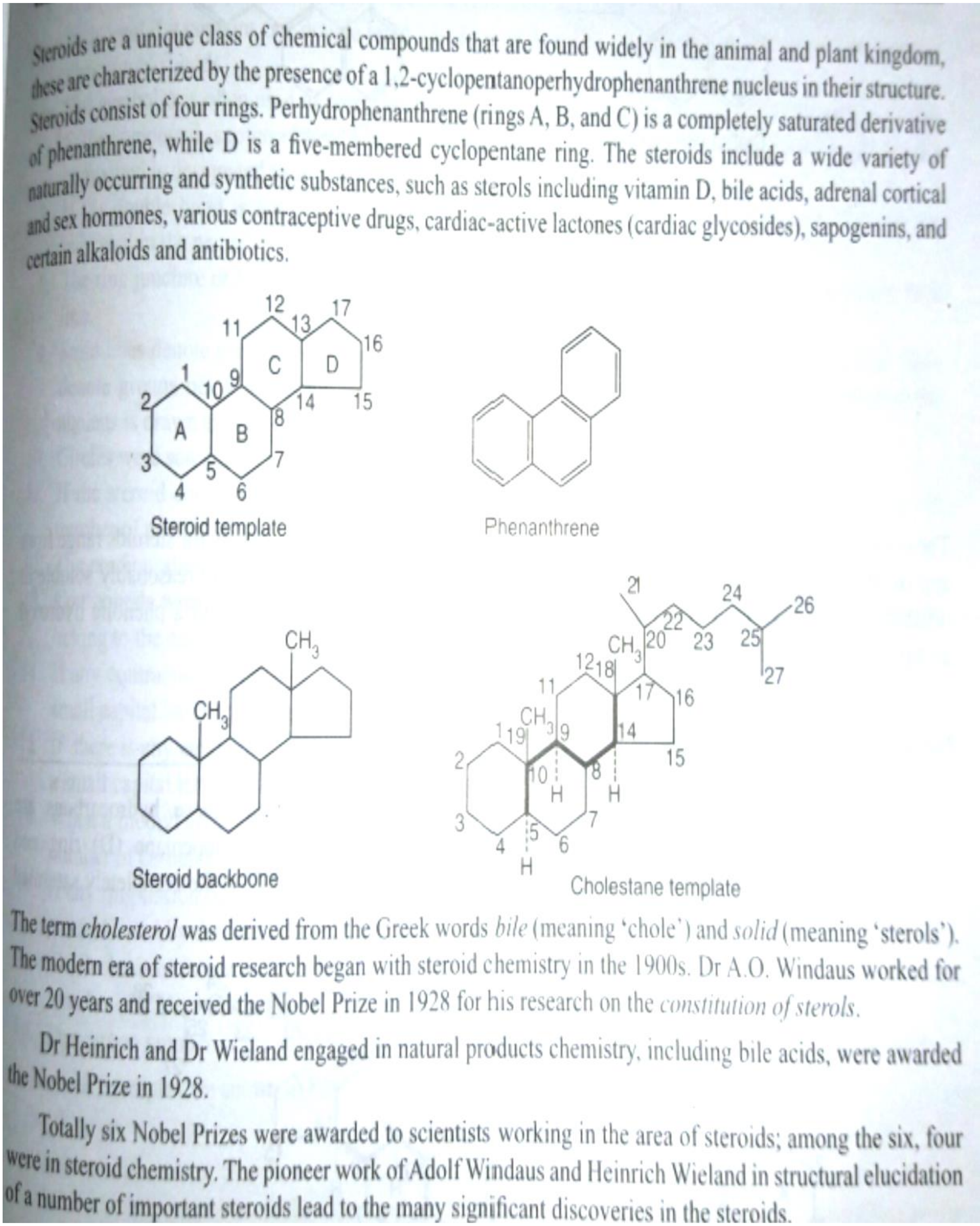
STEROIDS



Steroids are a unique class of chemical compounds that are found widely in the animal and plant kingdom, these are characterized by the presence of a 1,2-cyclopentanoperhydrophenanthrene nucleus in their structure. Steroids consist of four rings. Perhydrophenanthrene (rings A, B, and C) is a completely saturated derivative of phenanthrene, while D is a five-membered cyclopentane ring. The steroids include a wide variety of naturally occurring and synthetic substances, such as sterols including vitamin D, bile acids, adrenal cortical and sex hormones, various contraceptive drugs, cardiac-active lactones (cardiac glycosides), sapogenins, and certain alkaloids and antibiotics.

Steroid template

Phenanthrene

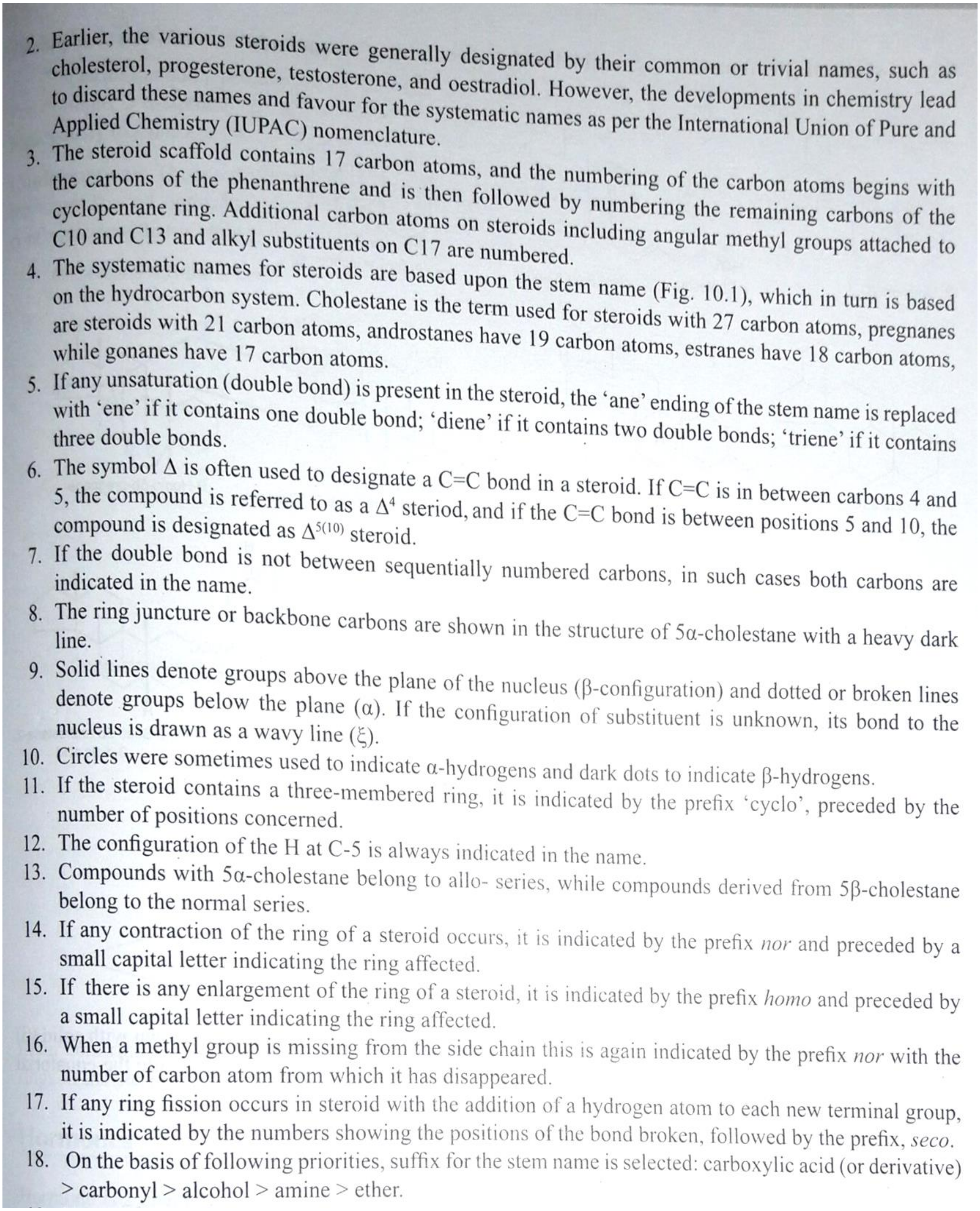
Steroid backbone

Cholestane template

The term *cholesterol* was derived from the Greek words *bile* (meaning 'chole') and *solid* (meaning 'sterols'). The modern era of steroid research began with steroid chemistry in the 1900s. Dr A.O. Windaus worked for over 20 years and received the Nobel Prize in 1928 for his research on the *constitution of sterols*.

Dr Heinrich and Dr Wieland engaged in natural products chemistry, including bile acids, were awarded the Nobel Prize in 1928.

Totally six Nobel Prizes were awarded to scientists working in the area of steroids; among the six, four were in steroid chemistry. The pioneer work of Adolf Windaus and Heinrich Wieland in structural elucidation of a number of important steroids lead to the many significant discoveries in the steroids.



