REACTION MECHANISMS IN ORGANIC CHEMISTRY

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STEROID REACTION MECHANISMS

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PREFACE

In writing this book we have assumed that the reader will consult the encyclopaedic account of Steroid Chemistry, Fieser and Fieser's *Steroids*, for detailed factual and historical aspects of the subject. More compact accounts of the steroids and their chemistry are available in monographs by Shoppee and Klyne. Valuable additional material is provided by Djerassi's *Steroid Reactions*.

Our aim has been to discuss the mechanisms of steroid reactions in language which should be largely familiar to undergraduates in chemistry, and also to biochemists. At the same time we have tried to show post-graduate students and research workers the extent to which current concepts of organic reaction mechanisms are relevant to, and have profited from, the study of steroids.

Our survey of evidence concerning mechanisms of reactions is intended to be both critical and constructive. Where experimental evidence is lacking or incomplete we offer possible interpretations of reactions, though realising that this must invite criticism. We feel, however, that our suggestions will serve a useful purpose even if their only effect is to stimulate further thought and experiment which ultimately prove them wrong!

Steroids are only a part of the large family of alicyclic compounds. The borderlines separating steroids from polycyclic triterpenes and similar structures are by no means clear, and we are well aware that supporting and even contrasting examples of some of the reactions we have discussed could be found among these related compounds. They are largely excluded here through lack of space, but we hope workers in those fields may find something useful in this survey of steroid reactions. Limited space also compels us to omit reactions involved in steroid biogenesis, and a few quite important steroid reactions which do not lend themselves to inclusion under the selected chapter endings.

Interest in Steroid Chemistry and in Reaction Mechanisms is growing so rapidly that parts of this text must quickly become out-of-date. To aid research workers we include, as an Appendix, a list of publications which appeared during the interval between completing the manuscript and reading the proofs.

It is a pleasure to acknowledge the invaluable help and encouragement of Professor W. Klyne, who read the entire draft manuscript and made many constructive suggestions for its improvement. Our thanks are also due to Dr. J. R. Hanson for numerous helpful comments and corrections to the manuscript, to Miss Patricia Browne, Mr. Alan Mudd, Miss Jennifer Wiles, and Mr. Malcolm Wilson, who shared the onerous task of hunting for errors in the typescript and references, and to Mrs. Bernice Benjamin for typing the manuscript, assisted by Mrs. Laura Grobler and Mrs. Wendy Mose.

Finally we acknowledge our debt to the writers of many earlier books which served as sources for much of our material. These are too numerous to list in full, but we mention below those books which were particularly useful, and which are recommended to the reader seeking further detailed information on aspects of steroid chemistry.

August, 1968

D.N.K.
M.P.H.

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CONTENTS

GLOSSARY

Configurations of substituents

α – substituent in *trans* relationship to the angular methyl groups in a normal steroid nucleus; indicated in projection diagrams by a broken line (– – – –)

β – substituent in a *cis* relationship to the angular methyl groups; indicated in projection diagrams by a full line. A wavy line (〰) in diagrams represents an undefined configuration or a mixture of epimers.

$C_{(20)}$ configurations are designated 20α- or 20β- according to Fieser and Fieser (*Steroids*, p. 337). Equivalent terms in the modern Cahn-Ingold-Prelog convention ("sequence rules") are:–

$$20\alpha \equiv 20(S) \qquad 20\beta \equiv 20(R)$$

but these apply only when $C_{(21)}$ is unsubstituted. A $C_{(21)}$-oxygen substituent, for example, reverses the "sequence rule" designations at $C_{(20)}$, with resulting confusion for steroid chemists.

Positions of substituents

"α", "β", "$\alpha\beta$", etc., refer to the position of a substituent or structural feature in relation to a particular functional group;

e.g. an "$\alpha\beta$"-unsaturated ketone (–C(=O)–C_α=C_β–)

Molecular models were constructed from Dreiding Stereomodels.

