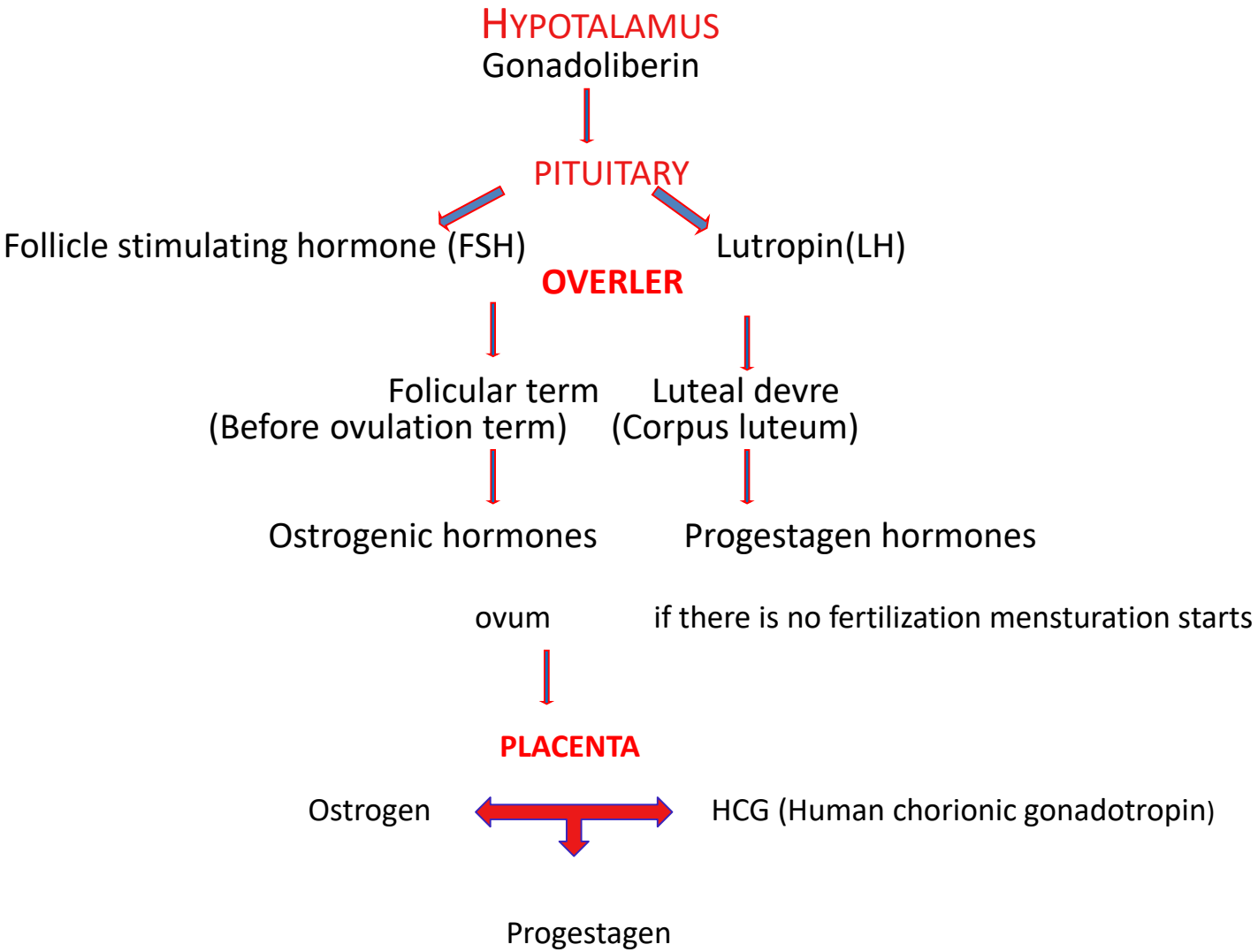
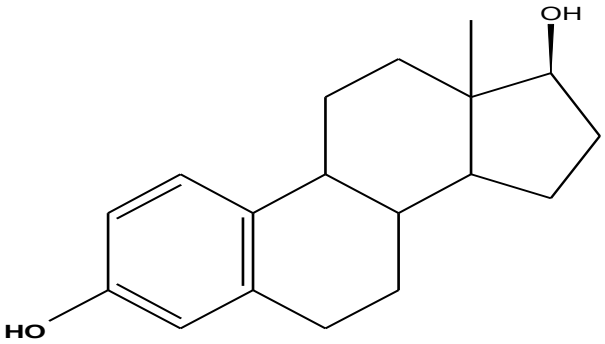
FEMALE SEX HORMONES and RELATED COMPOUNDS

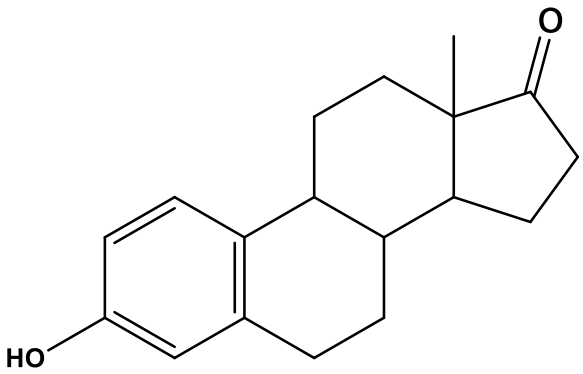

HYPOTALAMUS
Gonadoliberin
PITUITARY
Follicle stimulating hormone (FSH)
Lutropin(LH)
OVERLER
Folicular term
(Before ovulation term)
Luteal devre
(Corpus luteum)
Ostrogenic hormones
Progestagen hormones
ovum
if there is no fertilization mensturation starts
PLACENTA
Ostrogen
HCG (Human chorionic gonadotropin)
Progestagen

NATURE OESTROGENIC HORMONES

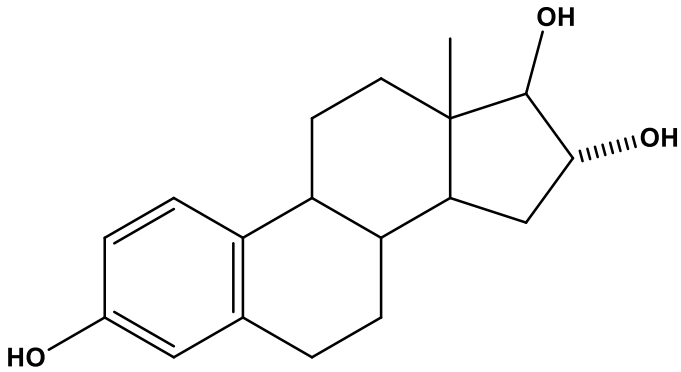
- **Ostradiol (Main base hormone)**
- **Oestron (Metabolite of Ostradiol)**
- **Ostriol (Metabolite of Ostradiol)**



ostradiol



oestron



ostriol

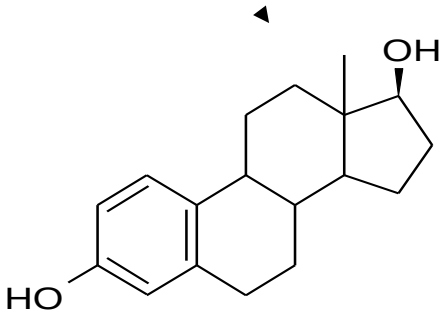
Biyosynthesis

Mainly they are synthesized at overium. In addition, in adrenal cortex, and placenta ve tiny amount in testicles in men.

Women are synthesized from childhood to menopause. During the ovulation period, level is max. In the menopausal period, estrogen synthesis is not performed in ovaries and is secreted only from the adrenal cortex.

The most synthesized hormone is estradiol, but the plasma has the highest concentration of oestrone.

OSTRADIOL

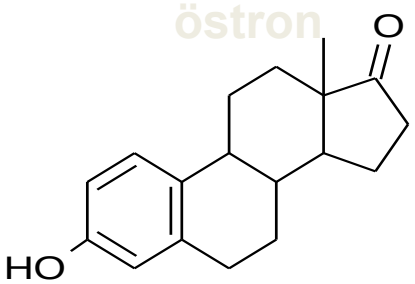


Östradiol

17-β-hydroxy dehydrogenas

Liver

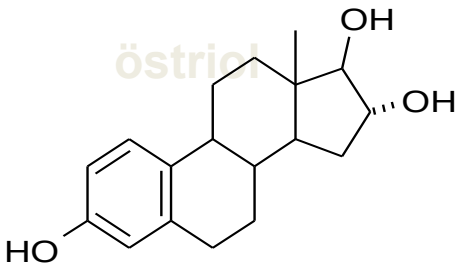
16-α-hydroksilas



Östron

(Activity is 1/3 of oestradiol)

Oestrojenik activity reduce



Östriol

(Activity is of 1/60 of oestradiol)

Synthesized hormon in overs are transported to the tissues as glucuronide or sulphate conjugates.

ACTIVITIES

- Before the maturation period; They regulate the development of the sexual organs and the secondary sexual structure (vagina, fallopian tubes, breasts and pubescence).
- In mature; It allows the endometrium to accept the fertilized egg, the normal functioning of the sexual organs and the stimulation of sexual instincts.