2. Earlier, the various steroids were generally designated by their common or trivial names, such as cholesterol, progesterone, testosterone, and oestradiol. However, the developments in chemistry lead to discard these names and favour for the systematic names as per the International Union of Pure and Applied Chemistry (IUPAC) nomenclature.
3. The steroid scaffold contains 17 carbon atoms, and the numbering of the carbon atoms begins with the carbons of the phenanthrene and is then followed by numbering the remaining carbons of the cyclopentane ring. Additional carbon atoms on steroids including angular methyl groups attached to C10 and C13 and alkyl substituents on C17 are numbered.
4. The systematic names for steroids are based upon the stem name (Fig. 10.1), which in turn is based on the hydrocarbon system. Cholestane is the term used for steroids with 27 carbon atoms, pregnanes are steroids with 21 carbon atoms, androstanes have 19 carbon atoms, estranes have 18 carbon atoms, while gonanes have 17 carbon atoms.
5. If any unsaturation (double bond) is present in the steroid, the 'ane' ending of the stem name is replaced with 'ene' if it contains one double bond; 'diene' if it contains two double bonds; 'triene' if it contains three double bonds.
6. The symbol Δ is often used to designate a C=C bond in a steroid. If C=C is in between carbons 4 and 5, the compound is referred to as a Δ^4 steriod, and if the C=C bond is between positions 5 and 10, the compound is designated as $\Delta^{5(10)}$ steroid.
7. If the double bond is not between sequentially numbered carbons, in such cases both carbons are indicated in the name.
8. The ring juncture or backbone carbons are shown in the structure of 5α-cholestane with a heavy dark line.
9. Solid lines denote groups above the plane of the nucleus (β-configuration) and dotted or broken lines denote groups below the plane (α). If the configuration of substituent is unknown, its bond to the nucleus is drawn as a wavy line (ξ).
10. Circles were sometimes used to indicate α-hydrogens and dark dots to indicate β-hydrogens.
11. If the steroid contains a three-membered ring, it is indicated by the prefix 'cyclo', preceded by the number of positions concerned.
12. The configuration of the H at C-5 is always indicated in the name.
13. Compounds with 5α-cholestane belong to allo- series, while compounds derived from 5β-cholestane belong to the normal series.
14. If any contraction of the ring of a steroid occurs, it is indicated by the prefix *nor* and preceded by a small capital letter indicating the ring affected.
15. If there is any enlargement of the ring of a steroid, it is indicated by the prefix *homo* and preceded by a small capital letter indicating the ring affected.
16. When a methyl group is missing from the side chain this is again indicated by the prefix *nor* with the number of carbon atom from which it has disappeared.
17. If any ring fission occurs in steroid with the addition of a hydrogen atom to each new terminal group, it is indicated by the numbers showing the positions of the bond broken, followed by the prefix, *seco*.
18. On the basis of following priorities, suffix for the stem name is selected: carboxylic acid (or derivative) > carbonyl > alcohol > amine > ether.

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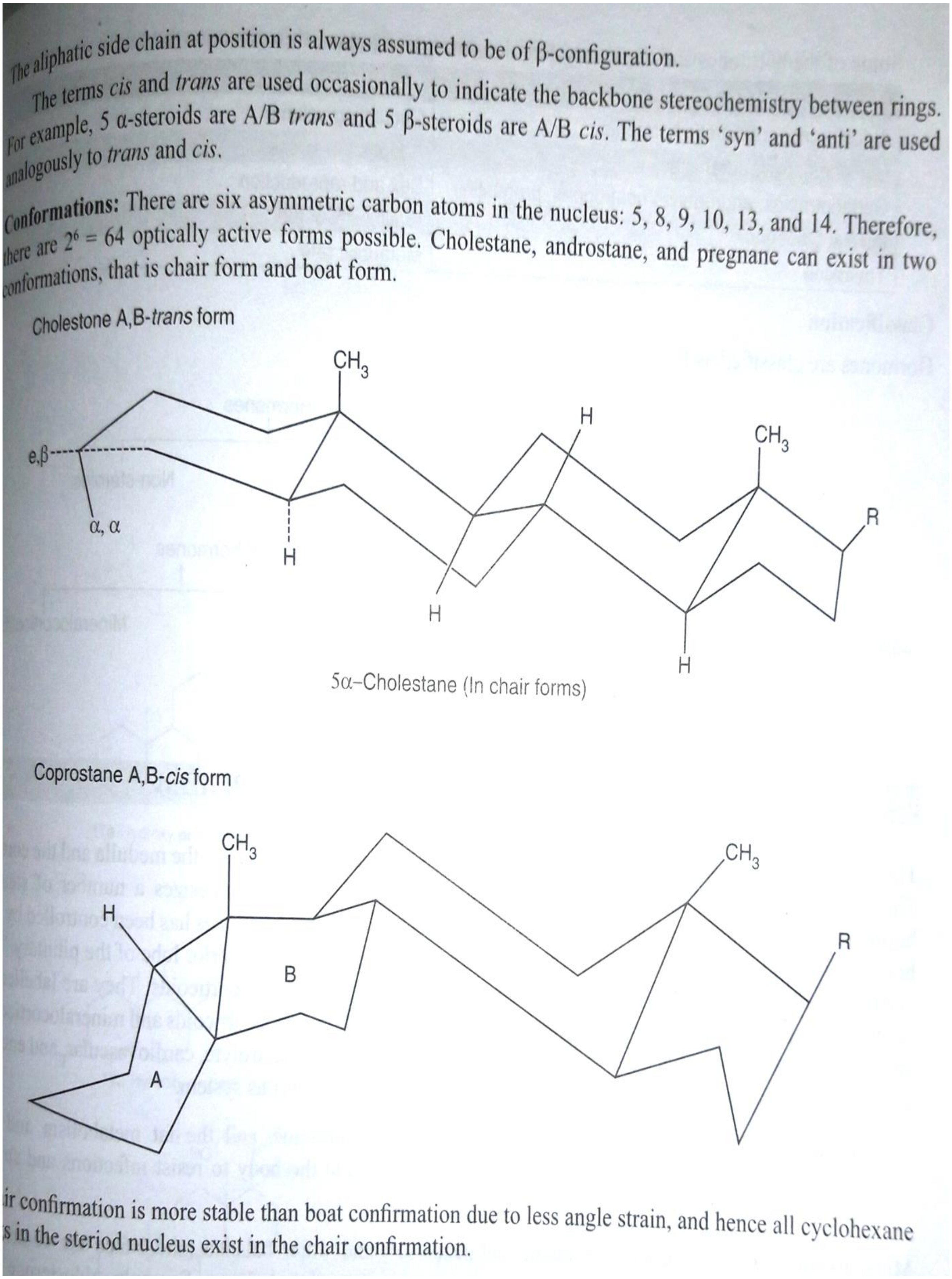


The aliphatic side chain at position is always assumed to be of β-configuration.

The terms *cis* and *trans* are used occasionally to indicate the backbone stereochemistry between rings. For example, 5 α-steroids are A/B *trans* and 5 β-steroids are A/B *cis*. The terms 'syn' and 'anti' are used analogously to *trans* and *cis*.

Conformations: There are six asymmetric carbon atoms in the nucleus: 5, 8, 9, 10, 13, and 14. Therefore, there are $2^6 = 64$ optically active forms possible. Cholestane, androstane, and pregnane can exist in two conformations, that is chair form and boat form.

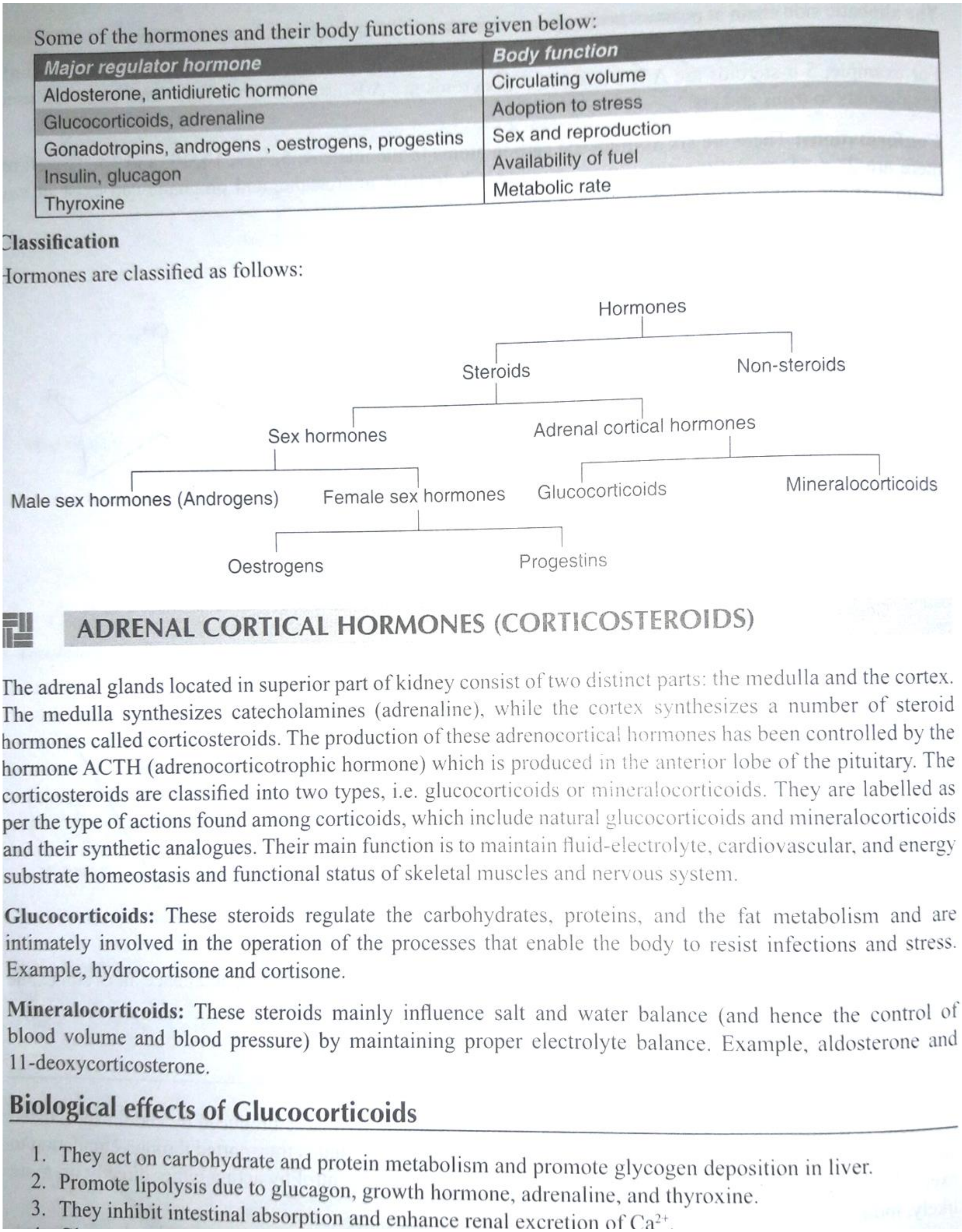
Cholestone A,B-*trans* form

5α–Cholestane (In chair forms)

Coprostane A,B-*cis* form

ir confirmation is more stable than boat confirmation due to less angle strain, and hence all cyclohexane s in the steriod nucleus exist in the chair confirmation.