Chapter 1

STEROIDS, REACTION MECHANISMS AND CONFORMATIONAL ANALYSIS

1. Introduction

Steroid chemistry before 1950 is a story of remarkable achievements with primitive tools. The unravelling of steroid molecular structures, their interconversion, and their synthesis during this period, demand the highest admiration for the early generations of steroid chemists, whose approach had to be largely empirical. Today's techniques of spectroscopy and chromatography were unknown or in their infancy, and the conformational aspects of steroids had not been realised. Very many steroid reactions were documented, but few were really understood. The study of reaction mechanisms lay in a specialised field which hardly impinged upon the chemistry of "natural products".

Nearly eighty years ago Sachse *[1]* laid the foundation of conformational analysis by proposing that a cyclohexane ring must exist in one of two unstrained forms, but the detailed shape of a ring must have seemed to most chemists hardly more than a matter for curiosity; it certainly excited little interest among organic chemists for several decades. In 1950, however, Barton *[2]* demonstrated the key role of conformational features in controlling many of the properties and reactions of alicyclic molecules, and was able to fit experimental data of many kinds into a single consistent pattern. Within a short space of time alicyclic chemistry, reaction kinetics and mechanisms, infrared and ultraviolet spectroscopy, thermodynamic properties, and a variety of other features of organic compounds, became firmly linked within the framework of conformational analysis.

Anybody reading an account of the development of conformational concepts since 1950 cannot help but notice the

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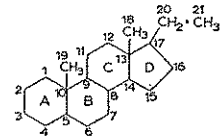
extent to which steroids figure in their rapid growth. Indeed Barton's first enunciation of the role of conformational features in determining the properties and reactions of organic compounds drew examples largely from the steroid field *[2]*. The prior existence of a large body of literature on steroids and related alicyclic compounds undoubtedly lay behind the immediate general acceptance of the new ideas, for already in 1950 data were available for many thousands of steroid compounds, from among which each new concept could find the support of an imposing range of examples. The number of known steroid compounds is now very large. The most comprehensive catalogue (Pouvoir Rotatoire Naturel *[3]*) lists in its first edition over 8000 steroids known up to 1953, and in its second edition (1961) over 21,000. This number has probably doubled by the present date (1967).

The original reason for the study of steroids, and the accumulation of so large a body of data, lay in their biological origins and activities. Once the correct structures of cholesterol and the principal steroid hormones had been discovered, there was a fresh impetus to the study of steroids from the need to develop practicable synthetic routes to the steroid hormones, and to study the effects of structural changes on their biological properties. With the arrival of conformational ideas, however, steroids were no longer to be the concern only of biochemists and "natural product" chemists, lying near what many workers in organic chemistry considered to be the outlying fringes of their subject. Barton's demonstration that the steroids have a chemistry which is not only logically predictable in many respects, but also intimately related to the general interests of organic and physical-organic chemists, has resulted in a surge of enthusiasm for the study of steroids which is now in full flood. This work has contributed much to the development of modern concepts of organic reaction mechanisms from the ideas first propounded in detail by Ingold *[4]*.

The steroid molecule provides, for example in the pregnane skeleton (1), twenty-one carbon atoms each unique in its steric environment. With simple functional groups (hydroxyl, carbonyl, olefinic, etc.) available at virtually every one of



(1)

these positions it is possible to test hypotheses concerning reaction mechanisms in a great variety of situations.

The crystallinity of most steroids, and the very convenient range of their melting points, were of immense value to early workers, and are still among the most attractive features of steroids for reaction studies. Steroid workers today have the added advantages of ultraviolet *[5,6]* and infrared spectroscopy *[7]*, both elaborately documented, and including structural correlations like those expressed in the "Woodward rules" *[6]* for ultraviolet spectra of conjugated systems. Optical rotatory dispersion and circular dichroism measurements *[8]* provide far more powerful tools for the study of stereochemistry than the earlier "monochromatic" optical rotations *[3]*. Nuclear magnetic resonance spectroscopy *[9]*, still only nine years from its introduction into steroid studies, is perhaps the most informative single technique available today; and mass spectrometry *[10]* is now in a phase of rapid development which may soon give it the dominant position among physical methods for structure determination. X-ray studies, using the power of modern computing techniques, have provided very close estimates of all bond angles and torsional angles in rings A, B, and C of a series of steroidal compounds *[11]*, and have revealed various possible conformations of ring D, depending on substitution patterns *[12]*. These finer details of molecular structure can have significant effects on chemical reactions.

