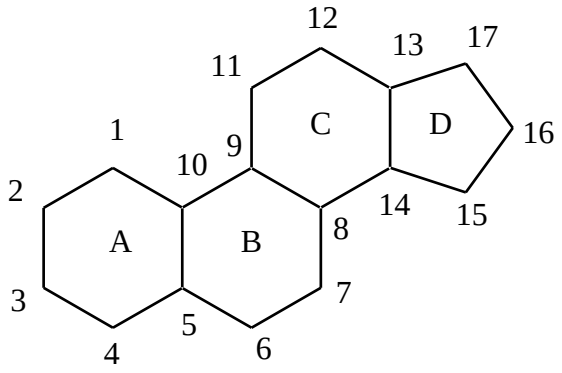
Steroidal hormones & related drugs

Abdu Tuha

Basic skeleton for steroids

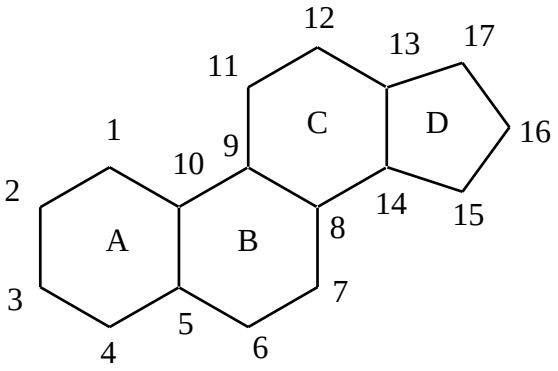


Cyclopentano perhydro-phenanthrene

Substituents indicated by

- Numbers to show their position
- α/ β or solid/ broken lines to show their configuration
  - α / broken line = $\downarrow$
  - β / solid line = $\uparrow$
- Methyl groups generally attached at 10 & 13
- If ring A is aromatic the C-10 methyl is absent
- Usually side chain at 17

Basic skeleton for steroids Cont.



Cyclopentano perhydro-phenanthrene

Stereochemistry

- Rings A & B
  - Fused cis or trans
    - Affording the 5 α or β series respectively
- Rings B & C are fused trans
- Rings C & D are fused trans

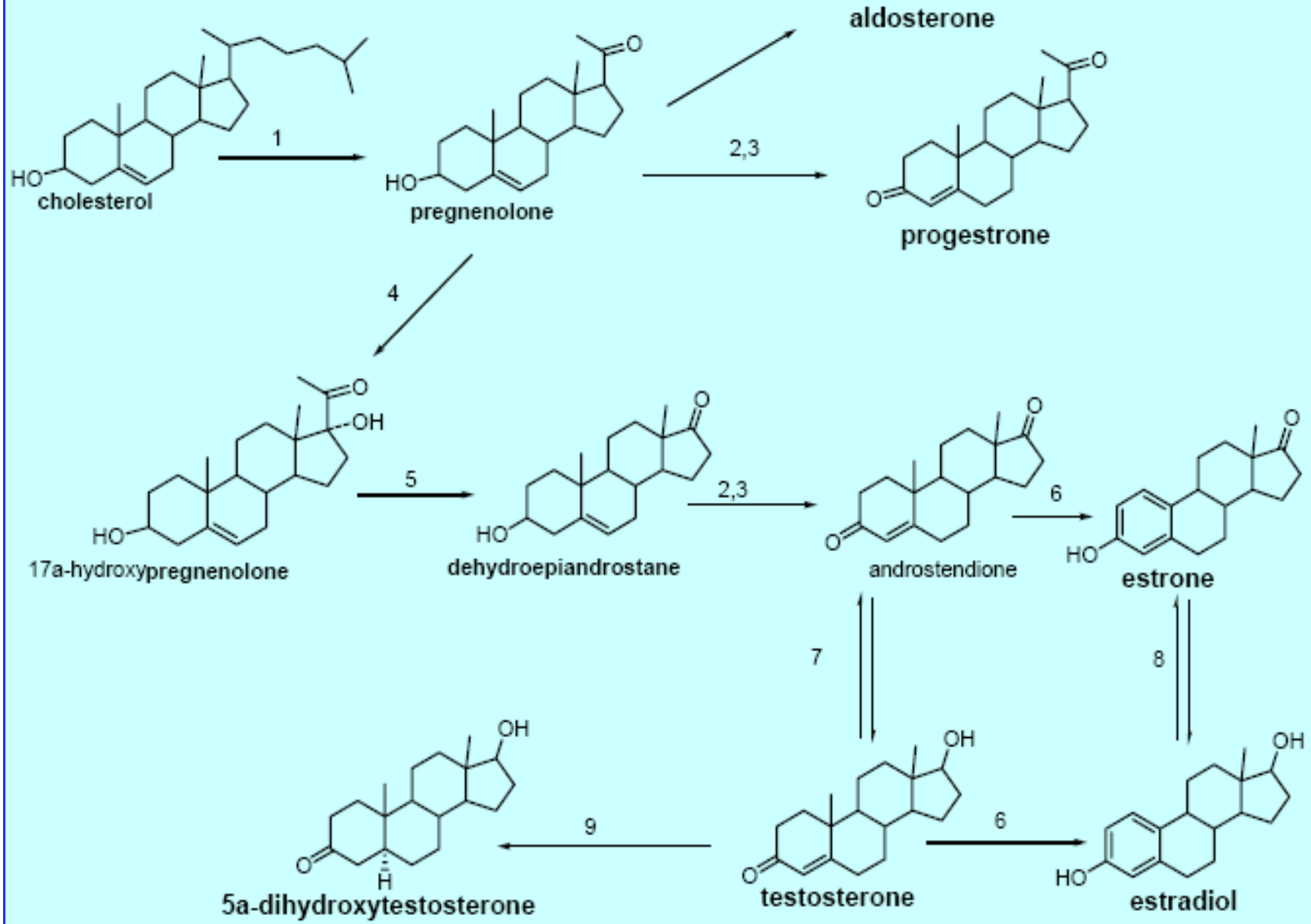
  except in
  - Cardiac glycosides
  - Toad poisons

Steroid Hormones

Steroid hormone biosynthesis

- common precursor is cholesterol
- first step is degradation of side chain via desmolase and formation of pregnenolone (C21)
- pregnenolone can then follow several pathways:
  - It can be converted to progesterone which can be converted into gluco and mineralocorticoids, **C21** (in the adrenal cortex)
  - It can also be converted through several steps into testosterone (**C19)** which in turn can be aromatized into estradiol (**C18**)

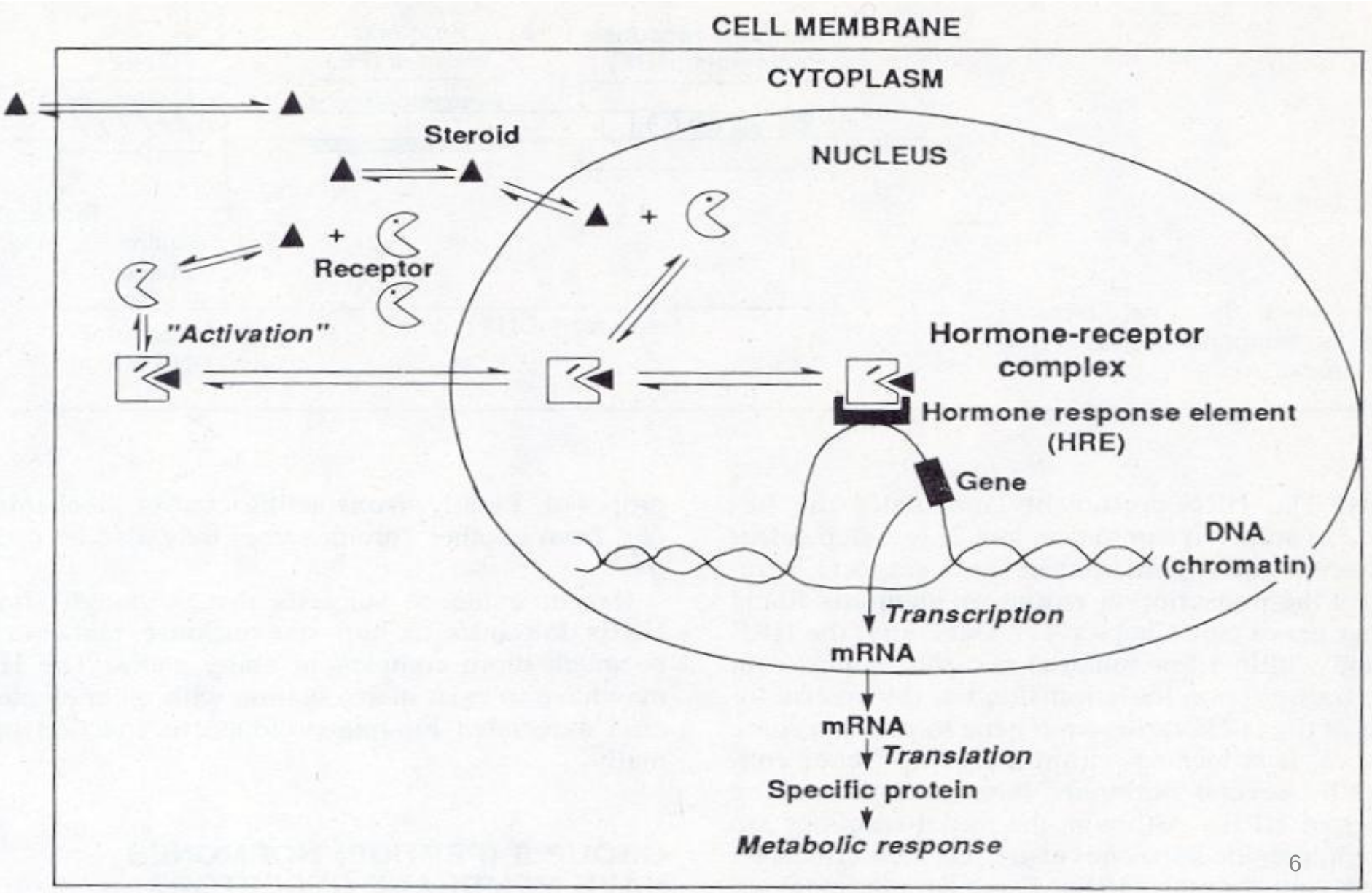
►Biosynthesis of sex hormones

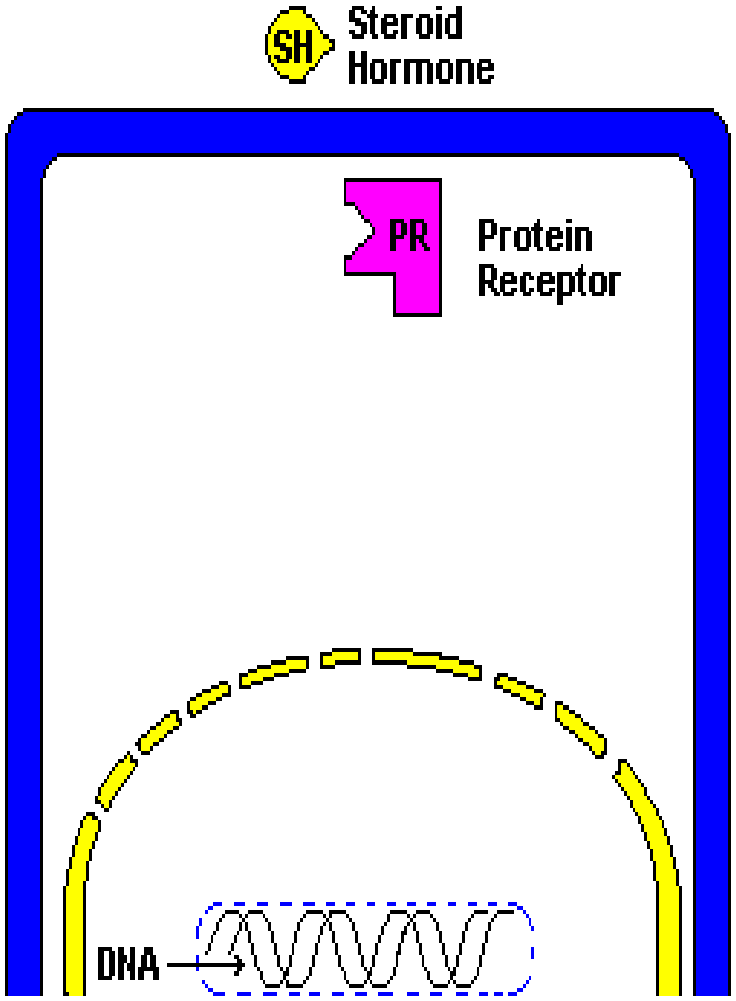


1-side chain cleavage 2- 5 ene-3B 3hydroxydehydrogenase 3-3 oxo 4-5isomerase 4- 17a-hydroxylase 5- 17-20-lyase

6- aromatase 7-17B-hydroxydehydrogenase 8-estradiol deyhdrogenase 9-5a- dihydrotestosterone