STEROIDS



Some of the hormones and their body functions are given below:

Major regulator hormone	*Body function*
Aldosterone, antidiuretic hormone	Circulating volume
Glucocorticoids, adrenaline	Adoption to stress
Gonadotropins, androgens , oestrogens, progestins	Sex and reproduction
Insulin, glucagon	Availability of fuel
Thyroxine	Metabolic rate

Classification

Hormones are classified as follows:

ADRENAL CORTICAL HORMONES (CORTICOSTEROIDS)

The adrenal glands located in superior part of kidney consist of two distinct parts: the medulla and the cortex. The medulla synthesizes catecholamines (adrenaline), while the cortex synthesizes a number of steroid hormones called corticosteroids. The production of these adrenocortical hormones has been controlled by the hormone ACTH (adrenocorticotrophic hormone) which is produced in the anterior lobe of the pituitary. The corticosteroids are classified into two types, i.e. glucocorticoids or mineralocorticoids. They are labelled as per the type of actions found among corticoids, which include natural glucocorticoids and mineralocorticoids and their synthetic analogues. Their main function is to maintain fluid-electrolyte, cardiovascular, and energy substrate homeostasis and functional status of skeletal muscles and nervous system.

Glucocorticoids: These steroids regulate the carbohydrates, proteins, and the fat metabolism and are intimately involved in the operation of the processes that enable the body to resist infections and stress. Example, hydrocortisone and cortisone.

Mineralocorticoids: These steroids mainly influence salt and water balance (and hence the control of blood volume and blood pressure) by maintaining proper electrolyte balance. Example, aldosterone and 11-deoxycorticosterone.

Biological effects of Glucocorticoids

1. They act on carbohydrate and protein metabolism and promote glycogen deposition in liver.
2. Promote lipolysis due to glucagon, growth hormone, adrenaline, and thyroxine.
3. They inhibit intestinal absorption and enhance renal excretion of Ca^{2+}.

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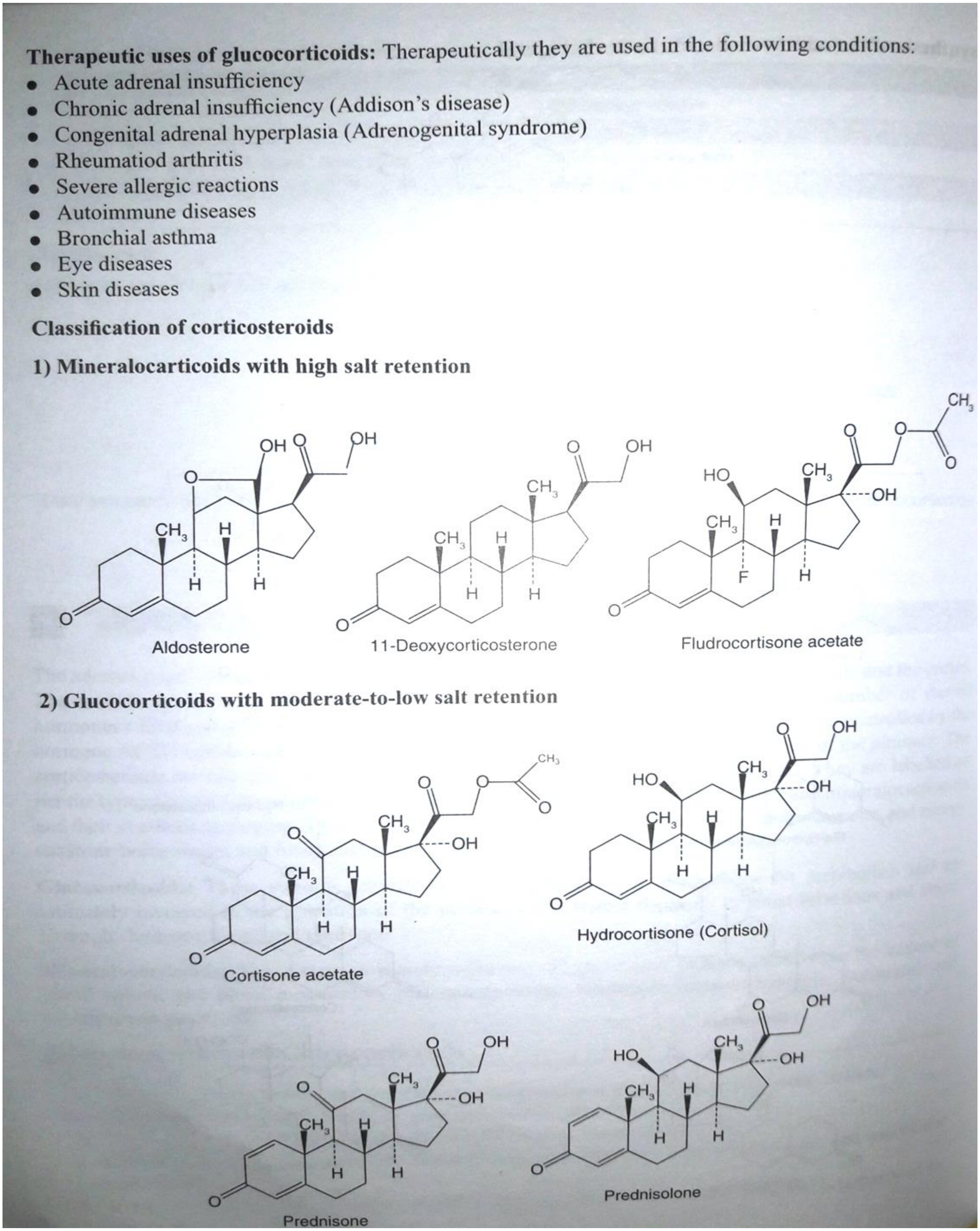


Therapeutic uses of glucocorticoids: Therapeutically they are used in the following conditions:

- Acute adrenal insufficiency
- Chronic adrenal insufficiency (Addison's disease)
- Congenital adrenal hyperplasia (Adrenogenital syndrome)
- Rheumatiod arthritis
- Severe allergic reactions
- Autoimmune diseases
- Bronchial asthma
- Eye diseases
- Skin diseases