Uses

In Women

- Treatment of diseases caused by hormone insufficiency or irregular secretion
- Elimination of menopausal problems directly or with androgens
- Lactation suppressant with androgens in postpartum painful nipples
- Postmenopausal breast cancer
- As an oral contraceptive with progestogens

In men

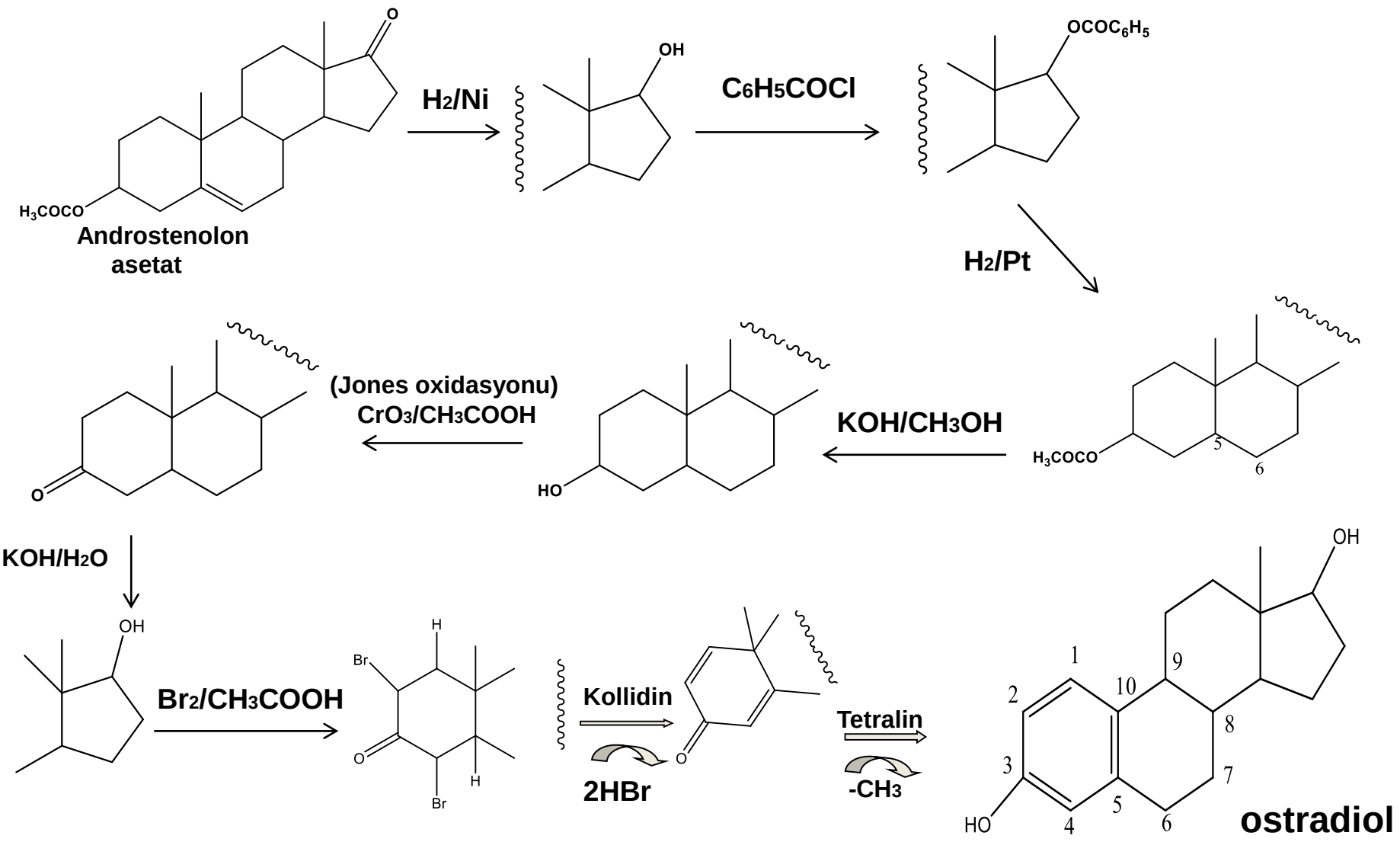
- Prostate cancer

They are contraindicated in renal and cardiac diseases, hypertension, premenopausal breast and uterine cancer.

Ostrogenic hormones

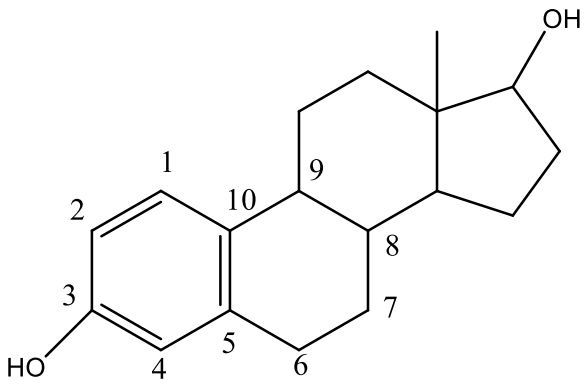
1)Steroidal oestrogens

Ostradiol (oestran-1,3,5(10)-trien-3,17β-diol)

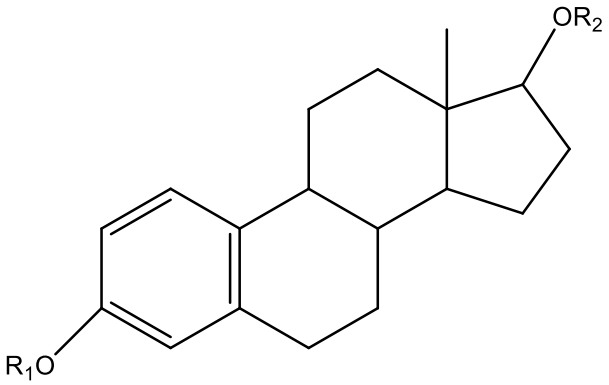


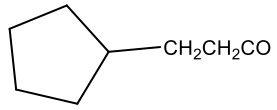
Tedavide doğrudan doğruya veya esterleri halinde kullanılır (3, 17, 3,17-diester).

Esterler; lipofilisiteyi ⟶ etki süresini artırır.