Model of steroid hormone action



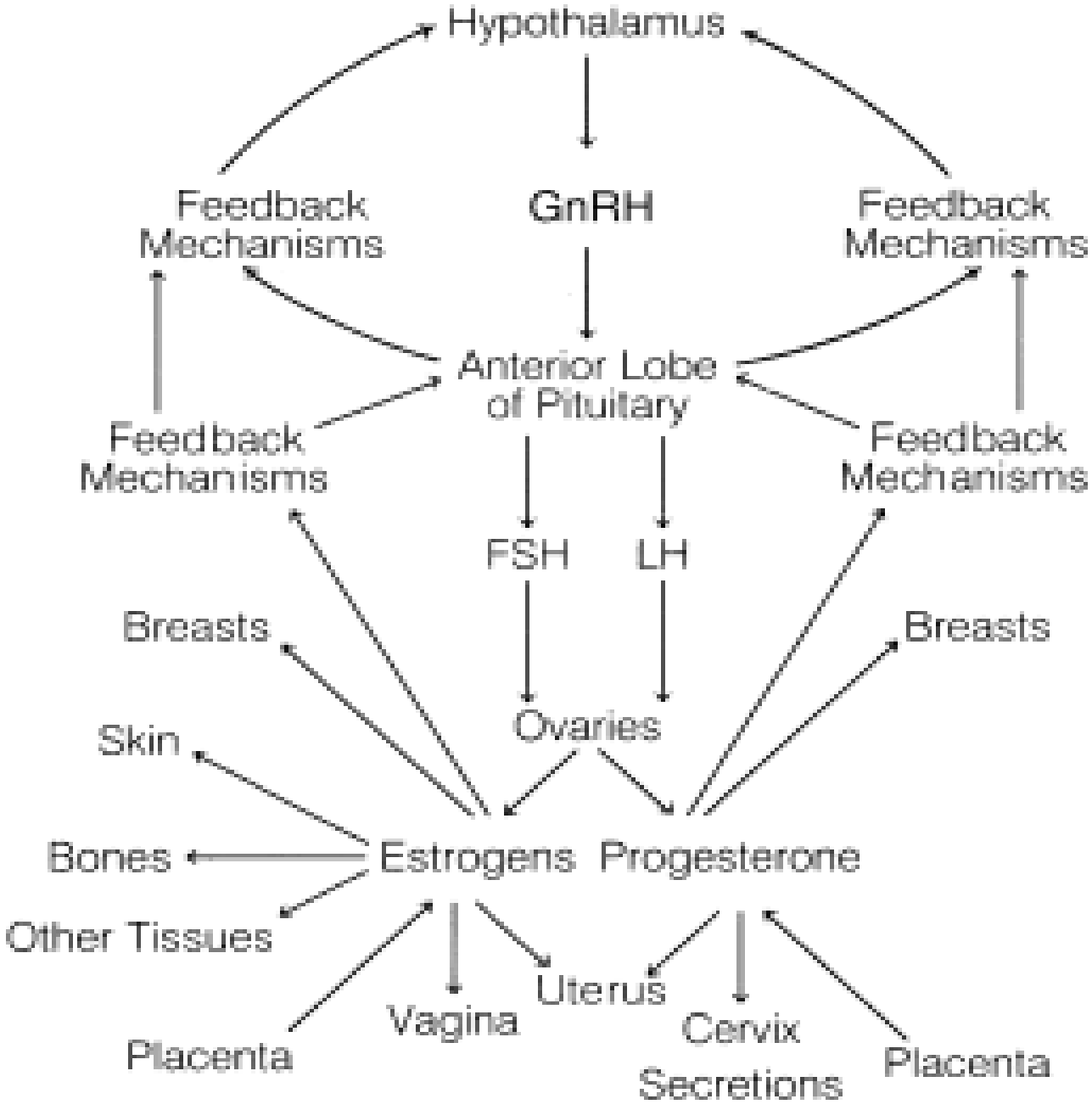

SH
Steroid
Hormone
PR
Protein
Receptor
DNA

Classification of steroidal hormones

- Sex hormones
  - Three groups produced by genital glands
    - Estrogens
    - Progestins
    - Androgens
- Adrenocortical hormones
  - Mineralocorticoids
    - Control salt and water balance in renal tubules
    - Cause retention of Na^-, Cl^- & water
    - Enhance elimination of K^+
  - Glucocorticoids
    - Facilitate production of glucose from non carbohydrate sources
    - Have lesser effect on salt & water balance
    - Inhibit response of tissue to inflammation

Sex hormones

- Anterior lobe of the pituitary gland liberates gonadotropic substances
  - Stimulate development of gonads of male & female
- In females- two gonadotropic hormones are involved
  - Follicle stimulating hormones (FSH) causes
    - Maturation of graafian follicle in which egg cells or ova develop
      - Cells surrounding graafian follicle produce an estrogen hormone (estradiol)
  - Luteinizing hormone
    - After ovulation LH stimulates development of
      - The corpus luteum from the graafian folicle
        - » Corpus luteum produces progestrone & released in to blood
    - If the egg get fertilized
      - Pregnancy occurs
        - » Corpus luteum grows for several months
    - If the ova is not fertilized
      - Pregnancy does not occur
        - » Corpus luteum degenerates
        - » Menstruation begins & the cycle repeated


Hypothalamus
Feedback Mechanisms
GnRH
Feedback Mechanisms
Anterior Lobe of Pituitary
Feedback Mechanisms
Feedback Mechanisms
FSH
LH
Breasts
Breasts
Ovaries
Skin
Bones
Estrogens
Progesterone
Other Tissues
Uterus
Vagina
Cervix
Placenta
Secretions
Placenta

Estrogens

Medical uses of estrogens

- As contraceptives in combination with progestins
- Ovarian failures
- To relief menopausal symptoms
  - Such as headache, dizziness, emotional instability
- In dysmenorrhea (painful menstruation)
- In cancer of the prostate gland & postmenopausal breast cancer
- Hirsutism (excessive hair on body & face) in women

Estrogens cont.

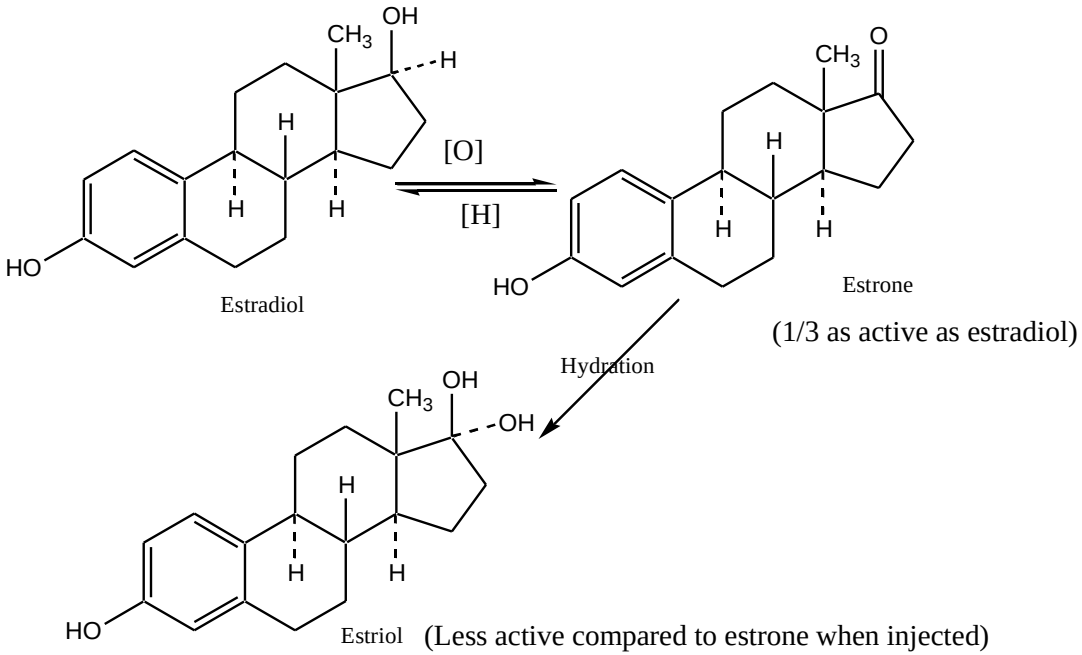
Physiologic Effects

Estrogens act on many tissues, such as those of the reproductive tract, breast, and CNS. They stimulate the development of secondary sex tissues. Another target of estrogens is breast tissue. Estrogens can stimulate the proliferation of breast cells and promote the growth of hromone-dependent mammary carcinoma.

- Types of estrogens
  - Natural estrogens
    - Estradiol
    - Estrone
    - Estriol
  - Semisynthetic estrogens
    - Ethinylestradiol
    - Mestranol
  - Synthetic non-steroidal estrogens
    - Diethylstilbestrol

Natural estrogens

- Estradiol
  - Most potent
  - Major secretory product of human ovary
    - Readily oxidized in liver to estorne that get hydrated to estriol



Estradiol

Estrone

(1/3 as active as estradiol)

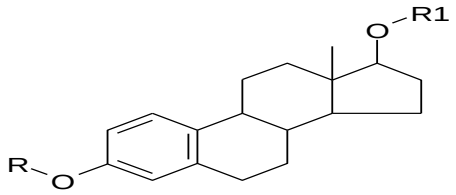
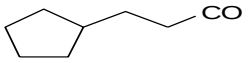
Estriol (Less active compared to estrone when injected)

(orally active)

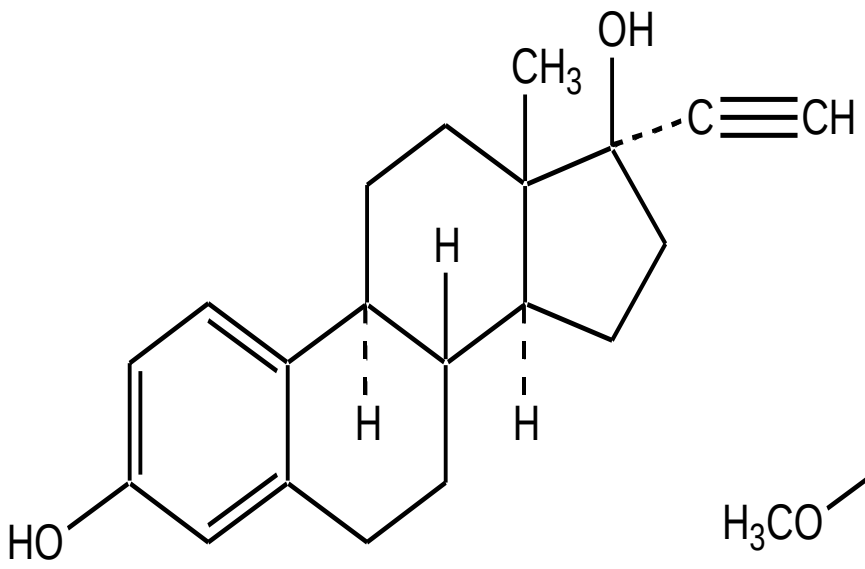
- In all naturally occurring estrogens
  - Ring A is benzoid
  - CH_3 at C-10 is absent
  - They lack a carbon side chain at C-17
  - All have a phenolic OH at C-3 (β-OH)

Semisynthetic estrogens

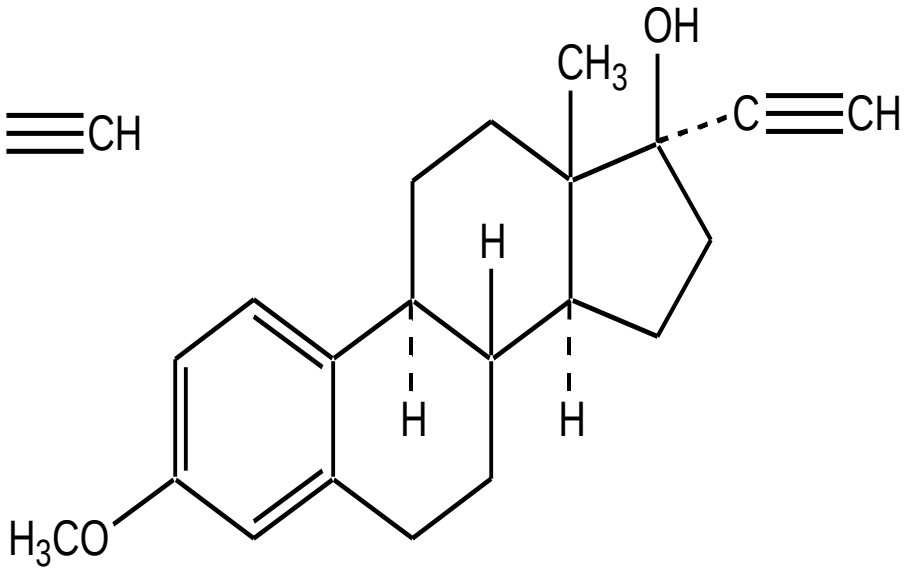
- It is already noted that estradiol, its 17β-OH is vulnerable to bacterial & enzymatic oxidation to estrone
  - But can be protected
    - Temporarily
      - As an ester

Estradiol 17β-valerate or Cypionate esters	
 ***Estradiol 17β-valerate*** R = H $R_1 = CH_3(CH_2)_3CO$ ***Estradiol 17β-cyclopentyl propionate*** R = H R1 = 	Estradiol cypionate or valerate esters may be thought of as pro-drugs, because they are administered intramuscularly, slow hydrolysis of the ester in vivo releases the free estradiol over a period of time Estradiol valerate has a duration of action of **14-21 days**. Estradiol cypionate has a duration of action of **14-28 days**.

- Permanently
  - By introducing 17α-alky group



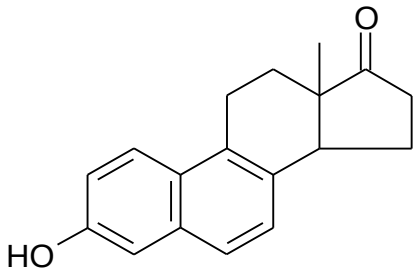
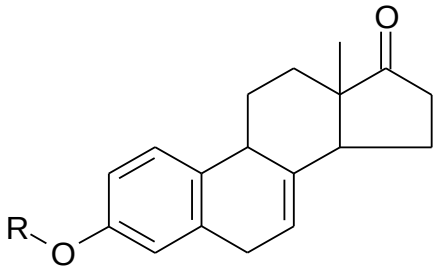
17α-ethinylestradiol



Mestranol

- Ethinylestradiol
  - 17α-ethinylestradiol
    - Formed from estrone by Grignard reaction
    - Has an advantage over estradiols in that it is orally active
      - 15-20X more active orally compared to estradiol
    - Equally potent by injection
- Mestranol
  - Inhibits the release of gonadotropins
    - Useful to suppress ovulation
      - Used as contraceptive
  - Metabolized to ethinylestradiol

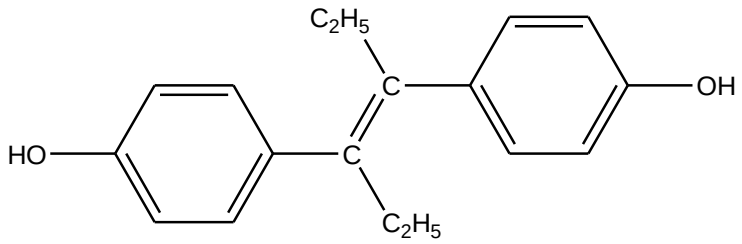
b) Conjugates Estrogens

 ***Equilenin***	Conjugated estrogens USP is a mixture of sodium salts of the water-soluble sulfate esters of estradiol metabolites derived wholly or in part from quine urine.
 ***Equilin*** R = H ***Equilin sodium sulfate*** R = $SO_3^-Na^+$	*Synthetic conjugated estrogens A* is a mixture of conjugated estrogens prepared synthetically from plant sources (i.e., soy and jams) It is a mixture of estrone sulfate, sodium equilin sulfate, 17α-dihydroequilin, 17α-estradiol sufate.