The modern experimental methods of separation and purification have been developed to a high degree for steroids. Chromatographic techniques, both column and thin-layer adsorption, and more recently gas-liquid chromatography, have reached the stage when the precise analysis of the composition of a reaction mixture is a practicable proposition. Some of the

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most valuable information on reaction mechanisms can be obtained by studying the effect on competing reaction paths of small changes in reaction conditions, or in the stereochemistry or substitution pattern of the original compound. Minor products from a reaction often provide a vital indication of factors deciding reaction paths, and detailed product-composition data frequently reveal and explain the interplay of both steric and electronic factors. A noteworthy feature of some very recent papers is the new light cast on steroid reactions first described years ago, now that gas–liquid and other chromatographic techniques permit analyses of previously intractable mixtures. Results obtained in this way are already compelling the revision of some old ideas, as will be apparent in the following chapters.

2. Reaction Mechanisms and Conformational Analysis

The structure and free-energy of the "transition state", and of any reactive intermediates, are the essential features in describing a reaction mechanism. The free-energy of a species is made up of terms representing its bonding energy, its interactions with surrounding molecules (*e.g.* solvation energy), intramolecular effects such as non-bonding (Van der Waals) interactions, bond-angle strains and torsional effects, and the electrostatic or transmitted inductive effects of polar substituents. Such intramolecular effects can only be assessed reliably if the geometrical arrangement of atoms and groups about the reaction centre is accurately known. The rigidity of steroid-like structures makes them particularly valuable in this respect, by permitting steric and polar effects to be assessed in a manner which is impossible for conformationally mobile and open-chain aliphatic compounds.

Geometric features of transition states for addition reactions of olefins (Chapter 3), bimolecular substitutions (S_N2 reactions; p. 36), bimolecular eliminations (E2 reactions; p. 101) and many other reactions have been defined from studies of a variety of steroid systems (*e.g.* Fig. 1a). Reactions proceeding through carbonium ions (*e.g.* Fig. 1b; see p. 228) are sensitive to

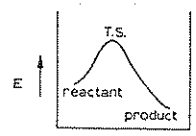


Fig. 1a. Energy diagram for one-step process.

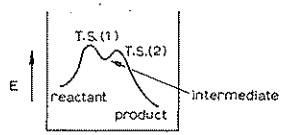
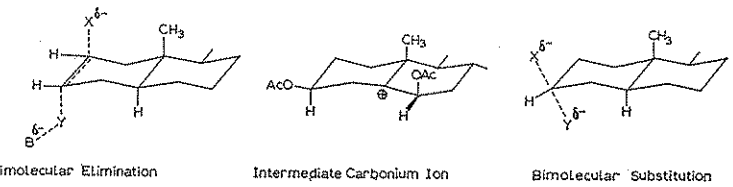


Fig. 1b. Energy diagram for two-step process.



electrostatic or inductive interactions with nearby polar groups; a rigid structure simplifies the assessment of such effects, and of steric interactions affecting the stabilities of the reactant and the intermediate. The ultimate fate of the carbonium ion may also be decided by the precise spatial arrangement of surrounding groups. The following chapters contain many examples of reactions governed by the spatial direction of the formally vacant *p*-orbital at a cationic centre in relation to the stereochemistry of its surroundings.

In order to appreciate the relationship between conformational features and reaction mechanisms it is necessary to understand the general principles of conformational analysis of cyclic structures. The reader is referred to other works for a detailed treatment of this subject *[13]*, but some of the main features relevant to steroids are summarised here.