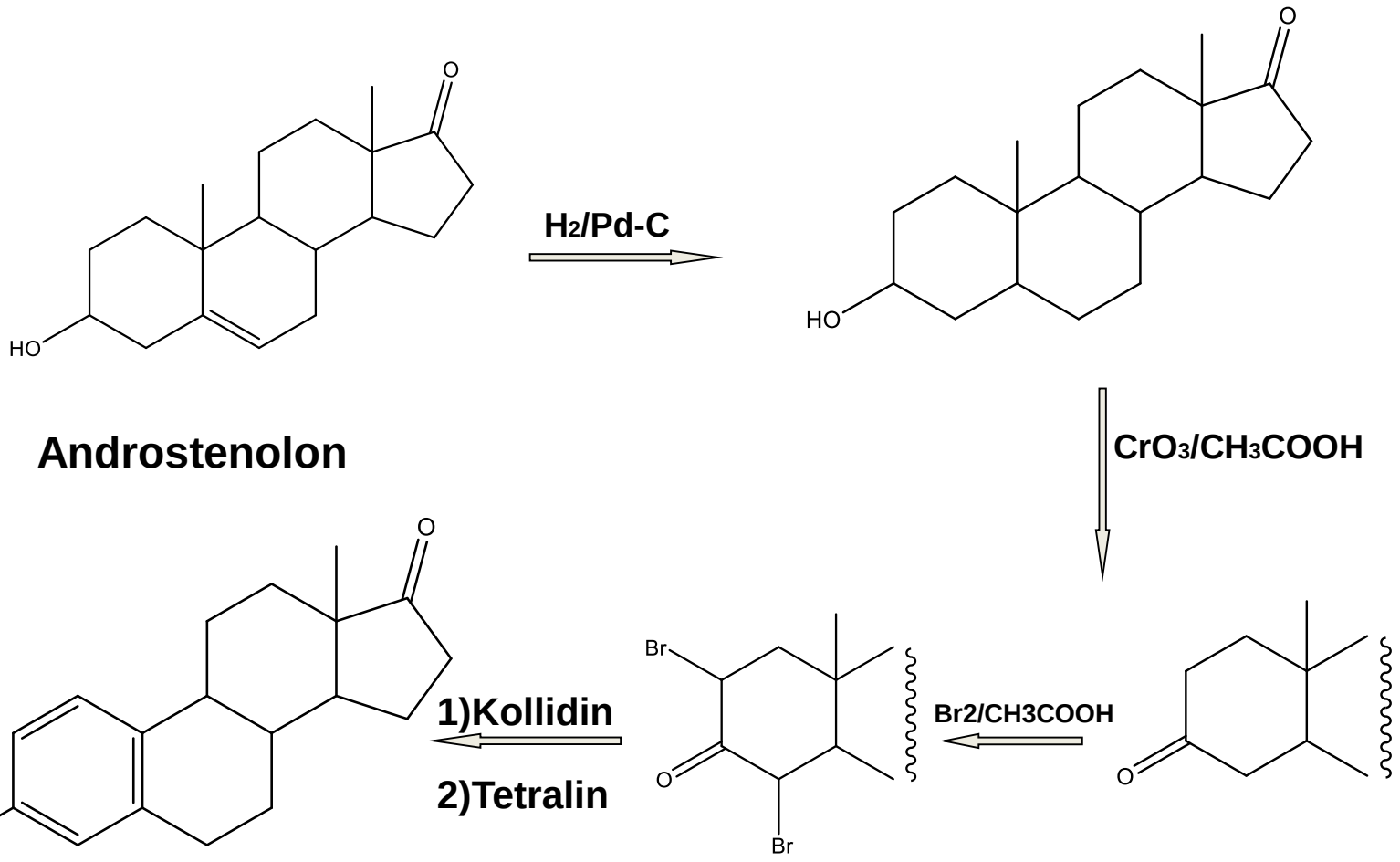


OSTRADIOL ESTER USED IN THERAPY



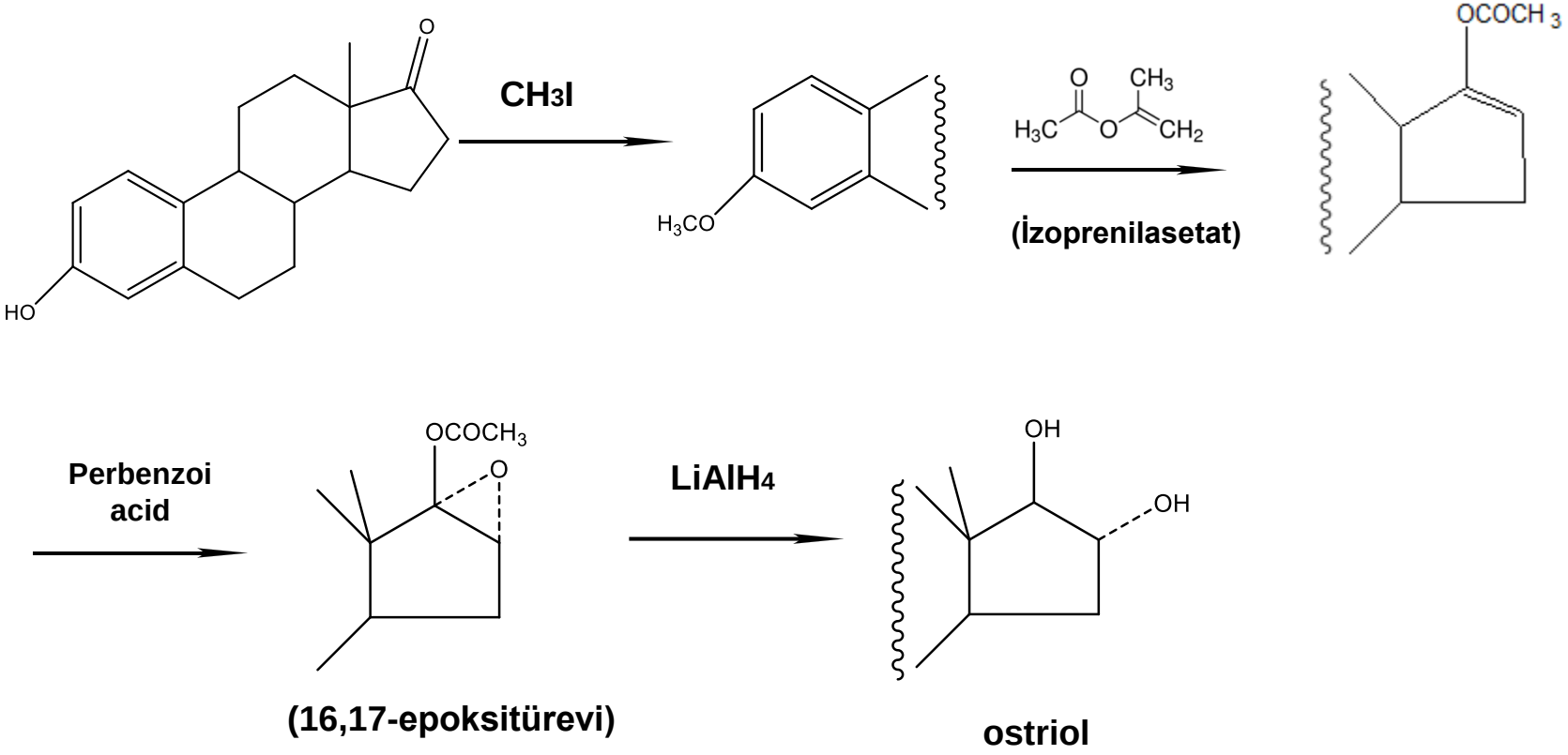
	R_1	R_2	
Ostradiol benzoate	**C_6H_5CO-**	**-H**	**Di-Pro oleosum,®**
Ostradiol dipropiyonate	**CH_3CH_2CO-**	**CH_3CH_2CO-**	
Östradiol valerate	**-H**	**$CH_3CH_2CH_2CH_2CO$-**	**Climen® Mesigyna®**
Ostradiol undesilate	**-H**	**$CH_3(CH_2)_8CH_2CO$-**	**Progynon-depot®**
Ostradiol spiyonate	**-H**		

Ostron (3-β-hydroxy-ostra-1,3,5(10)-trien-17-on)



When used orally, it loses activity in the intestine and liver. That is why it used as I.M.

Ostriol (ostra-1,3,5(10)-trien-16α,3,17β-triol)



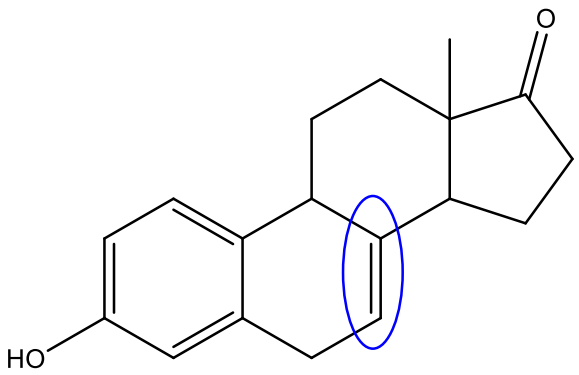
Conjuge ostrogens (Premarin®,Premella®)

It is a mixture of estrogen obtained by extraction from fresh or dried urine of pregnant mares. Other natural estrogens, including mainly estrone, also include equilin and equilenin. The estrogenic compounds contained are in the form of sodium salt.

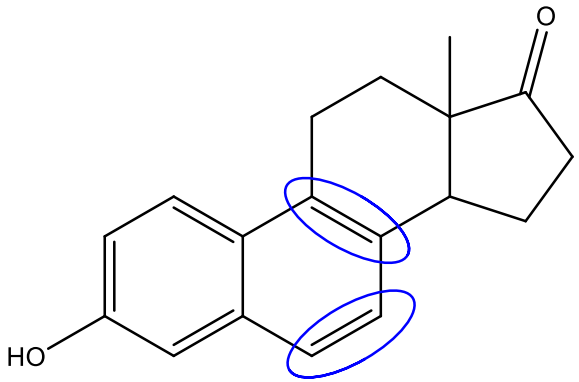
Total ingredinet of ostrojen ➔

- %50-65-»sodium oestron sulphate,
- %20-35-»sodium equilin sulphate

oluşturur.



Equilin



Equilenin

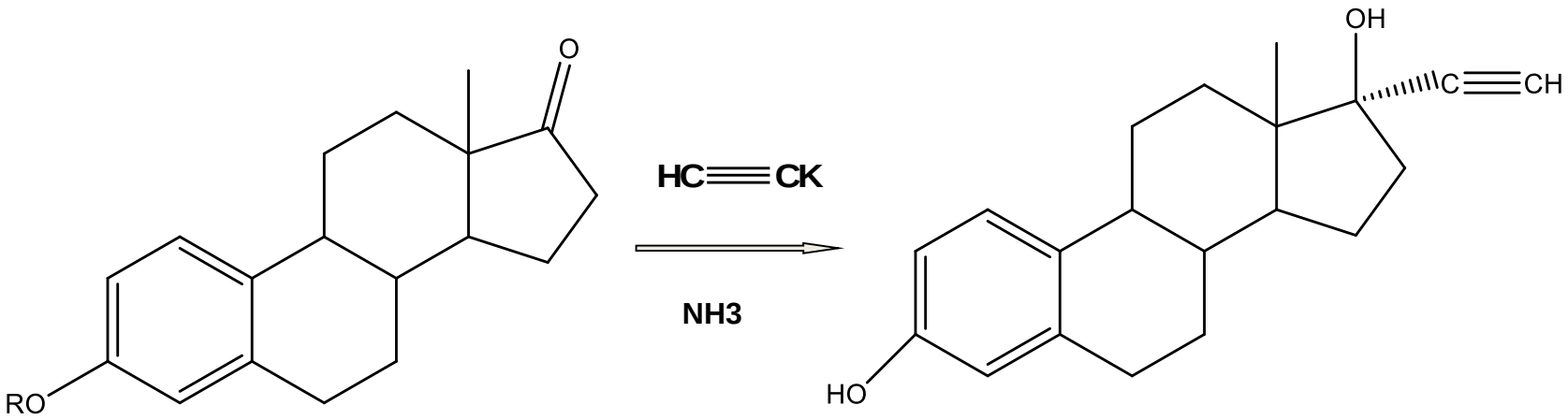
It is very fast to pass into absorption and circulation, it does not lose activity in oral use.

Synthetic ostradiol derivatives

17-α-ethynyl derivatives were prepared to prevent oxidation of OH group at 17th position of oestradiol.

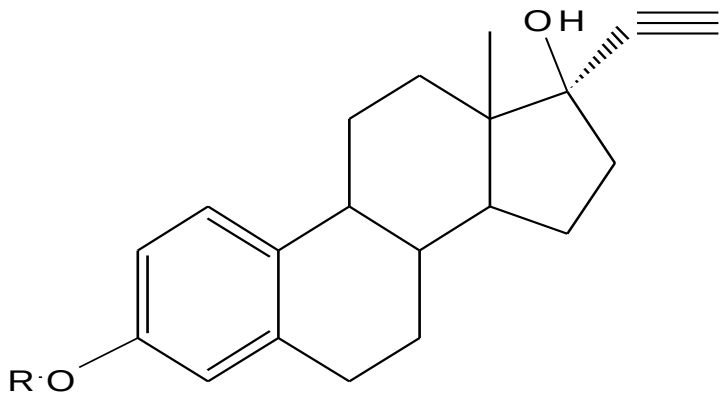
Activity is equal with oestradiol in parenteral uses

In oral uses is more than 15-20 times.



Oestron/oestron ether

Synthetic oestradiol derivatives used in Therapy

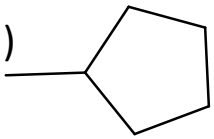


R

Ethinyl ostradiol (17α-ethynloestra-1,3,5(10)trien-3,17β-diol) -H

-Mestranol (3-metoksi-17-α-ethinylostra-1,3,5(10)-trien 17β-ol) $-CH_3$

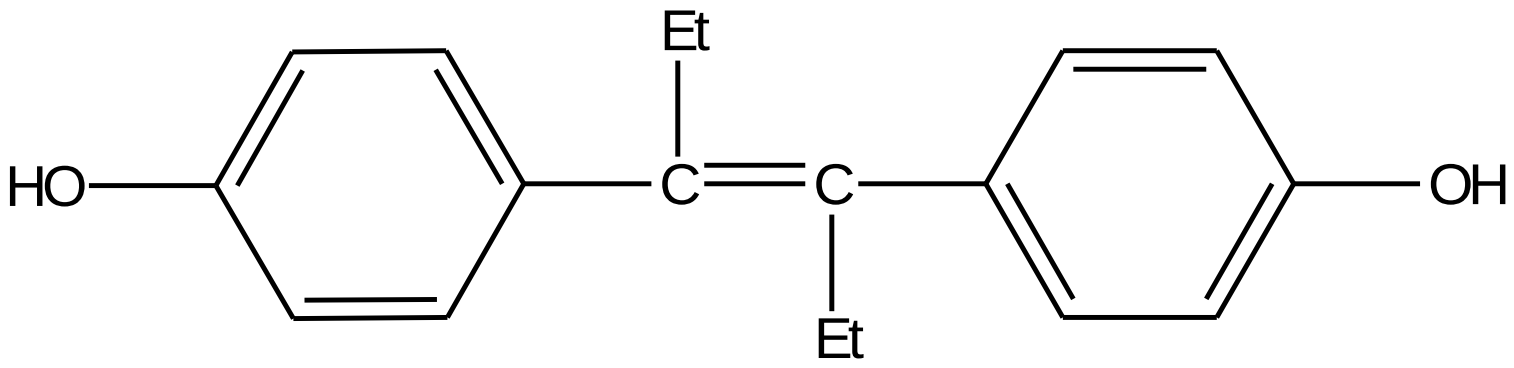
-Quinestrol (3-cyclopentyloxy-17-α-ethinyl oestra-1,3,5(10)-trien-17β-ol)

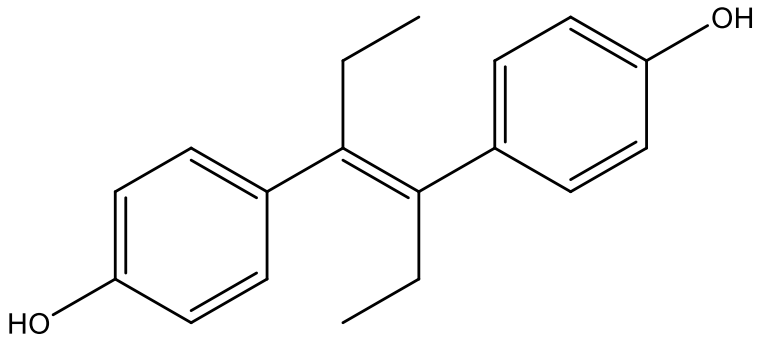


2) Nonsteroidal oestrogens

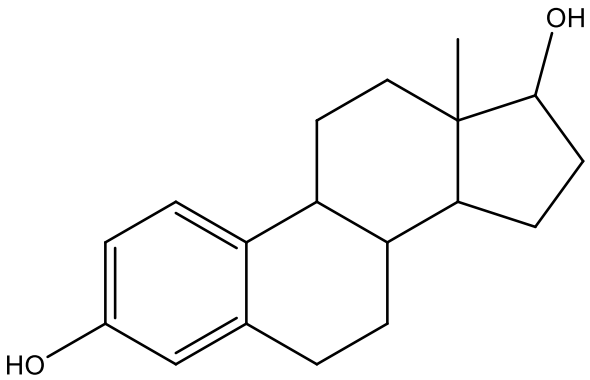
Diethylstilbestrol (trans-α,α'-diethyl-4,4'-stilbendiol)

It has an estrogenic effect although it doesn't carry a steroid ring.