Synthetic non steroidal estrogens

Diethylstilbestrol

- Have the advantage of being used orally
- The distance b/n the two DES phenol OH groups was the same as the 3 – OH to 17 – OH distance of estradiol
  - ➢ act on same receptors as natural the hormones
    - Diethylstilbestrol



Synthetic non steroidal estrogens cont.

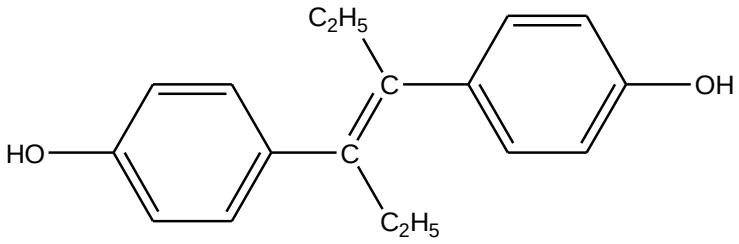
Diethylstilbestrol cont.

- The most active non steroidal estrogen
- Cis isomer 1/10 as active as the trans isomer
- Trans isomer
  - Well absorbed orally
  - Slowly metabolized
- Not to be taken during pregnancy and replacement theraphy
  - Risk of cervical cancer in female offspring
- Given in large dose as an emergency postcoital contraceptive
- It is used to treat prostatic cancer in male

Synthetic non steroidal estrogens cont.

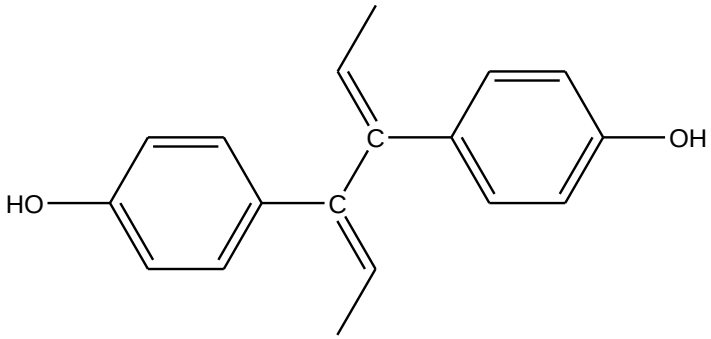
Diethylstilbestrol cont.

- SAR
  - Introduction of alkyl group on the aromatic rings
  - Acylation of phenolic OH
    - No significant impairment on estrogenic activity



Synthetic non steroidal estrogens cont.

- Dienestrol

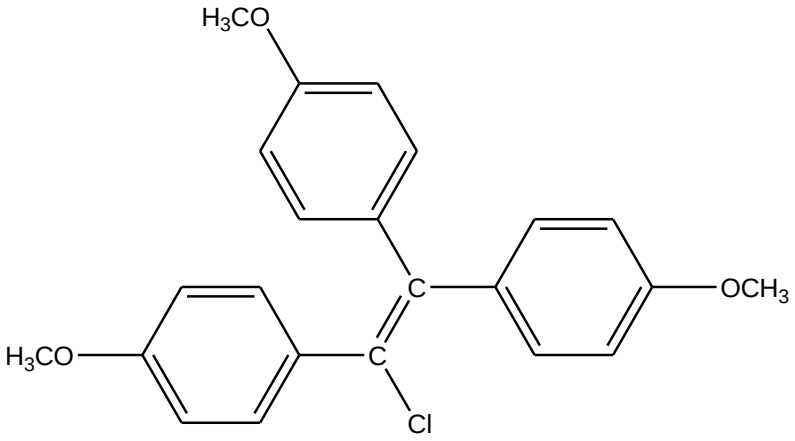


3,4-bis (p-hydroxyphenyl)-2,4-hexadiene

Can be synthesized from diethylstilbestrol diacetate

Can be intravaginally for in the management of vaginal and urethral atrophy

- Chlorotrianisane



- More active orally than by other route
- suggesting its being a prodrug

Estrogen Antagonists

Agents that antagonize the actions of estrogens are of particular interest for their ability to modify reproductive processes, and for the treatment of estrogen-dependent breast cancer.

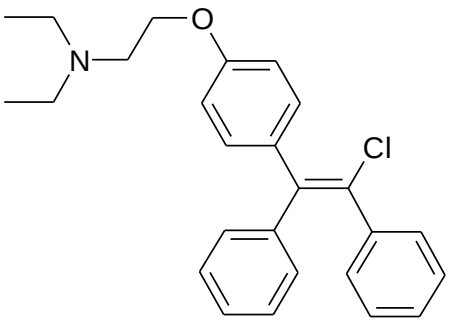
1) Impeded estrogens

These dissociate from the receptor too rapidly to produce any estrogenic effect.
They compete with decreasing the ***Estradiol*** effect the classical example is ***Estriol***
These are agents that interact with the estrogen receptor in target tissues

2) Antiestrogens Triphenylethelene Analogs

They exhibit a strong and pressistent binding to the estrogen receptor-producing antiestrogen receptor complexes.

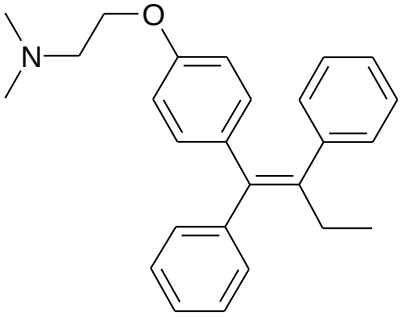
Clomiphene, *Clomid*®



2-[4-(2-chloro-1,2-diphenyl-ethynyl)phenoxy]-N,N-diethyl ethanamine

- ***Clomiphene*** citrate has both estrogenic and antiestrogenic properties (***partial agonist***) and is used to induce ovulation for the treatment of infertility. The usual dose is 50 mg daily for 5 days starting on the fifth day of the menstrual cycle.
- If ovulation does not occur the dose is increased to 100 mg daily for the next cycle.
- If menstruation does not occur pregnancy test should be conducted before additional ***clomiphene*** is taken.

Tamoxifen, *Nolvadex*®



It is an estrogen agonist-antagonist (***partial agonist***) that is used as an anti-estrogen in treatment of estrogen-dependent breast cancer.

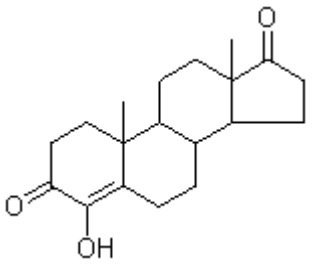
Antiestrogenic and estrogenic side effects can include hot flashes, nausea, vomiting, platelet reduction and (in patients with bone metastases) hypercalcemia.

3) Aromatase Inhibitors

These agents are either ***Androstenedione*** derivative or ***Triazole*** derivatives

a- Androstenedione derivatives

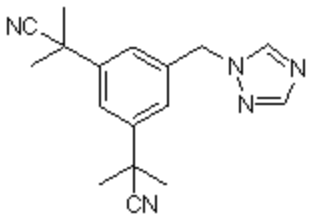
- These are inhibitors of aromatase, that block the conversion of androgens to estrogens and thus have therapeutic potential in the control of reproductive functions and in the treatment of estrogen dependent breast cancer.



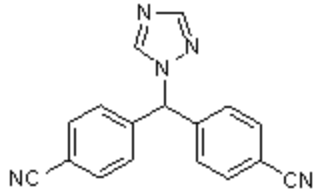
- These steroidal agents compete with androstenedione for binding to the active site of the aromatic enzyme e.g. ***4-Hydroxyandrostenedione***, ***4-OHA***. It acts as enzyme activated irreversible inhibitors (*suicide substrates*).

b- *Triazole derivatives (Letrozole, Anastrazole)*

- These drugs include the clinically available ***Anastrazole*** (*Arimidex*®) and ***Letrozole*** (*Femara*®).
- They are competitive inhibitors of aromatase that selectively inhibit the conversion of testosterone to estrogens in all tissues, reducing serum concentrations of circulating estrone, estradiol, and estrone sulfate, but do not affect the synthesis of adrenocorticosteroids, aldosterone or thyroid hormone.
- Both drugs are used for the treatment of advanced breast cancer in post menopausal women with disease progression following ***Tamoxifen*** therapy.



Anastrazole

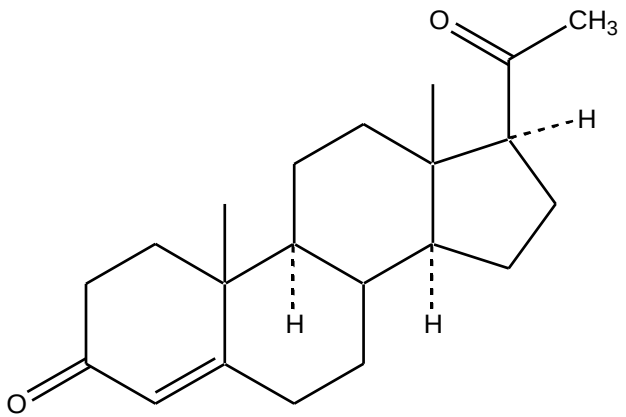


Letrozole

Progestins / Progestogens

Progesterone (the only naturally occurring progestin, not active orally)

- Produced by
  - Corpus luteum
  - Adrenal glands
  - The placenta
- Uses
  - As contraceptive
  - Excessive uterine bleeding
  - Dysmenorrhea
  - Amenorrhea
  - Diagnosis of pregnancy
  - Premenstrual tension
- Can be synthesized from
  - Stigmasterol
- Has short duration of action



Progesterone

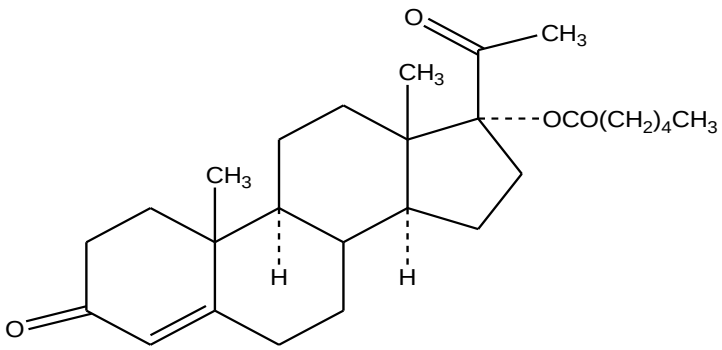
Synthetic Progestins :

The synthetic progestins can generally be divided into two classes of compounds, namely, the ***pregnanes*** (the *17α-hydroxyprogesterones*) and the ***androgens*** (the *19-norandrostane or estrane* derivatives).

1. Progestrone and its Derivative

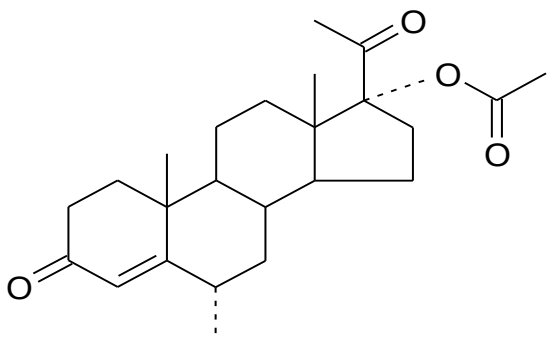
Hydroxyprogesterone caproate

- Compared to progesterone
  - More active
  - Longer acting
    - b/s of 17α-substituent that hinders red^{n} to 20-ol
- Given only im



Hydroxyprogesterone caproate

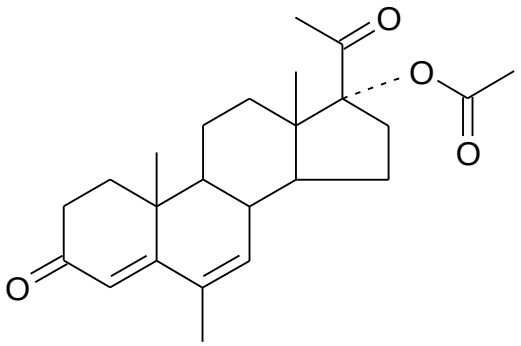
Medroxyprogesterone acetate (*Provera, Depo-provera, Amen)*



7α-Acetoxy-6α-methyl pregn-4-en-20-dione

- 17α-acetoxyprogesterone has enhanced oral contraceptive action.
- In addition, substitution at C_6 by a 6α-methyl grou hinders 6-hydroxylation of progestin and increase the lipid solubility.
- Medroxyprogesterone acetate is completely and rapidly deacetylated by first pass metabolism to medroxyprogesterone following oral administratio

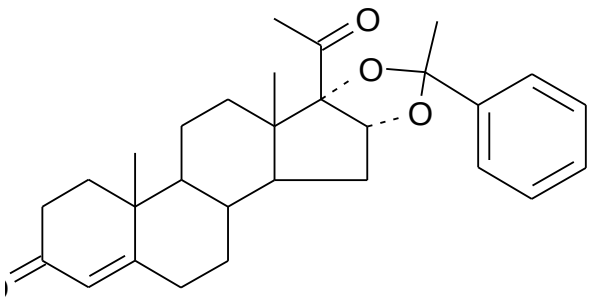
Megesterol acetate, *(Megace)*



7α-Acetoxy-6-methyl pregn-4,6-ien-3-20-dione

- Progestational activity is further enhanced with 6-substituted 17α-acetoxy progesterones when a double bond is introduced between C_6 and C_7.
- ***Megestrol*** is primarily used in the treatment of breast and endometrial carcinoma and in post menopausal women with advanced hormonally dependent carcinoma.