Classification of corticosteroids

1) Mineralocarticoids with high salt retention

Aldosterone

11-Deoxycorticosterone

Fludrocortisone acetate

2) Glucocorticoids with moderate-to-low salt retention

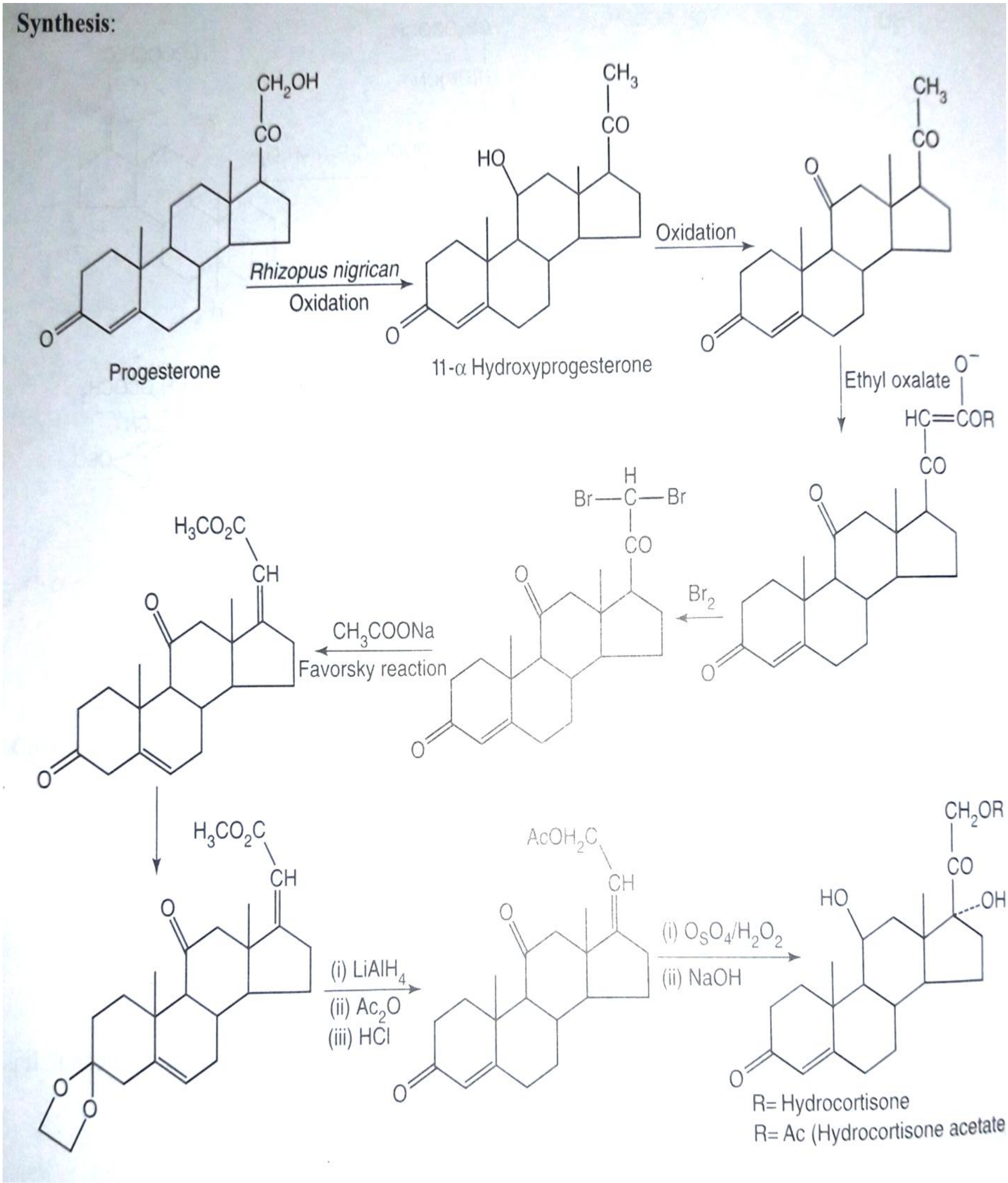
Cortisone acetate

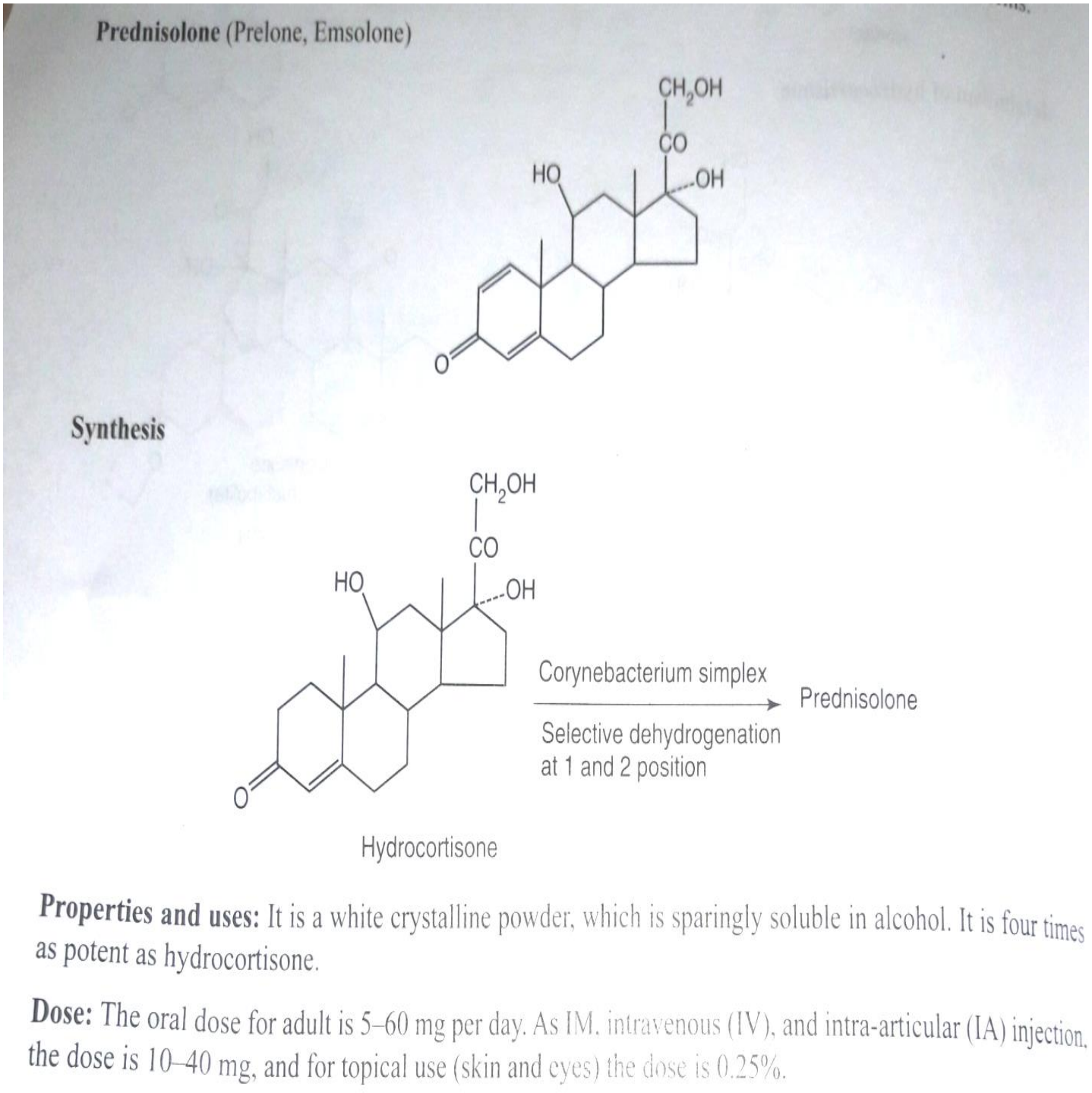
Hydrocortisone (Cortisol)

Prednisone

Prednisolone

Synthesis:


CH$_2$OH
CO
O
Progesterone
Rhizopus nigrican
Oxidation
CH$_3$
CO
HO
O
11-α Hydroxyprogesterone
Oxidation
CH$_3$
CO
O
O
Ethyl oxalate
O$^-$
HC═COR
CO
O
O
Br$_2$
H
Br—C—Br
CO
O
O
CH$_3$COONa
Favorsky reaction
H$_3$CO$_2$C
CH
O
O
H$_3$CO$_2$C
CH
O
O
O
(i) LiAlH$_4$
(ii) Ac$_2$O
(iii) HCl
AcOH$_2$C
CH
O
O
(i) O$_S$O$_4$/H$_2$O$_2$
(ii) NaOH
CH$_2$OR
CO
HO
OH
O
R= Hydrocortisone
R= Ac (Hydrocortisone acetate



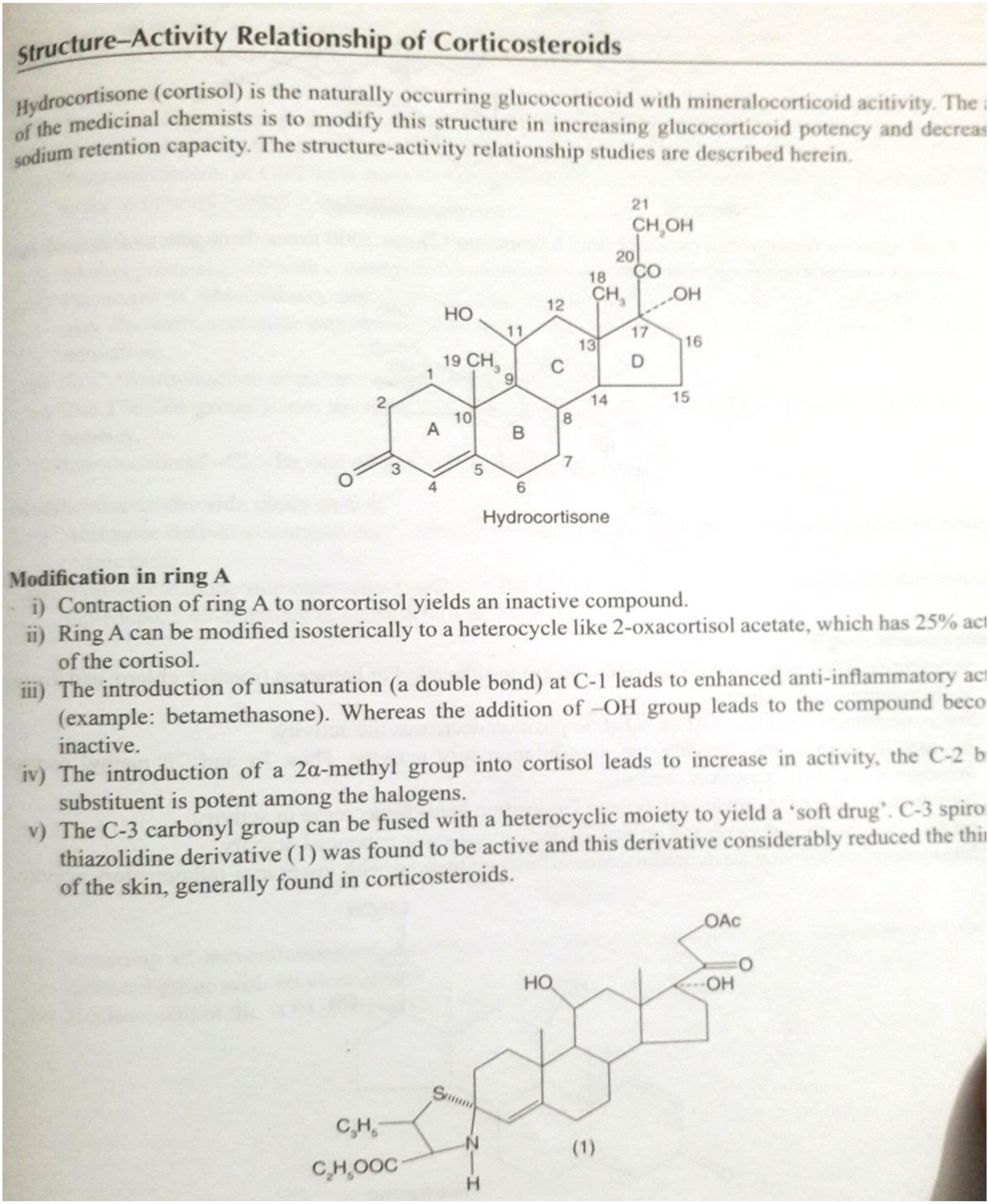
Prednisolone (Prelone, Emsolone)

Synthesis

Hydrocortisone

Properties and uses: It is a white crystalline powder, which is sparingly soluble in alcohol. It is four times as potent as hydrocortisone.

Dose: The oral dose for adult is 5–60 mg per day. As IM, intravenous (IV), and intra-articular (IA) injection, the dose is 10–40 mg, and for topical use (skin and eyes) the dose is 0.25%.



