Chapter 1
Structure and Nomenclature of Steroids

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1.1 Structure of the Steroid Skeleton

1.1.1 Parent Hydrocarbons

A formula of a steroid compound is easily recognized by its four-membered hydrocarbon core (Fig. 1.1a). My little grand daughter called it "a little cottage", more advanced beginners may recall the term "cyclopentenoperhydrophenanthrene". All the thousands of natural and synthetic steroids are derivatives of that core. Ring A is the cyclohexane ring on the left; it is attached to another six-membered ring B. The C ring follows, the D ring is a cyclopentane system.

Numbering of the core is shown in the most prolific steroid – cholesterol (Fig. 1.1b): it starts at the A ring, continues at B, C, and then D rings. Methyl groups at angular positions 13 and 10 are ascribed numbers 18 and 19, the numbering then continues in the side chain. The numbers are used to describe positions at which substituents or multiple bonds are attached in individual compounds.
Most steroid compounds are derived from the following six basic hydrocarbons:

Gonanes (Fig. 1.2a, $R^1 = R^2 = H$), having hydrogen atoms at carbons 13 and 10
Estranes, with $R^1 = H$, R^2 = methyl; the word rings in trivial names like estradiol, estrone (Applezweig, 1964)
Androstane, with $R^1 = R^2$ = methyl, reminds us of androsterone and androgens
Pregnane (Fig. 1.2b), its echo – pregnancy – points to gestagens
Cholane (Fig. 1.2c), found mainly in cholic alcohols and acids
Cholestane (Fig. 1.2d), the foundation of sterols and their derivatives

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H.L.J. Makin and D.B. Gower (eds.), *Steroid Analysis*,
DOI 10.1023/b135931_1,

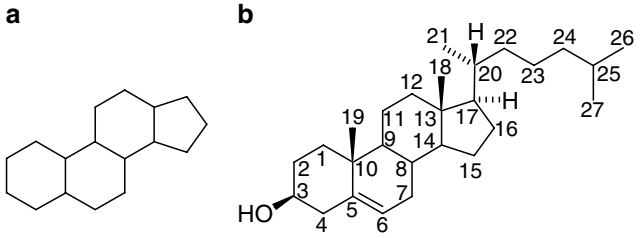

Fig. 1.1 (**a**) Perhydricyclopentenophenanthrene and (**b**) cholesterol and steroid locants

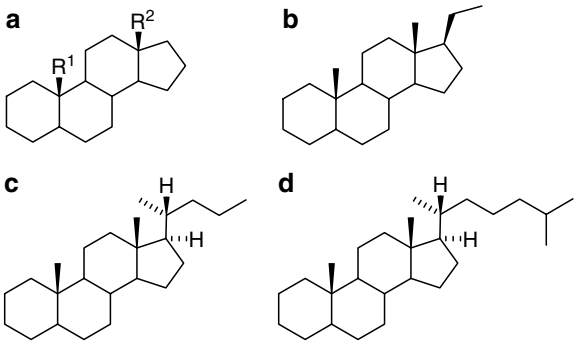

Fig. 1.2 Basic steroid hydrocarbons: (a) gonanes, estranes, androstanes; (b) pregnanes; (c) cholanes; (d) cholestanes

1.1.2 Configuration

(a) *Absolute Configuration* It is fortunate, for scientists and publishers alike, that the absolute configuration of the natural steroid molecule, established by X-ray analysis, corresponds to the one originally and arbitrarily chosen as the conventional representation when the structure of molecular framework in all other respects first became known.

While most steroids are directly or indirectly derived from a relatively small number of natural steroid raw materials, enantiomeric (i.e., mirror image molecules, not super imposable by any rotation of a molecule) steroids are available by total synthesis only. Before enantioselective reactions were contrived, products of total syntheses were 1:1 mixtures of standard steroids with natural absolute configuration and their enantiomers. These mixtures were called racemates. For example, estradiol thus formed was a mixture of estradiol and *ent*-estradiol (Fig. 1.3). It was designated by the prefix *rac*: as *rac*-estradiol, formerly, (±)-estradiol (the symbol indicates that racemates are not optically active).

For a long time, enantiomers were thought to be devoid of biological activity. Recent results, however, have suggested that enantiomers may be active though not via the usual steroid receptor route (Covey et al., 2001). Enantiomers of estradiol, androgens, and progesterone have all been shown to have neuroprotective actions

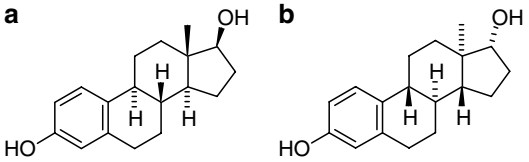

Fig. 1.3 (**a**) Estradiol and (**b**) *ent*-estradiol

as antioxidants or via GABA receptors (Klinger et al., 2002; Simpkins et al., 2004; Li et al., 2006; Van Landingham et al., 2006; Wang et al., 2006; Katona et al., 2007). Optimistic steroid chemists may find that Alice is not the only adventurer in the looking glass world …

(b) *Relative Configuration* Although steroids are in reality not planar molecules, they are represented on paper as planar projection, as illustrated in figures in this book. One has to keep in mind that hydrogen atoms or substituents bound to skeleton point either above the plane (in that case, the bond is drawn as a solid or preferably a wedged line) or below the plane (a broken or preferably a dashed line). The solid line bond is termed a "β-bond", the broken line an "α-bond". If the configuration at a certain point is not known, the bond is drawn as a wavy line and expressed by a Greek letter ξ ("xi").

For all single-bonded substituents at *secondary* carbon atoms in the ring structure, it is necessary to indicate the α- or β-configuration. It is often helpful, but is not obligatory, to include the stereochemical indicators for substituents at the tertiary sites (C-8, 9, 14, and 17), even when these correspond to the natural configuration, which is normally understood (e.g., 9α-fluoro- or 17α-hydroxy- in "17-hydroxyprogesterone").

These rules have been modified several times, however, not all users follow the most recent recommendations, and thus, one has to understand that formulae and names may be slightly different even in recent papers. For example, 3α-hydroxy-5α-pregnan-20-one (Fig. 1.4a), a steroid modulator of γ-aminobutyric acid in neurones, is only exceptionally not called "allopregnanolone". Equally, as another hormone – 3β-hydroxyandrost-5-en-17-one (Fig. 1.4b) – is most often named "dehydroepiandrosterone" (DHEA).

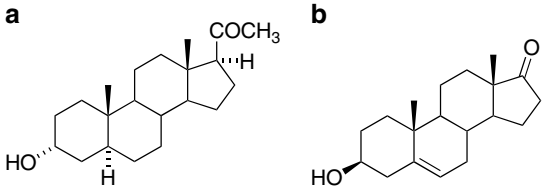

Fig. 1.4 (**a**) 3α-Hydroxy-5α-pregnan-20-one and (**b**) 3β-hydroxyandrost-5-en-17-one

Any steroid compound contains at least six chiral centers, which should theoretically lead to many configurational isomers. In reality, however, the situation is much simpler: configuration at several centers (8β, 9α, 10β, 13β) is constant in all natural

products and synthetic products based on them. The C14-configuration is α in most steroids; only a group of cardiac-active glycosides have the 14β configuration. Although a CIBA conference in 1950 defined the 5β configuration as "natural" (and their 5α – enantiomer as unnatural – allo, i.e. reversed), at the moment, the proportion of 5α and 5β steroids is almost equal. Thus a half of known steroids have the so-called all *trans* configuration: A and B rings are *trans* to each other (i.e., C10–C19 bond is *trans* to C5–H5); equally, B and C, and C and D rings are *trans*. The other half differ in the *cis* arrangment of A and B rings (see solid lines radiating from carbons 5 and 10). Therefore, C5 should be expressed always (with a solid or broken line connecting the hydrogen atom); some authors may forget this detail, which bears a great uncertainty on the whole conformation of the compound (see axial and equatorial bonds, page 8) because both isomers (see e.g. 5α-pregnane and 5β-pregnane in Fig. 1.5) greatly differ both in their chemistry and biological activity. The C5-configuration is not expressed if a compound contains a 4(5) or 5(6) double bond.