Following Sachse *[1]*, a saturated six-membered ring may assume either a rigid "chair" form or a so-called "flexible", "twist", or "boat" form. The chair form of cyclohexane is virtually strain-free, but torsional and Van der Waals strains (non-bonded interactions) make the "flexible" form less stable by some 5–6 kcal/mole *[14,15]*. Because of this free-energy difference, cyclohexane and most of its derivatives exist almost entirely in the more stable chair form (Fig. 2), the "twist" or "flexible" ring being encountered only when the "chair" form is destabilised by exceptionally large non-bonded interactions

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between substituents, or when the mode of fusion to other cyclic systems forces the ring into a strained conformation.

Two types of C–H bonds may be distinguished in the chair conformation: those more or less perpendicular to the ring

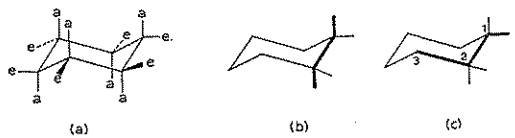

Fig. 2.

are called "axial" bonds ("a" in Fig. 2a), while bonds roughly in the plane of the ring are termed "equatorial" ("e" in Fig. 2a). This distinction is important in discussing mechanisms.

It is apparent from a molecular model that the two axial bonds on adjacent carbon atoms in the ring form a planar zig-zag with the bond linking the carbons (Fig. 2b; heavy lines), whereas an equatorial bond is in a similar relationship to the $C_{(2)}$–$C_{(3)}$ ring bond (Fig. 2c; heavy lines). In each case the "*anti*-coplanar" arrangement of four atoms leads to reactions having a common feature: the departure of an atom or group comprising one of the terminal positions of the four-atom system is accompanied by involvement of electrons associated with the other terminal group of the system (Fig. 3).

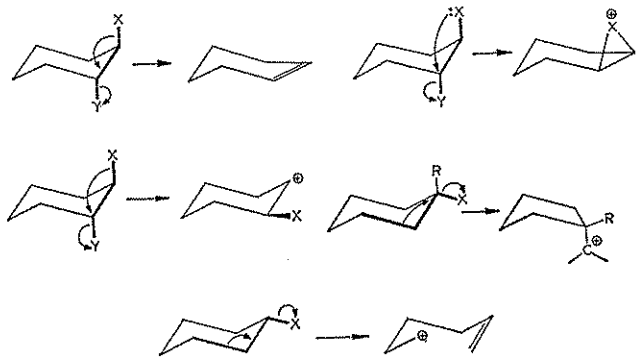

Fig. 3.

These electrons, according to the particular reaction involved, may come from the σ-bond between the third and fourth atoms of the system, when the over-all reaction will be one of elimination or rearrangement, or from a non-bonding orbital (lone-pair) associated with the fourth atom, when the product will be a cyclic derivative such as an epoxide. The generality of this "*anti*-coplanar" principle is well illustrated in reactions of steroids (see especially Chapters 3, 5, 6 and 8), and there are very few exceptions.

Further consequences of the distinction between axial and equatorial bonds lie in different rates of acylation of steroid alcohols, hydrolysis of esters, and oxidation of secondary alcohols, which were among the earliest steroid reactions to be interpreted in conformational terms. These reactions are discussed in Chapter 2.

The unsubstituted cyclohexane ring can exist in two distinct, but energetically identical, chair forms, their interconversion apparently proceeding through the "twist" form (1) (Fig. 4) *[15]*. This inversion causes bonds which previously were axial to become equatorial, and *vice versa*. The free energy barrier

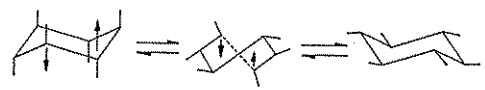

Fig. 4.

Fig. 5.

associated with the dynamic interconversion of the two chair forms has been estimated as *ca.* 10.1 kcal/mole (Fig. 5) *[16]*.

