives exclusively a cholestane derivative (XVI); hydroxylation with osmium tetroxide or permanganate gives the 3β,5α,6α-triol (XVII); reaction with perbenzoic acid gives chiefly the α-oxide (XVIII), which on hydrolysis yields the 3β,5α,6β-triol (XIX). Bromination of cholesterol has been shown by BARTON and MILLER[1] to yield the 5α,6β-dibromide (XXII); the reaction is here formulated as involving rear attack and fission of the α-bromonium ion XXI in the direction established for the α-oxide.

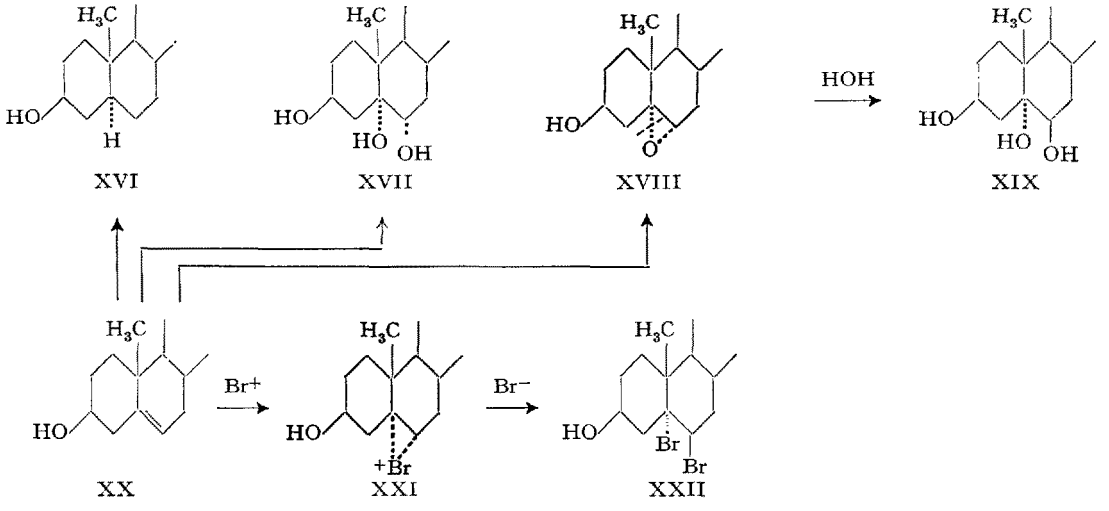
There is some reason to believe that both hydroxylation of ergosterol (XXIII) with lead tetraacetate or osmium tetroxide and reaction of the sterol with oxygen proceed by attack from the rear, as represented in formulas XXIV and XXV, since the ready dehydration of the triol-I (XXVI) on pyrolysis suggests that the hydroxyl group at C_8 is cis to the hydrogen atom at C_9.



Extraradial hindrance at C_5 operates to shield the front side of the molecule more than the rear side. Thus

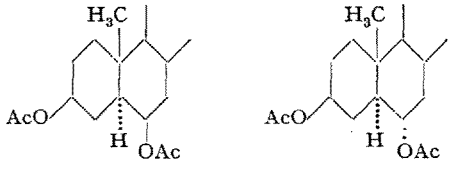


the 5α-hydroxyl group of cholestane-3β,5α-diol (XXVIII) is acylable whereas the 5β-hydroxyl group present in many cardiac aglycones (XXIX) is not. The relation-