Structure–Activity Relationship of Corticosteroids

Hydrocortisone (cortisol) is the naturally occurring glucocorticoid with mineralocorticoid acitivity. The
of the medicinal chemists is to modify this structure in increasing glucocorticoid potency and decreas
sodium retention capacity. The structure-activity relationship studies are described herein.

Hydrocortisone

Modification in ring A

i) Contraction of ring A to norcortisol yields an inactive compound.

ii) Ring A can be modified isosterically to a heterocycle like 2-oxacortisol acetate, which has 25% act
of the cortisol.

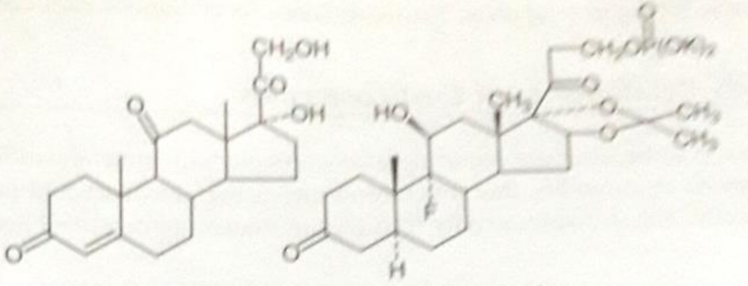
iii) The introduction of unsaturation (a double bond) at C-1 leads to enhanced anti-inflammatory act
(example: betamethasone). Whereas the addition of –OH group leads to the compound beco
inactive.

iv) The introduction of a 2α-methyl group into cortisol leads to increase in activity, the C-2 b
substituent is potent among the halogens.

v) The C-3 carbonyl group can be fused with a heterocyclic moiety to yield a 'soft drug'. C-3 spiro
thiazolidine derivative (1) was found to be active and this derivative considerably reduced the thi
of the skin, generally found in corticosteroids.

(1)

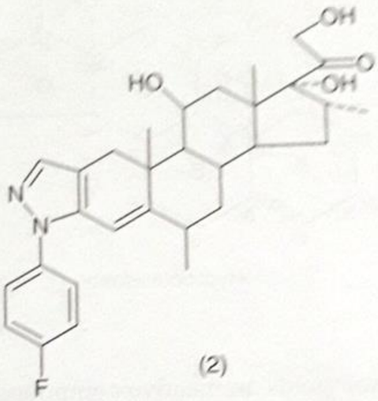
vi) The Δ^4 double bond is important but not essential for anti-inflammatory activity. Example: 5 α-pregnane-3-one is more active than cortisone.



Cortisone

5a-Pregnane-3-one

vii) Ring A can be fused with a pyrazole ring. Compound (2) has 2000 times the potency of cortisol, but also lacks mineralocorticoid activity.



(2)

Modification in ring B

i) Substitution of 6α position with hydrophobic groups like alkyl or halogens (methyl, chloro, and fluoro) leads to increase in activity.

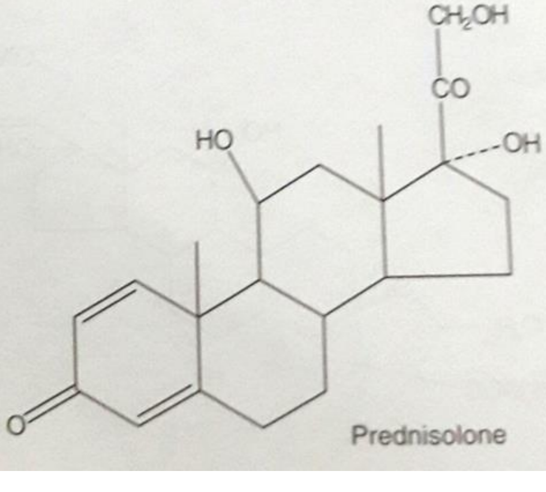
ii) Polar substituents such as –OH or =O at 6α position decreases the activity.

iii) 7α and 7β substituents decrease the anti-inflammatory activity. Thus 7α and 7β methyl cortisol derivatives are less potent than cortisol.

iv) Introduction of –OH group at both 6α and 7α position leads to decrease in activity.

v) 6α and 7α difluoromethylene and 6β and 7β derivatives show enhanced activity.

vi) Introduction of 8(9) double in prednisolone affords compound with lower anti-inflammatory activity.



Prednisolone

vii) Anti-inflammatory potency of corticosteroids drastically influenced by the substituents at C-9 position. The groups added were –F, –Cl, –Br, –I, –OH, and $–CH_3$. The activity of the compounds increases with increasing hydrophobic bonding of the C-9α substituents. The function of the electron withdrawing group at C-9 was to increase the acidity of the neighbouring 11β-hydroxy group which in turn leads to increase in corticoid activity.

viii) Removal of the C-19 angular $–CH_3$ group reduces anti-inflammatory activity.

ix) The H at C-10 should be in β-configuration for the optimal activity.

Modification in ring C

i) The C-11 oxygen group is not essential for anti-inflammatory activity. It can be replaced by groups like –Cl, which can be converted to the hydroxyl group *in vivo*.

ii) Ester substituents at C-12 have showed anti-inflammatory activity and the potency is in the following order: propionyl > butyl > isovaleryl.

Modification in ring D

i) Methyl group at C-15 with α configuration enhances anti-inflammatory activity.

ii) Placement of 16α-hydroxy and 17α-hydroxy groups yields potent compounds. These two groups may also form acetonide derivatives, which are more potent than the corresponding 16,17-dihydroxy derivatives.

iii) At C-16 introduction of chloro, methyl groups increase activity.

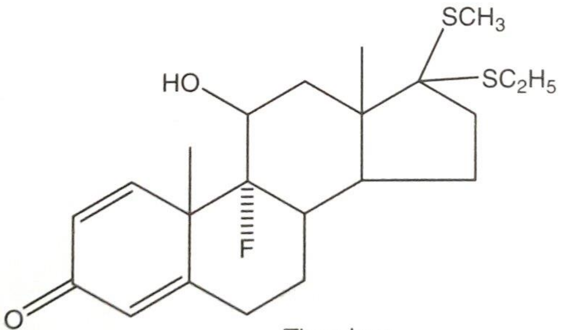
iv) The 17α-OH group is not essential for activity. Ketals and esters yield compounds with improved potency.

v) Introduction of –Cl, –Br, and –F at C-17α position lowers the activity.

Modification in the side chain at C-17

i) Acetonide derivatives across the 17,20-diol arrangement resulted in more potent analogues compared to free diols.

ii) Hydroxyethanone side chain attached at C-17 in the classical corticosteroid is not essential for activity. Tipredane, a 17-thioketal is a potent topical anti-inflammatory drug.

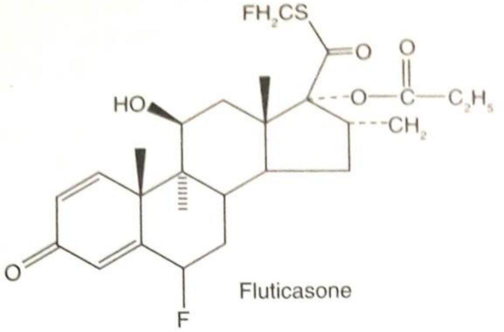


Tipredane

iii) Retaining of anti-inflammatory activity of corticosteroids observed upon ketalization of the C-20 carbonyl group with ethylene glycol.

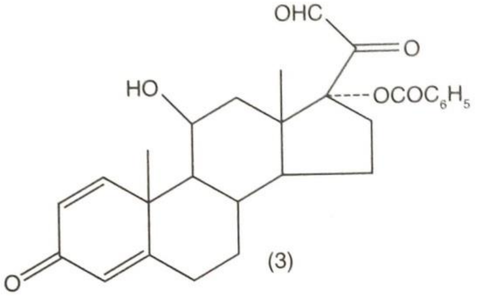
iv) Replacement of the –OH group at C-21 by –Cl or –F enhances activity.

v) Replacement of the C-21 carbon by sulphur (fluticasone) afforded 21-thioesters, also useful clinically.



Fluticasone

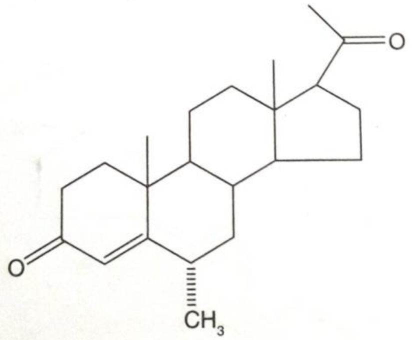
vi) Replacement of $-CH_2OH$ group with an aldehyde (3) leads to compound with some systemic absorption



(3)

vii) The C-21 –OH group can be esterified to afford lipophilic compounds that are meant for repository use.

viii) Introduction of activating groups at C-21; conversion of $-CH_2OH$ group to a $-CH_3$ group (medrysone) yields clinically useful ophthalmic anti-inflammatory compound with relatively little effect on intraoccular pressure.