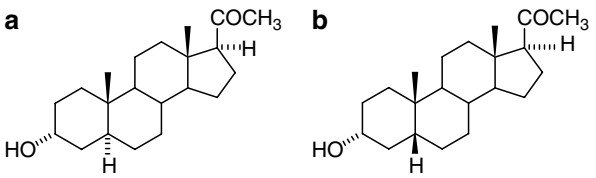

Fig. 1.5 (**a**) 3α-Hydroxy-5α-pregnan-20-one and (**b**) 3α-hydroxyandrost-5β-pregnan-20-one

When there is no ambiguity (i.e., if the C–H bonds are 8β, 9α, and 14α), hydrogen atoms at the bridgehead C8, C9, and C14 are omitted. Exceptionally, if in any of these cases, the configuration is different (unnatural), it must be shown in the name and formula.

Configuration of substituents at the side chain used to be based on a Fisher projection. Fieser and Fieser (1959) proposed an extension of the α/β system, based on the Fischer projection of the side chain, which has been widely used over many years, especially for the naming of such compounds as 'pregnanediol' (5β-pregnane-3α, 20α-diol, according to Fieser and Fieser). It is essential to this system that carbon with the highest number (i.e., the methyl group in Fig. 1.6) is placed on the top and groups projected to left and right are nearer the observer than groups projected in top and bottom positions. In such a conformation, 20α configuration has the substituent on the right side (Y = OH, X = H), 20β configuration is reversed (X = OH, Y = H).

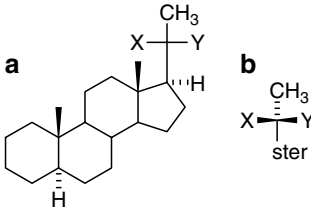

Fig. 1.6 (**a**) Fischer projection of 20 substituted 5α-pregnane derivatives; (**b**) a simplified scheme

The same applies to other positions of the cholestane side chain: always, the same trick is used: any molecule is reduced to a scheme like Fig. 1.7a in which a single carbon is considered and rest of the molecule – however complex – shrinks to four substituents: e.g., brassinolide – a plant growth hormone (Fig. 1.7b) has a complex structure of the steroid core, still, when C24 configuration is considered, its C24 configuration is expressed in the same simple manner: the single carbon 24 is arranged as in Fig. 1.7b: the highest number – C25 carbon – is put on top and below the plane of the paper; the 24-methyl group then appears at the right side and thus deserves the α configuration.

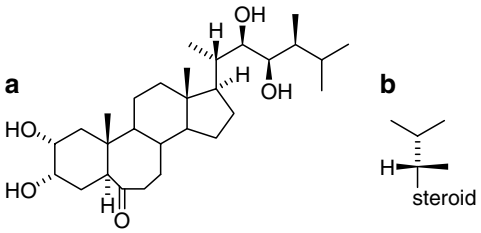

Fig. 1.7 (**a**) Brassinolide, a 24α-methyl steriol and (**b**) schematic view at carbon 24

More recently, International Union of Pure and Applied Chemistry (IUPAC) formulated a recommendation to conform to a wider use of the *R*/*S* system for designating the stereochemistry of the side chain. The procedure of assigning *R* or *S* configuration consists of two steps using the *sequence* and *conversion* rules.

According to the former one, "groups about an asymmetric atom shall be arranged in the order of decreasing atomic number of the atoms by which they are bound to it." This quotation of the IUPAC recommendation is simple e.g., for fluoro-bromo-chloro-methane (Br > Cl > F) or in isotopic derivatives (tritium > deuterium > protium) where priority is easily assigned. It is not so transparent if two or more atoms, attached directly at the chiral centre, are identical (e.g., carbon). Then continuation of the sequence rule should be applied. It reads, "if the relative priority of two groups cannot be thus decided, it shall be determined by a similar comparison of atom numbers of the next atoms in the groups, or, if this fails, of the next" (Cahn et al., 1966; Prelog V and Helmchen G, 1982).

In our former example of 20-hydroxy derivatives (Fig. 1.6) we easily assign the hydroxyl the highest priority (atomic number of oxygen and carbon is 16 and 12, respectively). The H-20 hydrogen atom (the atom number is 1) has the least priority. Two other substituents (carbons C-17 and C-21) compete and the race is decided at the second stage only: C-17 is bound to two other carbons, while C-21 to hydrogens only: C-17 has the second highest priority, C-21 is the third. If the priority were not decided by the second atom in each chain, the search would continue to the third atom in each chain until a deciding difference would be found.

Another rule should be mentioned here: Multiple bonds are treated as duplicated or triplicated single bonds: thus the carbon–carbon double bond counts as if each of the carbon atoms is attached to two other carbon atoms; similarly, the carbon–oxygen double bond is counted as if the carbon atom is bound to two oxygen

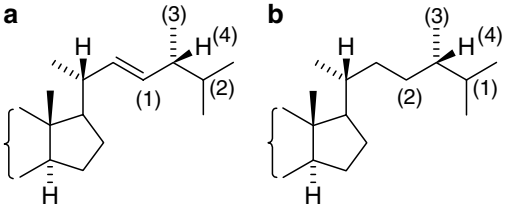

Fig. 1.8a The sequence rule in (**a**) ergosterol and (**b**) dihydroergosterol

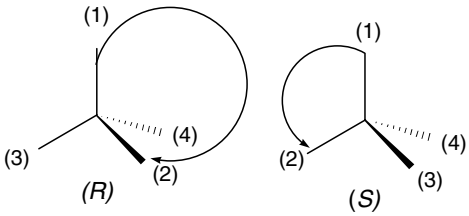

Fig. 1.8b The conversion rule

atoms. Thus, C-24 carbon is treated differently in ergosterol and dihydroergosterol (see Fig. 1.8a).

Having assigned priority to individual substituents at each centre, we turn to the *conversion* rule, which instructs us to view the substituents around the asymmetric atom in question (i.e., C-20 in this case) from an external point on the site remote from the substituent of least priority (usually a hydrogen atom): if then passing from the highest priority substituent to other two substituents according to decreasing priority has the clockwise sense, the configuration is defined to be *R* (from the Latin "*rectus*" meaning "right"). The reverse sense of order is defined as *S* (from the Latin "sinister", i.e., "left") (see Fig. 1.8b).

Motorists might prefer another model: the bond between the carbon considered and the least preferred substituent (usually hydrogen) can be visualized as a shaft holding a steering wheel which carries the remaining substituents; if one turns the wheel from the most preferred substituent to the less preferred one, and the sense is a clockwise one, the configuration is *R*.

The above operations must be carried out for each chiral centre in the molecule, except where the absolute configuration of the fundamental skeleton is implicit in the name, as it is for the skeletal structures of natural steroids. In this case it is necessary to designate *R* or *S* configurations only in side chains, or at any chiral centres not of fixed configuration defined by the class of compound. Thus if a polysubstituted side chain name is based on ergostane (e.g., epibrassinolide, Fig. 1.9), one need not express the C-24 configuration; if it is based on cholestane, the C-24 configuration has to be given.

While for the Fischer projection we had to abstract the particular segment of a molecule and put the highest carbon on top, there is no need to observe strict formalism in the *R*, *S* system: the sequence rule (the assignment of priority to substituents) can be done in any form of structure description, the conversion

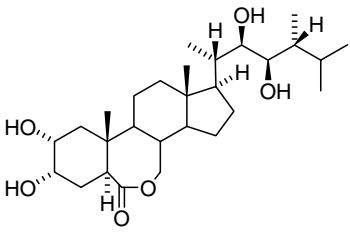

Fig. 1.9 (22*R*,23*R*,24*R*)-2α,3α,22,23-Tetrahydroxy-7-homo-24-methyl-5α-cholestabicarvi- 5,7-lcatone, or (22*R*,23*R*)-2α,3α,22,23-tetrahydroxy-7-homo-5α-ergostabicarbo-5,7-lactone (epibrassinolide)

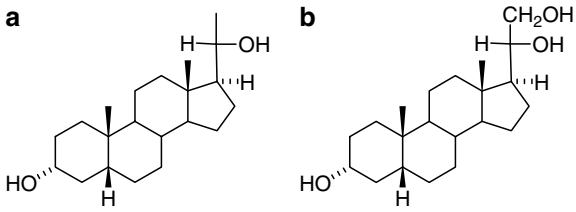

Fig. 1.10 (**a**) (20S)-5β-pregnane-3α,20-diol ('pregnanediol') and (**b**) (20*R*)-5β-pregnane-3α, 20,21-triol

rule (viewing of the space arrangement) can easily be applied anywhere without other requirements.

Although the *R*, *S* system is the most universal system capable of solving general problems with less simple skeletons, the Fischer system may seem favorable in some particular aspects. For instance, if configuration of a center remains constant throughout a reaction sequence, the Fischer-based configuration stays the same while the *R*, *S* description may change with changes of the vicinity of given carbon center. Thus, Fischer's 20β-alcohol (Fig. 1.10) keeps its unchanged configuration and configuration assignment through the hypothetical oxidation of compound (a) to compound (b), but its *R*/*S* assignment is changed.

