# Metabolism of Steroid Hormones

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1965

ACADEMIC PRESS New York and London

ACADEMIC PRESS INC.
111 Fifth Avenue, New York, New York 10003

*United Kingdom Edition published by*
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 65-14644

PRINTED IN THE UNITED STATES OF AMERICA

# Preface

Our first monograph on the metabolism of the steroid hormones published in 1953 and reprinted in 1954 represented information obtained from about 1500 reports with a listing of over 400 papers. This publication contains over 2000 literature citations reflecting still a greater number of papers actually consulted. During the intervening period, not only has the literature in the field of steroid hormone metabolism expanded enormously, but also additional areas of steroid research have undergone marked development, and information is constantly being added to swell the total body of knowledge in this field. This monograph presents a reasonably thorough but not necessarily complete coverage of the pertinent literature on the metabolism of the steroid hormones.

The basic plan of this work is to illustrate and tabulate the diverse aspects of steroid metabolism. In those instances where it seemed particularly appropriate we have made certain critical evaluations and have presented some theoretical considerations. In the over-all summaries presented as a complete system in Chapter 7 and in discussions of the tissue hormones and their metabolites we have considered the sum total of both *in vivo* and *in vitro* experiments as a body of composite information obtained from many species of animals. It is to be anticipated that in the near future sufficient information will become available to allow for a more detailed consideration of the comparative aspects of steroid metabolism.

As discussed and illustrated in Chapter 4, almost every position of the steroid molecule may be attacked by enzymes of microbiological origin. The imbalance between the practical and theoretical aspects of the science are striking when it is realized that only relatively few of the microbiological enzymes have been subjected to detailed biochemical study. Yet a few notable exceptions will be found such as the isolation of very active steroid isomerase and dehydrogenase enzymes from a microbiological source. We record with pleasure our indebtedness to Dr. Yuichiro Kurosawa, of the Tsurumi Chemical Research Laboratory, Yokohama, Japan, who so kindly helped search the Japanese literature for important steroid microbiological reactions and presented us with summaries for inclusion in this monograph.

Many steroids have been synthesized which are not naturally occurring and which are particularly important therapeutic agents. The *in vivo* and *in vitro* metabolism of these synthetic steroids has been documented to some extent. The knowledge of synthetic steroid hormone metabolism is expected to grow and become of particular value as it contributes to studies on the

mechanism of steroid hormone action and on the relationship between structure and biological activity, two important areas which are not directly covered in the present work.

A particular objective of this form of presentation, which has been clearly one of our primary considerations throughout, was the fashioning of a volume useful to the novice, and for that reason many structural formulas as well as a detailed treatment of the nomenclature have been included. This feature, with the more extensive documentation, we believe will be appreciated equally by the clinician, internist, endocrinologist, gynecologist, obstetrician, pediatrician, psychiatrist, urologist, and by the general practitioner who may desire a firm background in steroid biochemistry.

This publication should be considered to be primarily a qualitative treatment of steroid metabolism. Other reports in recent years have presented certain quantitative aspects of steroid metabolism with the available information on urinary and blood levels. We anticipate that the quantitative aspects and dynamics of metabolism, the relative pathways both of biosynthesis and catabolism, and the levels of steroid hormones and related substances in body fluid will be rapidly forthcoming in some detail and any future revision would deal with these matters at great length.

The staff of Academic Press has been particularly kind and helpful, and the difficult problems created by us were solved efficiently and in a most cooperative manner.

It is possible that in a volume such as this authors by acts of omission as well as commission manage to incorporate in the manuscript an untold number of errors; the bulk of these are detected and brought to our attention by our fellow co-workers and by the secretarial staff. This monograph is no exception and we accept full responsibility for whatever errors remain. To the degree to which the accuracy and the validity of the documentation has been preserved, full praise must go to Mrs. Iola Graton, Mrs. Elaine Joseph, Mrs. Madeline Daley, and Mrs. Marilyn Linn, who in good cheer and with meticulous care did all that was required to assist in preparing the manuscripts. For this we say "many thanks."

