3. CLASSIFICATION

Various authors have used slightly different means of classifying the **steroids**, but the one selected here divides them into *five* categories depending solely on the type of substituent group at C-17, *i.e.*, group R.

(*i*) **Sterols**—where R is an aliphatic side chain. They contain usually one or more hydroxyl groups attached in alicyclic linkage.

(*ii*) **Sex Hormones**—where R bears a ketonic or hydroxyl group and mostly possesses a two-carbon side chain.

(*iii*) **Cardiac Glycosides**—where R is a lactone ring. The **glycosides** also contain sugars linked through oxygen in other parts of the molecule. Normally on hydrolysis it yields this sugar together with the cardiac aglycone.

(*iv*) **Bile Acids**—where R is essentially a five-carbon side chain ending with a carboxylic acid moiety.

(*v*) **Sapogenins**—where R contains an oxacyclic (ethereal) ring system.

3.1. Sterols

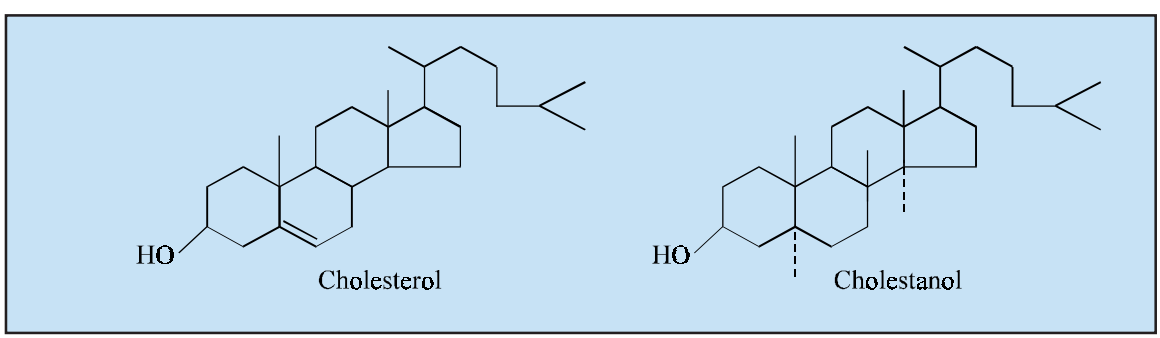
The term **sterols** has been coined from the words **'steroidal alcohols'**. They have been found to occur both in animal and plant oils and fats. These are usually crystalline compounds and mostly bear an alcoholic group. They may occur either as free or as esters of the higher fatty acids, and are isolated from the unsaponifiable fraction of oils and fats.

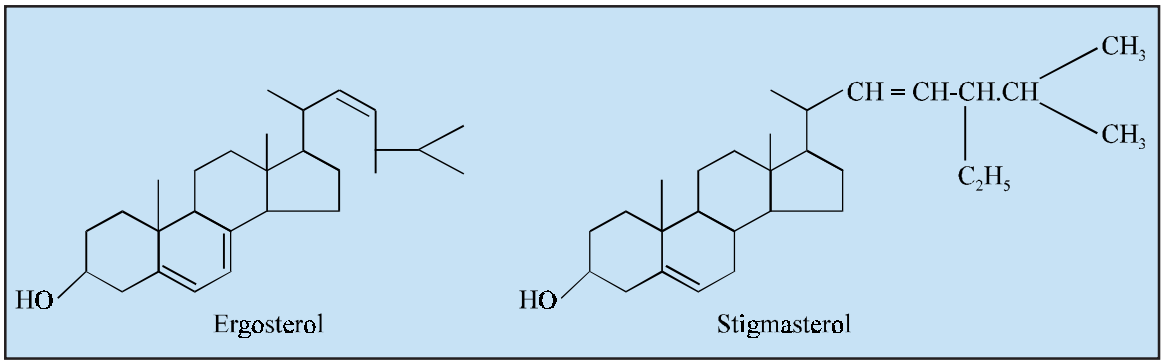
The **sterols** may be further sub-divided into the following ***three*** categories, namely :

(*a*) **Zoosterols**—such sterols those are obtained from the animal kingdom only, *e.g.*, **cholesterol**, **cholestanol**, **coprostanol (coprosterol)**, etc.