Analogously, the brassinolide side chain of Fig. 1.11a is derived of campesterol, i.e., of 24α-methylcholest-5-en-3β-ol (Fig. 1.11b): the Fischer projection shows the same assignment in both cases, the *R*, *S* system does not (24*S* for brassinolide, 24*R* for campesterol) in spite of the fact that C-24 configuration in both cases is the same.

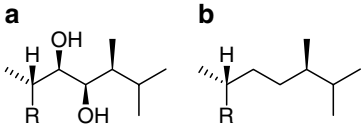

Fig. 1.11 (**a**) Brassinolide side chain and (**b**) campesterol side chain

1.1.3 Conformation: the Three-Dimensional Shapes of Steroids

The steroid ring system is represented in the formulae given in preceding figures as a planar projection but has, in reality, a 3D shape. Each saturated six-membered ring normally adopts a puckered shape like single-ring compound – cyclohexane.

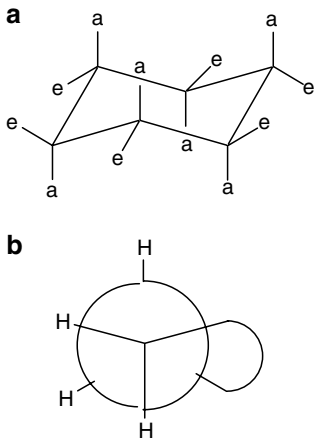

Fig. 1.12 (**a**) Chair conformation of cyclohexane; (**b**) Newman projection

The 'chair' form (Fig. 1.12a) is the most stable (minimum energy) conformation. It allows all the C–C–C bond angles to lie close to the tetrahedral value (~109.5°), and at the same time provides maximum separation of the bonds, which radiate from each linked pair of carbon atoms. This so–called 'staggered' or 'gauche' conformation, which minimizes torsional strains, is best seen from a 'Newman' projection of ethane (Fig. l.12b), in which the molecule is viewed along a C–C bond. The bonds at the front and rear carbon atoms in the diagram appear to make 60° angles with each other. Each ring is actually slightly flattened, so that torsion angles are close to, but not exactly, 60°.

Bonds to the cyclohexane ring fall into two groups, according to their geometric relationship to the ring structure. Those which lie close to the average plane of the ring are termed 'equatorial' bonds ('e' in Fig. 1.12a), and those, which are perpendicular to the average plane, are termed 'axial' bonds ('a' in Fig. 1.12a). The axial/equatorial distinction has considerable importance for chemical (i.e., reactivity) and physical properties (e.g., chromatographic behavior, spectroscopic characteristics) of steroids.

Whilst each six-membered ring approximates in shape to the chair conformation of cyclohexane, the five-membered ring D cannot form a complete chair. Like its monocyclic analogue – cyclopentane, it adopts a non-planar conformation which is often of 'half-chair' or 'envelope' type, adapting its shape in each individual steroid to minimize the strains associated with its mode of linkage to ring C and with any substituents present (Duax and Norton, 1975; Griffin et al., 1984).

The axial/equatorial classification of bonds is straightforward in 5α-steroids (Fig. 1.13a), where all the rings are similarly oriented. In the 5β-series, however, the A/B-*cis* junction causes a sharp bend in the ring structure, with ring A and the other three rings forming a roughly L-shaped whole (Fig. 1.13b). The difference between 5α- and 5β-steroids has a significant effect on their chromatographic mobilities and on their spectroscopic and chemical properties. One immediate consequence, apparent from an inspection of Fig. 1.13a and b, is that the respective axial or equatorial characters of the α- and β-bonds around ring A are reversed by the change of

configuration at C-5. This is easily seen, for example, by looking at the 3α-bond, which is axial in 5α-steroids but equatorial in 5β-steroids. A similar reversal of conformation with respect to ring A is seen at each of the other locants in ring A.

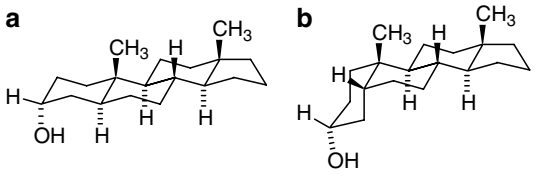

Fig. 1.13 (**a**) 5α-Androstan-3α-ol; (**b**) 5β-androstan-3α-ol

The bonds from five-membered ring D are not truly axial or equatorial: the terms quasi-axial and quasi-equatorial are commonly used to indicate their approximation to these conformations. Similar terminology applies in rings which contain unsaturation, and are partially flattened by the presence of a C=C double bond. Such rings are best described as 'half-chairs', with significant deviation from ideal chair geometry.

1.1.4 Functional Groups

Individual steroids of each skeletal class are characterized by the nature and locations of substituent groups, together with any unsaturation. These 'functional groups', as well as determining the overall shape of the molecule, determine its chemical and physical properties too, and contribute to its specific interactions with cell constituents, including hormone receptors and metabolizing enzyme systems.

Virtually all natural steroids have an oxygen function at C3, which may be in the form of a hydroxyl group in either 3α- or 3β-configuration or a phenolic (acidic) hydroxyl attached to an aromatic A ring in the estrogen series (Figs. 1.14 and 1.15). In certain natural products and in the main urinary metabolites of steroid hormones, the hydroxyl group may be masked by being in the form of a derivative (so called 'conjugates', see Section 1.1.3.1(e)); these derivatives are mostly of very polar nature; being more water-soluble, they are used as a means to rid the body of already spent steroids.

The other oxygen function commonly found at C-3 is a carbonyl (or 'oxo') group, where oxygen is double-bonded to carbon and the compound has the characteristics of a ketone (Fig. 1.15). All hormonally active steroids however, except estrogens, have the Δ^4-3-oxo group in the A-ring and catabolism of these active steroids involves inactivation by tetrahydro-reduction in the A-ring. 5α-Dihydrotestosterone formed in androgen-target cells is an exception to this, retaining potent activity even though the Δ^4 double bond is reduced. 5α-Dihydrotestosterone is even claimed to be the true androgen hormone (Degtyar et al., 2006).

Hydroxyl or carbonyl groups may, in principle, replace hydrogen at any of the skeletal sites where the requisite number of bonds is available. Examples of all possible

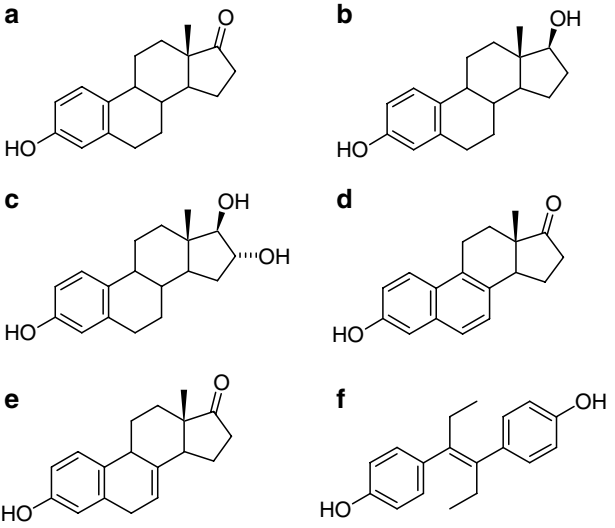

Fig. 1.14 (**a**) Estrone (3-hydroxyestra-1,3,5(10)-trien-17-one), (**b**) estradiol (estra-1,3,5(10)-trien-3,17β-diol), (**c**) estriol (estra-1,3,5(10)-trien-16α,17β-diol), (**d**) equilenin (3α-hydroxy-estra-1,3,5,7,9-pentaen-17-one), (**e**) equilin (3α-hydroxy-estra-1,3,5(10),7-tetraen-17-one), and (**f**) DES (diesthylstilbestrol)

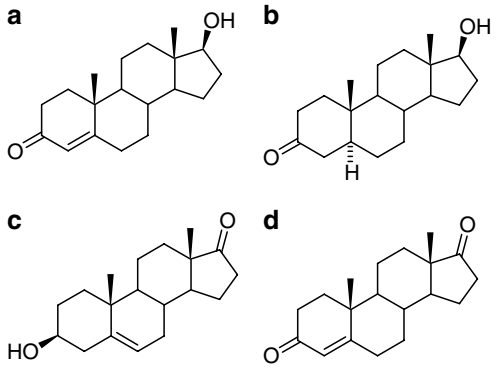

Fig. 1.15 (**a**) Testosterone (17β-hydroxyandrost-4-en-3-one), (**b**) dihydrostestosterone (17β-hydroxy-5α-androstan-3-one), (**c**) DHEA (dehydroepiandrosterone, 3β-hydroxyandrost-5-en-17-one), and (**d**) androstenedione (androst-4-en-3, 17-dione)

sites of hydroxylation, and of almost all possible sites for carbonyl groups, have been identified among the many steroids of natural origin. The most usual locants for substituents, other than C-3, include C-11, where the principal corticosteroids and their metabolites have either an 11-oxo or an 11β-hydroxy group, and C-17, where a 17-oxo group occurs in estrone and in various compounds of the androgen series, a 17β-hydroxy group in estradiol and testosterone, and a 17α-hydroxy group in some of the natural steroids of the pregnane type (e.g. the glucocorticoids, and 'pregnanetriol'). Whenever a single-bonded group like hydroxyl (OH) replaces one

of the hydrogen atoms at a methylene (CH_2) site of a steroid molecule, its configuration must be specified, as in the preceding examples.