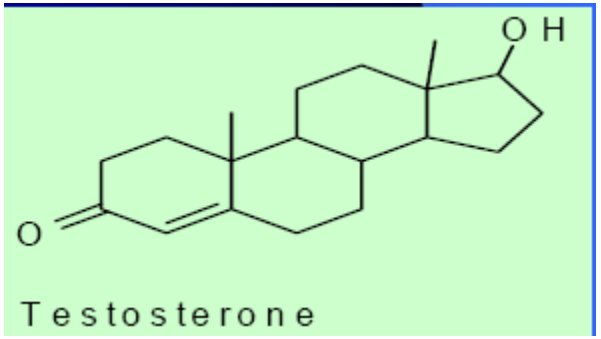
Dihydroxy progesterone acetophenide



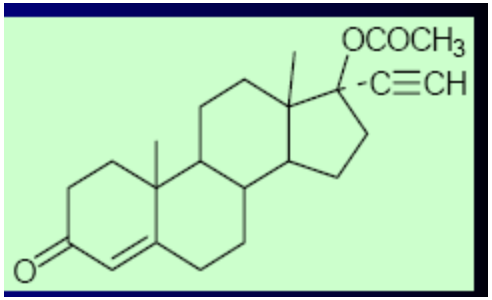
6α, 17α-dihydroxy progesterone acetophenide

A progestin with a prolonged duration of action. When given parentrally, this agent appears to be devoid of both androgenic and estrogenic activities.

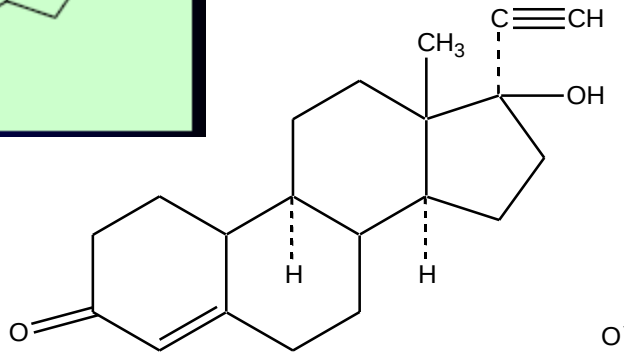
2. *19-norandrostane or estrane* derivatives



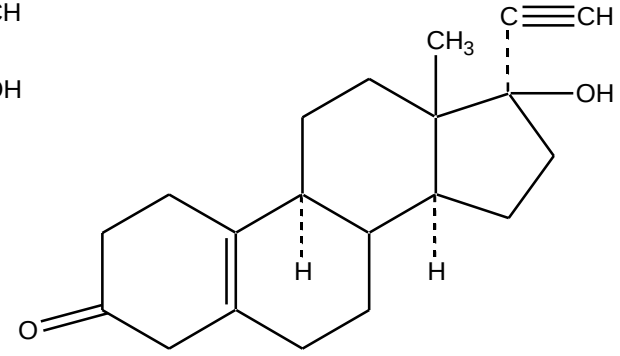
- Norethindrone & Norethynodrel
  - Are isomers
  - Used as oral contraceptives
  - Norethindrone is 10X more active than Norethynodrel



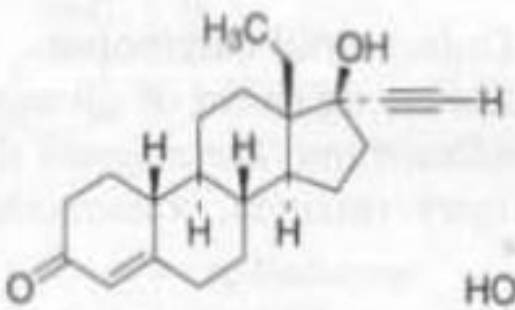
Ethisterone



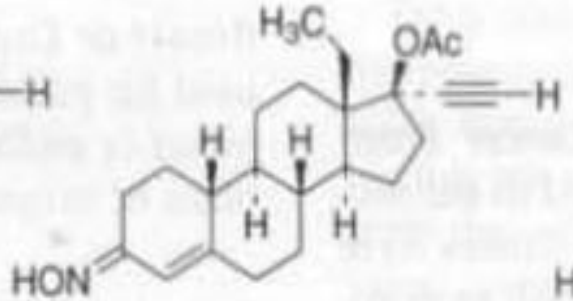
Norethindrone



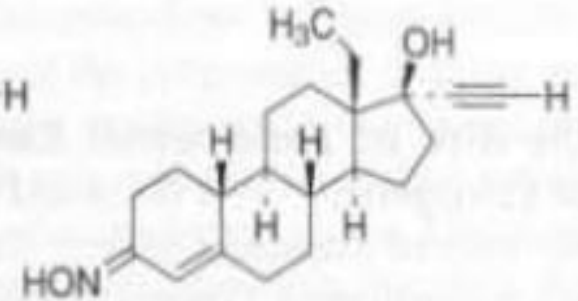
Norethynodrel



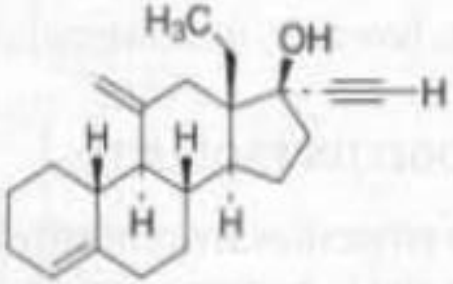
Norgestrel
(Levonorgestrel)



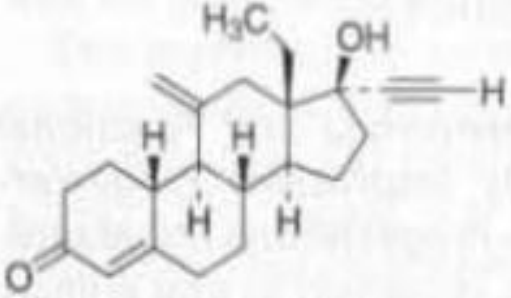
Norgestimate



Norelgestromin



Desogestrel

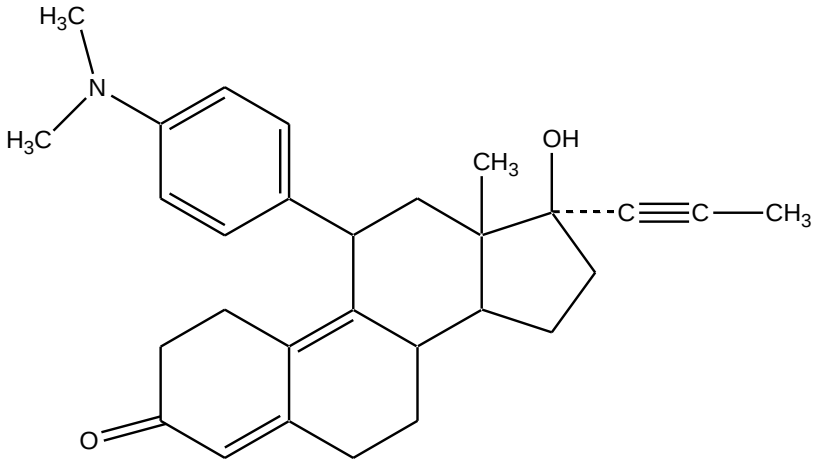


Etonogestrel

Antiprogestins

Mifepristone (RU 486)

- Can bind to both glucocorticoid & progesterone receptors
- Used together with prostaglandins
  - To terminate pregnancy within the first 9 weeks of gestation
- Used as post coital contraceptive via prevention of fertilized egg implantation
- Used to treat progesterone sensitive cancers



11β-(p-Dimethylaminophenyl)-17β–hydroxy-17-(1-propynyl) estra-4, 9-diene-3-one

Oral contraceptives

Combination

- Estrogen & progestin administered together in one tablet
  - Medication continued for 21 days
  - One tab /day from the first day of menses
  - 7 inert tablets are included in some preparations for this period
- Examples of preparations
  - Mestranol + ethynodrel
  - Mestranol + ethindrone
  - Ethinylestradiol + ethindrone
  - Ethinylestradiol + gestrel
  - Ethinylestradiol + ethindrone acetate

Mechanism of action

- Although the detail of the process are still not completely understood. it is now believed that the combination tablets suppress the production of LH, FSU. or both.

- An additional effect comes from the progestin causing the cervical mucus to become very thick providing barrier for the passage of sperm through the Cervics.

- Combination tablets are divided into three:

Monophasic (Fixed dose combination)

- The monophasic combination of progestin and estrogen contain the same amount of drug in each active tablet.
- As estrogen levels are reduced, breakthrough bleeding (spouting) becomes annoying side effect

Biphasic and Triphasic (Variable combination)

- The higher estrogen/progestrone ratio in early in the eycle is believed to assist development of endometrium
- The higher progestrone/estrogen concentration later contributes to the proliferation of endometrium and a resultant normal volume of menstrual flow
- The biphasic and triphasic combinations attempt to mimic the variation of estrogen/progestin, and thereby to reduce the incidence of spotting associated with low dose low dose monophasic combination

Extended oral contraceptive

- Clinical trial are currently in progress that use a 91-day cycle as opposed to the current 28 days cycle typically used for oral contraceptive.
- Instead of 2 1 days of hormone, followed by a week of inert tablets, these regimens have 84 days hormone followed by a week of inert tablet.
- The key difference is that the no of menustral cycle ,i.e reduced from 12 to 4 (reduced anemia, cramp)

How safe?

- Pills are excellently safe
- Products containing high level of estrogen exhibit higher incidence of tromboembolic disease (blood clot)
- Nausea, Vomiting, Break through bleeding , Breast tenderness & enlargement, Weight gain, Migraine headache ,and Depression

Single ingredient

- Progestin given alone in small doses (minipill)
  - One tablet given every day through out the year (at about the same time of the day)
- Drug examples
  - Norethindrone
  - Norgestreol

- *Depo-Provera:* Medroxyprogestrone acetate intramuscular (IM) injection (Depo provera) provides contraceptive for 3 months after a single 150 mg IM dose.
- Most women experience some irregular bleeding and slight weight gain
- Fertility regains with 12 months after discontinuation of the drug
- Contraception typically continues for a few weeks beyond a 3 month term to give a short grace period if subsequent IM dose is delayed.

Contraceptive implant

- Norplant: contains a set of six flexible silastic capsules that contain levonorgestrel.
- The capsule is implanted in the midportion of upper arm and provide contraception for 5 years.
- Most women experience changes in menstrual bleeding , ranging from irregular cycle to prolonged bleeding

Postcoital contraceptives

(morning after pills)

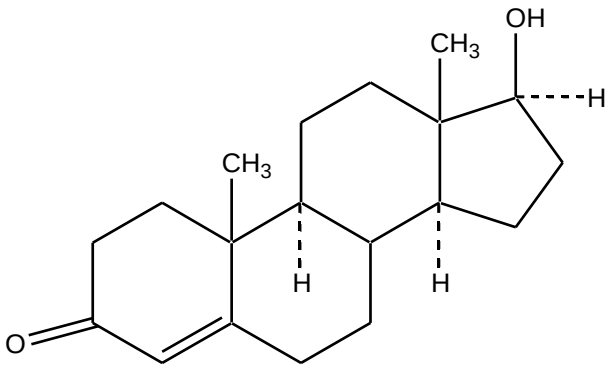
- Diethylstilbestrol (25mg) used within 24 - 72 hrs of unprotected intercourse twice daily for 5 consecutive days.
- Two Ovral (norgestrol,0.5mg + ethinyl estradiol,50µg) tablets within 72 hrs followed by two more tablets 12 hrs later.

- Treatment successful prevents pregnancy with about 90% of users
- This treatment is intended; however, only for use in short term emergency situation

Androgen & anabolic agents

Testosterone

- Natural androgen in men produced by testes
- Androgen: Any hormone with testosterone-like actions
- Androgens control development of male sexual characteristics
  - Serves as biosynthetic precursor to estradiol in women
- Androgen deficiency in men produces hypogonadism
  - Defects in sexual anatomy & physiology

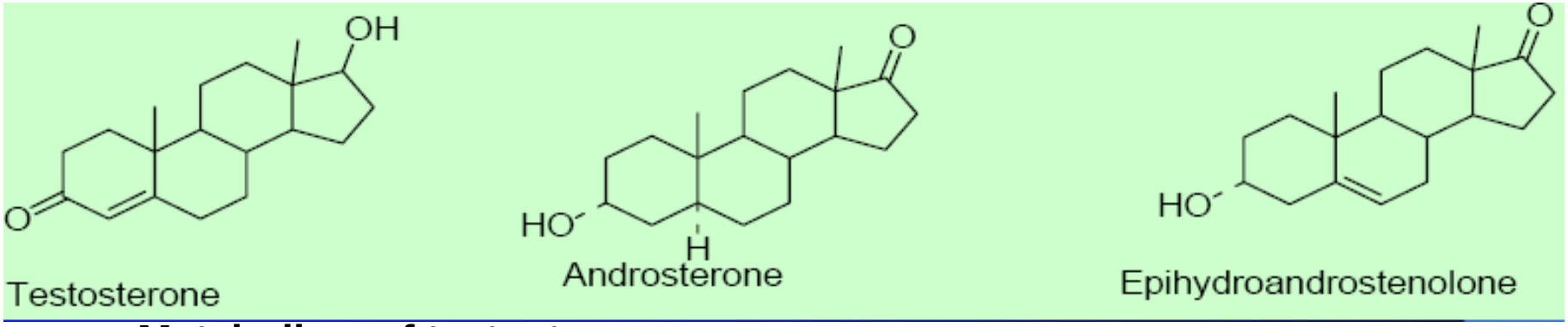


Testosterone

History of Anabolic Androgen Hormones

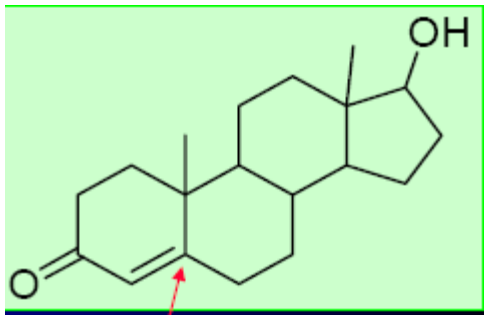
- Testosterone discovered in 1935 by independent European researchers .
  - All AAS are synthetic derivatives of testosterone.
- Anabolic steroids initially used in medicine to treat hypogonadism – a condition in which testes produce abnormally low testosterone levels .
- Bodybuilders and weightlifters first used anabolic steroids in 1930s to increase skeletal muscle mass .
- Current uses:
  - Serving medicinal purposes (treating delayed puberty, impotence and muscle deterioration brought upon by HIV infection).
  - Athletic manipulation and taboo.