(*b*) **Phytosterols**—such sterols those are derived exclusively from the plant sources, *e.g.*, **ergosterol**, **stigmasterol**, **sitosterols**, etc.

(*c*) **Mycosterols**—such **sterols** those are obtained from either yeast or fungi. It is pertinent to mention here that this particular classification is not quite rigid because of the fact that some sterols are obtained from more than one of these groups.





Ergosterol Stigmasterol

3.2. Sex Hormones

Generally, **hormones** are substances that are secreted by the ductless glands, and only minute amounts are necessary to produce the various physiological reaction in the body.

However, the **sex-hormones** belong to the steroid class of compounds and are produced in the gonads, *i.e.*, testes in the male and ovaries in the female. In fact, their activity seems to be controlled and monitored by the hormones that are produced in the anterior lobe of the pituitary glands. Perhaps because of this inherent characteristies the **sex hormones** are invariably termed as the secondary **sex hormones** and the **hormones** of the anterior lobe of the pituitary are called the primary **sex-hormones**.

A general survey of the literature stretching over the past three decades would reveal that a vast number of structural modifications of the steroid hormones have taken place. These newer compounds have been prepared with a view to enhance their biological activities, oral activity and duration of action, besides attributing better solubility properties, minimising the requirement for some essential perimeter functional group of the parent hormone and lastly to effect a marked separation of their biological activities.

These modifications have been duly accomplished through a number of means, for instance, protecting some vital moieties against the metabolic attack or attack by intestinal bacteria, prevention of the conversion *in vivo* of one **steroid hormone** into another steriod and lastly through alteration of physical properties by preparing their respective 19-nor analogues, ester derivatives, enol ethers, acetals and ketals, bringing about conformational changes and electron attracting effect.

3.2.1. Classification

Sex-hormones are usually classified under the following *three* heads, namely :

(*i*) **Androgens** (Male Hormones) *e.g.*, **androsterone**, **testosterone**.

(*ii*) **Oestrogens** (Female or Follicular Hormones), *e.g.*, **oestrone**, **oestriol**, **oestradiol**, **stilbesterol**, **hexesterol**.

(*iii*) **Gestogens** (The Corpus Luteum Hormones) *e.g.*, **progesterone**.

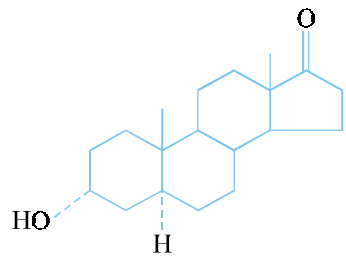
3.2.2. Androgens

Experiments with testicular extract has more or less enjoyed a chequered career. Veronoff successfully transplanted tested from monkeys into elderly men and claimed to rejuvenate them. Likewise, ligature of *vas deferens* which is known to cause atrophy of spermatogenic tissue and indirectly hypertrophy ofintestinal tissue which secrete **testosterone**. Another researcher Steinach carried out similar studies by ligaturing the *vas deferens* and obtained identical results.

Androgens besides showing a specific action on gonads, also stimulate production of elements that are absolutely essential for all tissue growth. This characteristic which the **androgens** share with other **steroidal hormones**, such as : **corticosterones** and **oestrogens** has paved the way towards synthesis of newer steroids that possess mainly metabolic activity without androgenic effect.

The *two* most important **androgens** are **androsterone** and **testosterone**.