The other most common sites for hydroxylation include C-21, in the corticosteroids, C-7 and C-12, in the principal bile acids, and C-1 and C-25, in the hormonally active metabolites of vitamin D (see Section 1.1.3.2).

Substitution of hydrogen atoms in the angular methyl groups (C-18 or C-19) is relatively frequent in metabolic processes. Even the conversion of testosterone into estradiol and estrone is launched by oxidation at the carbon C-19. The most important natural product of this type is aldosterone, where C-18 is oxidized to the level of an aldehyde (see Fig. 1.17f), although the aldehyde group is masked by hemiacetal formation (see Chapter 2, p. 62). Carboxyl groups are found mainly in the bile acids (Fig. 1.17), where the terminal C-24 position of cholane side chain is oxidized to a carboxyl group in the commonest series, the cholanic acids (cholic, deoxycholic, chenodeoxycholic, lithocholid and other). Carboxylic acids may also occur at other sites (e.g., C-18, C-19, C-21, C-26).

Unsaturation is the other most common feature found in steroids. Alkene-type double bonds (C=C) occur mainly at the 4,5- or 5,6-position. 7-Dehydrocholesterol and ergosterol, the provitamins D, are 5,7-dienes. Vitamins D_2 and D_3 themselves are conjugated trienes (see Section 1.1.3.2), whereas the estrogens (Fig. 1.14) have a fully unsaturated (aromatic) ring. In equilenin (Fig. 1.14d), both A and B rings are aromatic. Equilin (Fig. 1.14e), one of dihydro derivatives of equilenin, has become the most widely sought remedy against osteoporosis. The non-steroidal synthetic estrogen – diethylstilbestrol (Fig. 1.14f) also possesses aromatic rings, which appear to be essential feature for estrogenicity. Figures 1.4–1.7 illustrate some of the principal estrogen hormones and their metabolites. The system of nomenclature is discussed in Section 1.1.2.

The list of basic steroid structures should mention compounds which represent the source of material for large scale steroid production: nowadays, most steroids are produced by partial synthesis starting from diosgenin (Fig. 1.16a), which is degraded into dehydropregnenolone (3β-hydroxypregna-5,16-dien-20-one) and then converted into androstane and pregnane products. Sterols (e.g., sitosterol – Fig. 1.16c), present in industrial waste, can also be used as starting material for oxidation by *Mycobacterium* mutants into androst-1,4-diene-3,17-dione (ADD). Cholanic acids (e.g., Fig. 1.16e) were the starting material for the synthesis of 11-substituted pregnane compounds. Some other materials were also used but have been pushed out of business mainly due to low cost of diosgenin.

1.2 Steroid Nomenclature

In early days of steroid biochemistry, three major groups were involved in isolation and identification of naturally occurring steroids, allocating each new compound a letter of the alphabet in sequence as they were isolated. Inevitably steroids were not isolated in the same sequence and thus cortisol, the main glucocorticoid, was

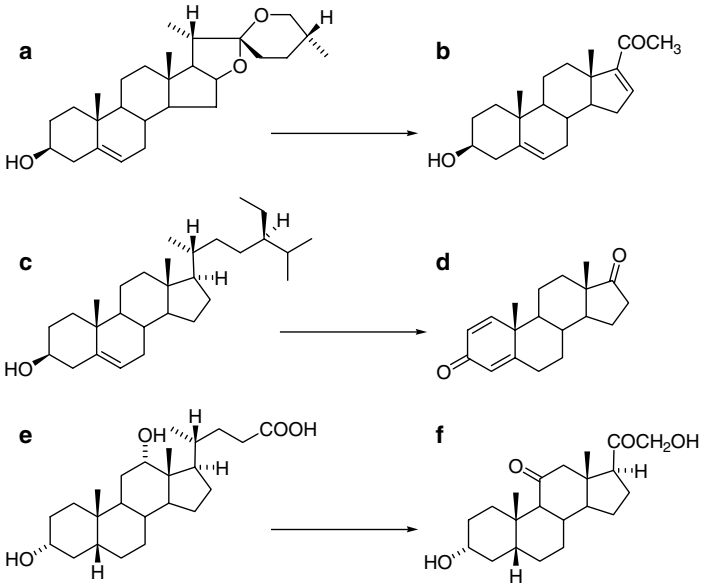

Fig. 1.16 (**a**) Diosgenin ((25*R*)-spirost-5-en-3β-ol), (**b**) dehydropregnenolone (3β-hydroxypregna-5,16,diene), (**c**) β-sitosterol (24*R*)-cholest-5-en-3β-ol, (**d**) ADD (androsta-1,4-diene-3,17-dione), (**e**) deoxycholic acid (3α-12α-dihydroxy-5β-cholanic acid), and (**f**) 3α-21-dihydroxy-5β-pregnane-11,20-dione

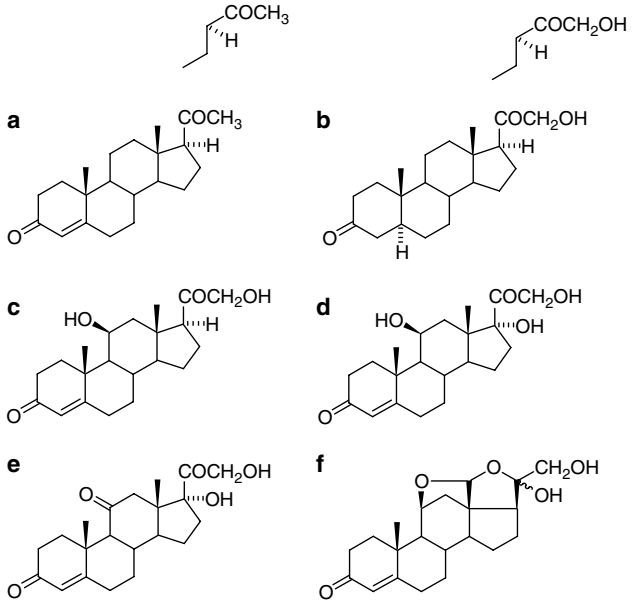

Fig. 1.17 (**a**) Progesterone (pregn-4-ene-3,20-dione), (**b**) deoxycorticosterone (21-hydroxy-pregn-4-ene-3,20-dione), (**c**) corticosterone, 11β,21-dihydroxypregn-4-ene-3,20-dione), (**d**) cortisol (11β,17,21-trihydroxypregn-4-ene-3,17-dione), (**e**) cortisone (17-hydroxypregn-4-ene-3,11,20-trione), and (**f**) aldosterone (11β,21-dihydroxypregn-4-ene-3,20-dione)

Kendall's compound F, Reichstein's compound M and Wintersteiner's compound F. This confusion is admirably resolved in a review by Reichstein and Shoppee (1943). Although these alphabetic designations have long since been formally replaced by IUPAC recommended names, elderly biochemists are still wont to use them as a convenient shorthand (e.g. THF is tetrahydrocortisol and THS is tetrahydro-11-deoxycortisol).

Many trivial names are still used more often than their orthodox equivalents; e.g., everybody speaks about progesterone but few name it as pregn-4-ene-3,20-dione (Fig. 1.17a). These names have faded out, though some other still linger on due to the increasing number of authors of medicinal and biological vocation who consult textbooks of their youth. Then 5α-androstane was called androstane, 5β-androstane was testane or etiocholane; 5α-pregnane was called allopregnane, 5β-pregnane was just pregnane; similarly, 5α-cholane was termed allocholane, and 5β-cholane cholane; cholestane meant 5α-cholestane, its 5β-isomer was called coprostane.

