International Journal of Chemical Studies

P-ISSN2349–8528
E-ISSN 2321–4902
IJCS 2016; 4(3): 124-132

Received: 18-03-2016
Accepted: 19-04-2016

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Systemic nomenclature of Steroids [Cyclopentaphenanthrene ring] their derivatives - An Overview

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Abstract
More than 25 million chemical compounds currently registered whole over world, about 20-25% contain heterocyclic systems and Cyclopenta [a] phenanthrene ring containing compounds. Cyclopenta phenanthrene rings (Steroids) are important, not only because of their abundance, but above all because of their chemical, biological and technical significance. The numbering, nomenclature and stereochemistry of Cyclopenta [a] phenanthrene ring effect their importance and count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as Pharmaceuticals aids.

Keywords: Steroids, Hydrocarbon, Heterocyclic, Hormone, Nomenclature

1. Introduction
Many naturally occurring Cyclopenta [a] phenanthrene (steroidal skeleton) are referred to by their common or trivial names, such as cholesterol, cortisol, progesterone, testosterone, and estradiol etc. As more steroid molecules were being discovered or synthesized, it became clear that a more systematic method for naming steroids was needed. Beginning in the 1950s, nomenclature rules for steroids were being developed, and the most recent IUPAC-IUB Joint Commission rules for systematic steroid nomenclature were published in 1989 [1-4]. The systematic names for steroids are based on the steroid hydrocarbon system, particular systematic name begins by selection of the stem name based on the hydrocarbon system, Steroid molecules possess a common chemical skeleton of four fused rings A/B/C, consisting of three six-membered rings and a five-membered ring,D (Figure1). Chemically, this hydrocarbon scaffold is cyclopentanoperhydrophenanthrene, describing the three rings of phenanthrene (rings A, B, and C) and the cyclopentane ring (D). In steroids, the phenanthrene ring system is completely saturated (hydrogenated) and is thus referred to as a perhydrophenanthrene [5-6]. This steroid scaffold contains 17 carbon atoms, and the numbering of the carbon atoms begins with the carbons of the phenanthrene ring A (Figure 2). Additional carbon atoms on steroids include angular methyl groups attached to C-13 (Carbon number) and C-10 and alkyl substituent's (methyl as in Androstane) on C17 (Figure 3) [3, 7-10].

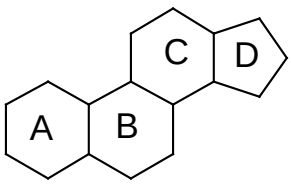


Fig 1

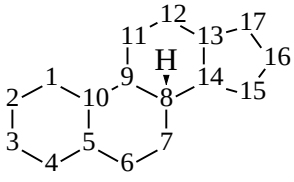
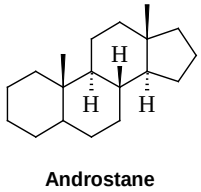


Fig 2



Androstane

Fig 3

Nomenclature designed by no of hydrocarbon, double bond, substituent's position, alteration in cyclopenta [a] phenanthrene affect physical, chemical as well as pharmacological properties of steroid scaffold, that why numbering and nomenclature of rings are important. Most of steroids are solid in nature because of melting points for steroids range between 100 to 260 °C [10-11]. Molecules of one particular steroid derivative may crystallize in either an anhydrous form or in a hydrated or solvated form, resulting in different melting points observed by the

two forms. Also, individual molecules of one steroid derivative may pack in different arrangements in crystals from different solvents, resulting in polymorphic forms. Steroids are generally insoluble in water, whereas they are reasonably soluble in organic solvents such as ethanol, acetone, chloroform and dioxane. Steroid has wide application in medicinal chemistry and is well known for their diverse therapeutic property which includes dyslipidimia, arthritis, antiinflammatory, antiobesity, antimicrobial, antihypertensive, pesticides, anti depressants, antioxidants etc. [12-16].

1.1 Orientation of projection formulae [3, 14-16]

When the cyclopenta [a] phenanthrene [steroid nucleus] is drawn in a two dimensional, the steroid nucleus appears planar and substituent's on carbons of the steroid skeleton may be located either above or below the "plane" of the steroid nucleus. Substituent's located above the plane are drawn with solid lines or with dark wedges [▬], and these steroid nucleus are referred to as (β) -configuration. Substituent's located below the plane are drawn with dashed lines [--------] or broken lines are referred to as (α) -configuration. The angular methyl groups numbered 18 and 19 are attached in the (β)-configuration (above the steroid plane) to C13 and C10, respectively. Side-chains at position 17 are always (β) unless indicated by dotted lines or in the nomenclature. The whole configuration has been shown below in [Figure 4 (4a and 4b)].

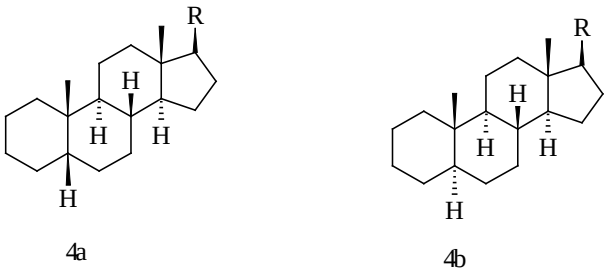


Fig 4

1.2 Nomenclature of hydrocarbon number containing cyclopenta [a] phenanthrene: Number of hydrocarbon in ring A/B/C/D, design or drive different steroidal derivatives i.e. C-17 named as Gonane, C-19 androstane etc.

Gonane

The parent tetracyclic hydrocarbon without methyl groups at C-10 and C-13 and no substitution at C-17 is named Gonane (Figure- 5).