The two chair conformations (Fig. 6) of a monosubstituted cyclohexane are not equivalent, for the substituent may occupy either an axial (2) or an equatorial position (3). Although the

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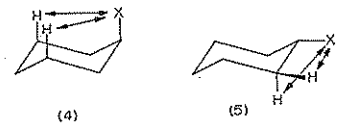
energy barrier to the interconversion of the two chairs remains essentially unchanged *[17]*, the free energies of the two chair

Fig. 6.

forms will differ. An axial substituent larger than hydrogen is



in a state of steric compression with the 1,3-related (*syn*-axial) hydrogen atoms (4), resulting in a repulsion which always exceeds the interaction between a similar equatorial (5) substituent and its adjacent hydrogen atoms. A bulky substituent is therefore normally more stable in the equatorial conformation.

The conformational equilibrium constant K, expressing the preference of a given substituent for the equatorial position, exceeds unity for all substituents larger than the hydrogen atom. The magnitude of the corresponding free-energy difference ($-\Delta G^{\circ}_{x}$) is indicated in Table 1 for a variety of substituents *[18]*. It represents the increase in potential energy of the system when an equatorial substituent is moved to an axial position. These values are used in discussing free-energy changes whenever a substituent suffers a conformational inversion during the course of a reaction. As an example, ΔG°_{x} for the acetoxy group enters into the energetics of any reaction of a 3β-acetoxy-5α-steroid in which inversion occurs at $C_{(5)}$, with a consequent change of conformation of the acetoxy group from equatorial to axial.

The steroid nucleus is built up of three cyclohexane rings and one cyclopentane fused in a *trans* sense at each ring junction (6). Each ring then includes bonds which are equa-

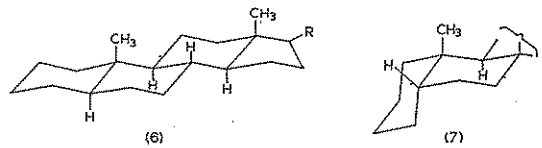
TABLE 1

CONFORMATIONAL FREE ENERGY DIFFERENCES FOR SUBSTITUENTS IN CYCLOHEXANES[a]

Substituent	$-\Delta G^{\circ}_{x}$ (kcal/mole)	Substituent	$-\Delta G^{\circ}_{x}$ (kcal/mole)
F	0.25	CH_3, C_2H_5	1.8
Cl, Br, I	0.4–0.5	iso-C_3H_7	2.1
OR[b]	0.7	$(CH_3)_3C$	5.6
NH_2	1.1	C_6H_5	3.1
$N(CH_3)_2$	2.1	CO_2R[c]	1.2
SR	0.8	C≡N, C≡C	0.2

[a] These values, which are approximate only, are taken from data given by E. L. Eliel *et al.* (Ref. *18*). [b] R = H, alkyl, acyl, toluene-*p*-sulphonyl, etc. [c] R = H or alkyl.

torially related to the adjoining ring or rings. The only common exception is in 5β-steroids where rings A and B are fused



in the *cis* sense (7). These rings then each include one bond axial to the other, making 5β-steroids generally less stable than the 5α-series. All the six-membered rings normally have the more stable chair conformation, and prefer to react in this conformation, although in rare circumstances, where the transition state for a reaction is more readily accessible from a flexible conformation of the ring involved, the reaction proceeds slowly through the less stable "flexible" conformation even though this is present in only low equilibrium concentration as compared with the unreactive chair form. The formation of an epoxide from a diequatorial halohydrin (p. 117) is such a reaction.