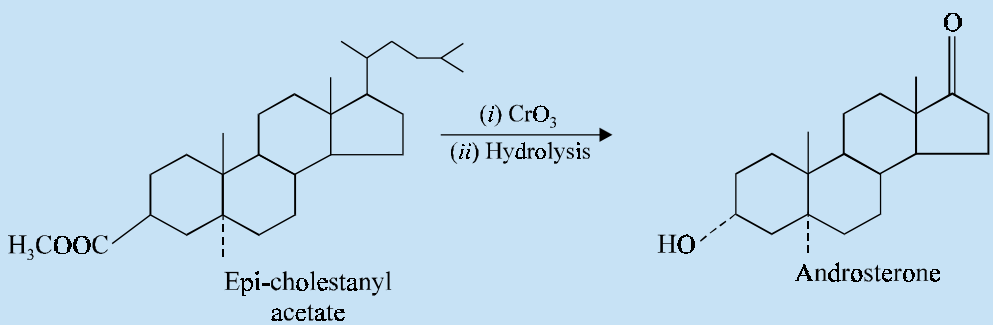
A. Androsterone



3α-Hydroxy-5α-androstan-17-one.

Androsterone (m.p. 185°C) is a **naturally occurring androgen** that may be isolated from male urine. It can also be synthesized from **epi-cholestanyl acetate** as given below :

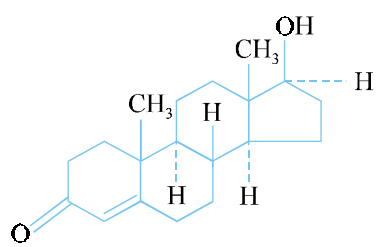
Synthesis



It may be synthesized from epi-cholestanyl acetate at two stages : *first*, by its oxidation with chromium-6-oxide and *secondly*, by subjecting the resulting product to hydrolysis to yield the desired product.

Butanandt and co-workers (1931) first isolated **androsterone** (15 mg) from 15,000 litres of urine.

B. Testosterone INN, BAN, USAN,



Testost. 17β-Hydroxyandrost-4-en-3-one ; Androst-4- en-3-one, 17-hydroxy-, (17β)- ; BP, USP ; Synadrol F(R) (Pfizer) ; Mertestate(R) (Sterling).

Synthesis

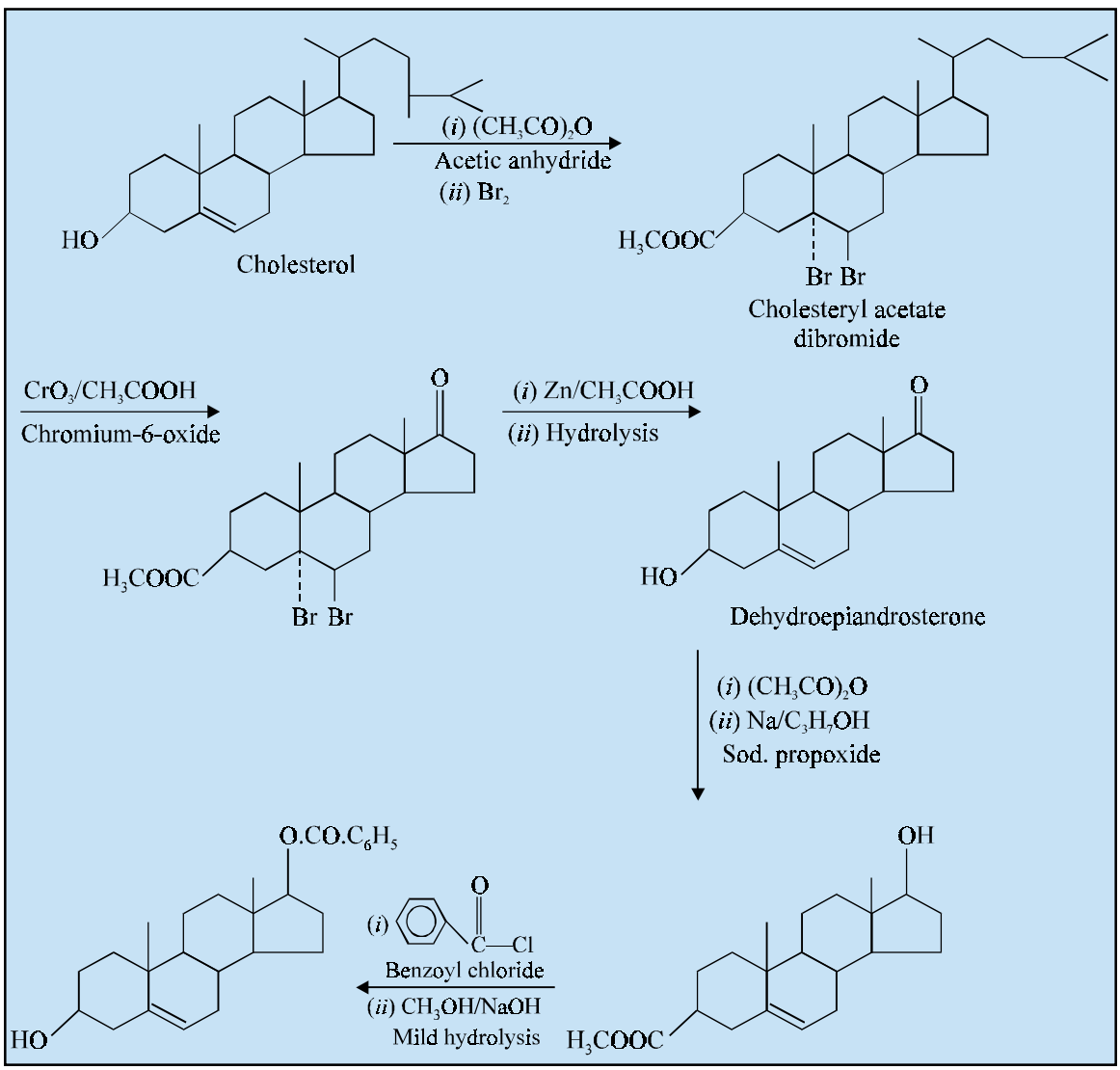
Testosterone may be synthesized from the following *two* starting materials, namely ;