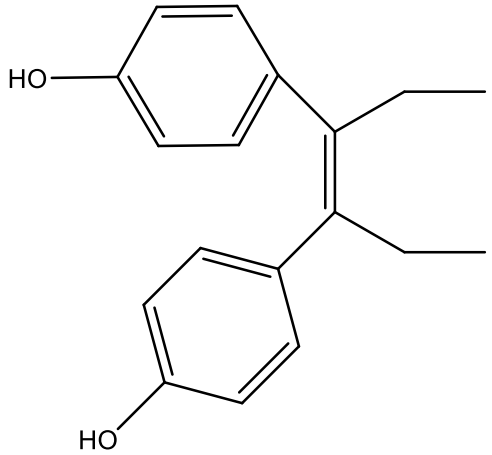




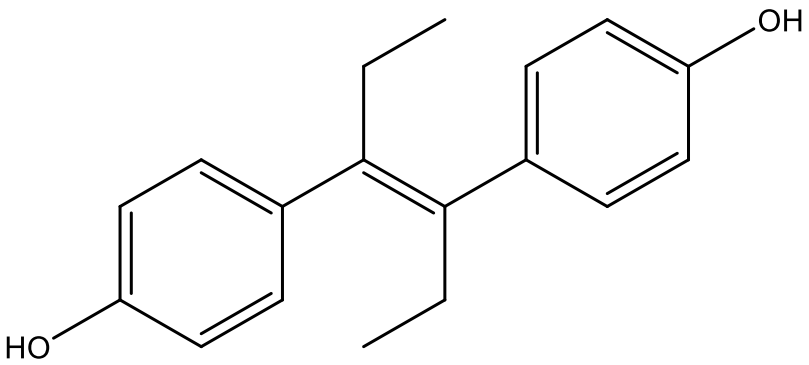
Trans-diethylstilbestrol



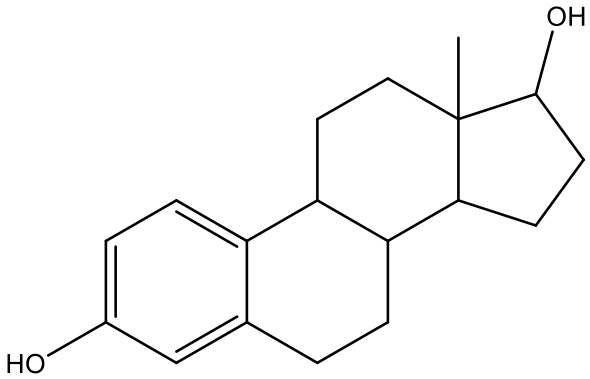
Ostradiol



Cis-diethylstilbestrol



Trans-diethylstilbestrol



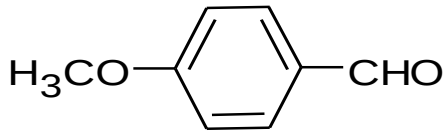
Oestradiol

Optimal oestrogenic activity a molecule should have a distance of about 8.55 Angstrom between the groups that can form H- bonds (e.g. Ketones, phenolic and alcoholic hydroxyl group) In DES this critical distance is 12.5 A and in oestradiol it is 10.9 A.

- It is the most active in nonsteroidal estrogenic compounds. 4 times estradiol or 10 times active more than estradiol. Dipropionate and diphosphate esters or directly are used. Oral, i.m and vaginal suppository forms are used.

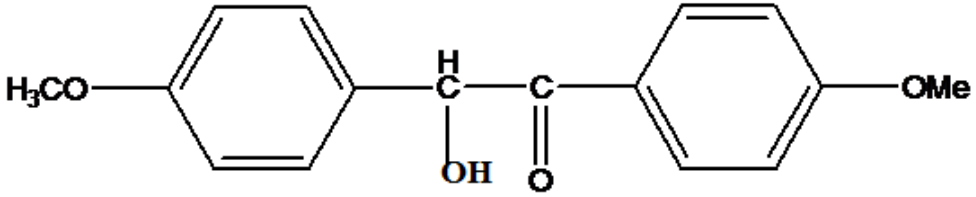
- It is used in advanced prostate cancer with postmenopausal breast cancer treatment.