Natural androgens



•Metabolism of testosterone

- 5-position of testosterone is attacked by reductase enzyme.
- If the attack takes place from the α-face by 5α-reductase enzyme, it will give 5α–Dihydrotestosterone (5αDHT)

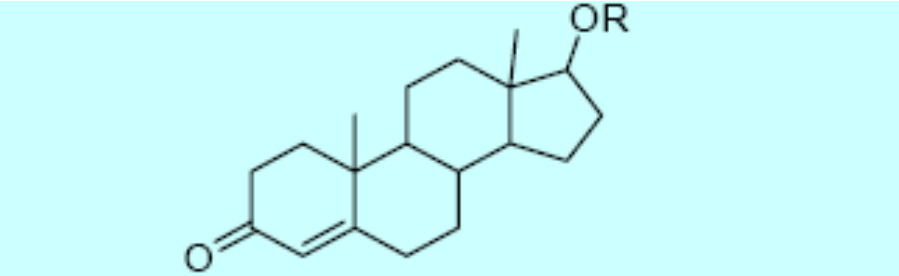


- If the reductase enzyme attacks take place from the β-face, it will give 5 β–Dihydrotestosterone (5βDHT) which is inactive metabolite.
- Testosterone also, can be converted to estradiol by aromatase enzyme**.**

Classification of androgens according to the androgenic / anabolic ratio

A) High androgenic / anabolic ratio

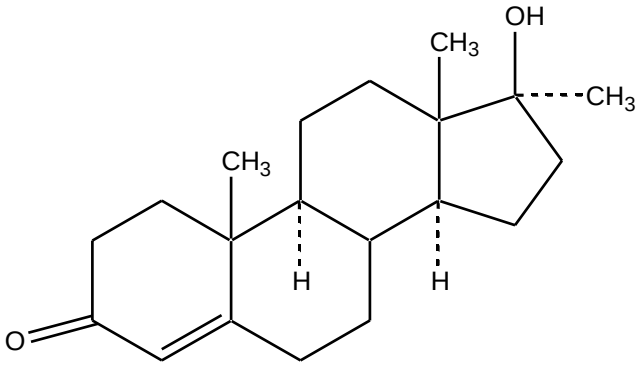
1) TestosteroneTestosterone is orally inactive because of rapid first pass metabolism to inactive 17-ketosteroid.



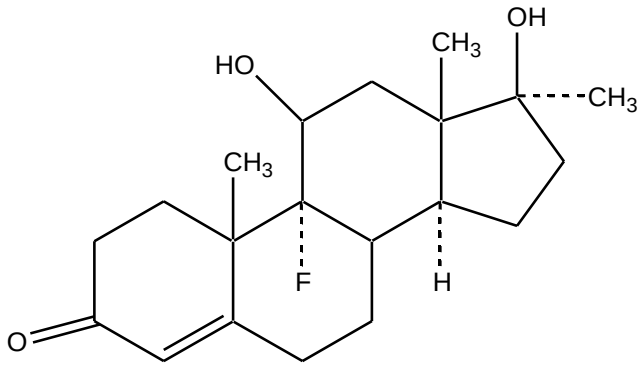
Pro - drugs

2 - 17α- Methyltestosterone

- Methyltestosterone
  - Produced synthetically from cholesterol
  - Active orally & im



- Fluoxymesterone
  - Obtained synthetically from 17α-methyltestosterone
  - 5-10X more potent than testosterone
  - Active orally

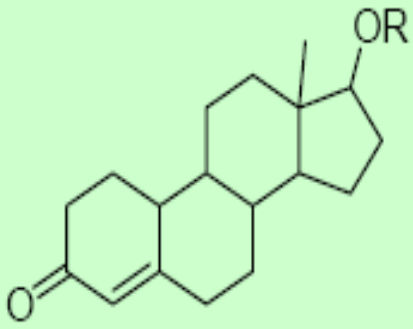


b) Anabolic steroids

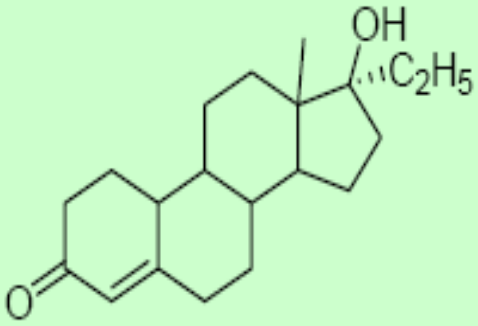
1) 19-norandrogens
2) 17α-Methyltestosterone derivatives
3) 17β-Testosterone acetate derivatives

1) 19-norandrogens derivatives

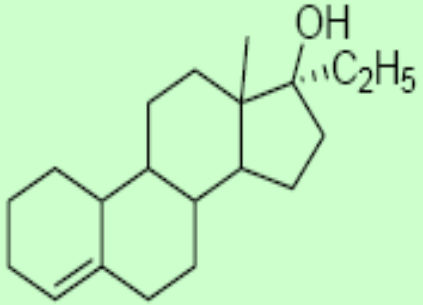
- Removal of the 19-CH3 group of the androgen results in reduction of its androgenic properties but retention of its anabolic, tissue-building proper.



Nandrolone R= H
Nandrolone decanoate R= $CH_3(CH_2)_8CO$
Nandrolone phenopropionate R=$C_6H_5(CH_2)_3CO$



Norethandrolone



Ethylestrenol

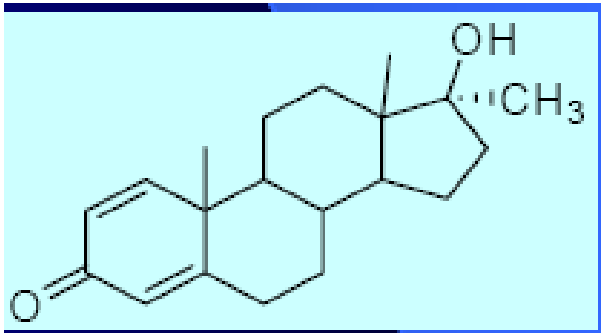
- Nandroloneanabolic/ androgenic ratio is 4/1.
- Norethandrolonehas oral and parentralanabolic activity without androgenic and progestational side effects.
- Ethylestrenol is more potent than Norethandrolone as an anabolic agent

2) 17α-Methyltestosterone derivatives

- insertion of a small alkyl group at 17α-position renders the compound to be metabolically stable and orally active

- Methandrostenolone

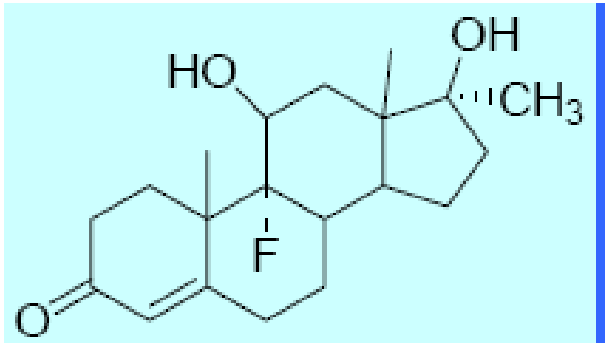
✓ has more potent anabolic activity with lower androgenic activity than 17α-methyltestosterone



Methandrostenolone

- Fluoxymesterone

✓ has 20 times the anabolic and 10 times the androgenic activity of 17α-methyltestosterone

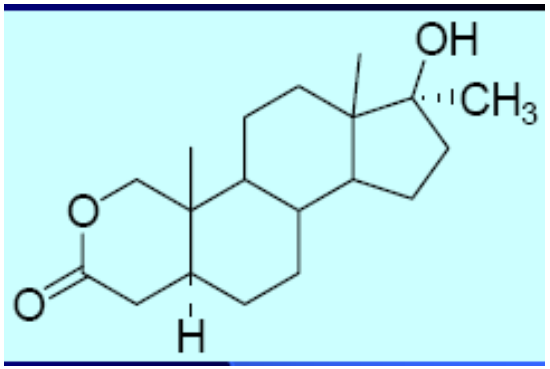


Fluoxymesterone

- Oxandrolone

✓ 2-oxasteroid analog of 17α-methyltestosterone which contains a lactone in the A ring

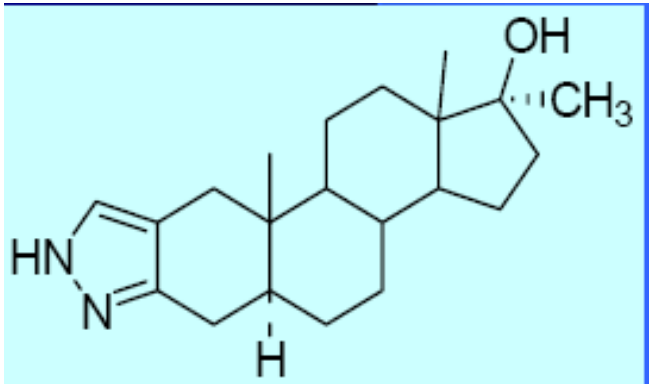
✓ it has three times the anabolic activity of 17α-methyltestosterone.



Oxandrolone

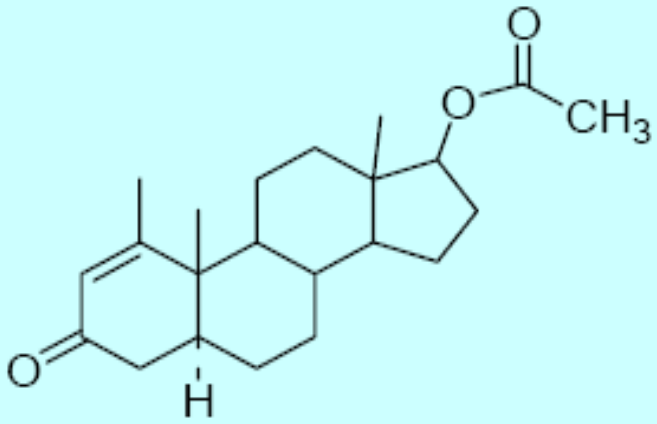
- Stanazolol

- another heterocyclic compound used for its anabolic effects and contain pyrazole ring.

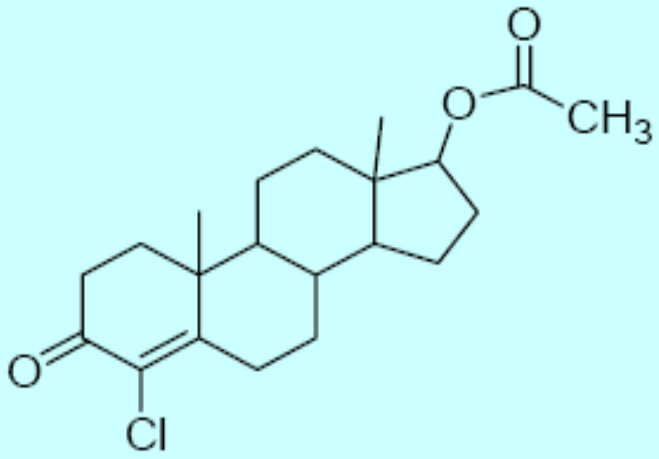


Stanazolol

3) 17β-Testosterone acetate derivatives



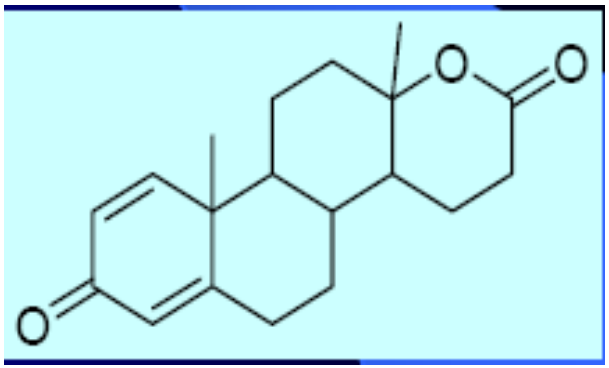
Methenolone acetate



Chlorotestosterone acetate

- Other testosterone derivatives

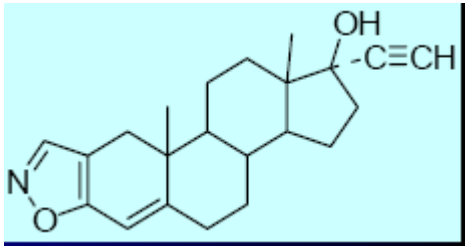
Testolactone(Teslac)

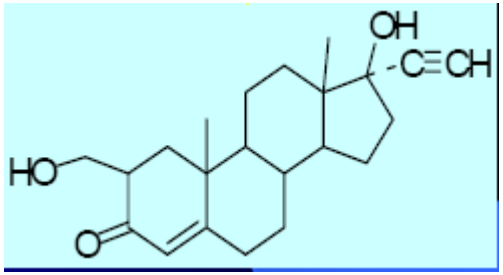


▪18-oxasteroid, is a D-homo oxoandrostandienedione

▪Testolactone(Teslac) D-homo-17α-oxoandrostan-1,4-diene3,17-dionepossesses some anabolic activity with weak androgenic effects, it is used primarily in the treatment of breast cancer as non-competitive irreversible inhibitor of aromatase**.**

•Danazol(Danocrine*)*





- Isoxazolederivative of ehtisterone-It binds to sex steroid receptors in the cytoplasmof target tissues and may thereby exhibit antiestrogen, anabolic and weakly androgenic effects
- Metabolized to 2-hydroxymethylethisterone.