(*i*) From Cholesterol, Butenandt (1935) ; Ruzica (1935) ; Oppenauer (1937) ;

(*ii*) From Dehydroepiandrosterone, Mamoli (1938).

(a) From Cholesterol

Cholesteryl acetate dibromide is first prepared by the acetylation of chloesterol and its subsequent bromination. This on oxidation with chromium-6-oxide reduces the 8-carbon side chain at C-17 to a mere CO moiety, which on reduction followed by hydrolysis yields dehydroepiandro-sterone. The resulting product on acetylation protects the acetyl moiety at C-3 and treatment with sodium propoxide introduces a hydroxy group at C-17. Benzoylation followed by mild hydrolysis causes the reappearances of free OH moiety at C-3 and a benzoxy function at C-17. **Oppeanauer oxidation** cuased by refluxing the resulting secondary alcohol with aluminium tertiary butoxide in excess of acetone affords a ketonic function at C-3, which upon hydrolysis in an alkaline medium yields the official compound.



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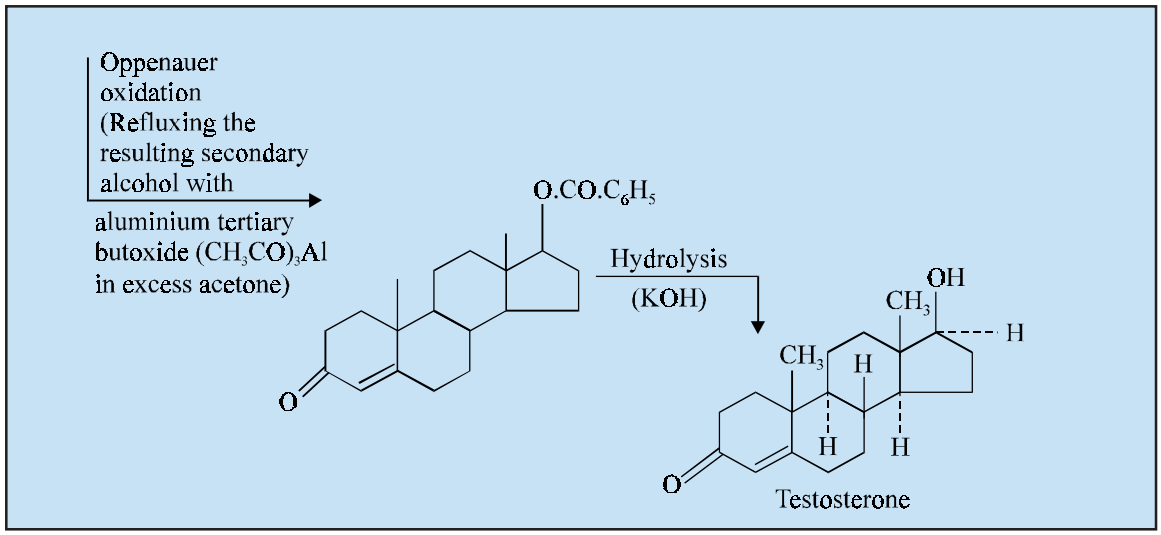
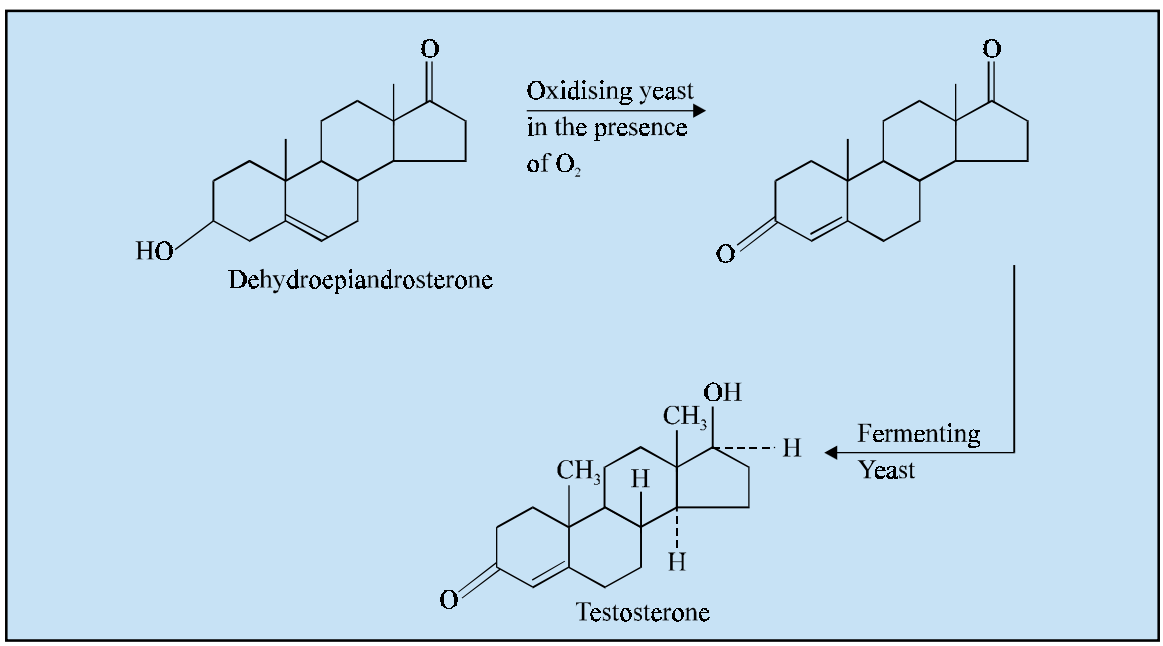


(*b*) *From Dehydroepiandrosterone*



Dehydroepiandrosterone first on being treated with oxidising yeast in the presence of oxygen and secondly by the fermenting yeast yields the desired official compound.

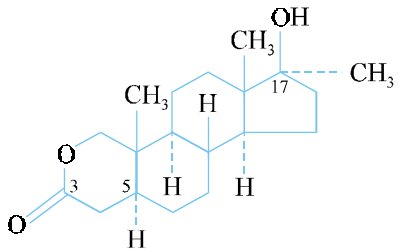
Testosterone controls the development as well as maintenance of the male sex organs and is solely responsible for the male secondary sex characteristics.

It also increases the size of the serotum, phallus, seminal vesicles, prostrate and enhances the sexual activity in adolescent males.