*Shrewsbury, Massachusetts,*
*Minneapolis, Minnesota*
*March, 1965*

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# CHAPTER I

## Introduction

The first steroid hormone, estrone, was isolated in 1929 at a time when the structure of the steroid nucleus was not yet established. Since then, the structure of the steroid nucleus has been elucidated, steroid chemistry has flourished, and four endocrine glands, the testis, the ovary, the adrenal cortex, and the placenta of pregnancy, have been identified as the steroid-producing tissues. In the years that have elapsed since the first crystalline steroid hormones were isolated from human pregnancy urine, many steroids with varying degrees of biological activities have been isolated from tissue sources. These studies have been supplemented with the isolation and identification of over 200 steroids from urine.

The isolation of the steroid hormones and the elucidation of their structure paved the way for intensive steroid metabolic studies. Significant work on steroid metabolism started in the 1930's with the use of the classical technic of administering large doses of known crystalline steroids to human subjects and experimental animals and isolating crystalline metabolites from body fluids, usually the urine. In this way the relationships of pregnanediol to progesterone (Venning and Browne, 1937), androsterone to testosterone (Callow, 1939; R. I. Dorfman and Hamilton, 1939), estradiol-17$\beta$ to estrone (Fish and R. I. Dorfman, 1941), and deoxycorticosterone to pregnanediol (rabbits: Westphal, 1942; Hoffman *et al.*, 1943; man: Horwitt *et al.*, 1944; chimpanzee: Fish *et al.*, 1943) were established.

An important phase of metabolism considered by early workers was the biosynthesis of the steroid hormones, including the possible conversion of androgens to estrogens. This conversion illustrates very well one aspect of the many problems that exist in the study of biosynthetic pathways.

Conversion of testosterone, the most active naturally occurring male sex hormone, into a substance possessing estrogenic activity was reported by Steinach and Kun (1937) to occur in men. These investigators reported an increase in urinary estrogenic material after the injection of testosterone propionate. In one case they reported a change from 36 to 1200 RU of estrogenic material per liter after the injection of 1 gm of testosterone propionate during a 6-week period. Since the estrogenic assays were made on the crude benzene extracts, there was a possibility that the activity was due to androgens, some of which are known to produce estrogenic or pseudoestrogenic effects on the vaginal epithelium.

R. I. Dorfman and Hamilton (1939), Hoskins *et al.* (1939), and Callow *et al.* (1939) obtained evidence by bioassay procedures for an increase in estrogens in the urine of human subjects with or without gonads after testosterone treatment. R. I. Dorfman and Hamilton (1939) were able to show the same effect in monkeys.

Nathanson *et al.* (1951) reported that the increase in phenolic estrogens after testosterone or dehydroepiandrosterone was actually due to the increased excretion of estrone and estriol, characterized by countercurrent distribution.

The results of these early studies were consistent with a biosynthetic pathway of estrogens from androgens but, since the yields of estrogens were low and many variables were not rigorously controlled, certainty of this biosynthetic route was not attained. It remained for more rigorous experimentation, as described in Chapter III, to establish beyond doubt that the conversion occurred. The decisive demonstration involved the conversion of a radioactively labeled androgen into a labeled estrogen.

In the middle of the 1930's two technical procedures were described which proved to be invaluable for steroid investigation. Girard and Sandulesco (1936) introduced the use of the two reagents known as Girard's reagents T and P, which are trimethylaminoacetohydrazide hydrochloride and pyridylacetohydrazide hydrochloride, respectively. These reagents efficiently separate ketonic steroids from non-ketonic substances, thus aiding immeasurably the fractionation procedures. Reichstein (1936) introduced the use of adsorption column chromatography for the separation of adrenocortical steroids, and Callow and Callow (1939) used this method for the fractionation of urinary steroids. The importance of the introduction of the two methods, the Girard and Sandulesco procedure and adsorption chromatography, can be appreciated from the following illustration. Butenandt (1931), working without these methods, needed about 15,000 liters to isolate 15 mg of androsterone (0.001 mg/liter) from normal men's urine, whereas Callow and Callow (1939) were able to isolate 0.3 mg of androsterone per liter with the use of the newer, more refined technics.

Further improvements in chromatographic technic which followed were adapted for steroid investigation. Paper chromatography, as applied to steroids by Zaffaroni *et al.* (1950), brought a new era of analysis and permitted experimentation at the microgram level. These advances continued with the use of partition columns and thin-layer chromatography. One of the newest and most striking developments concerns gas chromatography, where separations and identifications may soon be possible at the 0.01- to 0.001-$\mu$g level.