Table 1.1 gives trivial names that are still widely used for steroid hormones and for some of their principal precursors and metabolites. Some are contractions of the full UPAC/IUB-approved systematic names, while others derive from names of their source or biological activity. Many of the corticosteroids are also commonly

Table 1.1 Selected trivial names of some steroids

Aldosterone	11β,18-epoxy-18-hydroxypregn-4-ene-3, 20-dione (18,11-hemiacetal)
Androsterone	3α-Hydroxy-5α-androstan-17-one
Chenodeoxycholic acid	3α,7α-Dihydroxy-5β-cholan-24-oic acid
Cholesterol	Cholest-5-en-3β-ol
Cholic acid	3α,7α,12α-Trihydroxy-5β-cholan-24-oic acid
Corticosterone (Kendall's B[a], Reichstein's H)	11β,21-Dihydroxypregn-4-ene-3,20-dione
Cortisol[b] (hydrocortisone, Kendall's F[a])	11β,17,21-Trihydroxypregn-4-ene-3,20-dione
Cortisone (Kendall's E[a], Reichstein's F[a])	17,21-Dihydroxypregn-4-ene-3,11,20-trione
Dehydrocorticosterone (Kendall's A)	21-Hydroxypregn-4-ene-3,11,20-trione
Dehydroepiandrosterone (DHEA)	3β-Hydroxyandrost-5-en-17-one
Deoxycholic acid	3α,12α-Dihydroxy-5β-cholan-24-oic acid
Deoxycorticosterone (DOC, Reichstein's Q)	21-Hydroxypregn-4-ene-3,20-dione
Deoxycortisol (Reichstein's S)	17,21-Dihydroxypregn-4-ene-3,20-dione
Estradiol-17α[b]	Estra-l,3,5(10)-triene-3,17α-diol
Estradiol-17β[b]	Estra-l,3,5(10)-triene-3,17β-diol
Estriol[b]	Estra-1,3,5(10)-triene-3,16α,17β-triol
Lithocholic acid	3α-Hydroxy-5β-cholan-24-oic acid
Pregnenolone	3β-Hydroxypregn-5-en-20-one
Progesterone	Pregn-4-ene-3,20-dione
Testosterone	17β-Hydroxyandrost-4-en-3-one
Ursodeoxycholic acid	3α,7β-Dihydroxy-5β-cholan-24-oic acid

[a] Designation according to Kendall.

[b] Cortisol is identical with Reichstein's compound *M* and Wintersteiner's compound *F*.

designated by single letters of the alphabet, which originated from the order in which they were isolated from adrenal extracts by Kendall, Reichstein, or Wintersteiner (Fieser and Fieser, 1959). The trivial names of steroids, and the alphabetic designations of corticosteroids, are almost universally employed by those working in medical areas. International non-proprietary names (INNs) are available for many synthetic steroids in pharmaceutical use (Hill et al., 1991).

The nomenclature rules were put into detailed and definitive form in the early 1970s and were revised in 1989 (Moss, 1989). Steroids illustrated in this book are generally given both their full systematic names and their approved trivial names or INNs and common synonyms. The rules for steroid nomenclature follow quite closely those for other organic compounds, with special features to accommodate the stereochemical aspects and wide variety of structural and substitution types which come under the broad classification of steroids. We are concerned here only with those relatively straightforward rules that are sufficient for naming the steroids of biomedical importance that occur in the present text. The reader interested in more specialized aspects of nomenclature is referred to the full (40-page) statement of the rules (Moss, 1989; http://www.chem.qmul.ac.uk/iupac/steroids).

1.2.1 Procedure for Naming a Steroid

The system for naming a steroid is outlined in the following paragraphs. The reader should take note of punctuation, including hyphenation, of names that are given here as examples, and those which appear on later pages.

(a) *Hydrocarbon Class* Select the appropriate hydrocarbon skeleton (see Fig. 1.2). Note that the name of each saturated hydrocarbon follows the rule for simple hydrocarbons (methane, ethane, etc.) in having the ending '-ane'. If the steroid is saturated at C-5, prefix the skeletal name with C-5 configuration (e.g., 5β-pregnan-20-one). If there is an unnatural or uncommon configuration at any other ring junction position, indicate it (e.g., 5β, 14β, 17α-pregnan-20-one) (Fig. 1.18).

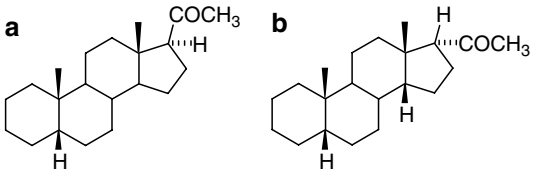

Fig. 1.18 (**a**) 5β-Pregnan-20-one and (**b**) 5β,14β,17α-pregnan-20-one

(b) *Unsaturation* Any unsaturation is indicated by replacing the terminal 'ane' by 'ene', 'diene', 'triene', 'yne', etc., according to the number of double (or triple) bonds present, preceded by locants. Unsaturation between consecutively-numbered carbon atoms (e.g. 5,6) is indicated by the lower locant (see cholest-5-ene

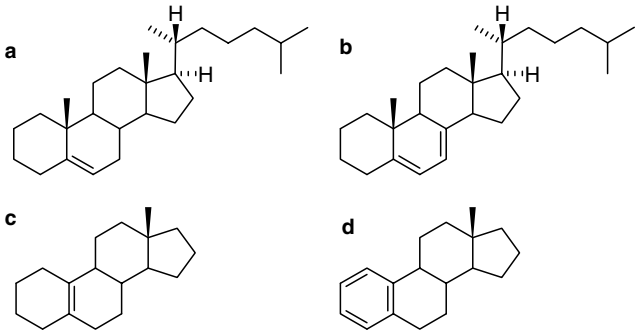

Fig. 1.19 (**a**) Cholest-5-ene, (**b**) cholesta-5, 7-diene; estr-5(10)-one, (**c**) estr-5(10)-ene, and (**d**) estra-1,3,5(10)-triene

and cholesta-5,7-diene; Fig. 1.19). Note, in the latter example, that 'a' (e.g., cholesta-5,7-diene) is added to the stem of the name when a consonant follows, to aid pronunciation. Non-consecutive locants, as, for example, a double bond between C-5 and C-10, both must be indicated, with the higher number in parentheses (e.g. estr-5(10)-ene). The aromatic ring A of estrogens is expressed as in 'estra-l,3,5(10)-triene' (Fig. 1.19). These locants for unsaturation are chosen in preference to those of the alternative Kekule form: 1(10),2,4.

However, when there is a possibility of using all single rather than compound locants, the former are preferred, as in estra-l,3,5,7,9-pentaenes (see equilenin, Fig. 1.14). The use of expressions like Δ^5 to denote unsaturation is no longer approved, except in generic terms (e.g., 'Δ^5 steroids').

The preceding two steps define full hydrocarbon skeleton of steroid. Further, it is necessary to designate all substituents, as described in the following paragraphs.

(c) *Substituent Atoms or Groups* Substituent groups are indicated either in suffix or in prefix form, as in general organic nomenclature. If more than one of the common types of substituent group is present it is necessary to select the one of highest priority, from those listed in Table 1.2, to comprise the suffix. Thus, for example, an oxo group has higher priority than a hydroxy group and so on: testosterone is named as 17β-hydroxyandrost-4-en-3-one and not 3-oxoandrost-4-en-17β-ol.

The selected suffix, in multiple form (di-, tri-, etc.) if necessary, and with locants, follows the skeletal hydrocarbon name, with omission of the final 'e' of the hydrocarbon if a vowel follows. Examples include 17β-hydroxyandrosta-4, 6-dien-3-one and androsta-1,4-diene-3,17-dione (Fig. 1.20), and pregn-4-ene-3, 20-dione (Fig. 1.17).