Testosterone *along with other androgens are invariably employed in the male for replacement therapy in hypogonadism, eunuchoidism, and the male climacteric.*

Dose : *For prolonged treatment, subcutaneously, 600 mg; For breast cancer up to 1.5g ; Alternatively 10 to 30 mg per day through the buccal administration.*

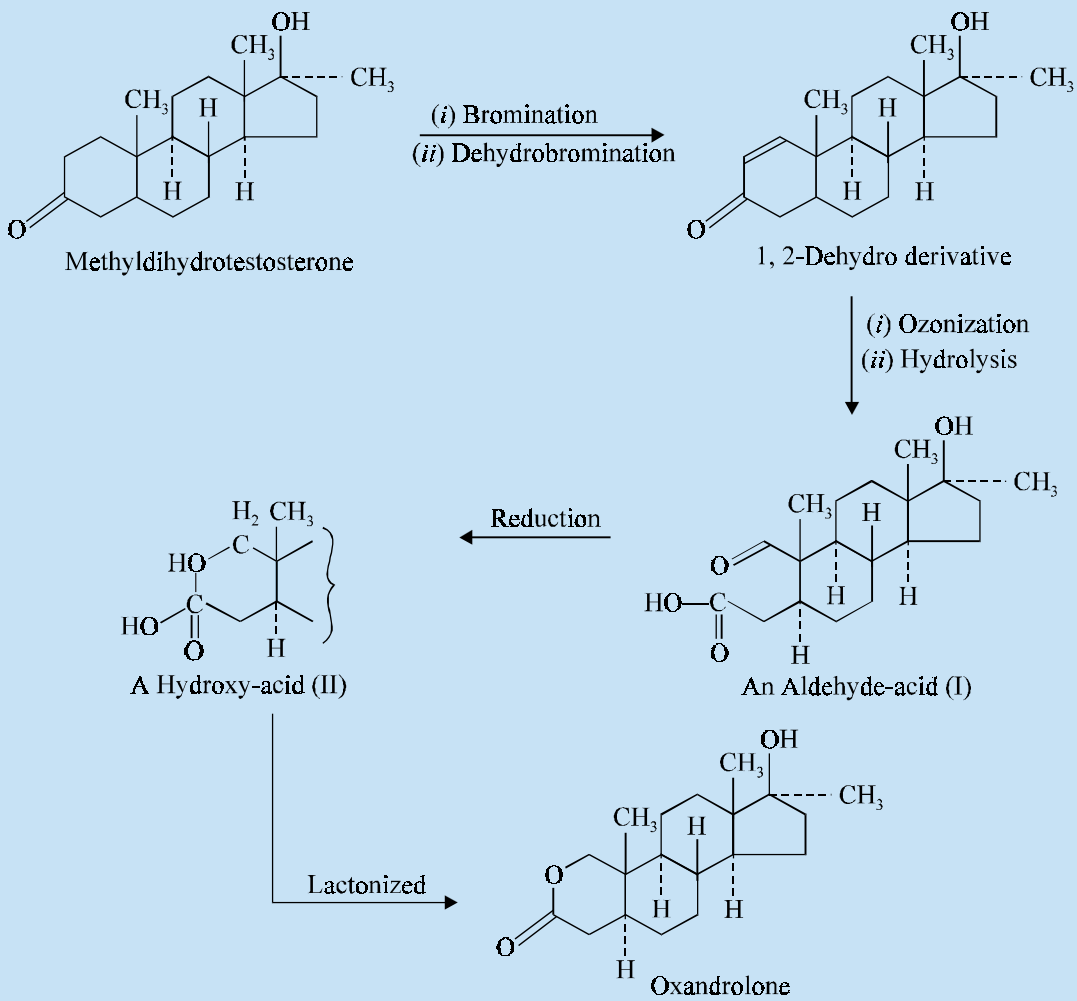
(*c*) *Oxandrolone* USAN, BAN, INN



(5α, 17β)-2-Oxandrostan-3-one, 17-hydroxy-17-methyl-; USP;

Oxandrin(R);