The angular methyl groups ($C_{(19)}$ and $C_{(18)}$ respectively) attached at $C_{(10)}$ and $C_{(13)}$ in the steroid nucleus are axial to the six-membered rings, with the exception of ring A in the

References p. 20

5β-series. This means that a significant Van der Waals interaction is inevitably present between the angular methyl groups and the 1,3-related (*syn*-axial) hydrogens (*e.g.* those at the 2β-, 4β-, 6β-, and 8β-positions in relation to $C_{(19)}$ in 5α-steroids). These modest interactions are much enhanced if any of the *syn*-axial hydrogens are replaced by larger substituents, for the system then corresponds to the energetically unfavourable conformation of a *cis*-1,3-disubstituted cyclohexane. Unlike the cyclohexane derivative, the steroid ring cannot relieve this strain by a conformational inversion, and may be compelled to accommodate it by distortions of bond angles. This can have a significant effect on reaction rates or even on the choice of reaction path. As examples of the magnitudes of *syn*-diaxial interactions, the OH/CH_3 interaction has been estimated at 1.9–2.4 kcal/mole, and the CH_3/CH_3 interaction as 3.7 kcal/mole *[19]*.

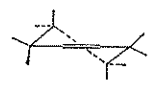
A carbonyl group causes only slight distortion of the carbon skeleton from normal cyclohexane geometry *[20,21]*, but a model reveals near-eclipsing between the carbonyl oxygen and the equatorial hydrogens on adjacent carbon atoms. This may involve non-bonded interactions in the cyclohexanone system which are absent in cyclohexane, and relief of these interactions has been suggested *[22]* to account for the greater reactivity of cyclohexanone as compared with simple aliphatic ketones, towards reagents which convert the sp^2-hybridised carbonyl C-atom into a state of sp^3-hybridisation. Steroid reactions of this kind, which include reductions of ketones to give secondary alcohols, are discussed fully in Chapter 4. Equatorial methyl groups adjacent to carbonyl seem not to introduce any larger interactions than equatorial H *[23,24,25]*, but the more bulky ethyl and isopropyl groups exhibit a significant "2-alkylketone effect" with values estimated *[26]* as 0.7 kcal/mole and 1.8 kcal/mole respectively*. The corresponding value for the tert-butyl group is not available, because of the tendency

* These values represent a lower conformational free-energy difference for the larger alkyl groups than for methyl in 2-alkylcyclohexanones, *i.e.* a reduced preference for the equatorial conformation of the alkyl group. For a recent more precise analysis of these effects see ref. *26a*.

of cyclohexanones bearing large substituents to exist partly in the "flexible" form.

Allinger *[27]* estimates that a carbonyl group reduces the difference in energy between the chair and flexible forms of a six-membered ring to only 2.7 kcal/mole, so that the flexible form becomes important in certain steroid ketones carrying bulky axial substituents *[28]*.

The skeletal geometry of cyclohexene and 1,2-epoxycyclohexane systems corresponds to a partially flattened chair or "half-chair" (8). The alternative "half-boat" conformation has



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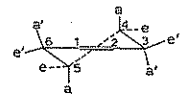

(9)

been estimated *[29]* to be some 2.7 kcal/mole less stable. Both the cyclohexene and epoxycyclohexane *[30]* molecules can exist in two enantiomeric "half-chair" conformations (8) and (9), which readily undergo chair inversion, but this is usually prevented in steroid derivatives, where the remainder of the molecule constrains the ring in one particular half-chair conformation. Such considerations of preferred conformations have recently advanced our understanding of the factors governing the rearrangement of steroid epoxides with Lewis acids (p. 357) *[31]*.

In the cyclohexene system (9) carbon atoms 1, 2, 3 and 6 are in one plane. Although normal axial and equatorial bonds are present at $C_{(4)}$ and $C_{(5)}$, the bonds at $C_{(3)}$ and $C_{(6)}$ have less clearly defined character and are termed "pseudo-axial" or "pseudo-equatorial" [a' and e' in (9)]. The effects of conformation on reactions of unsaturated steroids are discussed in Chapters 3 and 4.