Any remaining substituents are indicated as prefixes, in alphabetical order, multipliers (di-, tri-, etc.) are ignored in this alphabetical ordering (thus, 2β,3α-diamino-9α-fluoro-5α-androstan-17-one is correct and 9α-fluoro-2β,3α-diamino-5α-androstan-17-one not). Locants precede the substituent names to which they

Table 1.2 Substituents in order of priority for selection of suffix

Group	Suffix form	Prefix form
Carboxylic acid	-oic acid[a]	—
Lactone	-lactone[b]	—
Ester or salt (of carboxylic acid)	-oate[c]	—
Aldehyde	-al	oxo-
Ketone	-one	oxo-
Hydroxyl	-ol	hydroxy-
Amino	-amine	amino-

[a]The alternative suffix '-carboxylic acid' is used if the acid group represents a carbon atom additional to those of the parent hydrocarbon skeleton.
[b]The lactone locants are preceded by 'o', replacing the terminal 'e' of the hydrocarbon, e.g. cholano-24,17-lactone; the alternative suffix '-carbolactone' is used if the lactone carbonyl group represents an added carbon atom.
[c]The alkyl group or cation precedes the main part of the name, e.g. methyl 5α-cholan-24-oate, or sodium 5α-cholan-24-oate.

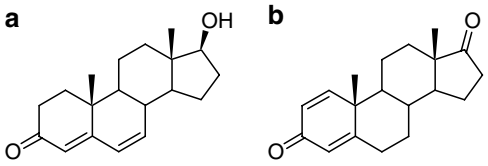

Fig. 1.20 (**a**) 17β-Hydroxyandrosta-4-,6-dien-3-one and (**b**) androsta-1,4-diene-3,17-dione

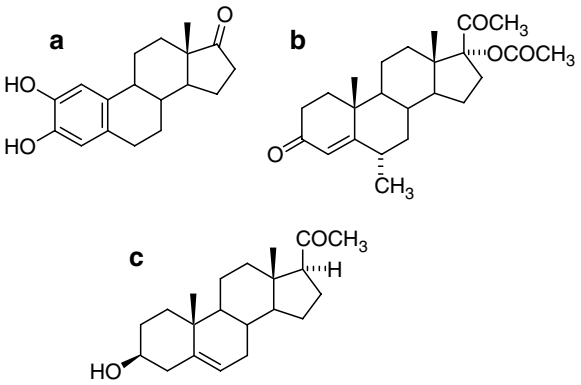

Fig. 1.21 (**a**) 2,3-Dihydroxyestra-1,3,5(10)-trien-17-one (2-hydroxyestrone), (**b**) 6α-methyl-3,20-dioxopregn-4-en-17β-yl acetate ('medroxyprogesterone acetate'), and (**c**) 3β-hydroxypregn-5-en-20--one ('pregnenolone')

refer. Composite suffixes (e.g. 'olone', as in 'pregnenolone'), are not permitted by IUPAC/IUB rules, although they are likely to remain in everyday use because of their convenience in trivial names like the one cited. Figures 1.4–1.7 contain several examples that illustrate use of prefixes. Others are given in Fig. 1.21.

(d) *Esters, Ethers, and Other Derivatives of Alcohols* In most recent recommendations, esters are named by replacing the terminal 'e' of the hydrocarbon name, or 'ol' of the alcohol name, by 'yl', to generate the radical name (compare 'ethane', which becomes 'ethyl'); 'yl' is preceded by its locant and any

multipliers, in the usual way. The acyloxy group is then indicated in anionic form, leading to names like cholest-5-en-3β-yl acetate ('cholesteryl acetate'; compare 'ethyl acetate').

Since esters take precedence over oxo (aldehyde or ketone) groups, systematic names of common steroidal esters do not necessarily derive directly from those of their parent alcohols. Thus medroxyprogesterone is 17β-hydroxy-6α-methylpregn-4-ene-3,20-dione, while its acetate is 6α-methyl-3,20-dioxopregn-4-en-17β-yl acetate (Fig. 1.21). Analogously, testosterone acetate is 3-oxoandrost-4-en-17β-yl acetate, the older form – 17β-acetoxyandrost-4-en-3-one – is no longer recommended.

For esters of diols and triols, names of the forms 'androst-5-ene-3α,17β-diyl diacetate' and '3α-hydroxyandrost-5-en-17β-yl acetate' are likely to be encountered. Where a steroid has an accepted trivial name, which implies the locants of any hydroxyl groups present, it is permissible and often convenient to use prefixes of the form '*O*-acyl' (e.g. '3-*O*-acetylcholic acid', Fig. 1.22).

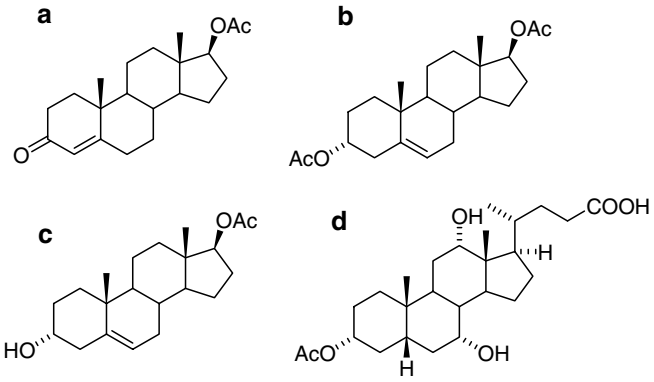

Fig. 1.22 (**a**) 3-Oxoandrost-4-en-17β-yl acetate (17β-acetoxyandrost-4-en-3-one; 'testosterone acetate'), (**b**) androst-5-ene-3α,17β-diyl acetate (3α,17β-diacetoxyandrost-5-ene), (**c**) 3α-hydroxyandrost-5-en-17β-yl acetate (androst-5-ene-3α,17β-diol 17-acetate), and (**d**) 3α-Acetoxy-7α,12α-dihydroxy-5β-cholan-24-oic acid (3-*O*-acetylcholic acid)

Steroid sulphates are named similarly. Thus sulphate of 3β-hydroxyandrost-5-en-17-one ('dehydroepiandrosterone'; DHEA) is 17-oxoandrost-5-en-3β-yl sulphate (more correctly, 'hydrogen sulphate' for the acidic form). Strictly, such names refer to the anion; the cation may be specified if appropriate (e.g. sodium 17-oxoandrost-5-en-3β-yl sulphate, sodium DHEA sulphate, DHEAS) (Fig. 1.23).

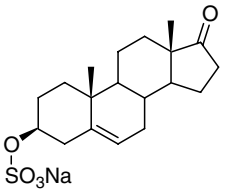

Fig. 1.23 Sodium 17-oxoandrost-5-en-3β-yl sulphate (sodium DHEA sulphate)

Ethers of hydroxy derivatives are indicated in prefix form (e.g., 3β-methoxy-, or 21-trimethylsilyloxy-). The nomenclature rules do not specifically cover the important urinary metabolites known as 'glucuronides', or similar sugar derivatives. The term 'glucuronide' is widely used and understood as an abbreviation for glucosiduronic acids, or even the fuller version glucopyranosiduronic acids, and their salts, the glucosiduronates (glucopyranosiduronates) (Fig. 1.24). Unless otherwise specified, these names refer to the β-D-isomers (Fig. 1.17), derived by linkage of a steroid alcohol to the hemiacetal carbon atom of D-glucuronic acid.

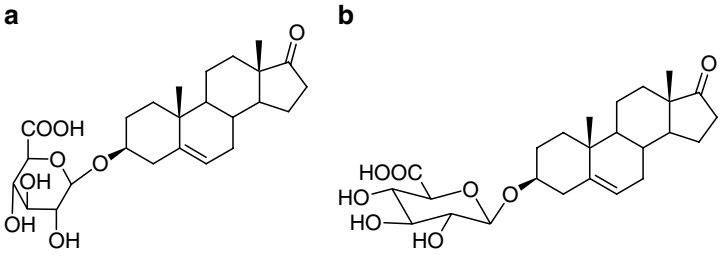

Fig. 1.24 A glucuronide, with the sugar moiety shown in (**a**) conventional and (**b**) conformational form

(e) *Derivatives of Carboxylic Acids* Esters and salts are generally named by use of suffixes (Table 1.2), as are amides (e.g., cholan-24-amide). The important conjugates of bile acids with glycine and taurine ($RCONHCH_2CO_2H$ and $RCONH(CH_2)_2SO_3H$, respectively, where R is the steroid residue) are not covered by the nomenclature rules: they are commonly indicated by the prefixes 'glyco' and 'tauro', respectively (e.g., glycocholic acid), or alternatively named as, for example, *N*-cholylglycine and *N*-cholyltaurine.

(f) *Geometric Isomerism* Unsaturation in the intact ring system needs no geometric indication, being fixed by ring geometry. In the side chain, the older terms *cis* and *trans* as descriptors of configurations about double bonds are now replaced by the more precise sequence rule terms (*Z*) and (*E*), respectively.