Synthesis of Trans-diethylstilbestrol

2 

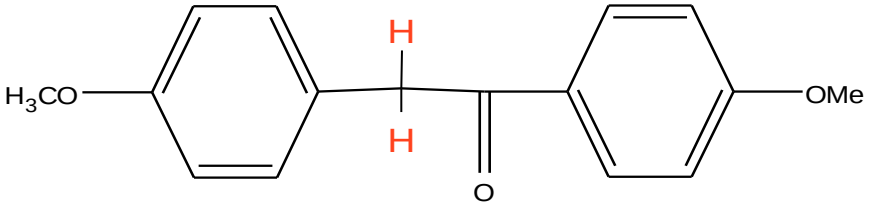
Anisaldehyde

KCN

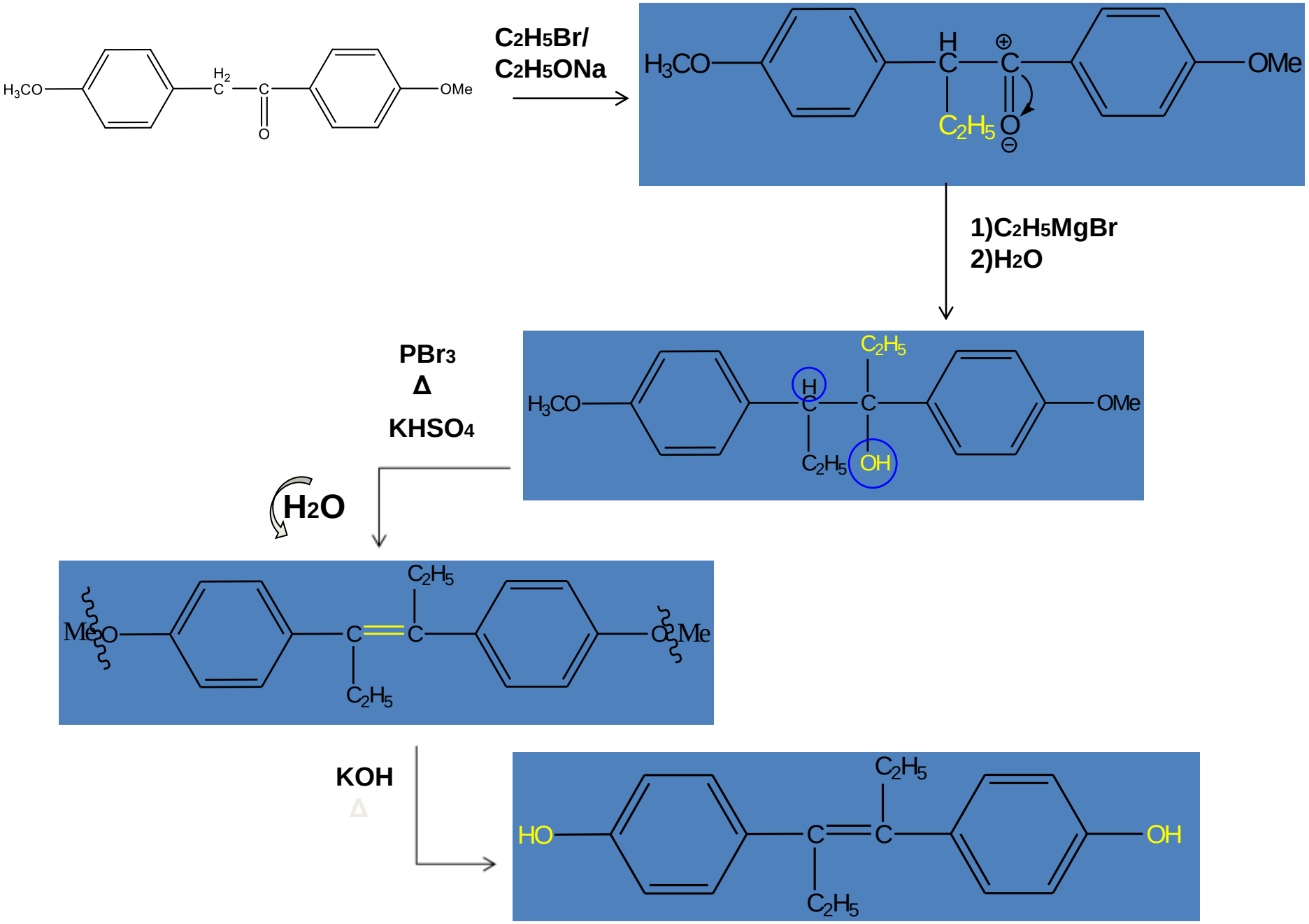


Anisoin

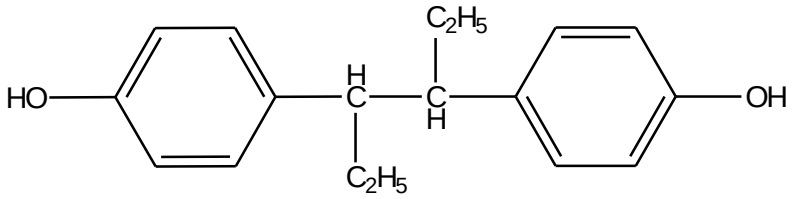
H_2



Dezoksianisoin


C2H5Br/
C2H5ONa
1)C2H5MgBr
2)H2O
PBr3
Δ
KHSO4
H2O
KOH
Δ

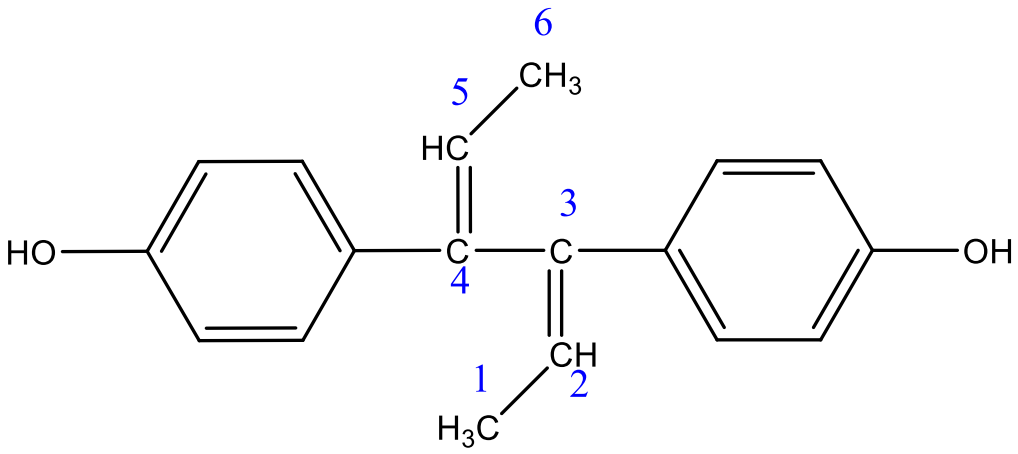
Hekzesterol 3,4-di(p-hydroxyphenyl)hexane.

Diethylstilbestrol $\xrightarrow{H_2}$ 

Hekzesterol

Its activity and toxicity are lower than diethylstilsterol.

Dienestrol **3,4-di(p-hydroxyphenyl)hexa-2,4-dien**



- **Activity and properties are similar to diethylstilbestrole.**

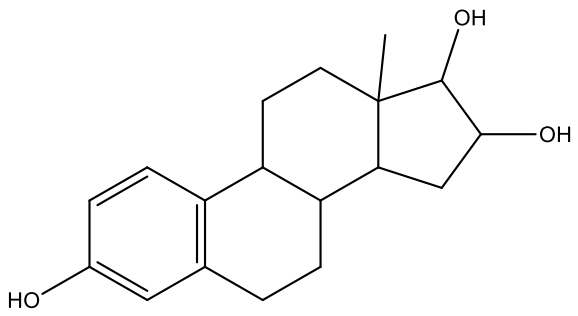
Estrogen antagonists

It is used to change the functions of natural estrogenic hormones related to sexual and reproductive activities and to treat breast cancer related to estrogens.

According to the activity mechanism

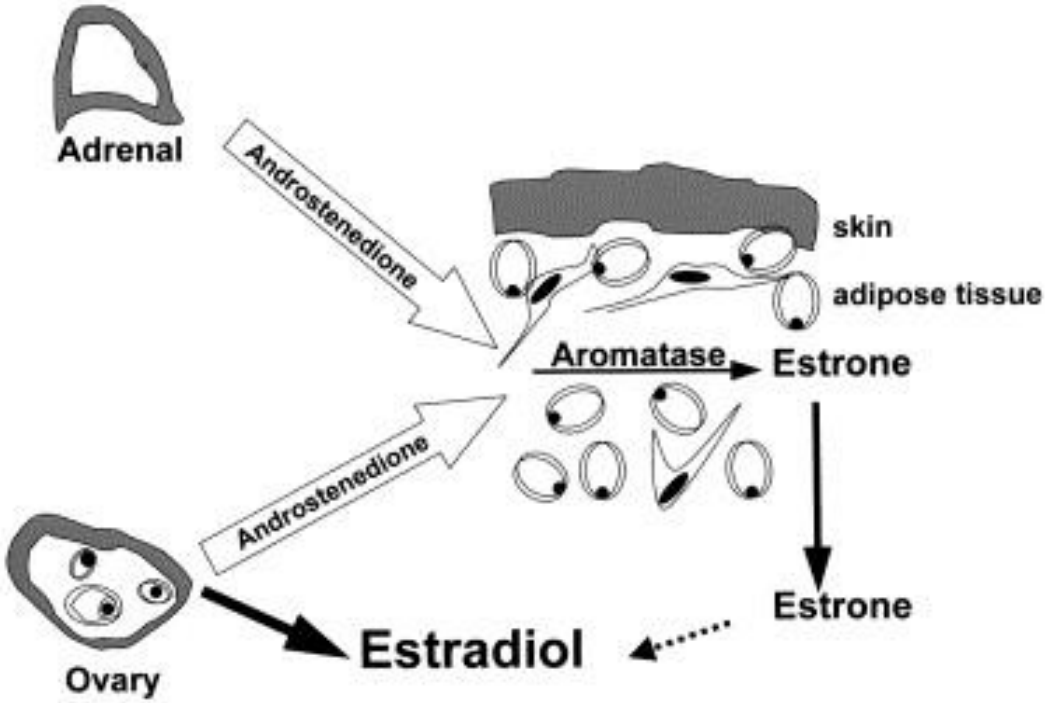
1)Compounds that inhibit estradiol

- It competes with estradiol in the target cells, but is rapidly detached from the receptor, so there is no strong estrogenic effect.
- They prevent interaction of estradiol with oestrogenic receptors, so estrogenic activity is decreased.

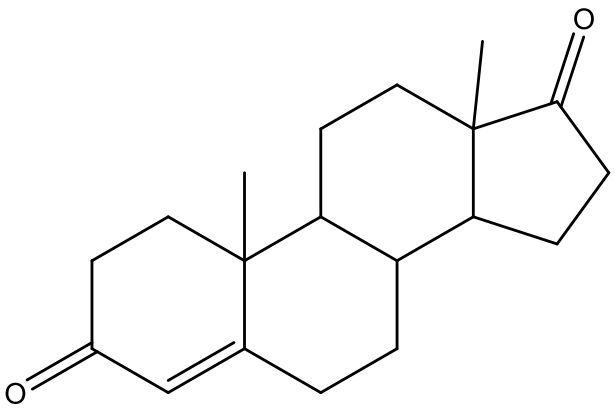


Ostriol

2)Aromatase Inhibitors

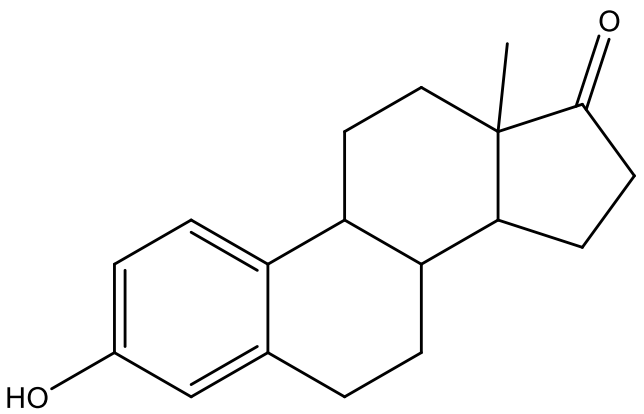


In the body, while estrogens are produced from ovaries at pre-menopausal term, whereas after menopause they are produced from androstendion in adrenal gland, via aromates enzymes.



androstendion

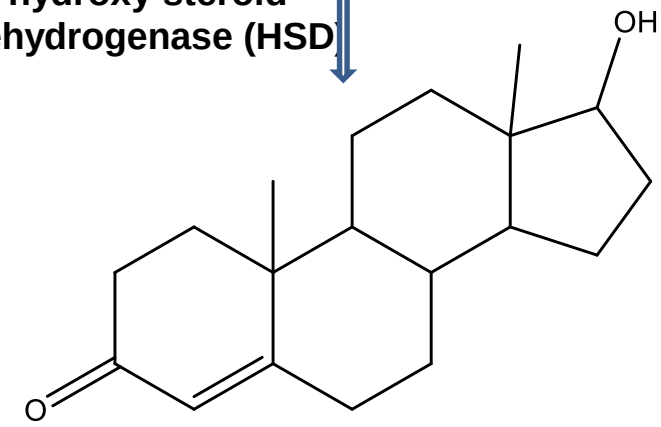
aromatase



östron

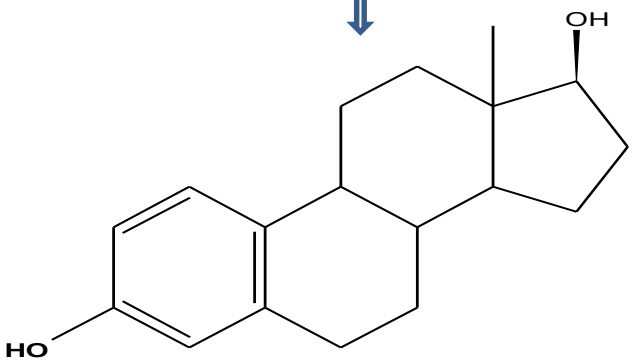
17-hydroxy steroid
Dehydrogenase (HSD)

17-hydroxy steroid
Dehydrogenase (HSD)



testosteron

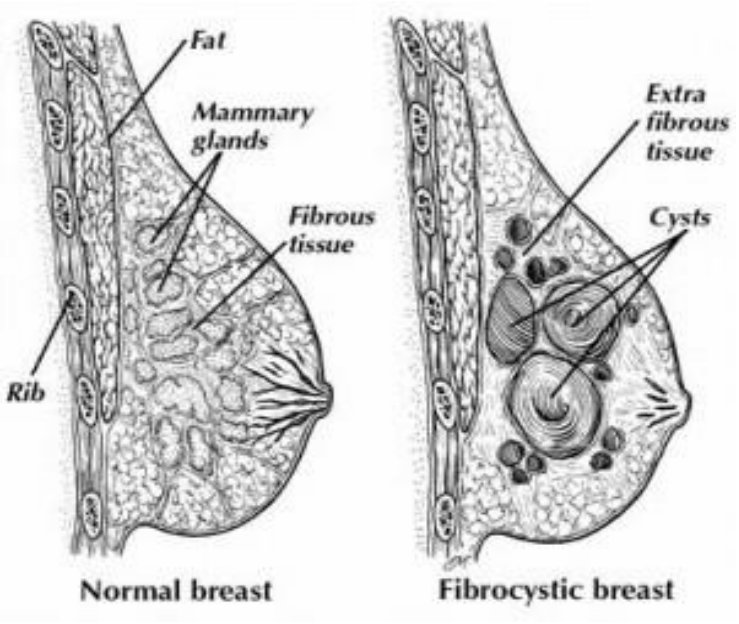
aromatase



östradiol

Breast cancer and estrogens

- Breast cancer is the leading cause of cancer among women. One out of every 8 women is at risk of developing cancer.