Countercurrent distribution has been brought to a high level of development for most steroids, starting with the pioneer work of Engel *et al.* (1950) with estrogens.

Structural proof for steroid compounds by physical means has kept pace with developments in separation and fractionation. The development of infrared spectroscopy by Furchgott *et al.* (1946) and by Jones and Dobriner (Dobriner *et al.*, 1948) was an important advance in the field of identification of steroids. Parallel roles have been shared for ultraviolet determinations (L. Dorfman, 1953; Bernstein and Lenhard, 1953), optical rotatory dispersion (Djerassi, 1957), nuclear magnetic resonance (Shoolery and Rogers, 1958), mass spectrometry (Reed, 1958), gas chromatography based on pyrolytic fission (Parsons *et al.*, 1955a, b, 1956, 1957), and X-ray crystallographic analysis (Bernal, 1932; Crowfoot and Dunitz, 1948; Crowfoot *et al.*, 1957).

The early development of certain color reactions, including the Kober reaction (1938), the Zimmermann reaction (1935), and the fluorescence analyses (Cohen and Bates, 1947), hastened progress immensely.

The field of analysis has developed considerably by the use of the technic of double labeling for aldosterone, estrogens, testosterone, cortisol, and progesterone. Methods of analysis have utilized enzymatic procedures (Hurlock and Talalay, 1958) and even steroid biosynthetic enzyme preparations as reagents (Finkelstein *et al.*, 1961, Forchielli *et al.*, 1963).

The metabolism of the steroid hormones and related substances has been studied by a variety of experimental procedures. These procedures have included the perfusion technic and various *in vivo* and *in vitro* preparations. The *in vivo* studies dominated the field at an early period with the administration, usually to humans, of relatively large amounts of steroid hormones and closely related substances. The metabolic products were then isolated from the urine. As the field developed, technics involving the use of perfusion of isolated intact glands, tissue slices, tissue homogenates, and tissue enzyme preparations were utilized.

The perfusion of an isolated single gland for studies on steroid metabolism was carried out by Danby (1940), who showed that liver obtained from a dog and the kidney of the cow could inactivate androgens. Certain $C_{19}$-steroids (dehydroepiandrosterone and androst-5-ene-3$\beta$,17$\beta$-diol), perfused through the isolated bull testis, showed increased androgenic activity. This technic was developed to a high degree of proficiency by investigators at the Worcester Foundation for the elaboration of the biosynthetic pathways for the adrenocortical steroids (Hechter *et al.*, 1949, 1951) and for studies of the metabolism by liver tissue of adrenocortical steroids (Caspi *et al.*, 1953).

A great part of our information on the metabolism of the steroid hormones was derived from *in vivo* experiments. This technic has been employed with relatively large doses of the steroid hormones as well as with more physiological concentrations of steroids bearing labeled atoms ($C^{14}$, deuterium, and tritium) at various points on the steroid nucleus and/or side chain. These *in vivo* studies have had a considerable utility and probably will continue to be of value in specialized types of experiments.

By means of this technic, the interrelationships that exist between certain steroid hormones produced in specific glands and urinary metabolites have been demonstrated. Thus, the determination of the urinary concentration of certain metabolites has made it possible to assess the functional status of a particular endocrine gland. The direct relationship between progesterone, the progestational hormone, and pregnanediol in the urine has been rigidly established. The urinary pregnanediol content during the luteal phase of the menstrual cycle in a nonpregnant woman indicates the quantity of progesterone produced by the ovary. In pregnancy, the massive amount of progesterone produced by the placenta is also converted to and excreted in part as pregnanediol. The concentration of urinary urocortisone plus urocortisol gives a reasonable measure of the cortisol produced by the adrenal cortex. These interrelationships were established by means of *in vivo* experiments. By the use of isotopic technics, *in vivo* studies give more decisive results, since the problems created by the presence of endogenous products are controlled. In addition, the formation of labeled metabolites, with proper specific activities, provide immediate answers to the many tissue hormone–urinary metabolite relationships. The interrelationships between the tissue steroids and their metabolites in blood and urine are considered in detail in Chapter VIII.