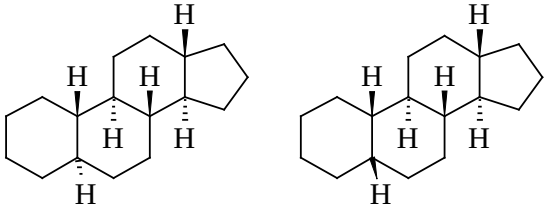


Fig 5

Estrane (oestrane)

The hydrocarbon with a methyl group at C-13 but without a methyl group at C-10 and no carbon substitution at C-17 is named estrane (oestrane), with an example of natural hormonal drug, Estradiol. (Figure- 6).

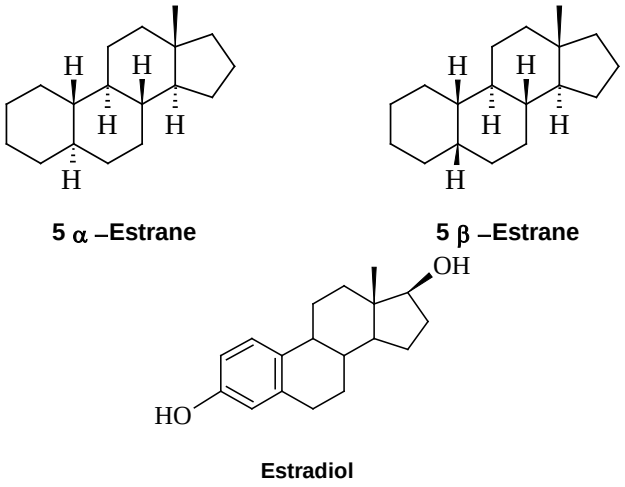


Fig 6

Androstane

The hydrocarbon with methyl groups at C-10 and C-13 but without carbon substitution a side chain at C-17 is named androstane, with drugs as example of C-19 derivatives (Figure- 7)

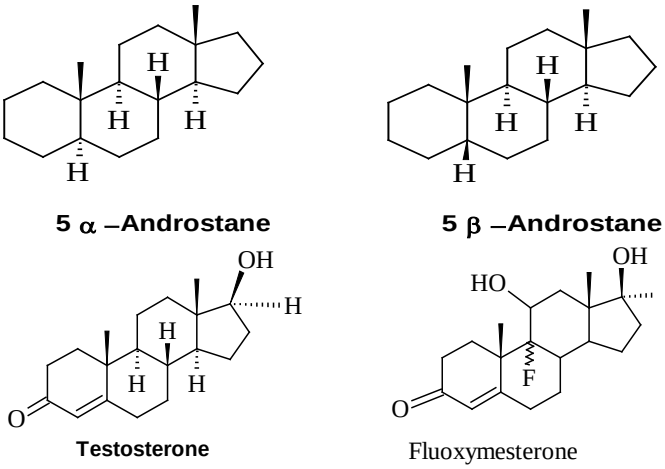


Fig 7

Pregnane

The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto C-21 containing is named Pregnane, with drugs as example of this class (Progestrone) (Figure- 8).

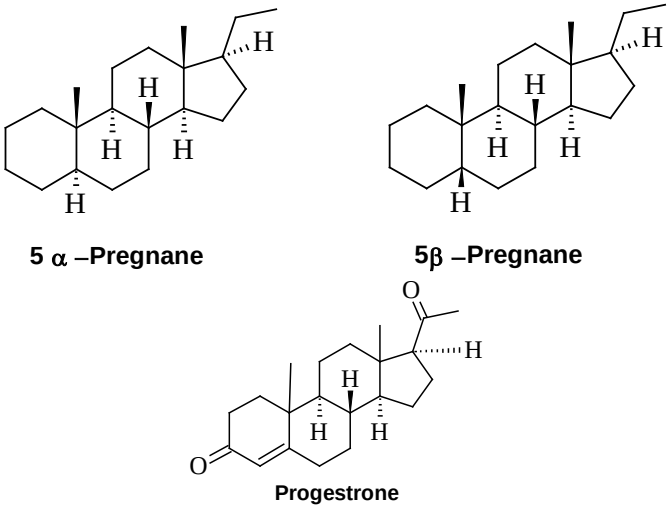


Fig 8

Cholane & Cholestane

The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto Carbon chain 24 is named Cholane and C-27 containing named Cholestane (Figure- 9).

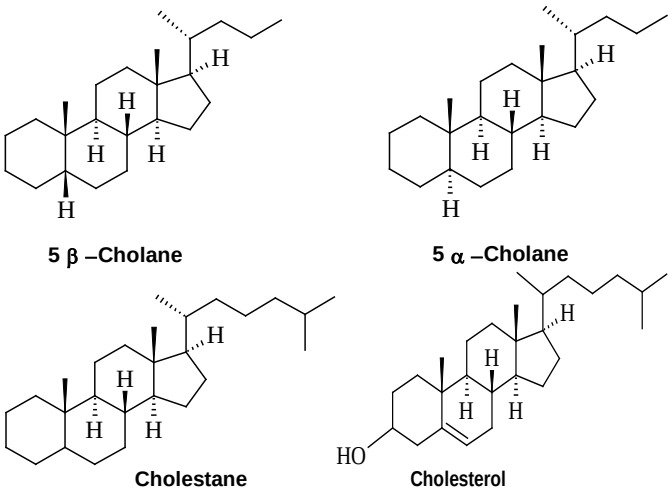


Fig 9

Ergostane

The hydrocarbon with methyl groups at C-10 and C-13, with a side chain at C-17 upto C-28 like similar manner cholestane named as Ergostane, with drugs as example (5α-ergostane-3β-ol) of this class (Figure- 10).