Structure activity relationship of androgen showed that :-

a)The steroid skeleton is essential for androgenic activity while the two functional groups at C-3 to C-17 are not.

b) Esterification of 17β-OH increases the duration of action, lipophilicityand oil solubility e.g. testosterone acetate, propionate, cypionateand enanthate. Some esters are orally active e.g. testosterone undecanoate.

c) Insertion of a small alkyl group at 17α position renders the compound to be metabolically stable and orally active, but increase the length of the alkyl group decreases the activity.

Alkylation at the 1, 2, 7, and 18 positions of the androstane molecule generally increase anabolic activity. While incorporation of a 17α-ethynyl group produces compounds with useful progestational activity e.g.ethindrone (ethisterone).

d) Introduction of 4β-OH group in methyltestosterone increases anabolic action e.g. oxymesterone. Further unsaturation in ring A enhances the activity several times e.g. methandrostenolone..

Further hydroxylation at C-11 and substitution with fluorine at C-9greatly increase the anabolic action e.g. fluoxymesteroneis 20 times the anabolic and 10 times the androgenic activity of methyltestosterone

However halogenation at any position except C-4 or C-9 decreases the activity.

e) Replacement of ring A by a hetero ring may produce potent anabolic agent e.g. oxandrolone and stanozolol

while saturation of ring A and epimerization or oxidation of 17β-OH decrease the activity

f) Removal of C-19 methylgroup drastically enhances the anabolic action and diminishes the androgenic one e.g. 19-nortestosterone. Further removal of C-18 methyl group produces compounds, which are devoid, both activities.

g) Contraction of the ring B leads to B-nor steroids which are lacking in androgen activity but having antiandrogeniceffects. On contrast, the B-homo steroids are weakly androgenics

h) Changing the position of the 3-keto function to C-1, C-2, or C-4 and alteration of ring A/B trans configuration to cis one drastically reduce the activity

Use of androgens

Medicinal:

Therapeutic effects of testosterone replacement

- Restore muscle mass in degenerative states, such as hypogonadism, HIV-related muscle wasting conditions, sarcopenia (age-related muscle loss) .

Performance Enhancing Effects

Commonly self-administered,

therefore little empirical evidence.

Increased strength and body weight

due to heightened skeletal muscle

mass

.

Side effects of androgens

a) Virilizing effects in women as represented by musclinization, coarsening of the voice, growth of the facial and body hair and acne, baldness, aggressive behavior and increased sexual drive

b) Edema due to retention of water and sodium chloride.

Common problems due to chronic abuse also include hypertension, atherosclerosis, blood clotting, jaundice, hepatic carcinoma, tendon damage, and reduced fertility in males

c) Cholestatic hepatitis and jaundice. Patients who have received prolonged androgenic therapy especially with 17α-alkyl derivatives may develop hepatic adenocarcinoma.

Antiandrogens

-useful in the treatment of hyperplasia, and carcinoma of prostate, acne, virilizing syndromes in women.

-They can be classified according their mode of action into the following classes:

-A) **Androgen synthesis inhibitors** -Gonadotropin-releasing hormone secreted by hypothalamus is an effective inhibitor of testosterone synthesis.

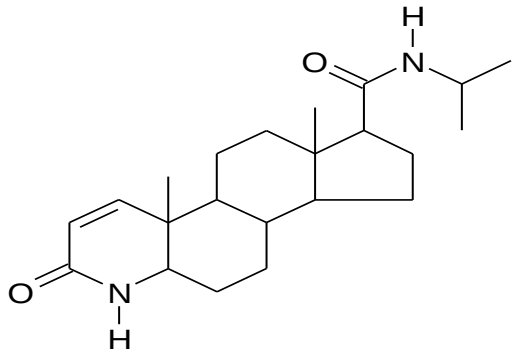
-**Imidazole antifungals** E.g. ketoconazole, have the ability to block CytP450 enzymes involved in steroid biosynthesis, but the GIT side effects and inhibition of adrenal glucocorticoides limit their use.

-**The aldosterone antagonist**, spironolactone,acts also as androgen biosynthesis inhibitor.

B-5α-Reductase inhibitors

inhibit conversion of testosterone to the more effective metabolite 5α-DHT azasteroide, finasteride.

Finasteride, *(Proscar®)*

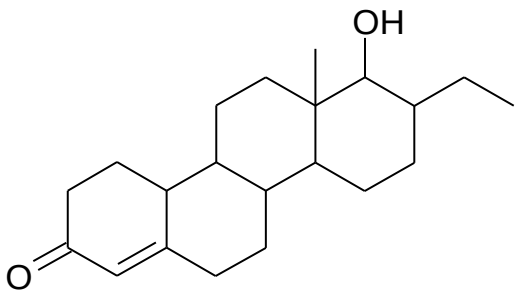


N-(1,1-dimethylethyl)-3-oxo-4-aza-androstano-7-ene-17-carboxamide

- This drug is approved for the treatment of symptomatic benign prostatic hyperplasia and management of alopecia in males.
- Since ***Testosterone*** has significant androgenic activity by itself, inhibition of its biosynthesis would be useful in treating androgen dependent diseases such as prostate cancer.

- C) Androgen-Receptor Antagonists

  - compete with dihydrotestosterone on the androgenic receptor and prevent binding of the hormone

Oxendolone	
	Acts by competing for the receptor binding sites.

Adrenocorticosteroids

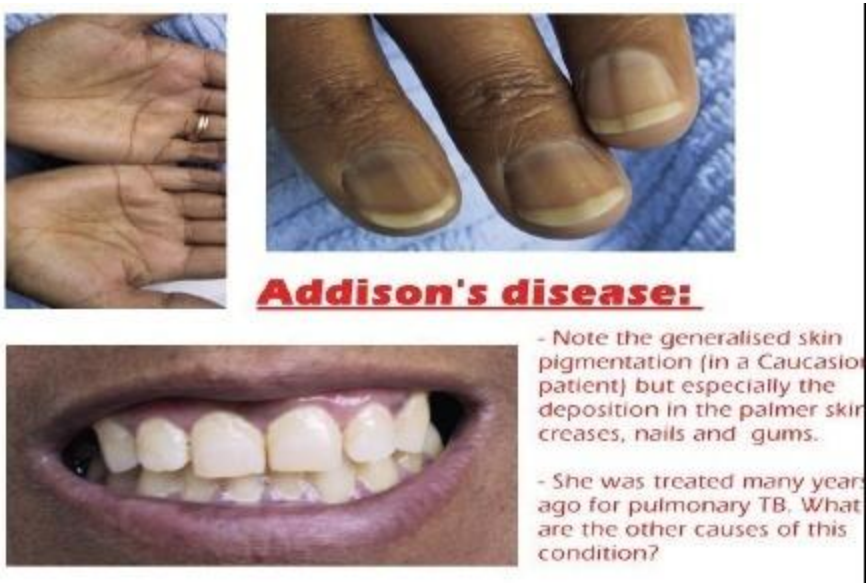
- They are synthesized in the cortex of the adrenal gland and secreted under the influence of hypothalamo-pituitary

- Can be classified in to glucocorticoids and mineralocorticoids**.**

Pathogenic condition

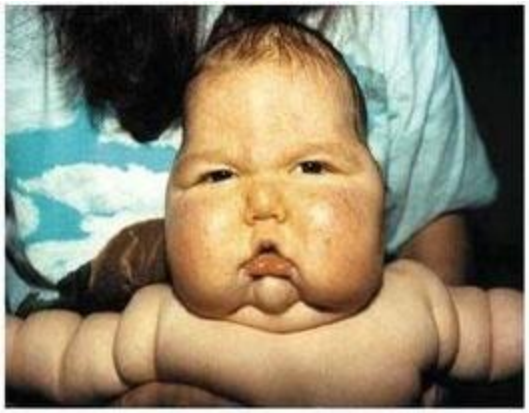
Addison‘s disease

- **Hypoadrenalism- weakness, anaemia, low Bp, Hyper-pigmentation of the skin, mental depression.**
- **Caused by destruction of the cortex by T.B or atrophy, ACTH**



Cushing‘s disease (Hyperadrenalism)

- Caused by (1) adrenal cortex tumors(2) Increased production of ACTH due to pituitary carcinoma.
- Characterized by :Hypertension , excessive retention of water



Conn ‘s syndrome

- Inability of the adrenal cortex to carry out 17α-hydroxylation in the biosynthesis of hormones, resulted in increase production of mineralocorticoids on the expense of glucocorticoids which cause -hypernatremia, polyuria, alkalosis and hypertension

I. Glucocorticoids

physiologic effects

- **Has phospholipase A2 inhibitory activity Both PG& leukotriens, so used as anti inflammatory and anti asthmatics**
- **Reduced migration of inflammatory cells to site of injury**
- Negative effect on lymphocytes, monocytes and macrophages
- Inhibit the release of IL-1, IL-2 and IL-6 and TNF-alpha
- Decreased lymphocyte production
- Impairment of delayed-type hypersensitivity

- permissive effects (glucocorticoids required for certain actions)
  - tissue effects
    - inhibit fibroblasts (connective tissue loss)
    - negative calcium balance (osteoporosis)
    - negative nitrogen balance (catabolism)
    - CNS: euphoria, behavioral changes, psychosis
    - GI: increase stomach acid and pepsin production
    - cardiovascular effects (inc. BP, heart rate)
    - uptake of fat by fat cells
    - gluconeogenesis
    - insulin release and glycogen deposition

Indications for systemic glucocorticoids

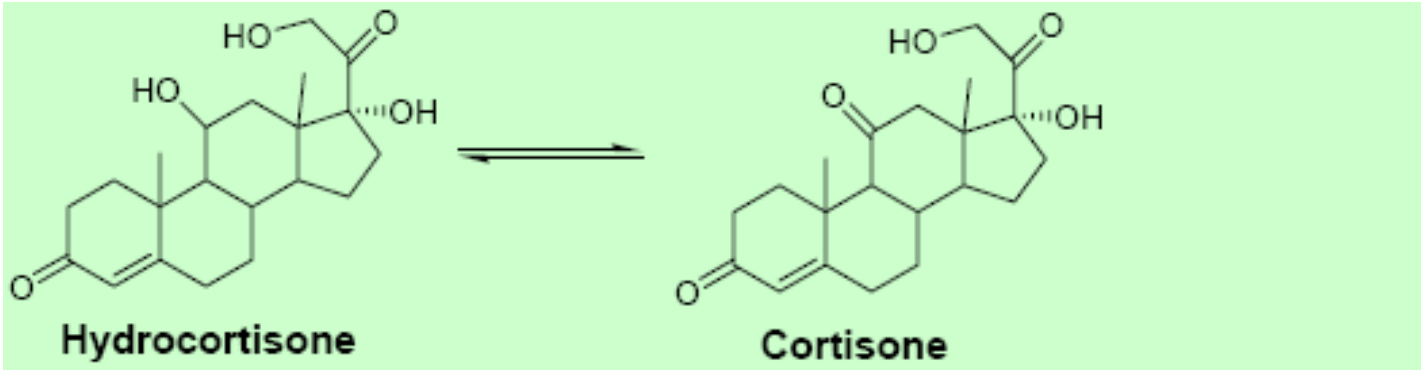
- Endocrine disorders
  - primary or secondary adrenocortical insufficiency
  - congenital adrenal hyperplasia
  - hypercalcemia associated with cancer
  - shock unresponsive to conventional therapy

- Rheumatic disorders
  - rheumatoid arthritis
  - ankylosing spondylitis
  - acute and subacute arthritis
  - acute nonspecific tenosynovitis

- collagen diseases
  - systemic lupus erythematosus
  - acute rheumatic carditis
  - systemic dermatomyositis

- allergic states
  - seasonal or perennial allergic rhinitis
  - bronchial asthma
  - contact dermatitis
  - atopic dermatitis
  - serum sickness
- drug hypersensitivity reactions, Dermatological diseases
  - pemphigus
  - bullous dermatitis herpetiformis
  - severe erythema multiforme (Stevens-Johnson)
  - exfoliative dermatitis
  - mycosis fungoides
  - severe psoriasis

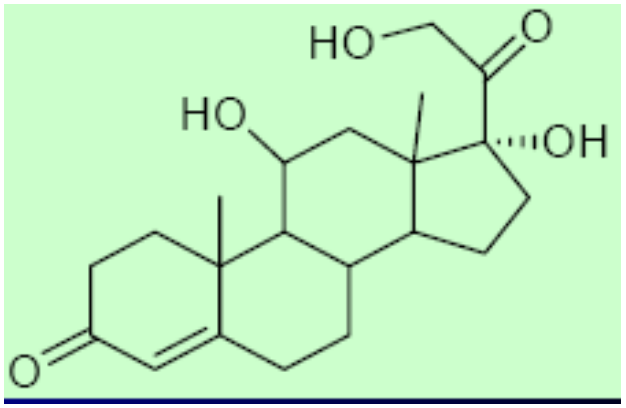
- respiratory diseases
  - symptomatic sarcoidosis
  - berylliosis
  - disseminated pulmonary tuberculosis
  - pulmonary emphysema
  - aspiration pneumonitis
- diffuse interstitial pulmonary fibrosisneoplastic diseases
  - leukemias and lymphomas in adults
  - acute leukemia of childhood
- hematological disorders
  - idiopathic and secondary thrombocytopenia in adults
  - acquired (autoimmune) hemolytic anemia



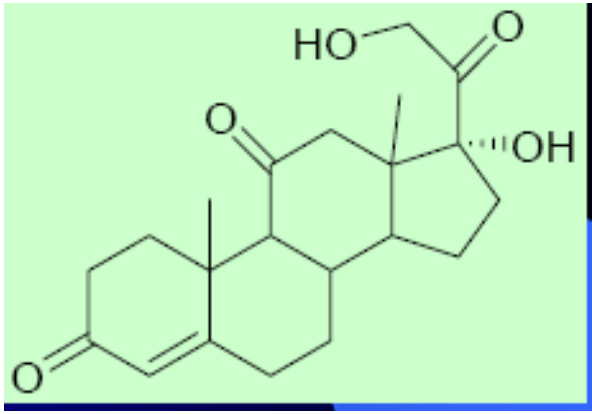
Hydrocortisone (Cortisol)

11β ,17,21-Trihydroxypregn-4-ene-3,20-dione

- Has 1:1 ant-inflammatory: salt retention
-11β-OH is important for binding with the receptor.
- Used in basic form or as acetate ester for injection and topically.