The *in vivo* technic has certain limitations, whether or not isotopically labeled hormones are employed. For examples, little can be learned of the intermediate steps in steroid reactions. Neutral steroid hormones which have at least three active centers may undergo reductive or oxidative changes leading to a variety of products. Frequently, alternative pathways are possible. The *in vivo* method of experimentation can only indicate likely possibilities. A further drawback is the fact that the tissue responsible for the transformation cannot be assessed with certainty.

The *in vitro* technic is capable of furnishing us with information, which supplements results obtained with *in vivo* methods, concerning the metabolic pathways of the steroid hormones and the specific tissues involved. Fractionation and purification of specific enzyme systems can provide the means for delineating the individual steps involved in the metabolic pathways of the steroid hormones, and the possible mechanisms involved.

Some of the technics employed in steroid investigation have been presented in order to illustrate their contributions to the understanding of the metabolism of the steroid hormones. By metabolism, we actually mean both the biosynthetic reactions leading to the production of a specific hormone and the transformations that the molecule, once formed, may undergo in peripheral tissues. This volume will be concerned primarily with reactions of the steroids in which the steroid nucleus remains intact. The extensive transformations of the steroid molecule after the disruption of the nucleus are essentially unknown. Studies employing labeled steroids have indicated that a small portion of administered steroids undergo

nuclear disruption. The incubation of testosterone-3-$C^{14}$ with human ovarian tissue resulted in the production of a small but significant amount of $C^{14}$-labeled carbon dioxide (Baggett *et al.*, 1956). Heard *et al.* (1954) have shown that, when estrone-16-$C^{14}$ was administered to a pregnant mare, a portion of the total estrogen administered was converted to $C^{14}O_2$, again demonstrating nuclear disruption.

Since more than 200 different steroids have been identified from tissue and urinary sources and since these compounds undergo many oxidative and reductive reactions, a classification or organization of the many diverse reactions involved becomes desirable. The question arises as to whether this complex of isolated facts may be put into a relatively logical and more useful form. It is the primary purpose of this volume to attempt some unified presentation of the material.

## Nomenclature of Steroids

The steroids are a class of organic compounds containing the perhydrocyclopentanophenanthrene nucleus. These substances include such important biological compounds as cholesterol, ergosterol, cardiac glycosides, bile acids, sapogenins, as well as androgens, adrenocortical hormones, estrogens, progesterone, and their metabolites. Figure 1 illustrates the structure of testosterone to indicate the basic common nucleus. The steroid structures are not usually written with all the carbon and hydrogen atoms illustrated, as in Fig. 1 for 5$\beta$-pregnane, but rather, as shown in Figs. 1, 2, and 3, with a hexagonal ring for each of the six-carbon rings and a pentagonal ring for the five-carbon ring. The hydrogen atoms are omitted and the representation of the nucleus as such indicates a fully reduced ring structure; that is, each carbon atom has its full complement of valence bonds satisfied by carbon or hydrogen atoms, or both. The carbon atoms represented in the nucleus are of three types: those that are linked to two adjacent carbon atoms and carry two hydrogen atoms; those that are linked to three carbon atoms and are common to two different rings so that they carry only one hydrogen atom; and, finally, the two carbon atoms (numbers 10 and 13) that are linked to four carbon atoms and carry no hydrogen atoms.

Figure 1 also indicates the manner of numbering the carbon atoms and designating the four rings. The carbon atoms are conventionally numbered from 1 to 17 and the rings are referred to by the letters A, B, C, and D. Carbon atoms 18 and 19 are located between rings C and D, and A and B, respectively. The methyl groups, containing carbon atoms 18 and 19, are frequently called angular methyl groups and are represented by solid straight lines between the respective rings. The side chain containing carbons 20 and 21 is attached to carbon 17.

All steroids of the androgenic, estrogenic, adrenocortical, and progestational series may be considered to be derived from the eight basic hydro-

carbons represented in Fig. 2. When the steroid molecule is depicted in the usual manner, the angular methyl groups (containing carbon atoms 18 and 19) may be considered to lie above the plane of the paper. Thus, in the pictorial representation of the steroid molecule, the entire nucleus, which is a relatively flat structure with the exception of the angular methyl groups, is considered to lie in the plane of the paper. The methyl groups are joined to the nucleus by means of solid lines designating a $\beta$-stereochemical configuration. The angular methyl groups serve as the reference groups for assigning stereochemical configuration. Thus, each time a solid line is used for a substituent group (where stereoisomerism is possible) it will mean that the group is above the plane of the molecule (or paper), it is on the same side of the molecule as the two angular methyl groups, and it has a $\beta$-configuration. If a substituent group is connected to the nucleus by means of a dotted line, it will mean that the group is below the plane of the molecule, on the opposite side with respect to the angular methyl groups, and has an $\alpha$-configuration. When two groups lie on the same side of the molecule they are said to be *cis* to each other and when they lie on opposite sides of the molecule they are referred to as being *trans* to each other.