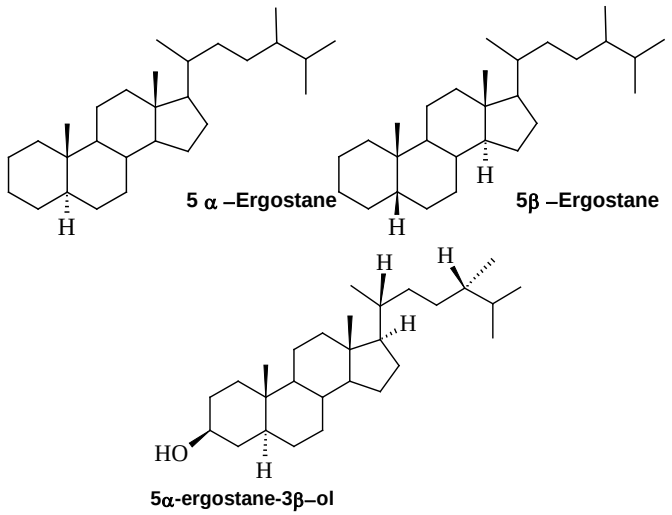
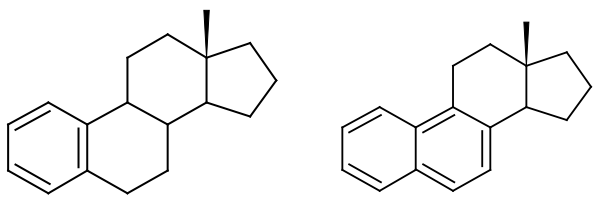
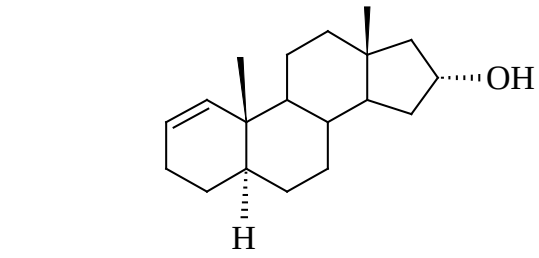


Fig 10

1.3 Unsaturation: Nomenclature of steroid scaffold containing double or triple bond:- Unsaturation is indicated by changing -ane to -ene, -adiene, -yne etc., or -an- to -en-, -adien-, -yn-, like Androst-5-ene, not 5-androstene 5α-Cholest-6-ene, 5β-Cholesta-7,9(11)-diene, 5α-Cholest-6-en-3β-ol and some of basic structure given below (Figure- 11 & 12).





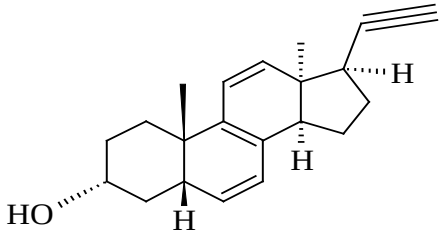


Fig 11

Sites of Unsaturation (*i.e.* double bonds) are often referred to using the Greek letter Δ. Thus, steroids containing the 5-6 double bonds, as in cholesterol, are designated Δ^5 steroids; those with a 4-5 double bond are called Δ^4 steroids. Unsaturation or double bond between C-5and C-10 final designations of steroid numbering confirmed as 5 $^{\Delta}$ 10. (Figure- 12).

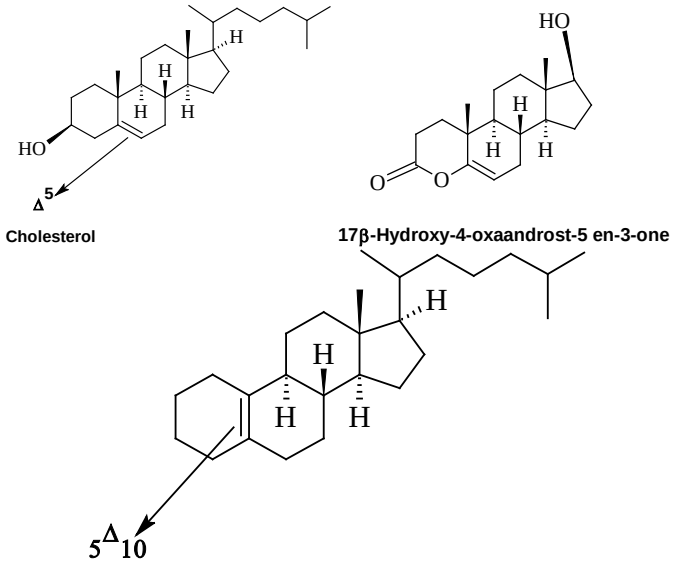
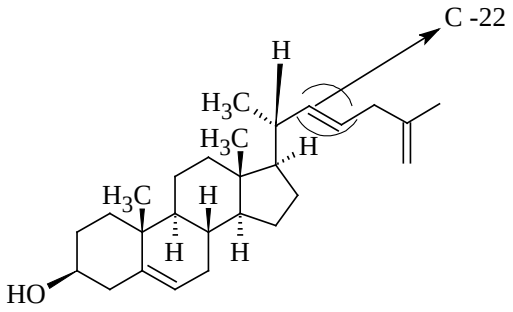


Fig 12

1.4 Stereochemistry of double bonds: [17-19]

The stereochemistry of double bonds in the side chain designated using the *E, Z* conformation. Example: (22 E) Chloesta-5,22,25 triene-3β-ol.(Figure- 13)