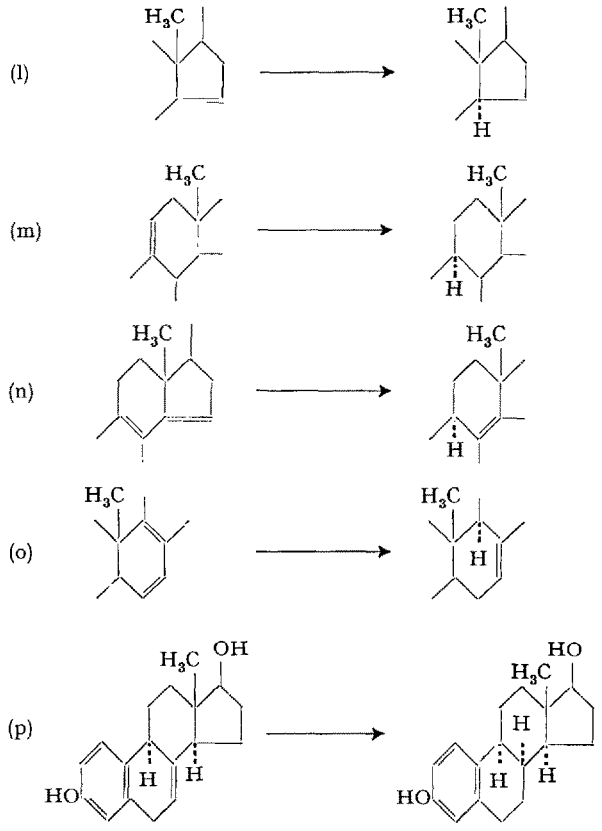
[1] D.H.R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).

ship is the same at position 6, since the 6β-acetoxy group of XXX is more resistent to hydrolysis than the 3β-acetoxy group, whereas in XXXI the 6α-acetoxy group is hydrolyzed at the same rate as the 3β-acetoxy group.



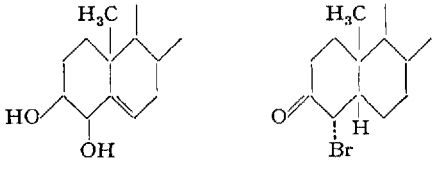
XXX XXXI

Hydrogenation. Instances cited above show that hydrogenation of a 16,17- or 5,6-double bond involve attack of the less shielded rear side to give products with a 17α- or 5α-hydrogen atom. In numerous examples of hydrogenation of a 14,15-double bond attack is likewise from the rear (l); reaction with perbenzoic acid similarly



gives the α-oxide. Rear attack is also the rule for hydrogenation of a double bond extending from C_9 to C_{11} or to C_8. Thus Δ^9-lithocholenic acid gives a 9α-dihydride (m); dehydroergostenol reacts in part by 1,4-addition to give $\Delta^{8\,(14)}$-ergostenol (n); isodehydrocholesterol reacts in part by 1,4-addition to give Δ^7-cholestenol (o). The 7,8-double bond in a stenol is not hydrogenable but migrates to the 8,14-position; however, the 7,8-double bond of dihydroequilin (p) is hydrogenable and the product probably has the unnatural α-configuration at C_8. Thus in the one known example position 8, like positions 5, 9, 11, 14, and 17 in the reactions cited, appears to be attacked by hydrogen from the rear.

Exceptions. Although rear attack in reactions at nuclear positions appears to be a rather general phenomenon, there are some exceptions to the rule. The 4,5-double bond of Δ^4-cholestene and of Δ^4-cholestenol suffers frontal attack on hydrogenation, for the products are coprostane and coprostanol. Hydrogenation of Δ^4-unsaturated 3-ketones usually gives mixtures in which coprostane derivatives predominate, but the direction of reduction varies with the structure and nature of the side chain and instances are known of reduction exclusively to members of the cholestane series. Frontal attack is noted in the reaction of Δ^4-cholestene-3-one with perbenzoic acid, for the product is the 4β,5β-oxide[1]. The steric course of reactions involving position 4 alone is not clear. Hydroxylation of cholesterol at C_4 by reaction with selenium dioxide gives a product of the probable configuration of XXXII, and hence appears to involve frontal attack. On the other hand, the chief



XXXII XXXIII

product of bromination of a 3-ketone of the coprostane series appears to be the 4α-derivative XXXIII, since it is subject to dehydrohalogenation, presumably by trans elimination.