In Fig. 2 the four-ring structures are modified in four ways. 5$\beta$-Gonane is a basic hydrocarbon, with no angular methyl groups, in which the hydrogen atom at carbon 5 projects in front of or above the plane of the molecule while, in 5$\alpha$-gonane, the hydrogen atom projects in back of or below the plane of the molecule. No naturally occurring derivative of this hydrocarbon is known at this time. The estrane series (5$\alpha$ and 5$\beta$) contains only one angular methyl group (carbon number 18) and includes, among its naturally occurring members, 19-norandrost-4-ene-3,17-dione and ring A and ring B unsaturated derivatives.

5$\beta$-Androstane and 5$\alpha$-androstane contain two angular methyl groups (carbon numbers 18 and 19) and differ only by the spatial configuration of the hydrogen attached to carbon atom 5. The 5$\alpha$-configuration of androstane is designated as "allo" in some of the older system of nomenclature. The 5$\beta$-configuration of androstane is sometimes referred to as the "normal" form. The same relationship exists between 5$\alpha$-pregnane and 5$\beta$-pregnane with respect to the spatial configuration of the respective hydrogens at carbon 5.

When 5$\alpha$-pregnane and 5$\alpha$-androstane are compared, it is found that the compounds differ in that the former compound has an ethyl ($C_2H_5$) side chain at carbon 17. A similar relationship exists between 5$\beta$-pregnane and 5$\beta$-androstane. The side chains in both 5$\alpha$-pregnane and 5$\beta$-pregnane are attached to carbon 17 with a solid line, indicating that the side chain is *cis* to the angular methyl groups and may be considered to lie above the plane of the molecule. This configuration is designated as beta ($\beta$), while side chains *trans* to the angular methyl groups are designated as alpha ($\alpha$). Actually all of the naturally occurring steroids in the sex hormone and

adrenocortical hormone series have side chains (when such are present) of the $\beta$-configuration. Derivatives of 5$\alpha$-androstane and 5$\beta$-androstane will be encountered among the androgens and their metabolites, while 5$\alpha$-pregnane and 5$\beta$-pregnane are important with respect to the adrenocortical hormones and progesterone.

Changes in stereochemical configuration at carbon 3 are encountered frequently in the steroids. Figure 3 illustrates this type of isomerism. The two compounds 5$\alpha$-androstan-3$\alpha$-ol and 5$\alpha$-androstan-3$\beta$-ol differ only in the spatial configuration of the hydroxyl group at carbon atom 3. In 5$\alpha$-androstan-3$\alpha$-ol, the hydroxyl group at carbon atom 3 is in a position *trans* to the methyl group on carbon atom 10. This *trans* position is designated as the alpha ($\alpha$) position, and compounds having this configuration usually do not form insoluble digitonides by the method ordinarily employed. In 5$\alpha$-androstan-3$\beta$-ol, the hydroxyl group is in a position *cis* to the position of the methyl group on carbon atom 10. This position is designated as beta ($\beta$), and compounds having a hydroxyl group of this configuration usually do form insoluble digitonides. The precipitation or nonprecipitation of a steroid by digitonin under specific conditions is presumptive, but not conclusive, evidence for the configuration of the hydroxyl group at carbon atom 3.

In addition to the stereoisomers in the steroid series at carbons 3, 5, and 17 which have been discussed, carbon atom 11 frequently carries a hydroxyl group. In the vertebrate animal the hydroxyl group at carbon 11 in all naturally occurring steroids has a $\beta$-configuration, i.e., the hydroxyl group is *cis* to the angular methyl groups. It is of interest to note that the 11$\alpha$-hydroxyl (*trans*) configuration can be formed by the actions of many microorganisms on suitable steroid substrates.