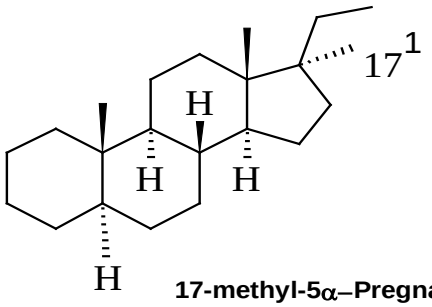


(22 E) Chloesta -5,22,25 triene - 3β – ol

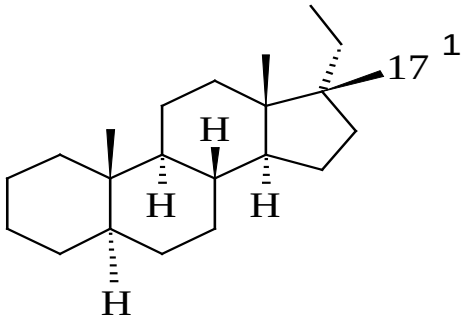
Fig 13

1.5 Nomenclature of alkyl substituent at C-17 in the scaffold: [18-19]

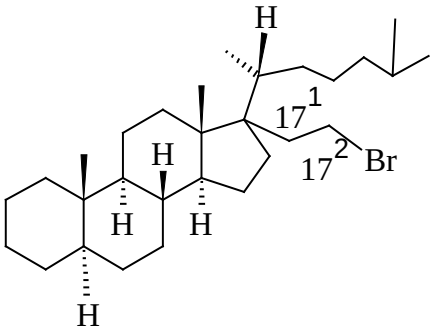
Steroid has two carbon chains attached at position 17 and the compound named as 17-alkyl derivative of that particular steroid skeleton. If both side chains at C-17, larger one is used, or the one in the normal configuration, e.g. 17-ethyl-5α-cholestane, 17-ethyl-5α-pregnane (not 17-ethyl-5α, 17α-pregnane). The carbon atoms of the alkyl substituent may be numbered by a superscript number added to the number of the atom to which it is attached, e.g. 17^1, 17^2 (Figure- 14).



17-methyl-5α–Pregnane



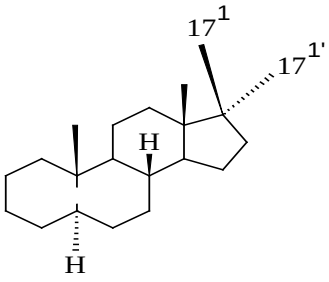
17-methyl-5 α ,17β Pregnane



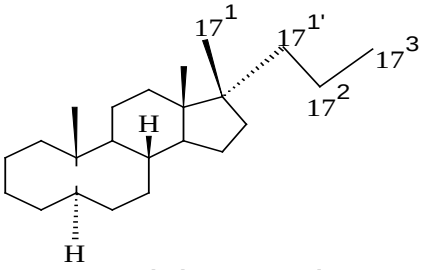
17(-bromoethyl)methyl 5 α ,17α-Cholestane

Fig- 14

The shorter of the two substituent chains receives primed superscript numbers. If the two substituent chains are of equal length and attached to the steroid ring system the substituent on the β-face has primed superscript numbers. If the two substituent chains are attached to the side chain of the steroid and are of equal length but one is further substituted the other chain has primed superscript numbers. (Figure-15).



17,17,Dimethyl -5α – androstane

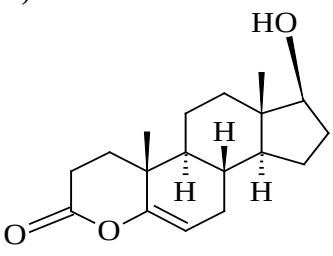


17β methyl,17α,propyl-5α - androstane

Fig 15

1.6 Replacement of carbon atoms by hetero atoms:-

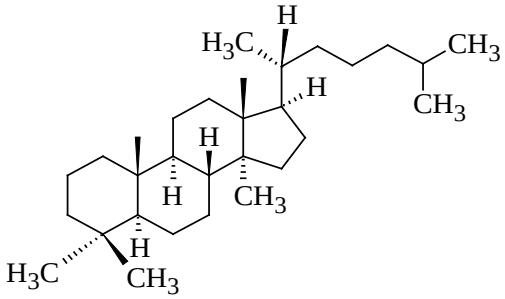
When the carbon skeleton of a steroid a carbon atom is replaced by a hetero atom [O, N, S] the replacement system of nomenclature is used with steroid names and numbering (Figure- 16).



17β - Hydroxy - 4 -oxaandrost - 5 en - 3 one

Fig 16

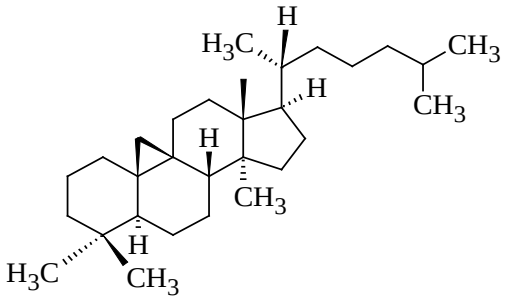
1.7 Nomenclature of steroid skeleton contain trimethyl scaffold: This type of nomenclature is especially useful for the parent hydrocarbons of biogenetic precursors of steroids. The tetracyclic triterpenoids can be represented as trimethyl steroids, the three additional methyl groups being numbered 28 (attached to C-4 with α-configuration), 29 (attached to C-4 with β-configuration) and 30 (attached to C-14); this numbering corresponds to that used for the triterpenoids.. For example, lanostane figure 17 is 4,4,14-trimethyl-5α-cholestane, the former name implying the 5α,8β,9α,10β,13β,14α,17β,20*R* configuration. The change of configuration at C-9 in cycloartane figure 18 is implied in the name, although it must be specified if called 4,4,14-trimethyl-9,19-cyclo-5α,9β-cholestane