Breast Cancer Etiology

- The cause of breast cancer in humans is unknown.

- Genetic, environmental, hormonal and psychological factors are considered to play a role in the formation, but 80 % of women with breast cancer do not have these risk factors.

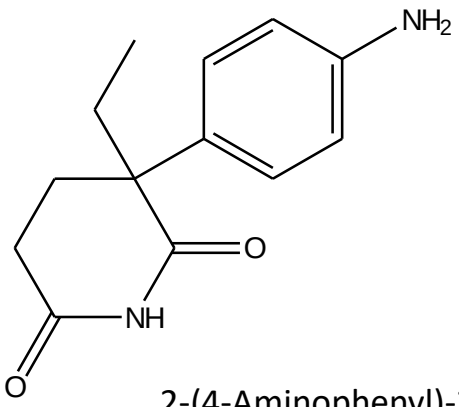
- It is reported that long-term and high exposure to endogenous estrogen hormone is one of the factors that increase the risk of breast cancer.

Drug used against breast cancer

Megestrol asetat		
Antioestrogenic Compounds	Estradiol-inhibiting Compounds	Oestriol
	Selective Estrogen Receptor Modulators	Tamoxifen Toremifen
	Oestrojen Receptor Antagonists	Fulverstrant
	Aromatase Inhibitors	Aminoglutetimit, Fadrozol, Anastrozol, Letrozol, Vorozol, Formestan, Eksemestan

1- Non-steroidal Inhibitors

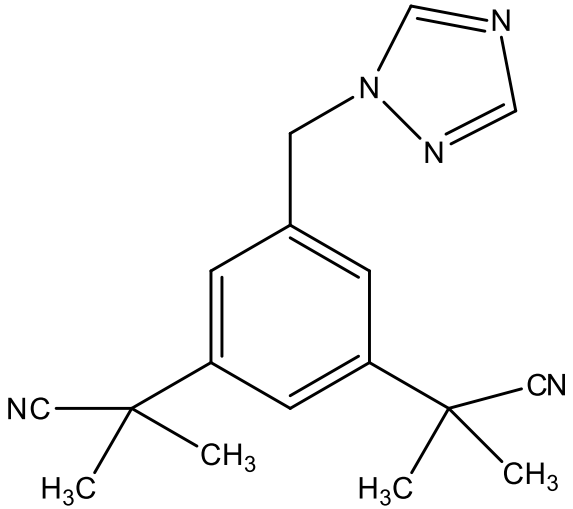
Aminoglutetimid



2-(4-Aminophenyl)-2-ethylglutetimid

- It inhibits the synthesis of glucocorticoids, mineralocorticoids, estrogens, androgens by inhibiting the enzymatic conversion of cholesterol to pregnonolon.

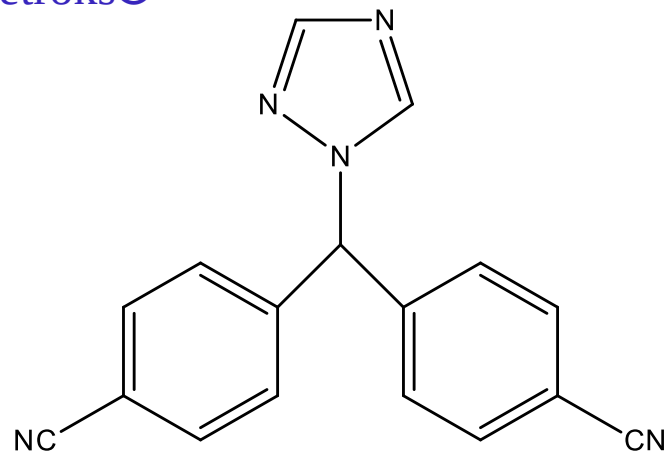
Anastrozol Arimidix®



2,2'-Dimethyl-2,2'-[5-(1H-1,2,4-triazol-1-yl-methyl)-1,3-phenylen]-bispropionitrile

Anastrazol does not inhibit adrenal steroid synthesis. Therefore, glucocorticoid or mineralocorticoid replacement therapy is not needed in patients receiving anastrozole. Anastrozole significantly suppresses serum estradiol levels and forms an alternative to tamoxifene to antagonize estrogen.

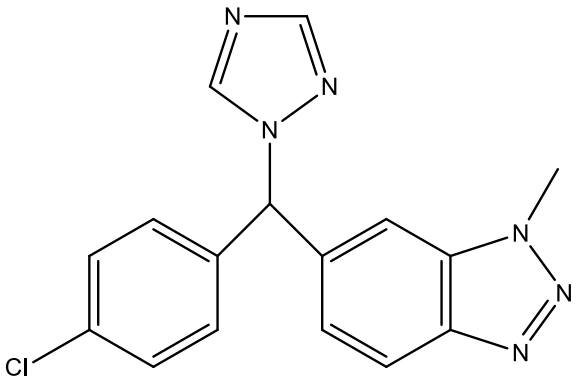
Letrozol Femara® Letroks®



4,4'-(1H-1,2,4-Triazol-1-yl-methylene)dibenzonitrile

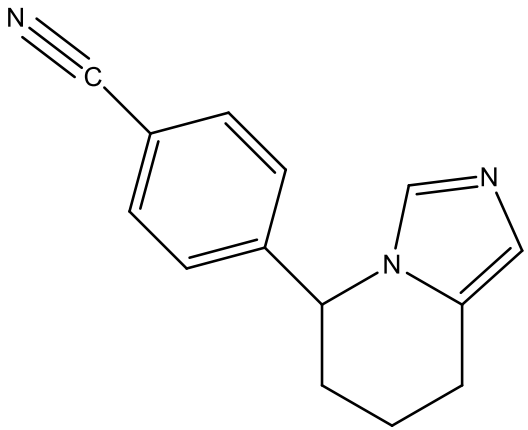
Letrozole is a highly selective nonsteroidal aromatase enzyme inhibitor that plays a key role in the biosynthesis of estrogen. In postmenopausal women, it is used to treat recurrent or progressive breast cancer despite antiestrogen therapy. Letrozole is better tolerated and more effective than megestrol acetate, a synthetic oral progestin.

Vorozol



(+)S-6-[(4-chlorophenyl)(1,2,3-triazol-1-yl)methyl]-1-methylbenzotriazole

Fadrozol

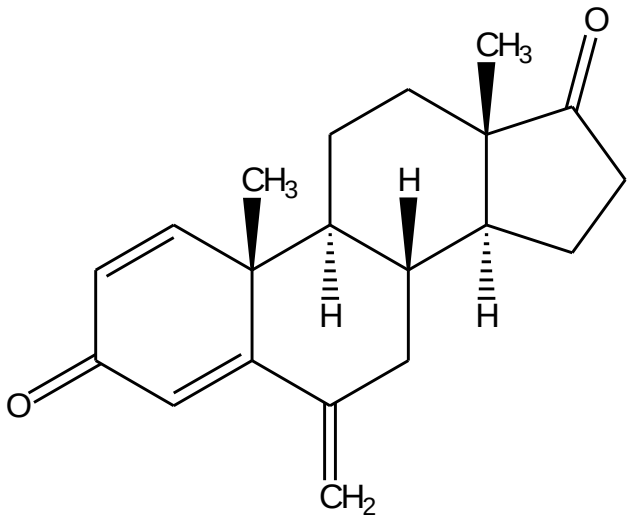


4-(5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-5-yl)benzonitrile

It is used in cases of postmenopausal advanced breast cancer.

2- Steroidal Inhibitors

Eksemestan- Aromasin®

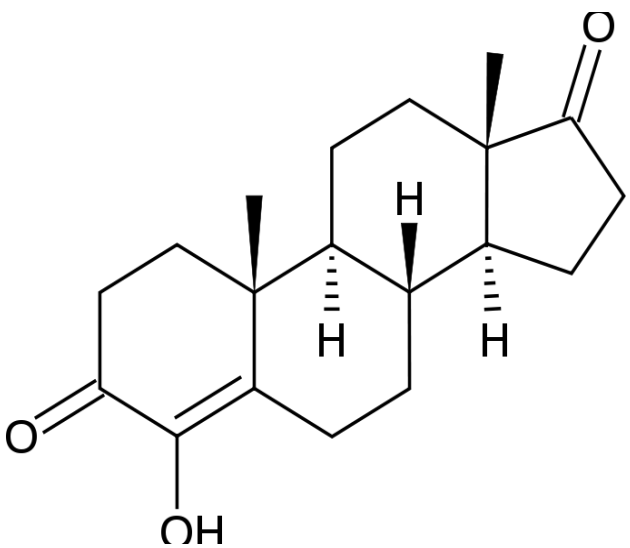


6-Methyleden-androst-1,4-dien-3,17-dion

- Exemestane is an irreversible aromatase inhibitor with steroid structure.

  It is used in the second line hormonal treatment of breast cancer.

Formestan Lentaron®



4-Hydroxyandrost-4-en-3,17-dion

- By competitively inhibiting the aromatase enzyme, it significantly reduces estrogen biosynthesis in all tissues.

It is used in cases of postmeno-pausal breast cancer.

- Aromatase inhibitors are intended to reduce estrogenic hormone levels by blocking the aromatase enzyme that provides estrogen synthesis.

- Most used aromatase inhibitors on today are Anastrozole, Letrozole and Exemestane.

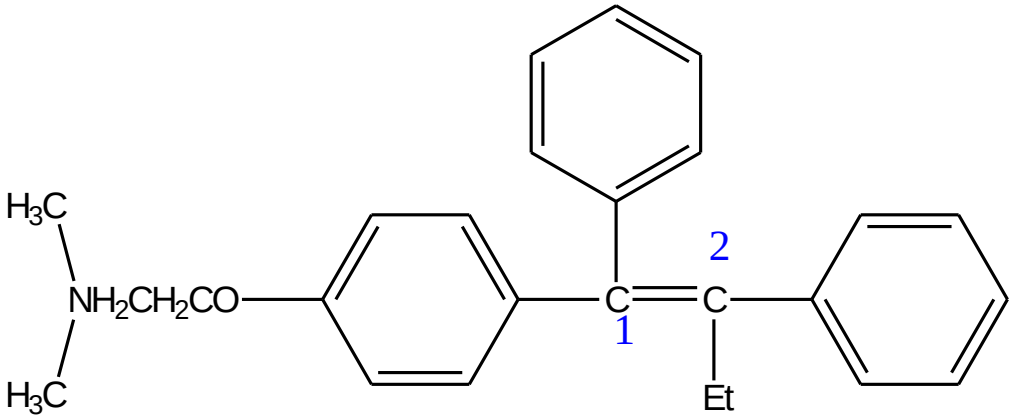
- AIl are used in ER (+) (Estrogen receptor positive) breast cancers because they significantly reduce estrogen production in the body.