Some ordor in the nomenclature of the steroid compounds has been finally achieved, The formal form of nomenclature to be discussed is that adopted by Commissions on the Nomenclature of Organic Chemistry and the Nomenclature of Biological Chemistry of the International Union of Pure and Applied Chemistry, 1957. These rules were published in London in 1958 by Butterworth's Scientific Publications under the title *Nomenclature of Organic Chemistry*.

In general, three types of steroid names are used. The common or trivial name has the advantage of simplicity but the disadvantage of not revealing the nature of the substitutions on the steroid nucleus, their position, or their spatial configuration. The second type of name is one which starts with a definite common name of a compound, and designates the compound to be named by changes in the common or trivial name. This practice has occurred particularly in the adrenocortical hormone series. Thus, corticosterone is the trivial name for 11$\beta$,21-dihydroxypregn-4-ene-3,20-dione and the name 11-dehydrocorticosterone (or dehydrocorticosterone), which is in common usage, indicates that the new compound is the same as corticosterone except for the loss of two hydrogen atoms at carbon atom

11 (actually one hydrogen is lost from carbon 11 and one is removed from the hydroxy group so the result is the formation of a ketone group). The third type of name emphasizes the parent hydrocarbon and designates the changes in the parent substances by the kind of change, the place of change, and the stereoisomerism involved. Thus, this name rigidly defines the compound in question.

The basic hydrocarbons and the possible stereoisomerism at carbon atoms 3, 5, 11, and 17 have been discussed. Nuclear modification also occurs and requires designation. A common type of nuclear modification is the presence of a double bond. The presence of the double bond is indicated in the spelling of the hydrocarbon. The term androstane represents the fully saturated hydrocarbon. The presence of one double bond changes the suffix "ane" to "ene" so that androstane, for example, becomes androstene. Two double bonds make the suffix "diene," and "triene" indicates three double bonds. Since the bond of unsaturation may occur at a number of places in the steroid, it is important to designate the position. This is done by a number designation and indicates that the double bond is present between the carbon atom named and the next carbon atom in order. Thus, "—3" indicates that the double bond should be placed between carbon atoms 3 and 4. In some instances, such as a double bond between carbon atoms 9 and 11, the double bond does not extend between consecutive carbon atoms. In these cases the numbers of both carbon atoms are used in the form "—9(11)." When more than one bond of unsaturation is present, as for example, between carbon atoms 3 and 4, and 5 and 6, the designation would be "—3,5." In naming compounds with a double bond the following order is used: The first part of the hydrocarbon name, the designation of the position of the double bond(s), followed by the suffix "ene." An example of this is androst-5-ene (Fig. 3). An older form of designation, commonly found in the literature, is the use of the symbol $\Delta$, followed by the carbon number involved, as a prefix to the hydrocarbon name; for example, $\Delta^5$-androstene. This designation is no longer preferred.

A second type of nuclear modification consists of a substitution of oxygen for hydrogen in the hydrocarbon. An alcohol or hydroxyl group is designated either as the suffix "ol" preceded by the number of the carbon atom to which it is attached or by the term hydroxy preceding the hydrocarbon name. An example of one unsaturated group and one alcohol group could be androst-5-ene-3$\beta$-ol (Fig. 3). A second type of oxygen substitution is a ketone group designated by the suffix "one" or, when preceding the hydrocarbon name, designated as keto or oxo. Other examples are presented in Fig. 3. Prefixes and suffixes are given in Table 1.

The prefix "nor" is used to designate shortening of the side chain or the elimination of a methyl group (Fig. 4).

Rings may be enlarged or contracted and, to designate these changes, "nor" is used when the ring is decreased, as in *A*-nortestosterone, and

"homo" is used when the ring is increased, as in *D*-homotestosterone (Fig. 5). The absence of a ring may be designated as "des" followed by the missing ring, as illustrated in Fig. 6. Here the D ring of the hydrocarbon, 5α-androstane, is absent and the compound is referred to as des-*D*-5α-androstane.

A ring may be opened, as shown in Fig. 7. In this example, the rupture in the steroid 5α-androstane is between carbon atoms 1 and 2 and the designation is 1 : 2-seco-5α-androstane.