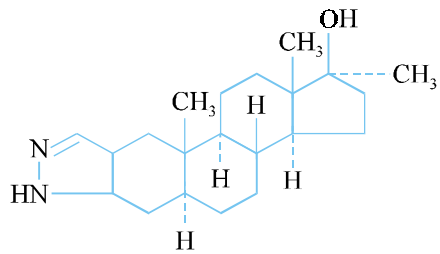
Synthesis



Methyldihydrotestosterone on being subjected to bromination followed by dehydrobromination gives rise to the formation of 1, 2-dehydro derivative, which upon ozonization and hydrolysis yields an aldehyde-acid (I). The resulting acid (I) on reduction produces the corresponding hydroxy-acid (II) which when lactonized produces the desired compound, **oxandrolone**.

It is an androgenic steroid having comparatively higher **anabolic activity** in relation to the **androgenic activity**. Hence, it is used mostly to promote nitrogen anabolism (protein synthesis) and weight-gain in cachexia* and other debilitating diseases and after serious infections, burns, trauma or surgical procedures. It may also be employed to relieve pain in some types of **osteoporosis** thereby augmenting Ca^{2+} retention and hence improving the condition of bone. It also finds its application for its predominant erythropoetic effects in the treatment of both **hypoplastic** and **aplastic anemias**.**

D. *Stanozolol* USAN, BAN, INN



(5α, 17β)-2′H-Androst-2-enol [3, 2-C] pyrazol-17-ol, 17-methyl ; USP ;

Winstrol$^{(R)}$;

It is an androgen having comparatively *strong anabolic* and weak **androgenic activity**. Its uses are almost identical to that of oxandrolone. Besides, it is also employed in the prophylaxis of hereditary angiodema, which is presently the only approved use.

3.2.2.1. Mechanism of Action

The mechanism of action of the various compounds described under Section 23.3.2.2. shall now be treated individually as under :

3.2.2.1.1. Androsterone

Being one of the naturally occurring androgens it exerts widespread anabolic effects. The '**drug**' also affects hypopituitarism and with **Addison's disease**, relief of impotence not associated with evidence of testicular underactivity, pituitary dwarfism to accelerate growth, and in functional dysmenorrhea giving relief through an antiestrogenic action.

3.2.2.1.2. Testosterone

The '**drug**' undergoes metabolism that may lead to either pharmacologically **active steroids** *e.g.*, **estradiol**, **5α-dihydrotestosterone** (or **5α-DHT**), and **androsterone** ; or to **inactive steroids** *e.g.*, **6α-hydroxytestosterone**, **epitestosterone**, and **etiocholanolone**.***

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*A state of ill-health, malnutrition, and wasting (*e.g.*, chronic diseases, certain malignancies and advanced pulmonary tuberculosis.

***Hypoplastic i.e.*, aplastic anemia ; *Aplastic :* Anemia caused by deficient red cell production due to bone-marrow disorders.

***RW Brueggemier, **Burger's Medicinal Chemistry**, 5th edn, Vol : 3, ME Wolff ed., John Wiley & Sons, NewYork, pp 445-510, 1996.

However, the enzyme **5α-reductase** brings about the following changes, namely :

(*a*) In prostate gland (an androgen target tissue) testosterone gets converted to 5α-DHT, which enjoys the reputation of being the *most potent endogenous androgen metabolite of* **testosterone**, *and*

(*b*) It helps to catalyze an irreversible reaction for which it essentially needs NADPH as a cofactor that strategically provides the H-atom at C-5.*

It is found to be not effective when administered orally as it almost gets destroyed in the liver on absorption. Its plasma half-life ranges between 10-20 minutes.

3.2.2.1.3. Oxandrolone

The '**drug**' exerts its action by virtue of its inherited protein catabolism associated with long-term usage of **corticosteroid**. Besides, it is also indicated in HIV wasting syndrome and alcoholic hepatitis.

Note. Strictly speaking it is not a 'steroid', and its configuration is that of a 17-methyl androgenic steroid.

3.2.2.1.4. Stanzolol

The '**drug**' acts by significantly lowering the frequency and severity of attacks in angioedema ; and it is now the only approved application.