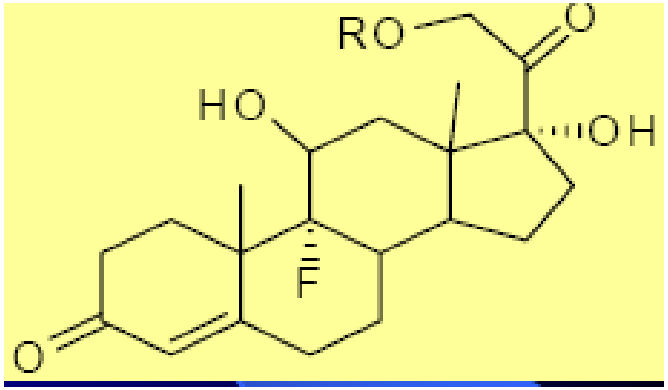
Cortisone



- Cortisone17,21-Dihydroxypregn-4-ene-3,11,20-trione
- Used as its 21-acetate ester because of its high stability and high duration of action when used by injection, also available in tablet or in ophthtalmic suspension.
- *Cortisone has no topical activity. Why???*
- *11-keto function reduced invivo to the 11β-OH.*
- *Sod. Succinate derivative at 21 regarded as bifunction gp(for iv).*

Glucocorticoids with enhanced anti-inflammatory

- Essential features for superior glucocorticoid activity:
  - C=O at C3
  - a double bond bet. C4 &C5
  - Oxygen a C11 (C=O or OH)
  - β-ketolside chain at C17



Fludrocortisone **9α-Flurohydrocortisone**

- Fludrocortisone H
- Fludrocortisone acetate CH3CO

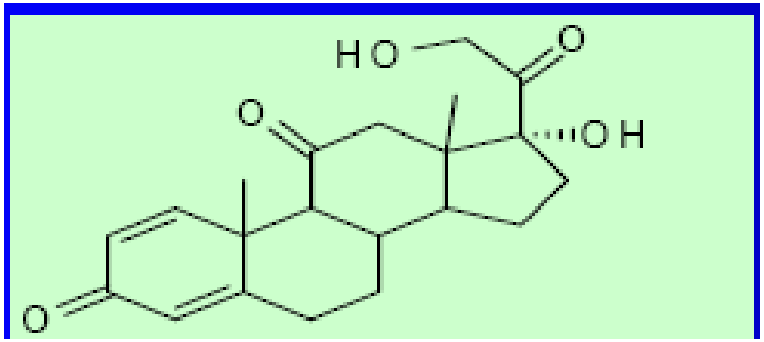
Flurohydrocortisone

- Insertion of F increase glucocot. Activity 11 fold, but mineralocort.activity is also increased 300-800 times that lead to edema
  - ➢ so, fludrocortisone acetate is used topically as anti-inflam. and used in tab. form for treatment of addison's disease
- 9α-Fluro:
  - prevent metabolic oxidation of 11 β-OH to C=O
  - Increase activity by its inductive effect, by increase dissociation of 11 β-OH so, increase formation of H-B to biological receptor

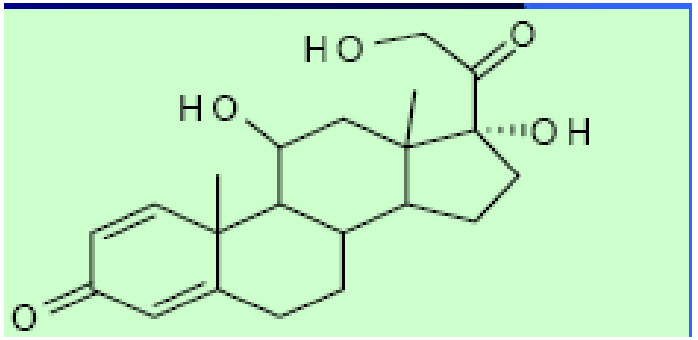
Δ-Corticoids

Cortisone $\xrightarrow{\Delta}$ Prednisone

Cortisole $\xrightarrow{\Delta}$ Prednisolone



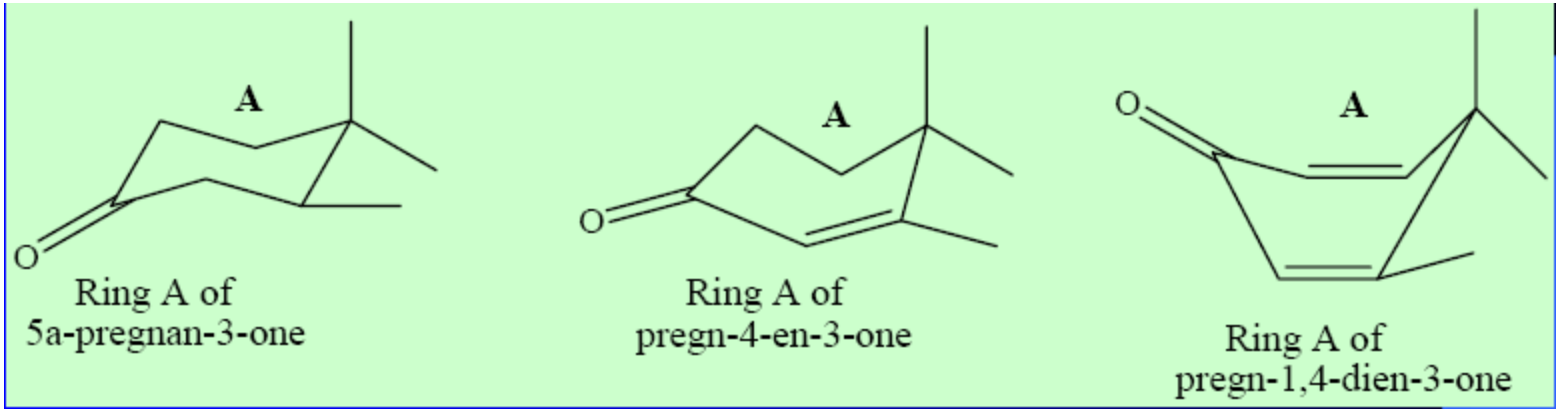
Prednisone



Prednisolone

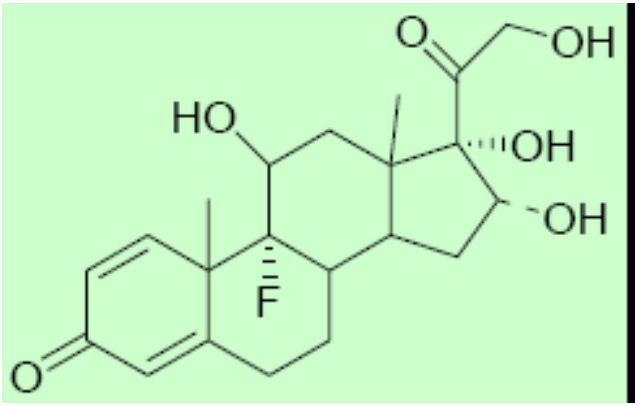
- They have 3-4 times more potent as anti-rheumatic and anti-allergic. While the electrolytes activity not increased
- sod. Phosphate ester (21) is water soluble.
- Δ-Corticoids may be used continuously, in patients with rheumatoid arthritis without gastrointestinal hazard.

- The increased potency due to the change in geometry of ring A.



Triamcinolone (kenacort)®

- 9α-Fluoro-11β, 16α,17, 21 tetrahydroxy Pregna-1,4-diene-3,20-dione
- This drug combines the structural features of both Δ-Corticoids and 9α-Fluorocorticoid

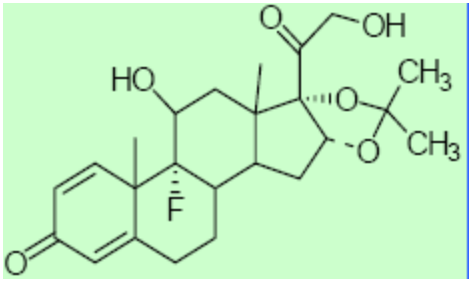


- 16α –OH decrease the mineralocorticoid activity and causes sodium excretion
- used in the form I.M injection in treatment of dermatosis

  -more safe.

Triamcinolone acetonide

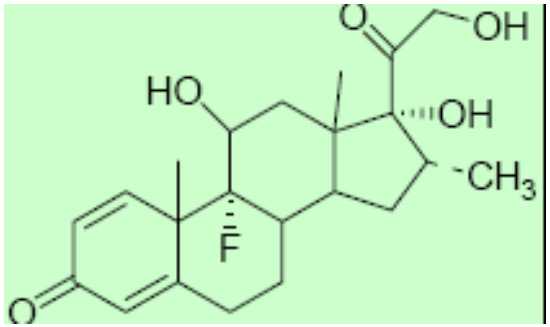
- 9α-Fluoro-11β, 21 dihydroxy16α,17 α- isopropylidinedioxy Pregna-1,4-diene-3,20- dione



- 16α,17α cyclic ketal or acetal derivative.
- Prepared by condensation of acetone with triamcinolone
- Has more potent anti-inflamatory activity than triamcinolone
- Used for treatment of dermatological condition.

Dexamethasone

- 9α-Fluoro-16α-methyl 11β,17, 21 trihydroxyPregna-1,4-diene-3,2
  dione



- 16α-methyl : increase anti - inflammatory.

  decrease salt- retention.

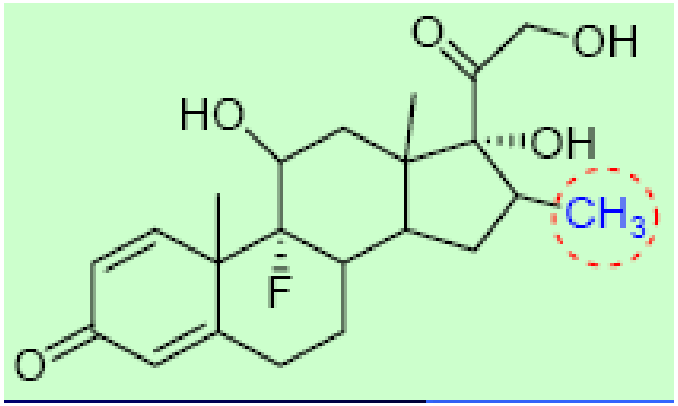
- Has 7 times more active as anti-rheumatic of predinsolone

Side effects:

- facial mooning acne
- excessive appetite and weigh gain

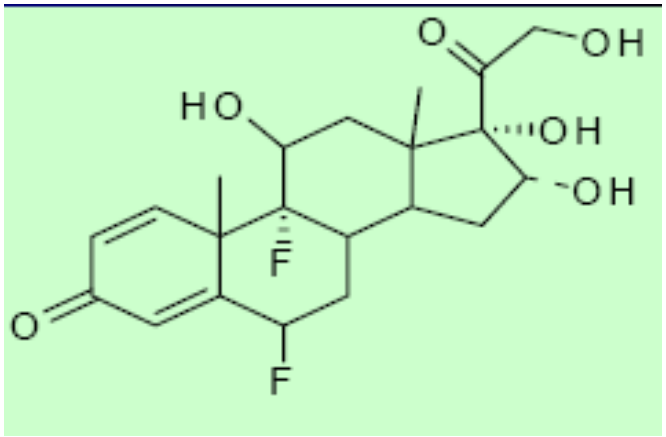
Betamethasone

- 16 CH3 group is in β-configuration
- Slightly more active than dexamethasone



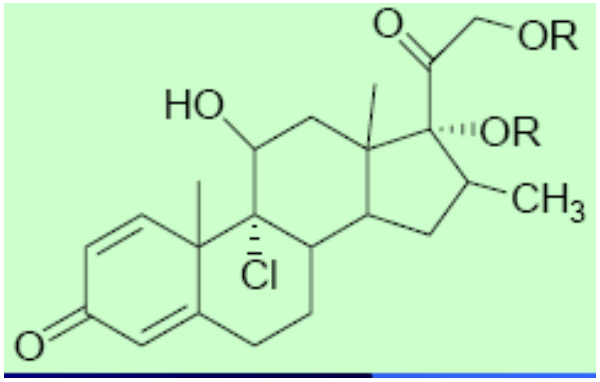
Fluocinolone

- 6α,9α-Difluoro-11β, 16α,17, 21 tetrahydroxyPregna-1,4-diene-3,20-dione



- 6α-fluoro has less salt retention properties than 9α-fluoro.
- Has potent ant-inflammatory activity and is applied topically.
- It is also used as acetonide analog .
- Effective in the treatment of psoriasis.