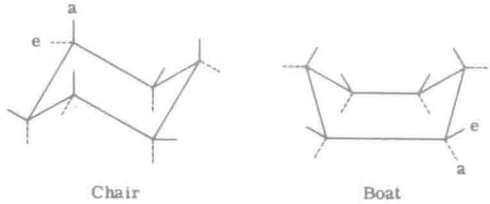
Other conventions include a symbol for an unknown configuration which is drawn with a wavy line and designated as ξ (Greek xi); "deoxy," indicating replacement of a hydroxyl group by a hydrogen atom; the prefix "*di*hydro," indicating addition of 2 hydrogen atoms to a double bond; "*de*hydro," indicating the loss of 2 hydrogen atoms; "epi," meaning the inversion of a substituent; and "deoxo," indicating the replacement of an oxo (ketone) group by two hydrogen atoms.

In the interest of efficiency, the common or trivial names have been employed frequently in this book and are given in Table 2 together with their systematic names.

Table 3 lists some general steroid metabolism reviews.

## Conformational Analysis

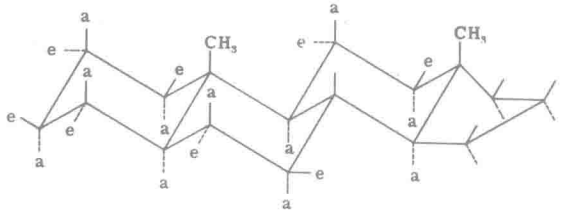
The steroid nucleus is composed of three cyclohexane rings and one cyclopentane ring. The six carbon atoms of the cyclohexane ring are not fixed but can assume various arrangements owing to twisting or turning, with consequent strain on the ring. These different arrangements in space are called conformations. The chair (1) and boat (2) forms of the cyclohexane ring are good examples.



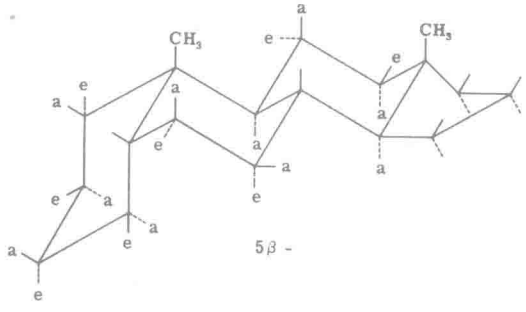

Chair (1) Boat (2)

The valencies of the carbon atoms of the cyclohexane ring can exist in the general plane of the ring, and are called equatorial (e); or they are perpendicular to the plane of the ring and are called axial (a). In depicting the equatorial or axial bonds as lying parallel or perpendicular to the plane of the ring, the convention and significance of writing the bonds extending above the plane of the ring as a solid line (β-configuration) and

those below the plane of the ring as a broken line (α-configuration) is still retained. The equatorial and axial connotations describe more accurately the spatial relationships of the substituents and the carbon atoms between themselves and the ring system of which they are a part.




5α -




5β -

| | 5α ($\Delta^4$ or $\Delta^5$) | 5β |
|---|---|---|
| Carbon 1α | a | e |
| 1β | e | a |
| 2α | e | a |
| 2β | a | e |
| 3α | a | e |
| 3β | e | a |
| 4α | e | a |
| 4β | a | e |
| 5α | a | – |
| 5β | – | a |

| | 5α – and 5β – Steroids | |
|---|---|---|
| | α | β |
| 6 | e | a |
| 7 | a | e |
| 8 | – | a |
| 9 | a | – |
| 10 | – | a |
| 11 | e | a |
| 12 | a | e |
| 13 | – | a |
| 14 | a | – |
| 15, 16 and 17 | indeterminate or quasi – | |

The most stable conformation of the cyclohexane ring and of the ring system in steroids is the chair form, and because of the greater interatomic distances, the equatorial substituents on the molecule confer greater stability than do the corresponding axial substituents, owing to differences in repulsion between atoms. The chair forms of the rings A, B, and C can be depicted for 5α- and 5β-steroid forms as shown in the accompanying illustration with the equatorial and axial substituents indicated. Since the conformations on the cyclopentane ring D are nearly at 45° angles, their valencies have been called indeterminate (i), or quasiequatorial or quasi-axial. The conformations for carbons 6 to 17 are the same for steroids with 4- and 5-double bonds as well as for 5α- and 5β-oriented compounds.