3.2.2.2. Derivatives of Testosterone

There are, in fact, quite a few improtant derivatives of testosterone that have been used extensively in therapy ; and these are summarized in Table 23.1.

Table 23.1. Derivatives of Testosterone

Approved Names	Official Status	Proprietary Names	Dose
Testosterone Acetate	—	Cetovister(R) (Substancia, Spain)	—
Testosterone Cypionate	USP ;	dep Andro 100(R) (Forest)	50 to 200 mg/ml in oil solution
Testosterone Decanoate	BP ;	—	—
Testosterone Enanthate	BP ; USP ;	Delatestryl(R) (Squibb)	100 to 400 mg every 2 to 4 weeks
Testosterone Isocaproate	BP ;	—	—
Testosterone Ketilaurate	—	—	—
Testosterone Phenylacetate	—	—	—
Testosterone	BP ;	Tess PP(R)	—

(*Contd...*)

*P Ofner, *Vit Horm*., **26,** 237, 1968.

Phenylpropionate		(Organon)	
Testosterone Propionate	BP ; USP ; Eur. P. ; Int. P. ; IP. ;	Synadrol(R) (Pfizer)	5 to 20 mg daily as buccal tablets
Testosterone Undecanoate	—	Restandol(R) (Organon, UK)	40 to 160 mg daily

3.2.3. Oestrogens

The **oestrogens** are mainly concerned with growth and function of the sex organs.

In general, they are classified under *two* sub-heads, namely :

(*a*) Steroidal Oestrogens

(*b*) Non-steroidal Oestrogens

(*a*) Steroidal Oestrogens

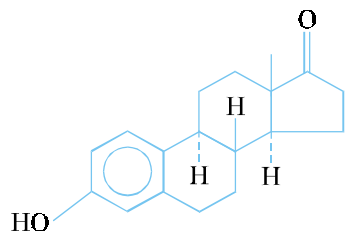
All of them essentially possess a steroidal nucleus and attribute oestrogenic activity.

Examples : Oestrone, oestriol, oestradiol.

***A.* Estrone INN, USAN Oestrone, BAN,**

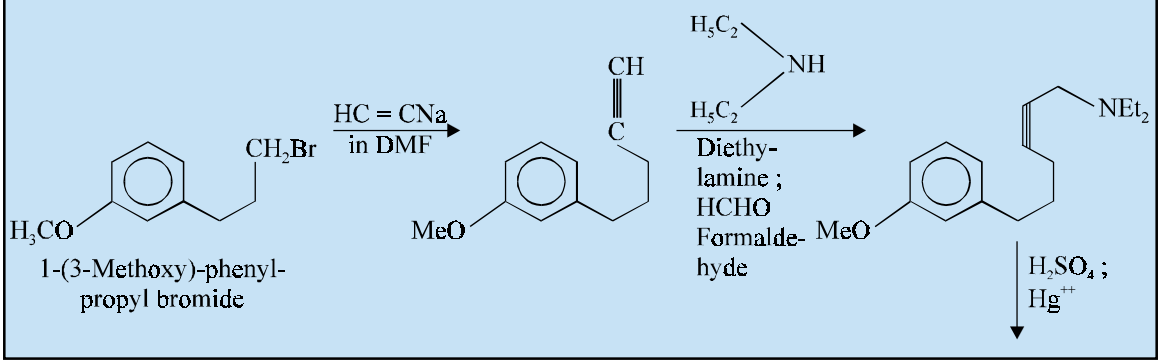
3-Hydroxyestra-1, 3, 5 (10)-trien-17-one ; Estra-1-3, 5(10)-trien-17-one, 3 hydroxy-; Oestrone Eur. P. ; Estrone USP ;

Theelin(R) (Parke-Davis).



Synthesis

Johnson and co-workers (1958, 1962) have carried out a total synthesis of **oestrone** ; each step in their synthesis was **stereoselective**, but Hughs and co-workers (1960) have put forward a total synthesis of oestrone which appear to be comparatively simpler than any other previous method.



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