- Aromatase inhibitors can now be used in the treatment of women with hormone receptor-positive breast cancer menopause. In the hormonal treatment of premenopausal women, antiestrogens are still the treatment of choice.

3) Antioestrogen Compounds

a)-Triphenylethyelen antiestrogens

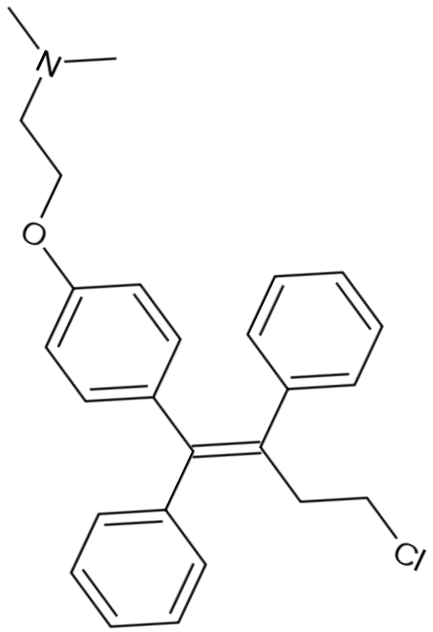
Tamoxifen Sitrat➔Apo-tamox®, Nolvadex®, Tamox®



(Z)1-[(p-dimethylaminoethoxy)phenyl]-1,2-diphenyl-2-ethylethylene

- It blocks the estrogen receptor in target cells - not an estrogenic response.
- It is used in the treatment of infertility. Tamoxifen has been shown to effectively stimulate ovulation in women who do not ovulate on a regular monthly basis.
- It is used to help breast surgery in breast cancer and breast cancer in women with risk of breast cancer.

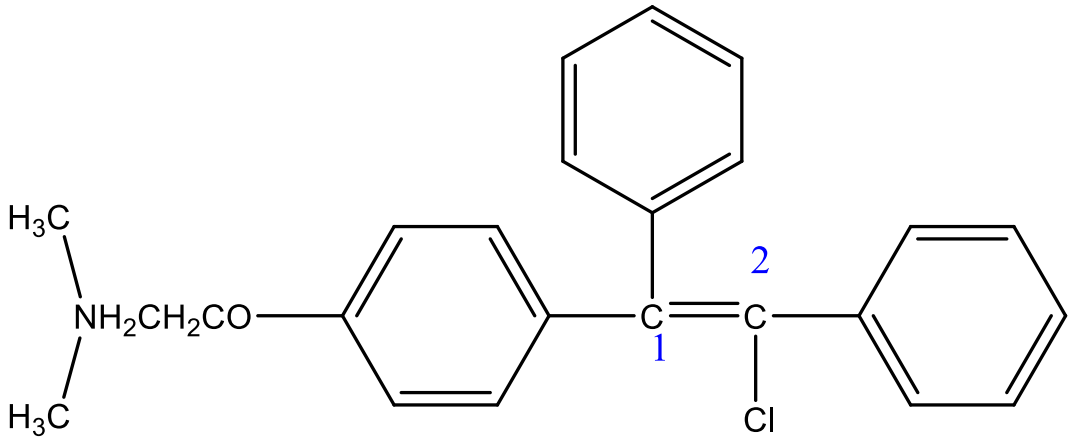
Toremifen Fareston®



(Z)1-[(p-dimethylaminoethoxy)phenyl]-1,2-diphenyl-2-(2-chloroethy) ethylene

It is a selective estrogen receptor modulator. It is used in the treatment of breast cancer and prevention of prostate cancer.

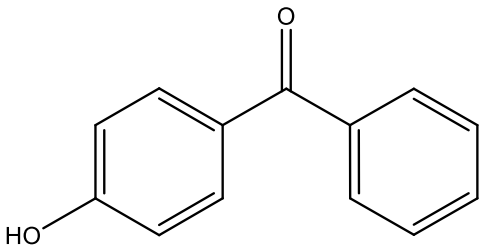
Chlomiphen citrate **Fertilin® , Klomen ®**



1-[(p-dimethylaminoethoxy)phenyl]-1,2-diphenyl-2-chloroethylene citrate

Amenorrhea or anovulator is used to treat infertility due to menstrual cycle.

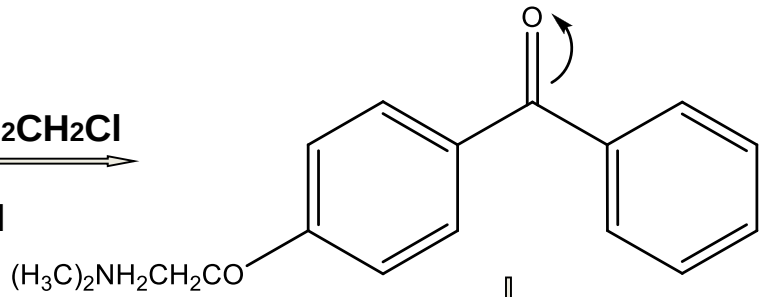
As a result of the blocking of the estrogen receptor in the pituitary, the ovaries are stimulated and enlarged with the effect of excessive secretion of follitropin and lutropin - usually more than one follicle matures unovulation is stimulated.

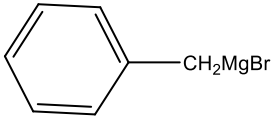


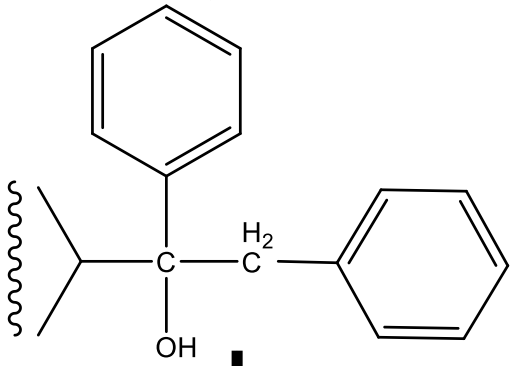
4-hydroxy benzophenon

$(CH_3)_2NCH_2CH_2Cl$

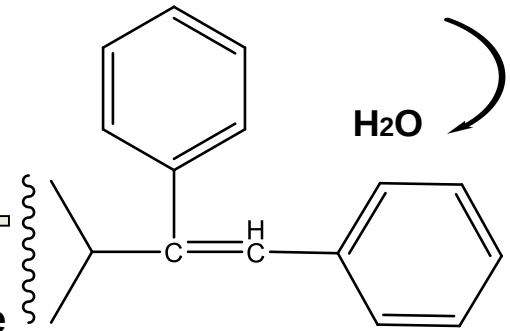
-HCl





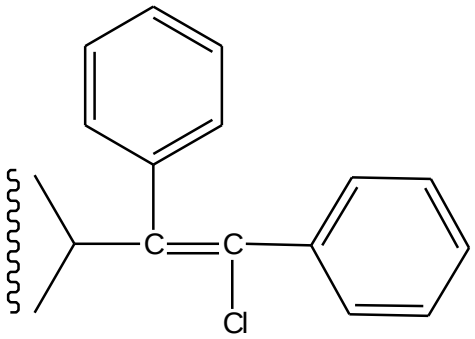


H_2O



NCS

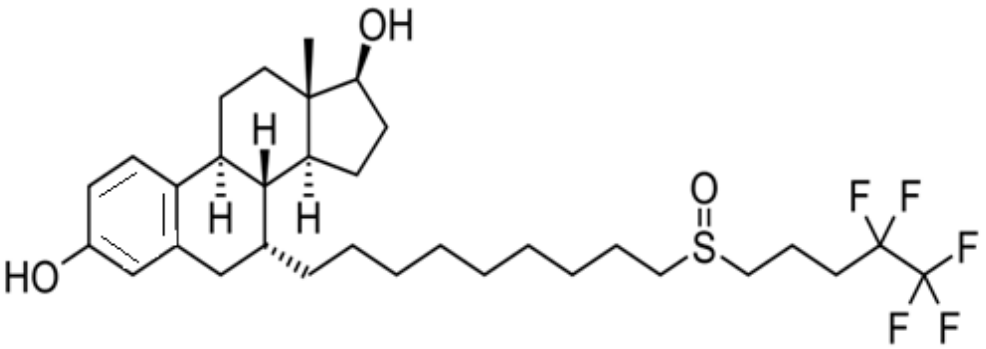
N-chloro succinimide



It is the mixture of isomers.

b- Ostrogen Receptor Antagonists : Antiostrogens

Fulvestrant Faslodex®



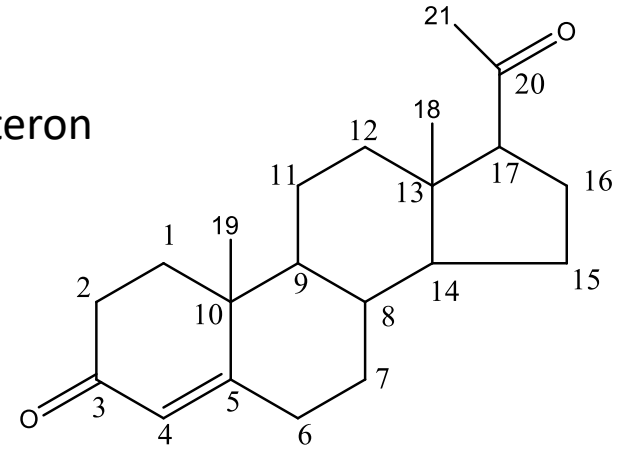
(7α,17β)-7-{9-[(4,4,5,5,5-pentafloropentyl)sulfinil]nonil}oestra-1,3,5(10)-trien-3,17-diol

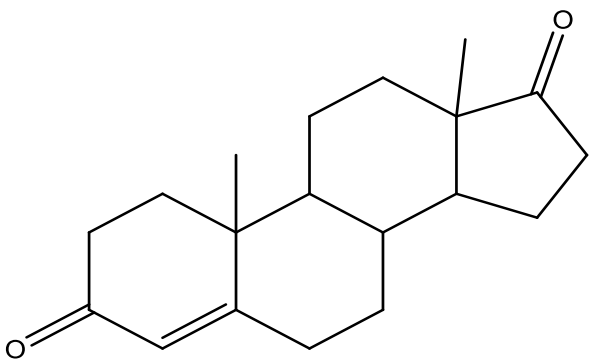
It does not block estrogen receptor such as tamoxifen, it breaks down the receptor and shows antagonistic effect. It is used in the treatment of advanced and metastatic breast cancer.