Not much consistency is apparent in available evidence concerning the steric course of reactions at positions 6 and 7. The primary product of bromination of 7-ketocholestanyl acetate is probably the 6β-bromo derivative; that obtained from 6-ketocholestane-3β,5α-diol diacetate is probably the 7β-bromo derivative[2]. In apparent contradiction to the last observation, reduction of the 7-keto group of 7-ketocholestanyl acetate with lithium aluminum hydride occurs chiefly by rear-bond attack, and allylic bromination of cholesteryl esters gives the 7α-bromo derivatives[3].

Zusammenfassung

Der sterische Verlauf von Reaktionen an einem gegebenen Kohlenstoffatom des Steroidgerüstes hängt von Hinderungseffekten ab, welche innerhalb des van der Waalsschen Radius des betreffenden Kohlenstoffatoms wirken. Diese Effekte werden daher als intraradiale bezeichnet. Eine zweite Klasse von Effekten, die als extraradiale zu definieren sind, beeinflussen den sterischen Verlauf von Reaktionen funktioneller Substituenten, wie z. B. von Azetylgruppen oder Carboäthoxylgruppen, am Sterinkern.

In Stellung 17 und 12 wirken der intraradiale und der extraradiale Effekt gegeneinander, während sie in Stellung 11 und 5 im gleichen Sinne wirksam sind.

Von sehr wenigen Ausnahmen abgesehen wird bei intraradialer Hinderung vorzugsweise die Rückseite des Moleküls angegriffen. Daher erhält man in Substitutionsreaktionen vornehmlich Produkte mit dem Substituenten auf der α-Seite. Auch Anlagerungen an Doppelbindungen finden hauptsächlich durch Angriff auf die α-Seite statt.

[1] Pl. A. Plattner, H. Heusser, and A. B. Kulkarni, Helv. chim. acta *31*, 1885 (1948).

[2] L. F. Fieser and S. Rajagopalan, J. Amer. Chem. Soc. *71*, 3938 (1949).

[3] A. E. Bide, H. B. Henbest, E. R. H. Jones, R. W. Peevers, and P. A. Wilkinson, J. Chem. Soc. 1783 (1948).

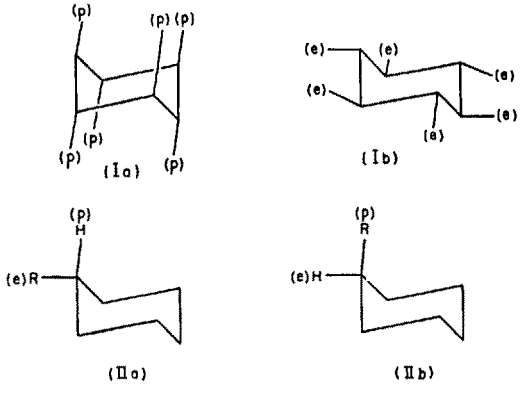
STUDIORUM PROGRESSUS

The Conformation[1] of the Steroid Nucleus

By D. H. R. BARTON[2], Cambridge, Mass.

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.

[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.

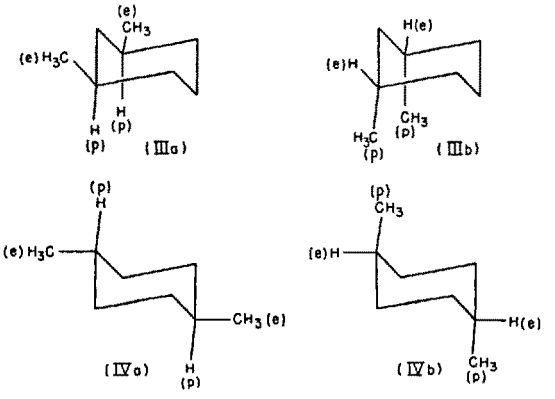
[3] C. W. BECKETT, K. S. PITZER, and R. SPITZER, J. Amer. Chem. Soc. *69*, 2488 (1947).

[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.

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] 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