Conformations of the five-membered ring D are not clear-cut. Two "envelope" forms (10) and (11), and a "half-chair" conformation (12) *[32,33]* have been proposed, each for a specific group of compounds. Experimental evidence (spectroscopic and other physical data *[34,35,36]*), supported by cal-

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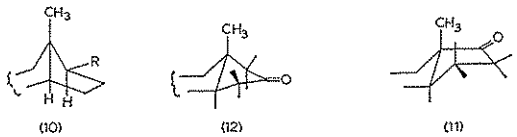
culations of bond-angle strains and non-bonded interactions



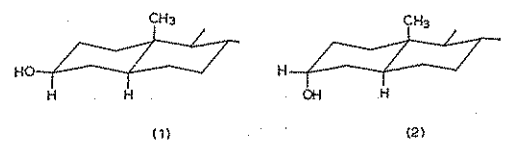
(10) (12) (11)

[32], suggests that ring D will assume, in any particular compound, the conformation which best accommodates the various strains due to the substituents present. Recent evidence from X-ray diffraction data substantiates this view *[12]*.

The steroid side chain (at $C_{(17)}$) also deserves mention. The two-carbon chain in the pregnane series possesses a certain conformational mobility, but interactions with the rest of the molecule make this markedly less than in a simple aliphatic compound. Physical measurements have demonstrated distinct preferences for particular conformations in various $C_{(20)}$-substituted pregnanes *[37,38]*, and these conformations are significant in interpreting reactions of these systems. Reduction of a 20-oxo group, for example, occurs with a fair degree of stereospecificity as a result of its asymmetric environment when considered in relation to the neighbouring parts of the steroid skeleton (p. 139).

3. Conformation and Stability of Substituents

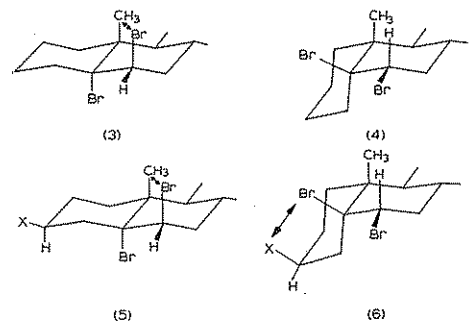
The preference of a bulky substituent for the equatorial position in a cyclohexane ring often results in the establishment of a conformational equilibrium for the mobile monocyclic system, but the rigidity of a steroid molecule prevents conformational inversion. Thus the epimeric 5α-cholestan-3β-ol (1) and 5α-cholestan-3α-ol (2) have conformations in which the hydroxyl group is respectively held in the equatorial and



(1) (2)

axial conformation. The greater stability of the hydroxyl group in the equatorial position is demonstrated by vigorous treatment of the alcohols with sodium alkoxide, when each isomer undergoes a partial inversion of configuration at $C_{(3)}$ to yield an equilibrium mixture of epimers in which the equatorially-substituted 5α-cholestan-3β-ol (1) predominates *[39]*. Similar treatment of 5β-cholestan-3β-ol (coprostanol) and 5β-cholestan-3α-ol (epicoprostanol) results in epimerisation of the less stable axial alcohol to give a mixture rich in the equatorial epimer, in this case the 3α-alcohol.

The relative stabilities of axial and equatorial substituents are revealed in an interesting set of data for equilibration of the bromo-substituents in 5α,6β-dibromocholestane (3) and its 3β-substituted derivative (5) *[40]*. In the dibromide (3) not only do the bromine atoms occupy axial positions and so suffer considerable steric compression, but the structure is further destabilised by the *syn*-diaxial interaction between the axial bromine at $C_{(6)}$ and the angular methyl group at $C_{(10)}$. A solution of this dibromide exhibits mutarotation and



(3) (4) (5) (6)

an equilibrium is established between the diaxial dibromide (3) and the diequatorial dibromide (4), in which inversion has occurred at both $C_{(5)}$ and $C_{(6)}$. The position of equilibrium for the 3-deoxy compounds (3) and (4) favours the diequatorial compound to the extent of 99:1, but the introduction of a 3β-hydroxyl group into the system changes the position of equilibrium to one where (6) is favoured with respect to (5) by only 85.5:14.5 *[40]*. This change is due to the hydroxyl group, initially present in the 5α,6β-dibromide (5) as an equa-

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torial substituent, occupying the less stable axial position in the product (6), and suffering additional steric compression due to its interaction with the bromine at $C_{(5)}$. The mechanism of this reaction, and of analogous rearrangements involving compounds derived from 5α-cholest-2-ene, is reviewed in Chapter 9.