Beclomethasone



Beclomethasone H

Beclomethasone dipropionate C2H5CO

- 9α-chloro derivative of betamethasone

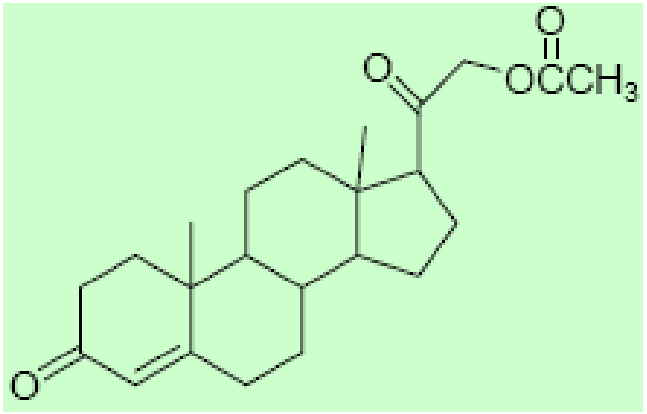
Role of dipropionate

- Increase stabilization of comp. , increase lipophilicity, increase

  Bronchial tissue absorption, duration of action.
  - used in inhalation aerosol therapy for treatment of asthma &rhinitis

Mineralocorticoids

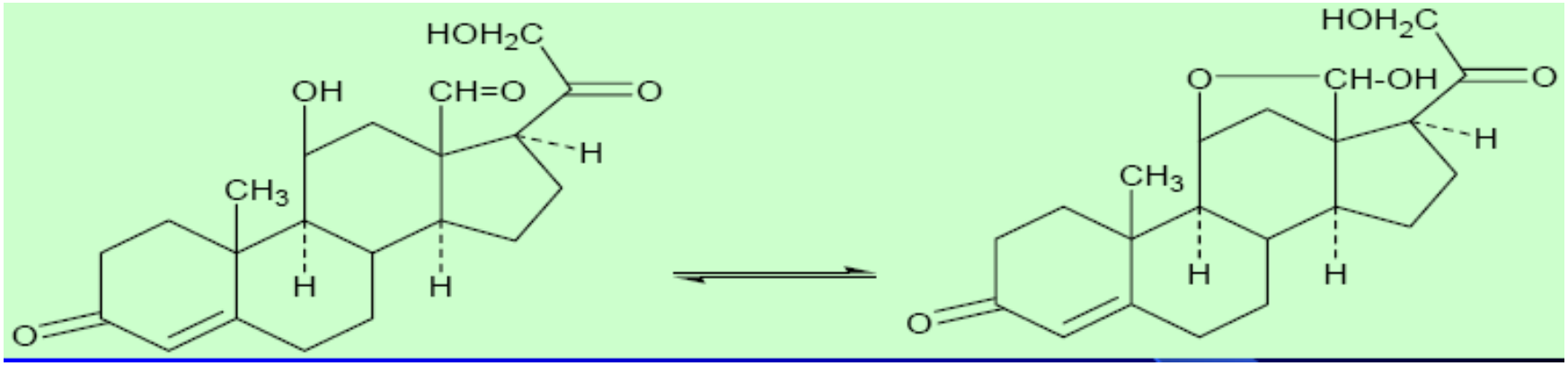
11-Deoxycorticosteron acetate (DOCA)



- 21-Hydroxy-4-pregnene-3,20-dione acetate
- Shows 40 times the salt retention activity of hydrocortisone and has zero anti-inflammatory activity.
- It used for treatment of Addison's disease

Aldosterone

- 11β,21-Dihydroxy-18-aldo-4-pregnen-3,20-dione

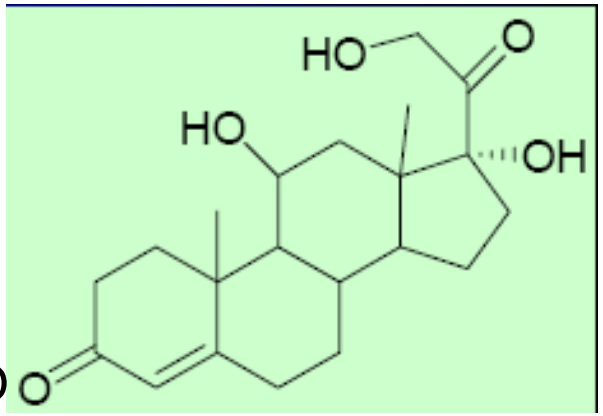


(Aldol form)

(Hemi acetal form)
Active form

- Aldosterone is known as anti-diuretic hormone secreted by adrenal cortex.
- It has 300 times the mineralocortical activity of hydrocortisone only 0.2 times its anti-inflammatory activity

SAR of corticosteroids



1) 11-keto group in cortisone must reduced in vivo to OH group (Hdrocortisone) to be active.

(2) 9α-Fluro:

a) prevent metabolic oxidation of 11 β-OH to C=O

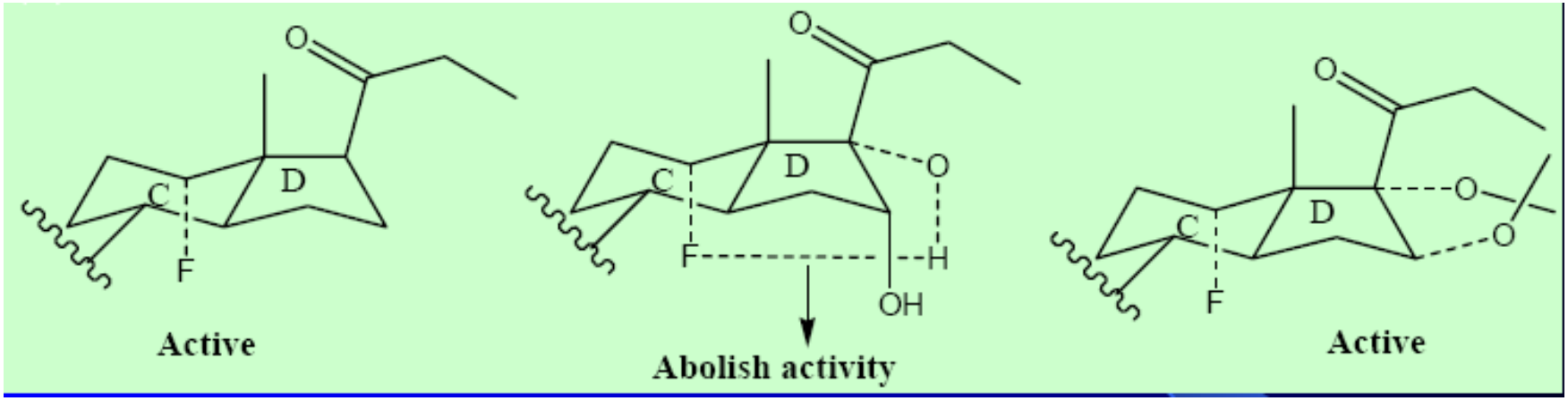
b) Increase activity (glucocorticoid) by its inductive effect, by increase dissociation of 11 β-OH so, increase formation of H-B to biological receptor.

(3) OH group in position 11,17 reduces the Na retention activity so, mineralocorticoids have no OH at this position.

(4) 9α-Fluro> *9α-Cl> 9α-Br in retention of sod.*

(5) Insertion of 16α-OH gp decrease sod. Retention by a) opposite The effect of 9α-Fluro b) increase sod. excretion.

6.


O
C
D
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OH
Abolish activity
O
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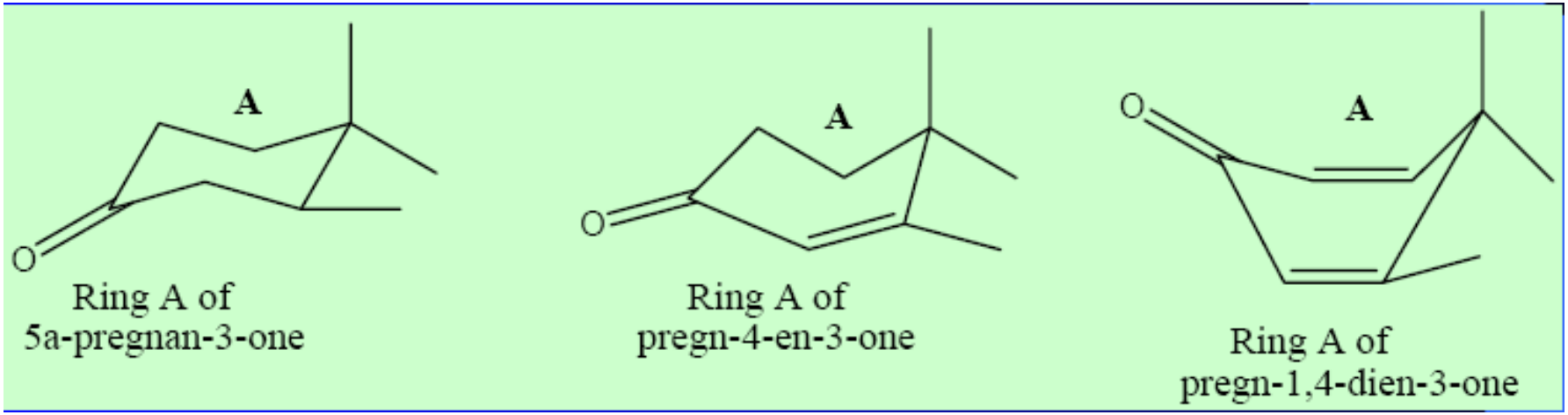
Active

7.


A
O
Ring A of
5a-pregnan-3-one
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Ring A of
pregn-4-en-3-one
O
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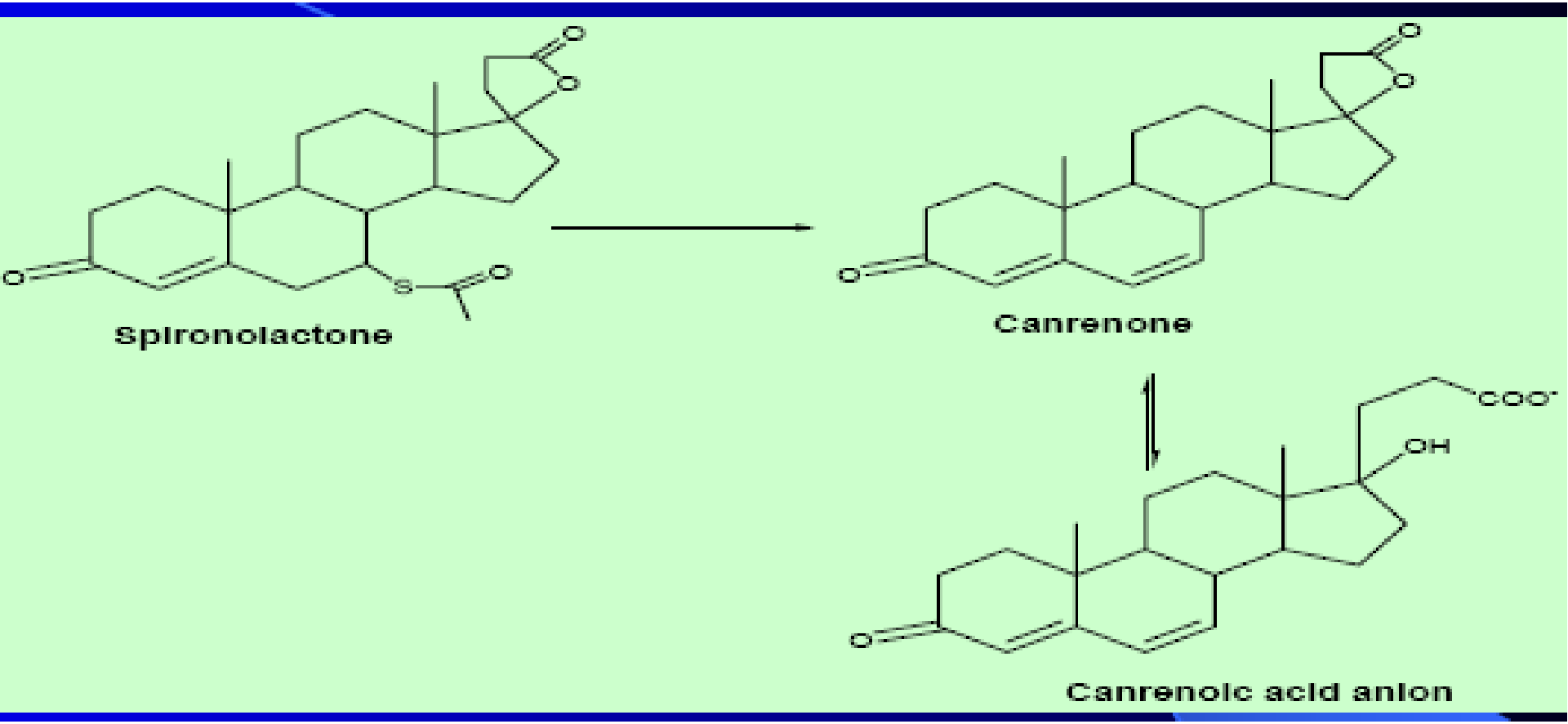
Ring A of
pregn-1,4-dien-3-one

Adrenocorticoid Antagonists

Spironolactone



- a competitive antagonist of aldosterone
- action occurs in the distal portion of tubule
- only effective if sufficient sodium reaches the distal tubule and

  if excess aldosterone is present
- has demonstrated tumorigenic action in rodents; not humans
- causes occasional hormonal problems, i.e. gynecomastia in males
- has gradual onset; activity peaks in 2 - 3 days
- 80% is metabolized to canrenone

- useful in patients with gout or diabetes, since it causes no hyperuricemia or impairment of glucose tolerance

- do not administer potassium supplement - hyperkalemia
- effective in the management of primary and secondary aldosteronism

- dosage: 10 mg/day initially for edema; for essential hypertension: 100 - 400 mg
- frequently combined with HCTZ (Aldactazide)