4,4,14 -Trimethyl -5α cholestane

Lanostane

Fig 17



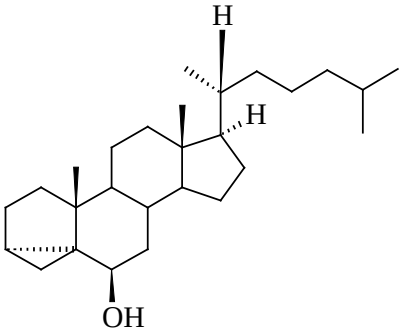
4,4,14 -Trimethyl -9,19 cyclo-5α, 9β cholestane

Cycloartane

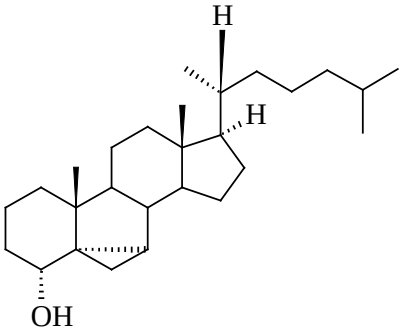
Fig 1**8**

1.8 Additional rings formed within the steroid skeleton:-

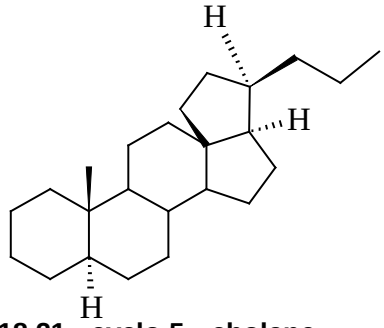
When an additional ring in between any two carbon atoms of the steroid ring system or the attached side chain, the steroid named **cyclo**; used as prefix, is preceded by the numbers of the positions joined by the new bond and Greek letter α, β denoting, with the new bond, unless that designation is already contained in the name. (Figure- 19)



3α,5–Cyclo 5α Cholestan 6β –ol



5α,7,5–Cyclo 5α Cholestan 4α –ol

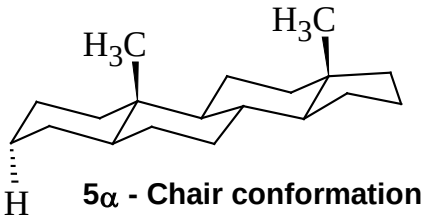


18,21 - cyclo 5α cholane

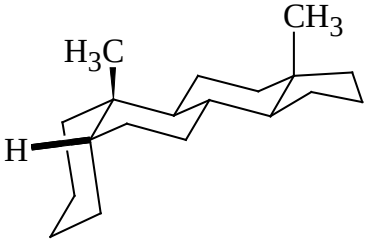
Fig 19

2. Conformational stereochemistry: Chair and boat structure [20-26]

The three-dimensional shapes of the rings in the steroid skeleton are not planar. So that, substitutents on the rings (A/B/C) can be positioned on the axial or the equatorial of the ring (Figure 20) The cyclohexane ring experienced flip conformation and ring D exists in a half-chair conformation. The steroids are rigid in structures because of trans fused-ring system, and these rings must be diequatorial to each other. Endogenous steroid skeleton contain two trans fused rings, one diequatorial trans fusion between rings B and C (C- 8 and C-9) and diequatorial trans fusion between rings C and D (C-13 and C-14).



5α - Chair conformation



5β - boat conformation

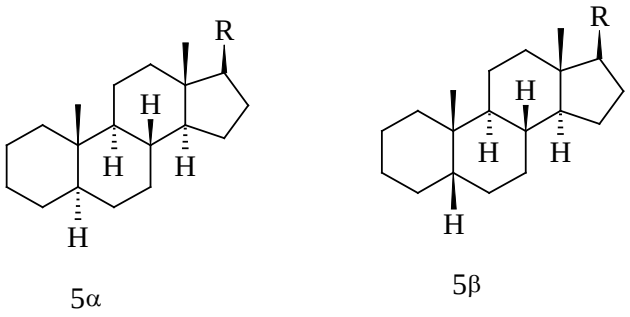


Fig 20

There is two ring fusions are seen in steroidal skeleton between rings A and B. The diequatorial trans fusion between rings A and B results in the hydrogen atom at position 5 being on the opposite side of the rings from the angular methyl group at position 19, 5α designation used for this hydrogen. So that three-D shape of the 5 α -steroid is a nearly flat. (Figure 21).

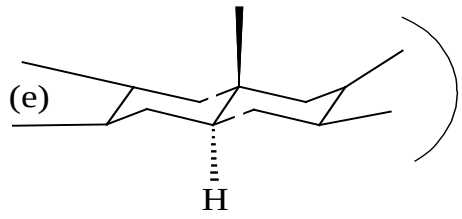


Fig 21

The axial-equatorial cis fusion between rings A and B results in the hydrogen atom at position 5 being on the same side of the rings with the angular methyl group at position 19; the 5β designation is used for the hydrogen. The two-D and three-D representations for the 5 α -steroid and the 5 β –steroid (Figure-22).