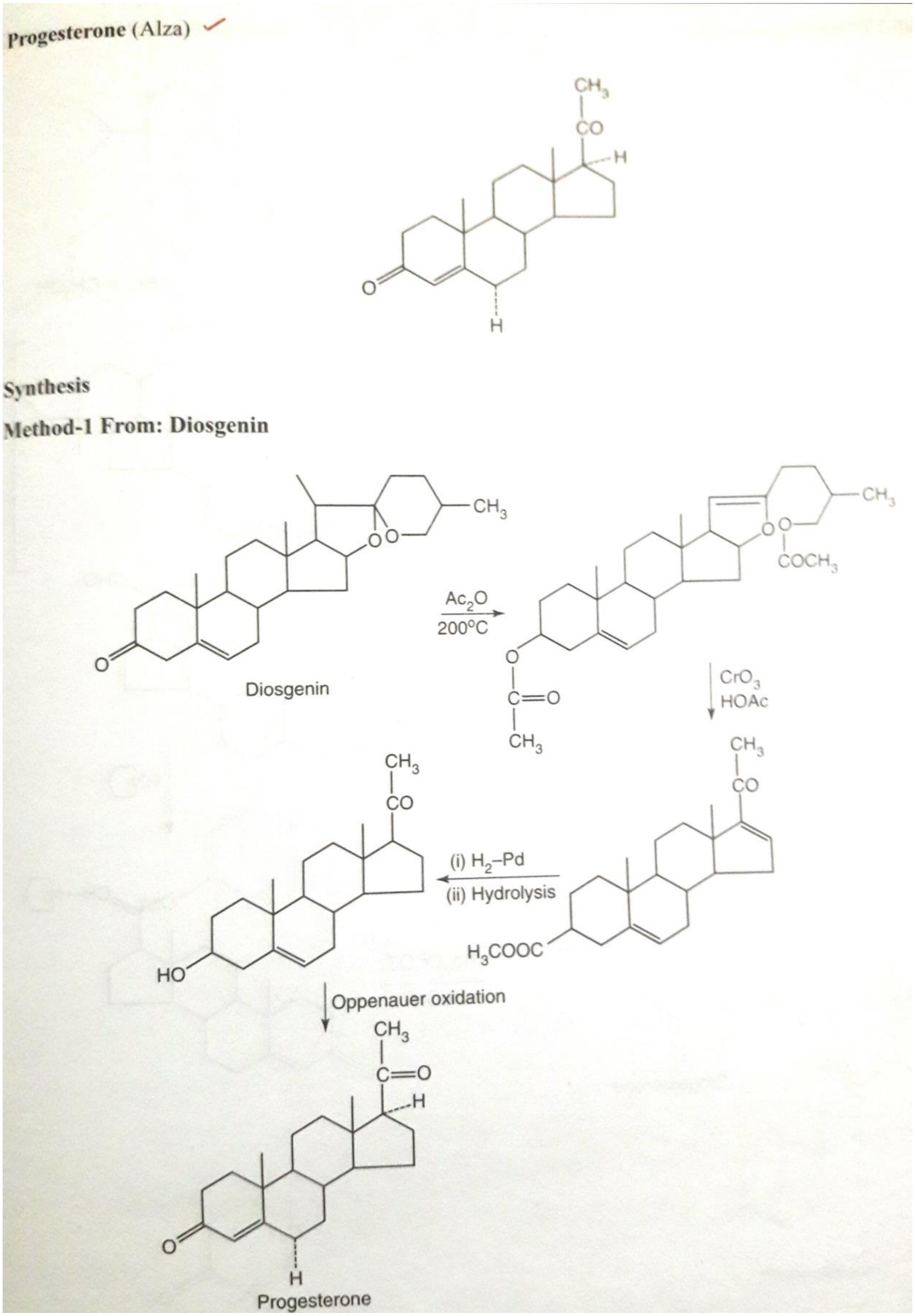


Medrysone

SEX HORMONES

These are a group of steroids biosynthesized in the testes, ovaries, adrenals, and placenta of pregnancy. The activity of these sex hormones is controlled by the hormones that are produced in the anterior lobe of the pituitary gland.

The sex hormones regulate reproductive functions and sexual processes and are responsible for the development of secondary male and female sex characteristics.



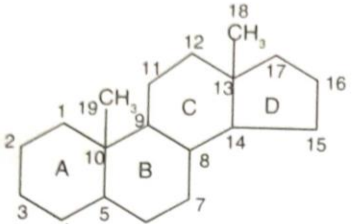
Progesterone (Alza) ✓

Synthesis

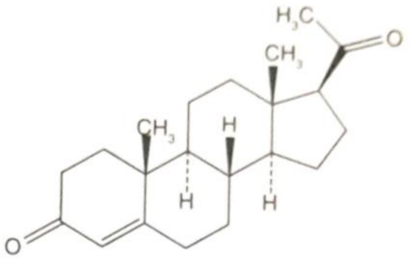
Method-1 From: Diosgenin

Structure–Activity Relationship of Progesterones

Presence of steroid nucleus (cyclopentanoperhydrophenanthrene ring) is compulsory for pharmacologica activity of progestins.



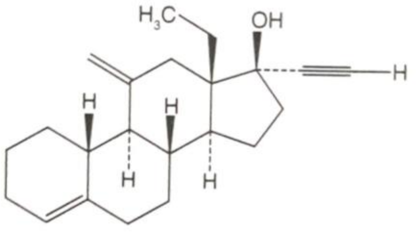
Steroid nucleus



Progesterone

- Ketone group at C-3 is not essential for the activity of progesterone, because removal of it retains the progesterone activity.

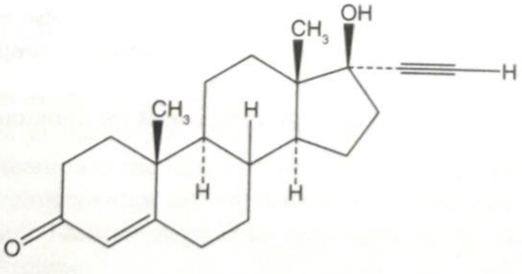
  Example,



Desogestrel

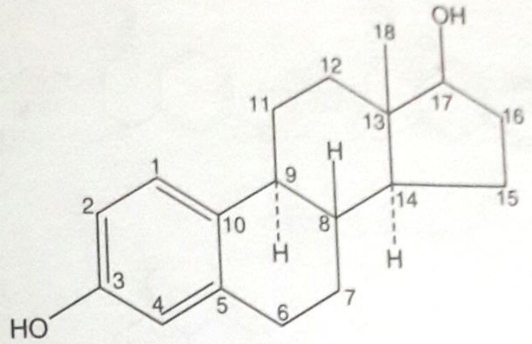
- Presence of ethyl or ethinyl or diethyl group at C-17 in α configuration increase bioavailability through oral route, but decreases by subcutaneous route.

  Example,



Ethisterone

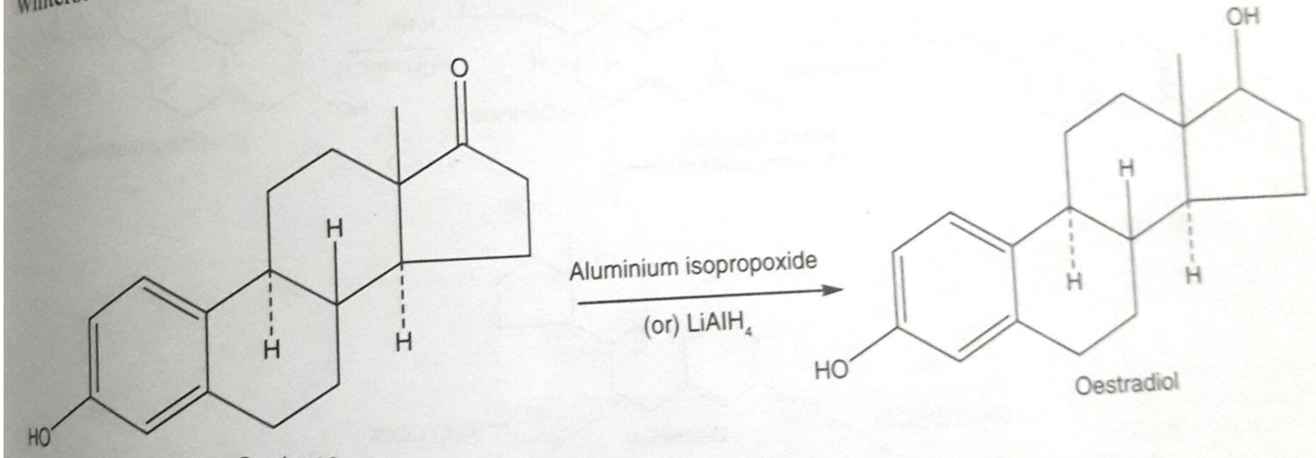
- The l-enantiomer of the compound resulting from substitution of ethyl group at C-ring juncture is found to be active.
- Derivatives of the progestins like 3-oxime-17-ester decreases androgenic side effect, while retaining the progestin activity.



Oestrogen (or) (9*S*, 14*S*)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3,17-diol

It exists as two stereoisomeric oestradiols (i.e. α and β). Among them β-isomer is much more active than oestrone whereas α-isomer is much less active.

Doisy et al., in 1935, isolated the β-isomer from the ovaries of cow. The α-isomer was isolated by Winterstein and co-workers in the year 1938 from the pregnancy urine of mares.

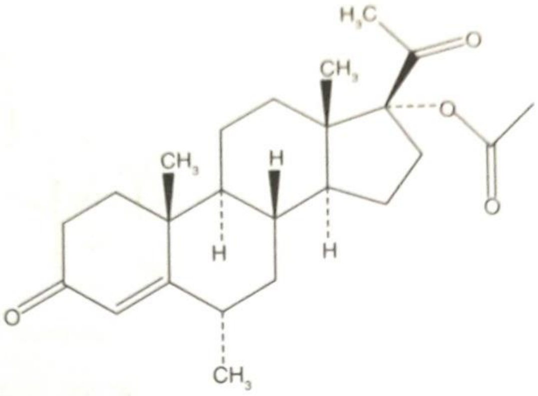


Oestrone

Oestradiol

- Introduction of halogen or CH$_3$ at C-6 or C-7 atoms in α configuration increases hormonal activity of progestins.

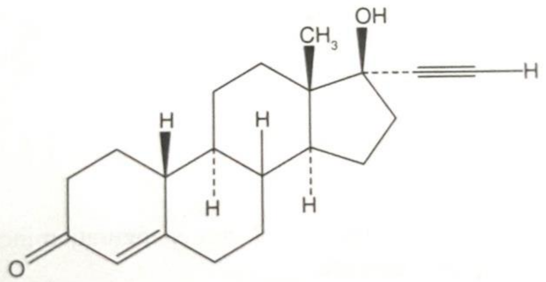
Example



Medroxy progesterone acetate

- Presence of methyl at C-19 is not essential for activity because its removal leads to formation of compound with increased activity.