The four bonds that radiate from the two ends of a C=C double bond are coplanar. Since rotation about the double bond is prevented by π-bonding, the possibility of isomerism arises. In simple cases of 1,2-disubstituted alkene-type bonds, substituents may be *cis* or *trans* related. However, these terms are not applicable when three or four substituents are present on the unsaturated centers.

The following system is now preferred for use in all cases. The sequence rules, as summarized above (see Section 1.2b), are applied in turn to the pair of atoms or groups at each end of double bond. If atoms or groups of higher priority at each unsaturated atom lie on the same side of double bond, the configuration is *Z* (German: *zusammen*, together). If higher-priority atoms or groups are on opposite sides the configuration is *E* (German: *entgegen*, opposite). In 1,2-disubstituted

C=C bonds, *Z* corresponds to *cis*, and *E* corresponds to *trans* (Fig. 1.25) (Figures A.4 and A.5). Similar principles are used in defining the configurations about C=N bonds in oximes and related compounds.

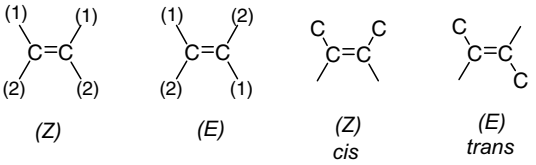

Fig. 1.25 *Z* and *E* configurations

The rules as summarized above should enable the reader to understand the assignments of configuration that occur in Table 1.3 and elsewhere in this chapter. Note that systematic nomenclature places *R*/*S* and *E*/*Z* descriptors, with locants if necessary, in parentheses at the beginning of the name of a compound.

Ergosterol (Fig. 1.26), for example, has the (22*E*)-configuration. The sequence rule is recommended also for describing the configuration around double bonds in vitamin D series (Section 1.1.3.2).

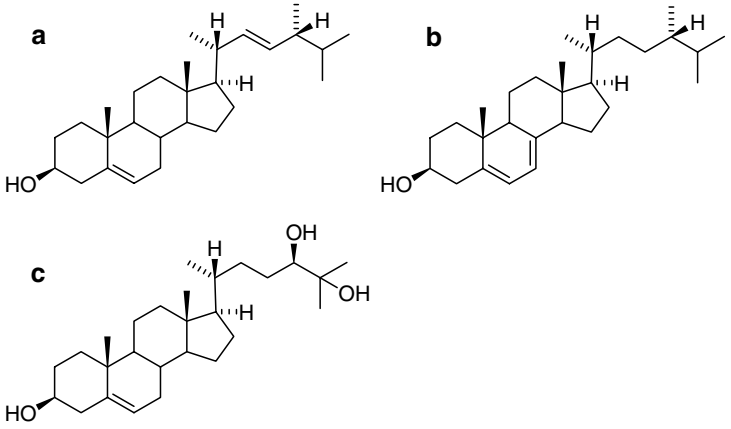

Fig. 1.26 (**a**) (22*E*)-Ergost-5,7,22-trien-3β-ol (ergosterol), (24*R*), (**b**) ergosta-5,7-dien-3β-ol (22,23-dihydroergosterol) (24*S*), and (**c**) (24*R*)-cholest-5-ene-3β,24,25-triol ((24*R*)-24,25-dihydroxycholesterol)

(g) *Skeletal Modifications* Absence of a carbon atom from one of the fundamental hydrocarbon structures is indicated by the prefix nor-, preceded by the locant of the missing carbon atom. The use is illustrated by 19-norpregnane (Fig. 1.27). Several of the synthetic ovulation inhibitors are strictly 19-nor-17α-pregnane derivatives: the simplest is 'norethisterone' (17β-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one; Fig. 1.27). 'Ethynylestradiol' (Fig. 1.27) is named systematically as 19-nor-17α-pregna-l, 3,5(10)-trien-17-yne-3,17-diol (17β- can be stated for clarity if desired). Note that 'estrane' is used in preference to '19-norandrostane',

although the trivial name '19-nor-testosterone' is commonly used for the anabolic steroid 17β-hydroxyestr-4-en-3-one.

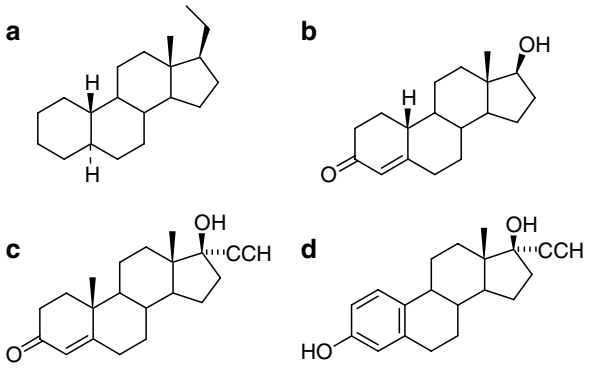

Fig. 1.27 (**a**) 19-Nor-5α-pregnane, (**b**) 17β-hydroxyestr-4-en-3-one (19-nortestosterone), (**c**) 17β-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one (17α-ethynyl-17β-hydroxyester-4-en-3-one, 19-norethisterone), and (**d**) 19-nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17β-diol (17α-ethynylestra-1,3,5(10)-triene-3,17β-diol; ethynylestradiol)

Other uses for the nor- prefix occur if a ring is contracted (e.g. 4-nor-5α-androstane, or 7-norcholesterol, see Fig. 1.28). Formerly, these compounds were termed A-nor-5α-androstane and B-norcholesterol, respectively, which is not recommended any more. Missing carbons in the side chain are also termed in this way (e.g., in 24-nor-5β-cholan-23-oic acid or 23,24-dinor-5β-cholan-22-oic acid, Fig. 1.28).

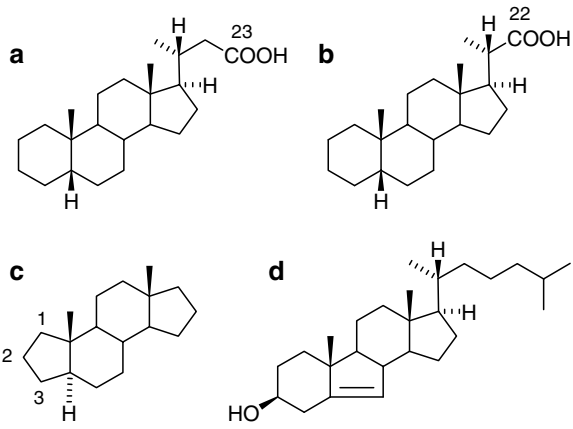

Fig. 1.28 (**a**) 24-Nor-5β-cholan-23-oic acid, (**b**) 23,24-dinor-5β-cholan-22-oic acid, (**c**) 4-Nor-5α-androstane (A-nor-5α-androstane), and (**d**) 7-norcholest-5-en-3β-ol

The prefix homo- similarly indicates added carbon atoms. Until recently an enlarged ring has been indicated as, for example, 'D-homoandrostane', but it is now recommended that the extra carbon be specified instead by its locant (Fischer et al. 2003).

This results in names of the form '17a-homo-5α-androstane' (Fig. 1.29). Scission of a ring is signified by the prefix seco-, with the locants of two carbon

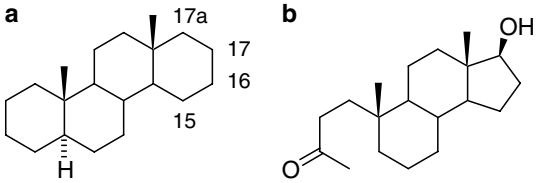

Fig. 1.29 (**a**) 17a-Homo-5α-androstane (D-homo-5α-androstane) and (**b**) 17β-hydroxyl-4(5) secoandrostan-3-one (4,5)-secodihydrotestosterone

atoms where the break occurs (Hu Y and Covey DF, 1993). The best known examples are the compounds of the vitamin D3 series (Fig. 1.30), which are derivatives of 9,10-secocholesta-5, 7,10(19)-triene, or the corresponding 9,10-secoergostanes.

1.2.2 Nomenclature of the Vitamin D Series

On UV irradiation of 5,7-unsaturated steroids, corresponding photoisomers are formed. History of D vitamins knows lumisterols, tachysterols, precalciferols and eventually calciferols (IUPAC-IUB, 1982). 7-Dehydrocholesterol eventually yields cholecalciferol or calciol, its systematic name being (5*Z*,7*E*)-(3*S*)-9,10-secocholesta-5,7,10(19)-trien-3-ol, Fig. 1.30b, $R^1 = R^2 = R^3 = H$. Since the B ring is split and the A ring is rotated, the substitutents which used to be above the plane are below and use of Greek letters is ambiguous. Therefore, the (*R*/*S*) system is also used for designating configurations of substituents in ring A. Other photoisomers are not given in this brief summary, they differ in the position and configuration of the double bonds between rings A and C (see Fig. 1.7).