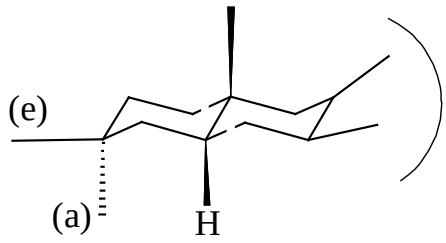
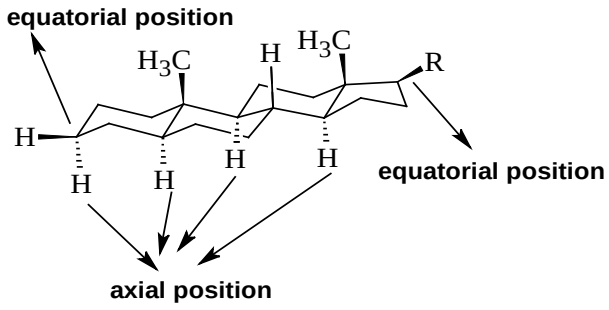


Fig 22

The chair conformation of the cyclohexane rings showing the rigidity of steroid scaffold because of ring positioned between ring A/B and B/C. The minor flexibility is experienced in the D ring conformation due to the angular methyl groups at positions 18 and 19 are β and perpendicular to the plane of the rings (axial orientation) (Figure 23).



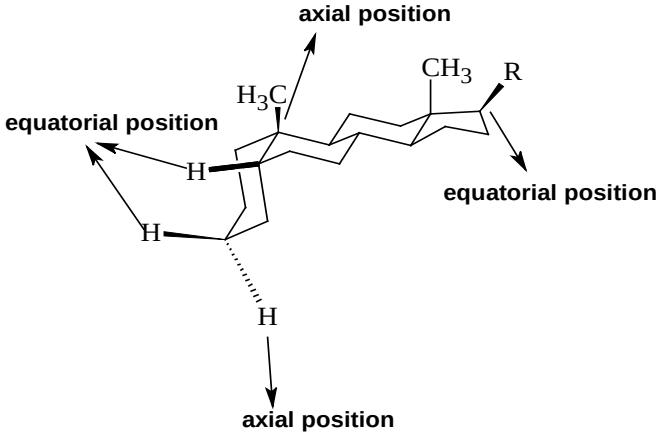


Fig 23

The position and orientation of the remaining bonds on a steroid scaffold determine by the positioned groups on carbon atoms of cyclohexane ring i.e vicinal, -C,H-C,H-, are trans if their relationship is 1,2-diaxial or 1,2-diequatorial.(Figure 24)

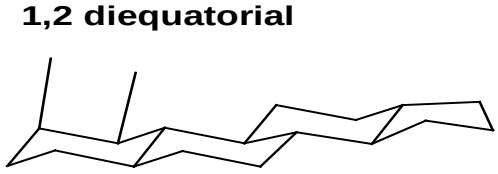


Fig 24

The position and orientation of the remaining bonds on a steroid scaffold determine by the positioned groups on carbon atoms of cyclohexane ring i.e vicinal, -C,H-C,H-, are cis if their relationship is 1,2-equatorial-axial.(Figure 25)

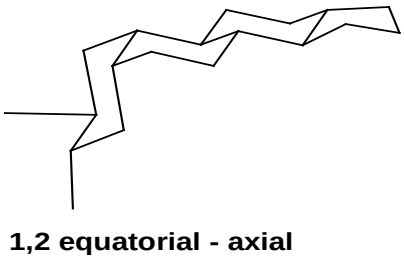


Fig 25

The backbone of the steroid scaffold confirmed by a series of carbon-carbon bonds and the cis or trans relationship of the rings A/B/C/D. The 5α-steroid skeleton having trans-anti-trans-anti-trans backbone. In this structure, all the fused rings have trans (diequatorial) stereochemistry (i.e., the A/B used ring, the B/C fused ring, and the C/D fused ring are trans). The term anti word showing the orientation of rings that are connected to each other (Figure 26).

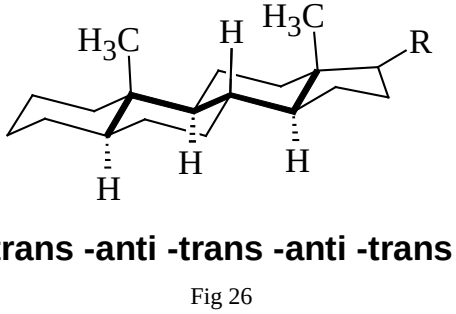
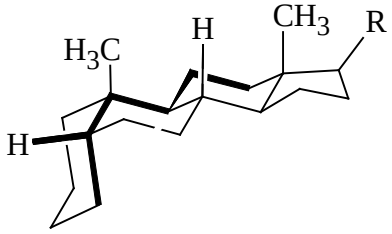


Fig 26

A 5β-steroid has a cis anti- trans-anti-trans backbone, in which the A/B rings are fused cis conformation. These derivatives are chemically synthesized only, no one having natural occurrence (Figure 27).



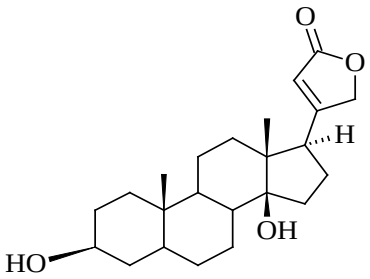
Cis -anti -trans -anti -trans

Fig 27

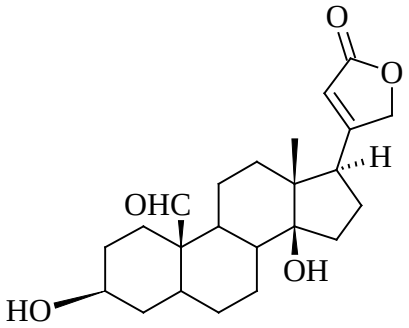
Only saturated position at carbon -5 describe either 5α or 5β steroid scaffold and the traditional drawing of the steroid skeleton is the natural conformation and does not show the hydrogen's at the 8β,9α, 14β positions.