Example

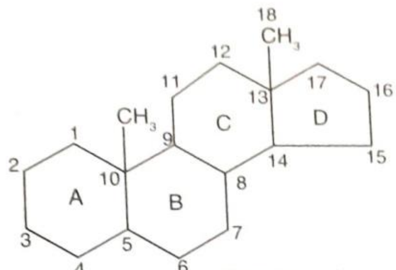


Norethindrone

- Addition of Cl or F at C-21 prevents metabolic hydroxylation, which also enhances oral effectiveness.
- Unsaturation at ring A and B enhances activity of 19-norethindrone. Example: Trimegestone.
- Addition of methyl at 18th position increases the activity.
- In ring D at C-17, acetylation of 17α-hydroxyl group increases the duration of action.

Structure–activity relationship of oestrogens

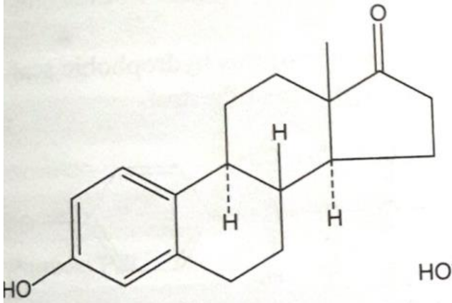
Presence of steroid nucleus (cyclopentanoperhydrophenanthrene ring) is essential for pharmacological activity of oestrogens.



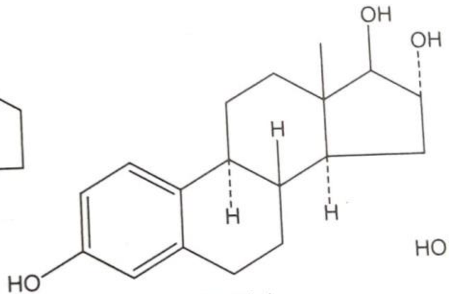
Steroid nucleus

Modification of Ring A

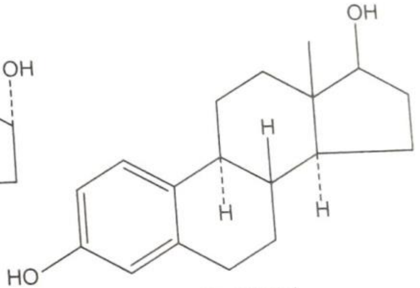
- Ring A is aromatic in nature in all the oestrogens, which is essential for oestrogenic activity.
- –OH group at C-3 is also essential for oestrogenic activity. Removal of this –OH group leads to great loss of activity.
- Substitution at C-1 reduces the activity.
- Smaller groups can be substituted at positions C-2 and C-3. Example: 2-hydroxy ethinyl oestradiol.



Oestrone



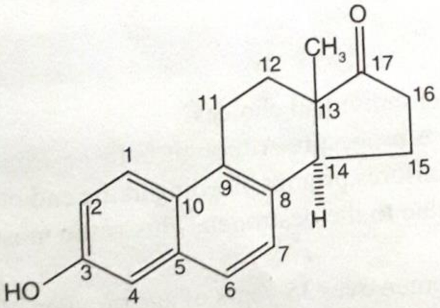
Oestriol



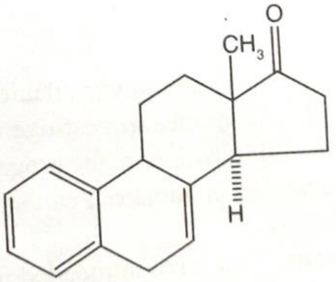
Oestradiol

Modification of Ring B

- Presence of unsaturation at positions C-6 and C-7 increase the potency of drug, similarly additional double bond between C-8 and C-9 positions further increase the activity. Example: equilin, equilenin.
- 7α-Substituents show increased oestrogenic activity.



Equilenin



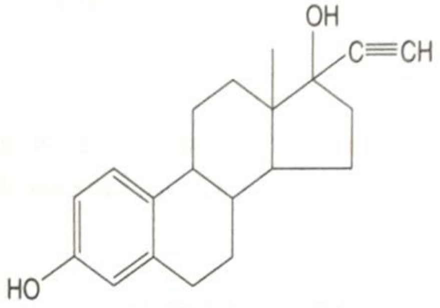
Equilin

Modification of Ring C

- Substitution of –OH groups at C-6, C-7, and C-11 position reduces the activity.
- Substitution at C-11 β-position with alkyl group or alkoxy groups which has 17-ethinyl group greatly increase affinity for the oestrogenic receptor compared to oestradiol. Example: 11β-methoxy or 11β-ethyl oestradiol.
- $-CH_2Cl$ group at C-11 with β-configuration shows more potent activity.
- Larger substituents, example *N*,*N*-dialkyl undecylamides, show antagonistic activity.

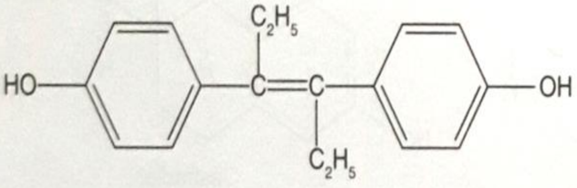
Modification of Ring D

- 17β-OH is essential for oestrogenic activity.
- Epimerization of 17β-OH to α-configuration results in the formation of less active analogues.
- 17α-Ethinyl or 17α-vinyl groups provide greatest activity due to increase in polarity. Example: Ethinyl oestradiol.

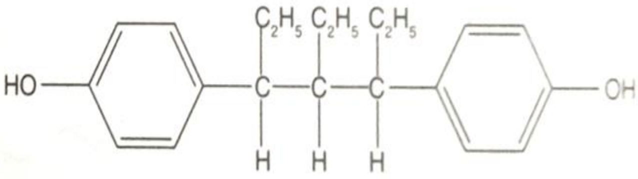


17a-Ethinyl oestradiol

- Reversal of configuration of C-2 or replacement of H for ethynyl in D ring leads to loss of oestrogenic activity or increase in androgenic activity.
- The distance between C-3 and C-17 –OH groups should be 10–12 Å, presence of this hydrophobic scaffolding helps to optimize oestrogenic activity. Example: all oestrogens and diethylstilbestrol.



Diethylstilbestrol



Benzoestrol

Hormonal Contraceptives

Because of our alarming population trend, antifertility drugs are the need of the day. These are hormonal preparations used for reversible suppression of fertility. In the year 1955, successful use of an oral progestin for contraception was found, soon it was discovered that addition of a small quantity of an oestrogen enhances their efficacy.

STEROIDS

Classification

1. **Androgenic or male sex characteristics promoting activity:** Compounds with androgenic activity are called androgens. It includes normal development, functioning, and maintenance of the male sex organs and sexual characteristics.
2. **Anabolic or muscle building activity:** Compounds with anabolic activity are called anabolic agents. It causes nitrogen retention by increasing the rate of protein synthesis, decreasing the rate of protein catabolism, and thus promotes laying down of new tissues. It also stimulates the thickness rise and linear growth of the bones to some extent. The distinction of anabolic therapy of such wasting conditions as cancer, trauma, osteoporosis, and effects of immobilizations are also treated by the anabolic agents.

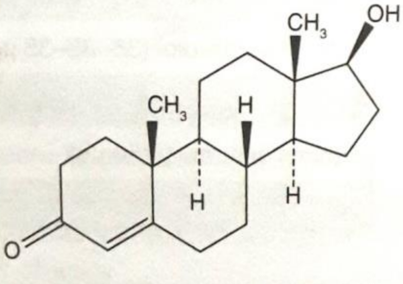
Biological Activities of Androgens

Testosterone and DHT cause masculinizing effects, even in the male foetus. They induce the development of prostate, penis, and related sexual tissues at puberty. The secretion of testosterone by the testes increases greatly, leading to an increase in facial and body hair, deepening of the voice, increased protein anabolic activity and muscle mass, and increase in the size of sexual organs. Spermatogenesis begins, and the prostate and seminal vesicles increase their activity. The skin becomes thicker, and sebaceous glands increase in number leading to acne in many young people. The androgens also play important roles in male psychology and behaviour. Testosterone plays a role in libido, mood, muscle mass and strength, as well as bone density of women.

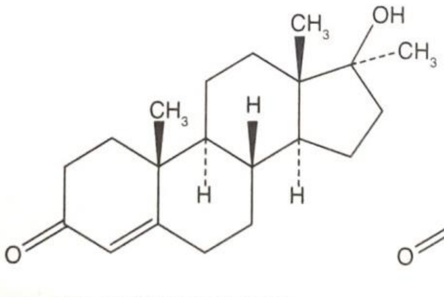
Therapeutic Uses of Anabolic–Androgenic Steroids (AAS)

- Mainly used in androgen replacement therapy in men, either at maturity or in adolescence.
- Used in advanced or metastatic breast carcinoma of selected patients.
- Used to relieve bone pain associated with osteoporosis and to treat certain anaemias.

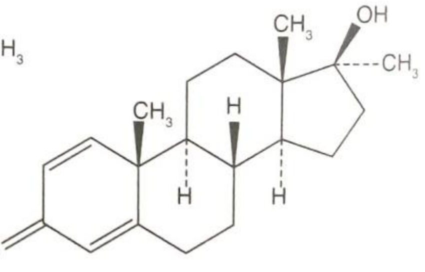
Following are the testosterone and its synthetic anabolic–androgenic steroids.