The conformational analysis of "α"-halocyclohexanones has been the subject of a great deal of work involving infrared, ultraviolet, and n.m.r. spectroscopy, dipole moments, optical rotatory dispersion and circular dichroism measurements *[41]*. In addition to the normal steric effects relevant to conformational analysis there is a new variable in the interaction between dipoles of the C–halogen bond and the carbonyl group. Steric interactions are maximal for an axial halogen atom, while the dipolar repulsion is minimal. For "α"-haloketones in the steroid series, provided there are no bulky groups in the *cis*-1,3-diaxial position with respect to the halogen atom, the halogen prefers to occupy the axial position where dipolar interactions are minimised *[42]*. In such circumstances the epimer with an axial halogen atom will be the major product of reactions subject to thermodynamic control. However, an axial and β-orientated halogen atom in rings A, B and C, is subject to at least one *cis*-1,3-diaxial interaction with an angular methyl group. Under such circumstances the energy of the axial haloketone will be higher than that of the equatorial haloketone, which becomes the principal product after equilibration.

The relative stabilities of olefinic bonds at various positions in the steroid nucleus have a direct bearing on reactions of several kinds, including elimination reactions (Chapter 3), enolisation of ketones (Chapter 4) and the equilibration of olefinic structures (Chapter 5). Infrared absorption spectra in the region 1600–1700 cm^{-1}, which for cyclohexene (1650 cm^{-1}) and cyclopentene (1613 cm^{-1}) reflect the greater strain (5–6 kcal/mole) present in cyclopentene *[43]*, have been employed *[44,45]* to obtain some indication of the relative stabilities of *cis*-disubstituted and trisubstituted double bonds. The data are summarised in Table 2.

Heats of hydrogenation *[46]* are available for several

TABLE 2

INFRARED ABSORPTION DATA *[44, 45]* AND HEATS OF HYDROGENATION *[46]* OF OLEFINS

	i.r. spectrum (C=C stretch, cm^{-1})	Heat of hydrogenation (kcal/mole)
cis-Disubstituted olefins		
Cyclopentene	1613	25.67
Cyclohexene	1650	27.10
5α-Cholest-1-ene	1644	27.30
5α-Cholest-2-ene	1653	25.85
5α-Cholest-3-ene	1647	27.97
5α-Cholest-6-ene	1637	27.36
Δ^{11}-Steroid	1623	28.93
Trisubstituted olefins		
Δ^{4}-Steroid	1657	—
Δ^{5}-Steroid	1670	25.85
Δ^{7}-Steroid	1668	—
$\Delta^{9(11)}$-Steroid	1646	—
Δ^{14}-Steroid	1647	—

cholestenes, again in comparison with similar data for cyclopentene and cyclohexene. These are included in Table 2.

Heats of hydrogenation measure the *total* energy differences between the steroid olefins, taking into account the energy involved in minor conformational distortions needed to accommodate the half-chair geometry of the unsaturated ring in the polycyclic framework. The infrared data, in contrast, probably indicate only the amount of strain in the double bond itself. The results of olefin isomerisation experiments have not really helped to clarify the situation among the commoner cholestenes, for acidic conditions sufficiently drastic to cause double-bond migration are liable to promote a complete rearrangement of the molecule (see p. 291).

A carbonyl group adjacent to a ring junction bearing a hydrogen atom allows conformational equilibration to take place at the ring junction through enolisation (p. 154). For the 4-oxocholestane system (7), optical rotatory dispersion measurements *[47]* have indicated the presence of 99% A/B *trans*-isomer (5α) at equilibrium. In contrast, similar data *[47]* for

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