Skeletal aspects of vitamin D nomenclature are discussed above. Table 1.3 gives trivial and systematic names for some of the more important compounds, by way of illustration. Additional hydroxyl groups may be indicated by prefixing the recommended trivial names, e.g. (1*S*)-l-hydroxycalciol.

Table 1.3 Nomenclature in the vitamin D series

Current trivial name[a]	Recommended trivial name[a]	Systematic name[a]
Cholecalciferol (vitamin D3)	Calciol or cholecalciferol	(5*Z*,7*E*)-(3*S*)-9,10-secocholesta-5,7,10(19)-trien-3-ol, Fig. 1.30b, $R^3 = H$
25-Hydroxycholecalciferol	Calcidiol	(5*Z*,7*E*)-(3*S*)-9,10-secocholesta-5,7,10(19)-triene-3,25-diol, Fig. 1.30b, $R^1 = OH$, $R^2 = R^3 = H$
lα,25-Dihydroxycholecalciferol	Calcitriol	(5*Z*,7*E*)-(l*S*,3*R*)-9,10-secocholesta-5,7,10(19)-triene-l,3,25-triol, Fig. 1.30b, $R^1 = R^2 = OH$, $R^3 = H$
(24*R*)-1α,24,25-Trihydroxycholecalciferol	Calcitetrol	(5*Z*,7*E*)-(l*S*,3*R*,24*R*)-9,10-secocholesta-5,7,10(19)-triene-l,3,24,25-tetrol, Fig. 1.30b, $R^1 = R^2 = R^3 = OH$

[a]Corresponding names in the ergosterol series are ergocalciferol (vitamin D2), ergocalciol, ergocalcidiol, etc., with systematic names based upon (22*E*)-9,10-secoergosta-5,7,10(19),22-tetraene.

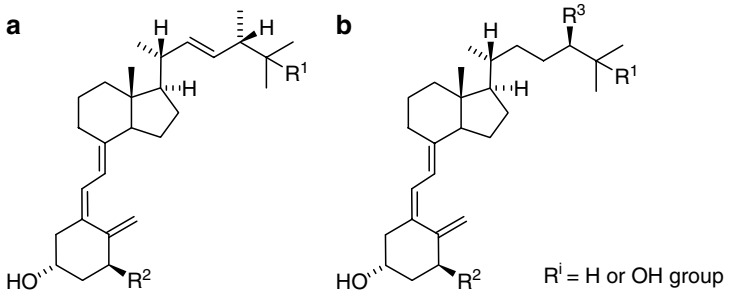

Fig. 1.30 (**a**) Ergocalciferol (D2 vitamin) and its hydroxyl and dihydroxy derivatives and (**b**) cholecalciferol (D3 vitamin) and its hydroxy, di- and trihydroxy derivatives

1.2.3 Nomenclature of Steroids Derived of a Heteroatom-Containing Skeleton

Although even other compounds can be classified as derivatives of basic steroid hydrocarbons, it would be cumbersome in some cases. Although diosgenin is actually a derivative of the cyclic form of 3β,16β,26-trihydroxycholest-5-en-22-one, the IUPAC rules recommend the use of (25ξ)-5ξ-spirostane as the ground for

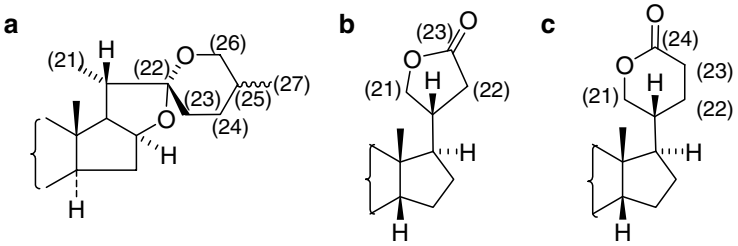

Fig. 1.31 (**a**) Spirostane, (**b**) cardanolide, and (**c**) bufanolide

naming these compounds (Fig. 1.31a).

Similarly, cardanolide is a lactone derived of 24-nor-14β-cholanic acid (Fig. 1.31b), as well as bufanolide is a lactone derived of 14β-cholanic acid (Fig. 1.31c).

Notice the 14β-configuration in cardanolide and bufanolide: this configuration is considered "normal" in cardioactive glycosides. Aglycons of some of them (strophantidin and scillarenin) are shown in Fig. 1.32.

In spirostans, both 25*R* and 25*S* derivatives are found in the nature, thus C-25 configuration has also to be specified. Figure 1.32a shows the structure of diosgenin, the most important raw material for industrial production of steroids. The chair conformation of the spirostane six-membered ring means that the 25-isomers differ in having the 25-methyl group in axial (25*S*) or equatorial (25*R*) position.

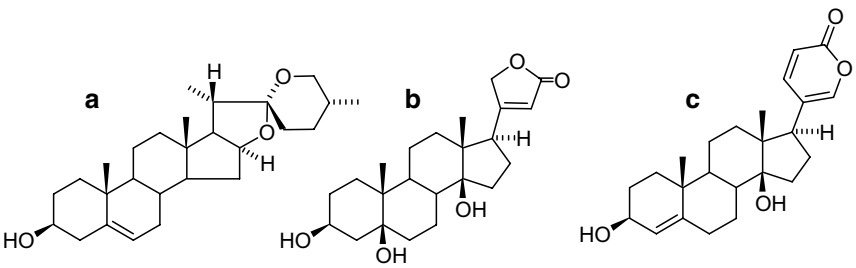

Fig. 1.32 (**a**) Diosgenin, (**b**) strophantidin, and (**c**) scillarenin

Another biogenic element can be found in steroids: nitrogen. Plants of the genus *Solanum* contain glycosidic alkaloids whose aglycons can also be named as cholestane derivatives. In spite of that new names were designed: 5ξ-solanidan and 5ξ-solasodan (Fig. 1.33). Solasodin and solanidin are the most frequently found aglycons of this kind.

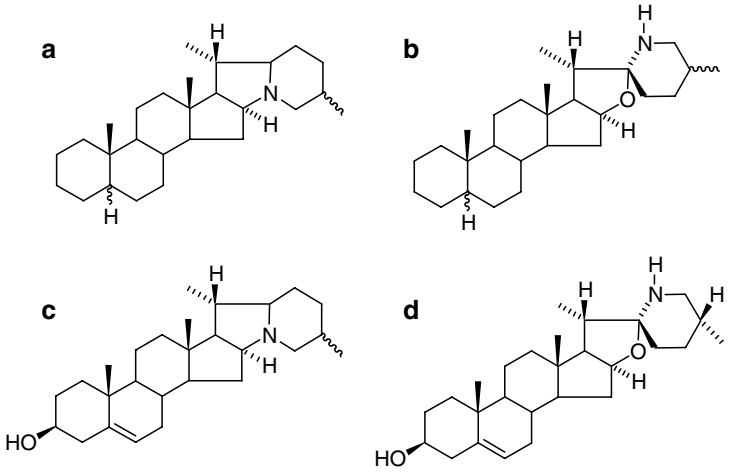

Fig. 1.33 (**a**) 5ξ-Solasodan, (**b**) 5ξ-solanidan, (**c**) solasodin, and (**d**) solanidin

Steroid skeleton can be found in yet another group of alkaloids: several alkaloids from *Holarrhena antidysenterica* and others are derivatives of (20*S*)-*N*-methyl-18,20-imino-5α-pregnane (Fig. 1.34), the steroid core, however, is called 5α-conane. The most abundant alkaloids of this family are conessine and holarrhimine.

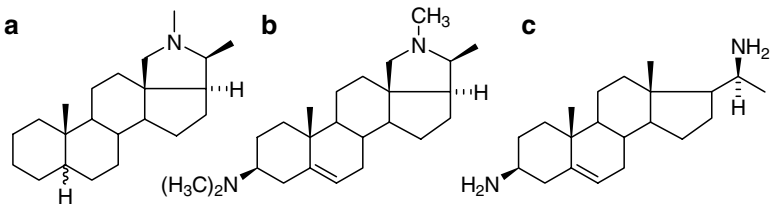

Fig. 1.34 (**a**) 5ξ-Conane, (**b**) conessine, and (**c**) holarrhimine

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