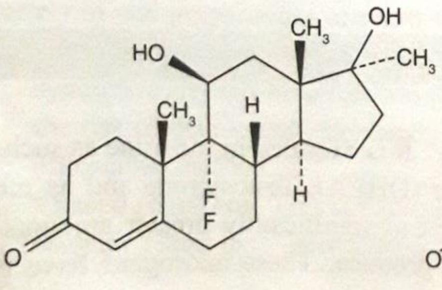
Testosterone



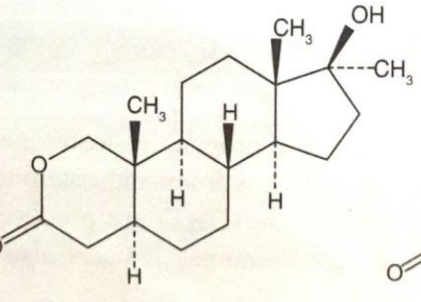
17a-Methyltestosterone



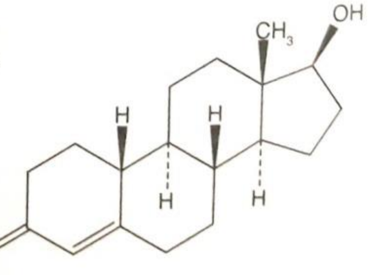
Methandrostenolone
(Dianabol)



Fluoxymesterone



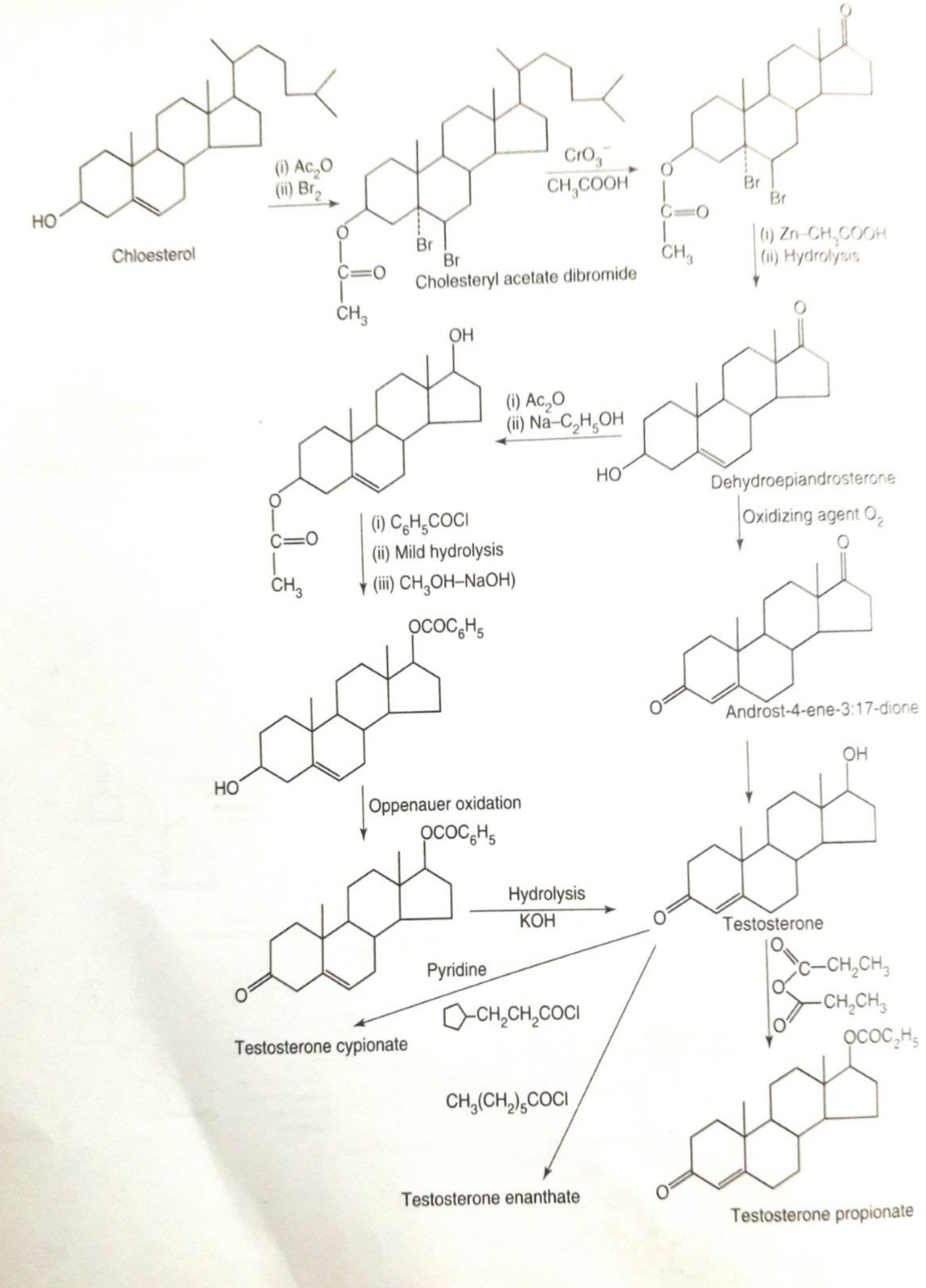
Oxandrolone (Oxandrin)



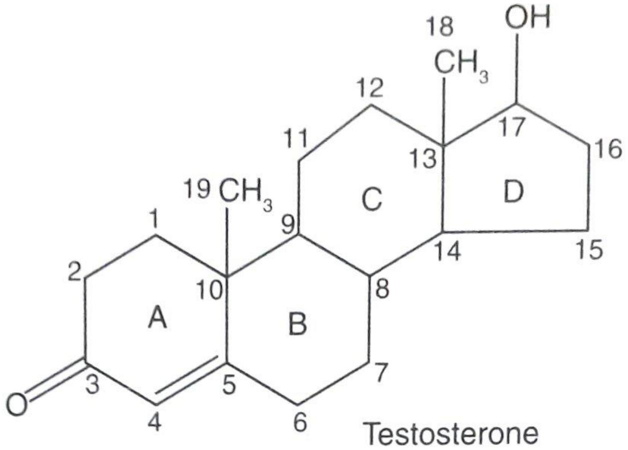
Nandrolone

STEROIDS

Synthesis

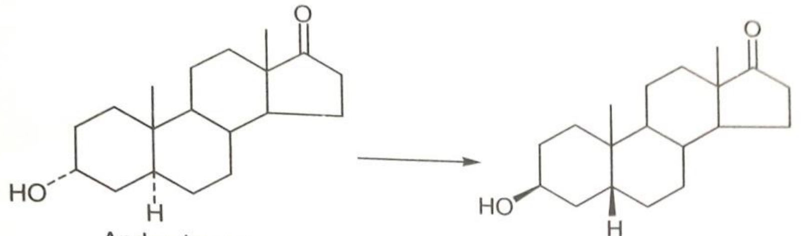


Structure–Activity Relationship of Androgens

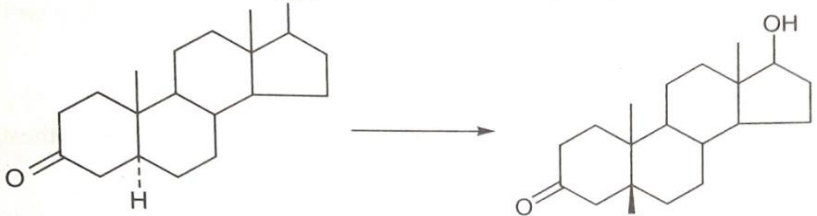


Testosterone

Conversion of testosterone to dihydrotestosterone (DHT) has little effect or may increase potency. Changing the A/B *trans* stereochemistry of known androgens such as androsterone and DHT to the A/B *cis*-derivative 3β-hydroxy-5β-androstane-17-one and 17β-hydroxy-5β-androstan-3-one, respectively, reduces both the anabolic and androgenic properties drastically.

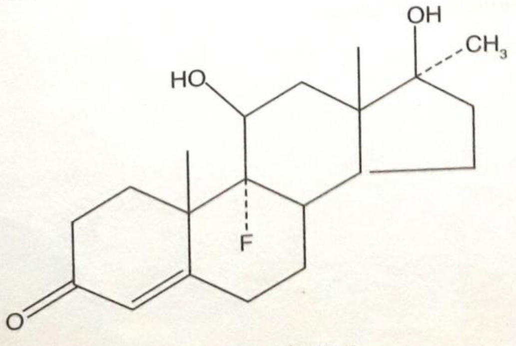

Androsterone

3b-Hydroxy-5b-androstane-17-one


51-Dihydro testosterone

17b-Hydroxy-5b-androstane-3-one

- These observations indicated the importance of the A/B *trans* ring juncture for activity.
- Oxygen function at C-3 can be removed from testosterone with little reduction in androgenic activity, removal of the –OH group from C-17 sharply reduced the androgenic activity.
- The position of the oxygen atom is important. The substitution of oxygen at C-2 affords the most active compound and the order of activity is $2 > 3 > 4$.
- The relative androgenicity of the olefins of 3-deoxy testosterones is in the order of $\Delta^1 > \Delta^2 > \Delta^3 > \Delta^4$. But the Δ^2-isomer displayed the greatest anabolic activity.
- On the basis that sulphur is bioisosteric with CH=CH Wolff and co-workers have synthesized the thia, seleno, and tellurio androstanes, which displayed androgenic activity.
- Esterification of testosterone prolonged the activity significantly when it was administered parenterally. Long-chain aliphatic or aryl aliphatic acid such as propionic, heptanoic (enanthoic), decanoic, cyclopentylpropionic (cypionic), or β-phenylprorpionic acid are used for esterification of testosterone.
- Placement of a 9α and an 11β-OH substituents (analogous to synthetic glucocorticoids) gives fluoxymesterone (9α-F-11β,17β-dihydroxy-17-α-methylandrost-4-en-3-one), which is an orally active androgen showing approximately four times the oral activity than that of 17α-methyl testosterone.


Fluoxymesterone