3. Steroids with heterocyclic rings in the side chain [2-4, 11, 26]

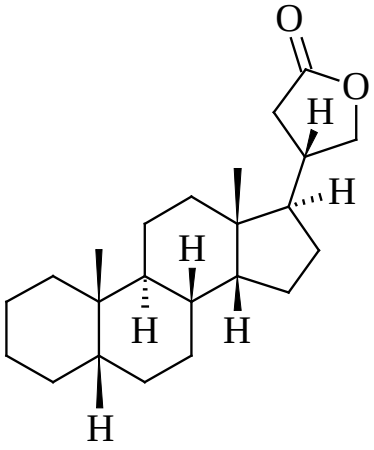
3.1 Cardanolides



3β,14 - Dihydroxy 5β card -20(22) -enolide

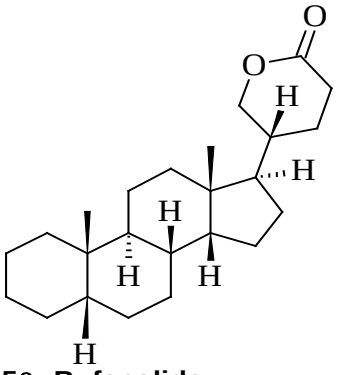


3β,5,14 - Trihydroxy -19 oxo 5β card -20(22) -enolide

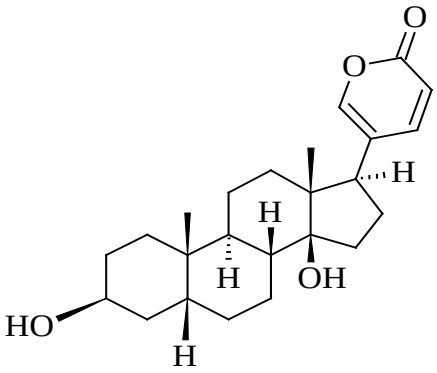


5β Cardanolide

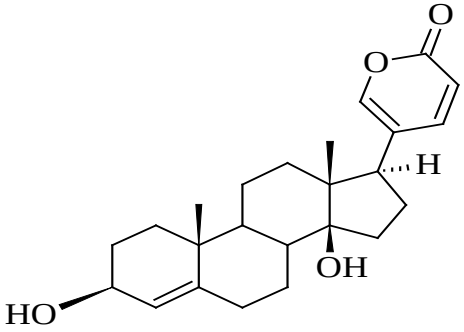
3.2 Bufanolides



5β -Bufanolide

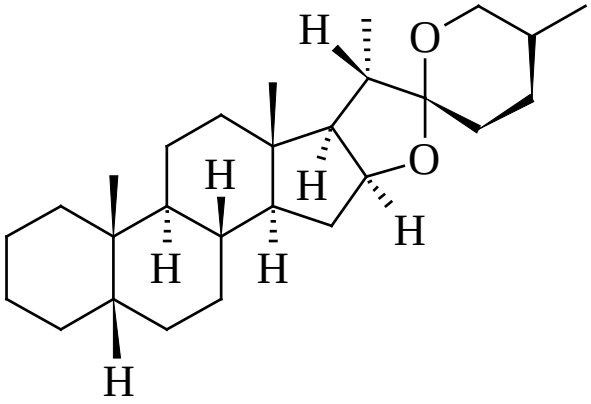


3b,14 - Dihydroxy -5β -Bufa -20(22) dienolide

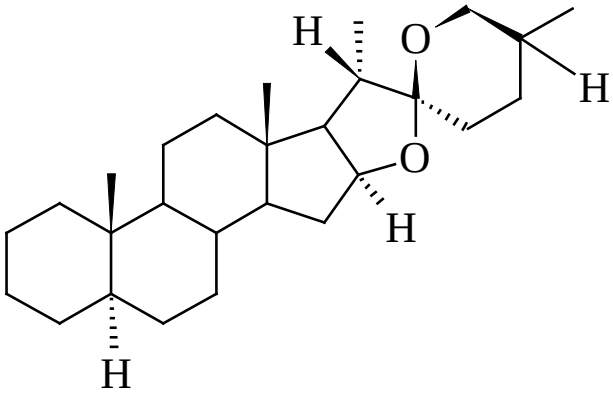


3b,14 - Dihydroxybufa -4,20,22 trienolide

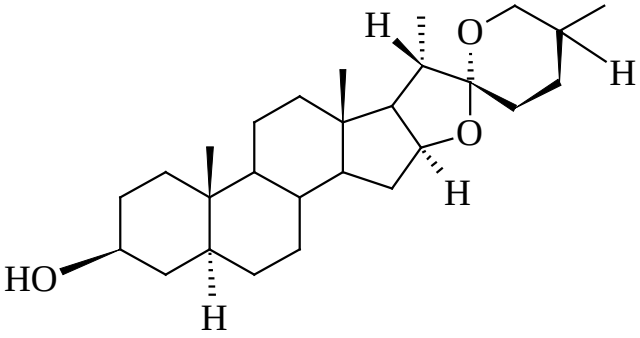
3.3 Spirostans



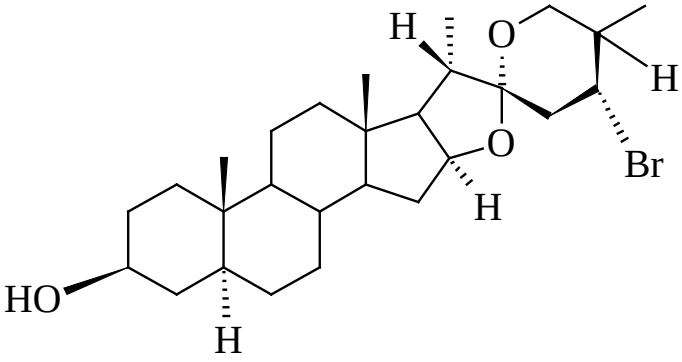
5β - spirostan



5α - spirostan

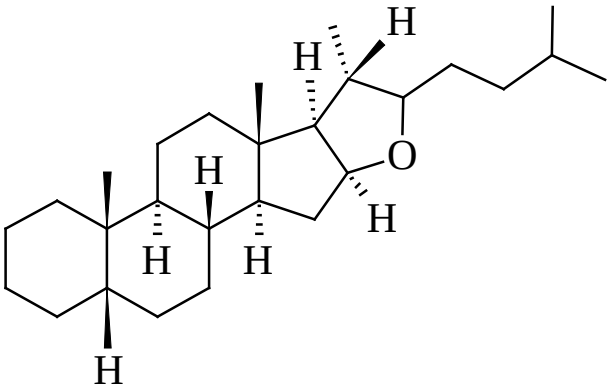


5β- spirostan-3β -ol

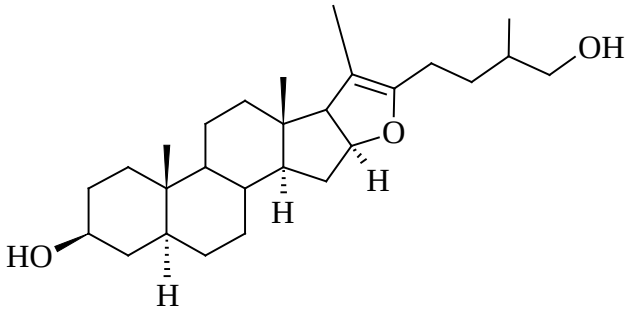


24α Bromo -5β- spirostan-3β -ol

3.4 Furostans

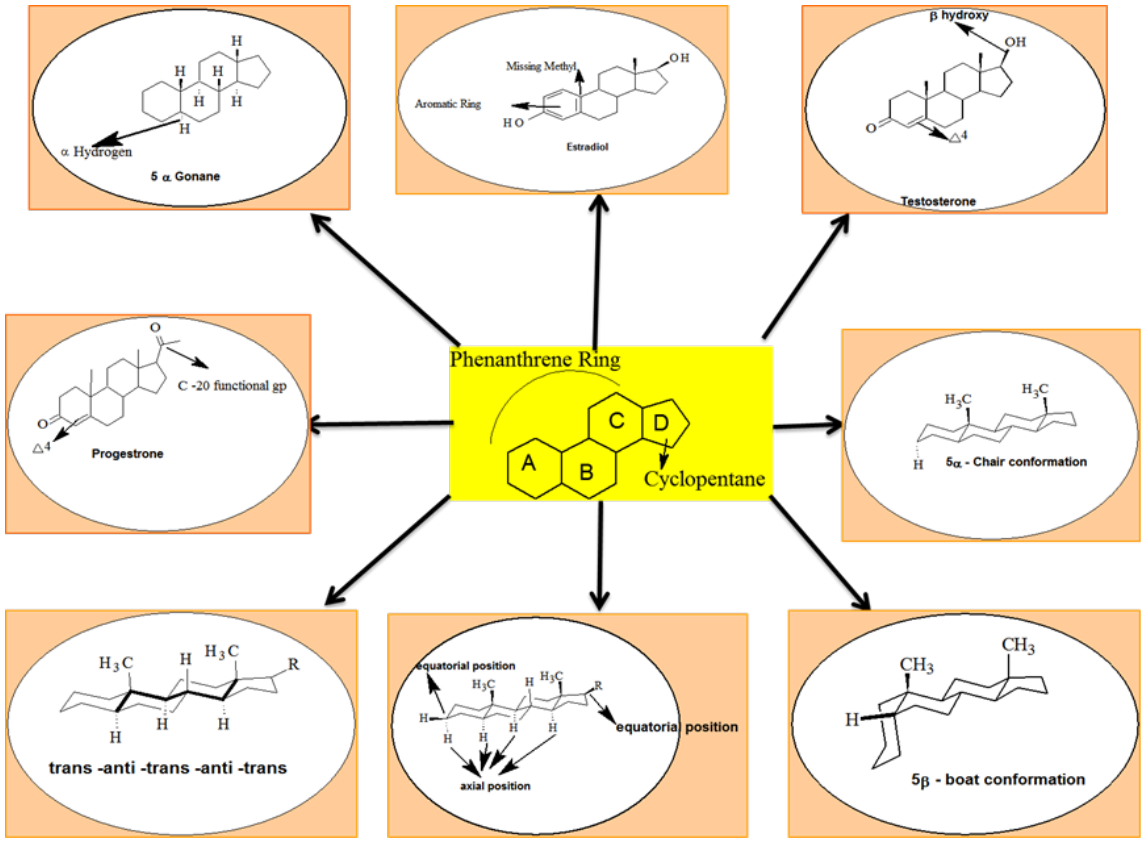


5β -Furostan



5α-Furos-20(22)-ene 3β,2,6–diol

Conclusion: The chemistry of steroidal skeleton play significant role in synthesis and pharmacological role. The chemical nature of formulated steroidal drug depends upon numbering and stereochemistry of steroids. Hundreds of steroids are found in plants, animals and fungi. All natural steroids are manufactured in cells from the sterols lanosterol (animals and fungi) or cycloartenol (plants), Lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene. This review reveals how hydrocarbon numbering and stereochemistry drive different steroids and affect their chemical and biological activity.



Graphically representation of steroid nomenclature of different derivatives

Acknowledgment: I would like to express my gratitude and appreciation to all those (teachers, librarian, technical staff, and office staff) who gave me the possibility to complete this nomenclature review. A special thanks to Principal, whose help, stimulating suggestions and encouragement, helped me to provide College facilities to writing this Review.

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