Progestagens Hormones

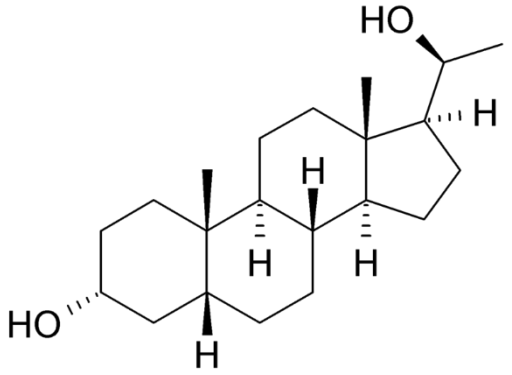
Progesterone is a naturally occurring progestative hormone in humans. Its half-life is very short (a few minutes), it undergoes rapid metabolic inactivation (Androstan-3,17-dione and 5-β-pregna-3α-20-diol).

Progesteron





Androstan-3,17-dion

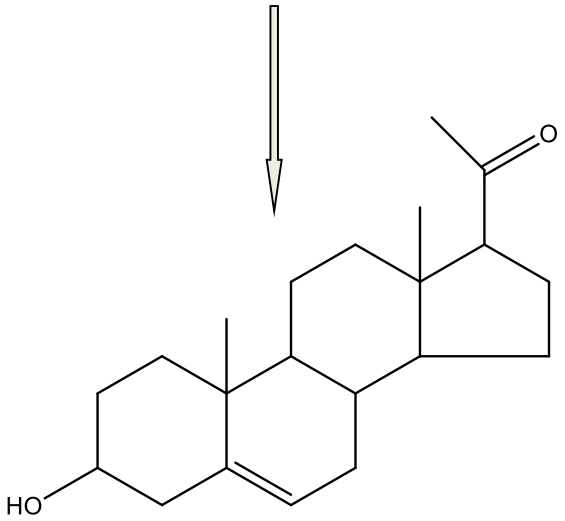


5-β-pregna-3α-20-diol

- Women in the ovaries,
  placenta in pregnancy,
- A small amount of testicles in men,
- Synthesized in the adrenal cortex in both sex.

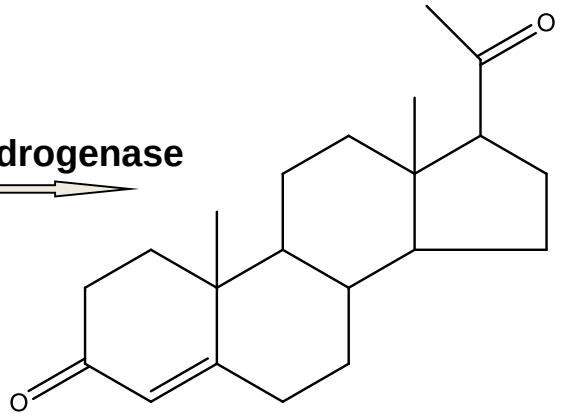
Biosynthesis

Cholesterol



pregnenolon

3β-hydroxy
Steroid dehydrogenase



progesteron

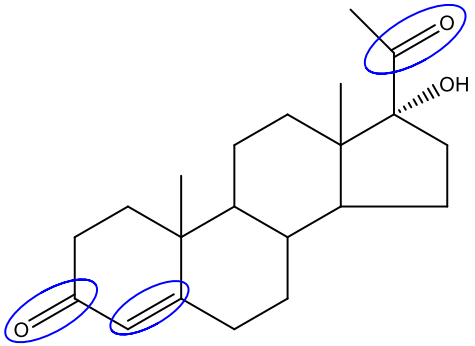
Effects

- Accelerates the formation of alveolar breast tissue in teenagers
- Regulates menstrual cycle in women,
- It affects to the endometrium in the uterus, a significant effect is the reduction of contractility of the uterus. Because of its effects on the uterine, progesterone is necessary for the implantation of the fertilized ovum into the uterine and continuation of pregnancy.
- Interaction with receptors in the hypothalamus inhibits gonadotropic hormone secretion.

- Functional uterine haemorrhages, including estrogens or androgens;
- in amenorrhea
- dysmenorrhea
- In premenstrual blood pressure,
- In the treatment of infertility,
- In endometrial cancer
- They are used directly or mostly as oral contraceptives with estrogens.

- The oral activity of natural progestogen hormone progesterone is low, and a variety of compounds with high oral activity have been developed by synthetic means.

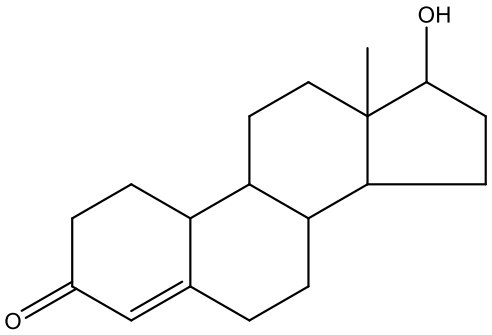
1) 17-α-Hydroxy progesteron derivatives



- 3 okso, Δ^4, 20 okso➔main structure
- Δ^6, 6-CH_3 or X➔activity increases
- 17α OH➔ main structure

If it is converted to ester (prevent reduction of keton group) activity increase. It can be used orally avaliable.

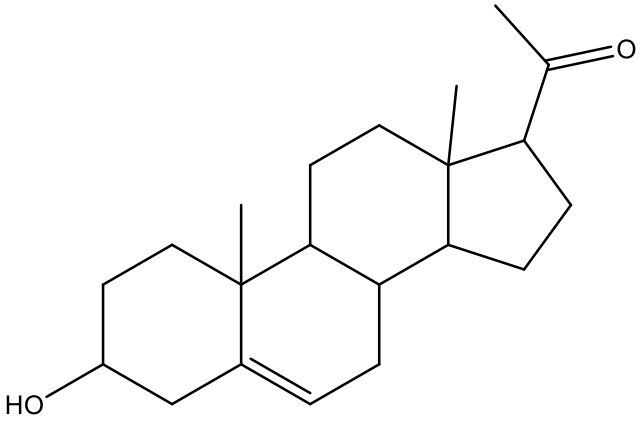
2) Androgenic progestagens



- 19-nor → progestagen akt. ↑
- 3 okso,Δ^4,17β OH➔main structure
- 17α alkyl➔provide oral uses
- 17β OH convert to the ester ➔ effect duration increases
- Δ^6,6-CH_3 or X➔activity increase
- 3 desoksi➔androjenic activity decrease.

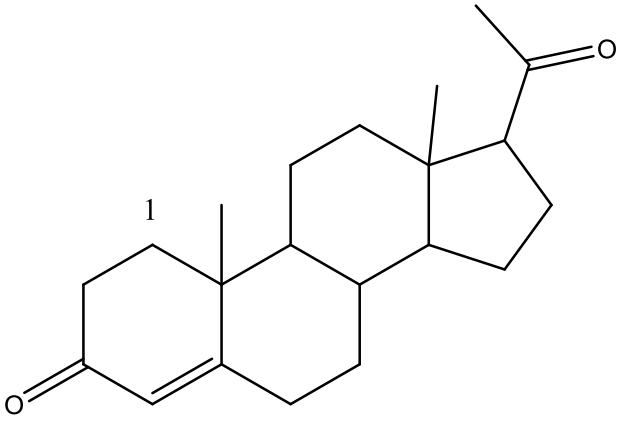
Progestagen Drugs

Progesteron Progestan®



pregnenolon

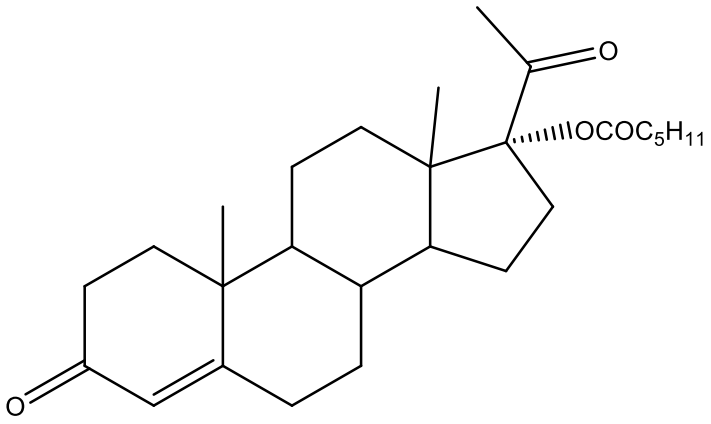
Oppenauer ox.



pregn-4-en-3,20-dion

No oral uses, I.M. Oral activity is 12 times lesser than I.M.

Hydroxyprogesteron caproate Proluton-depot®

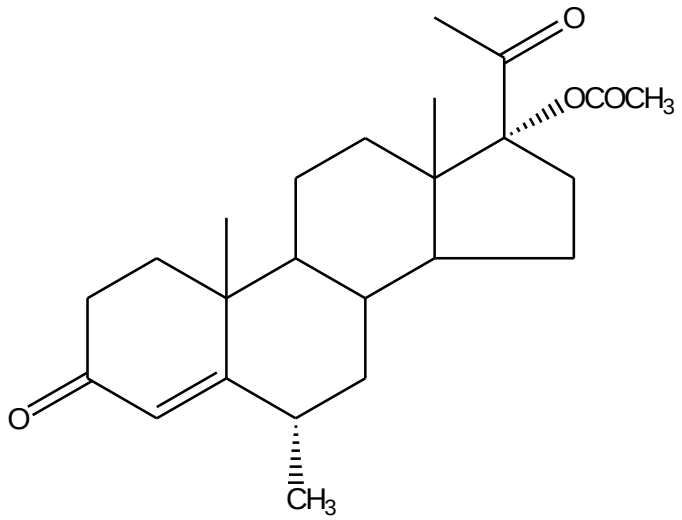


17-α-hydrokxypregn-4-en-3,20-dion hekzanoat

4-10 times active than progesteron

Menstruel disorders and uterine cancer are used

Medroksiprogesteron acetate Depo-provera®



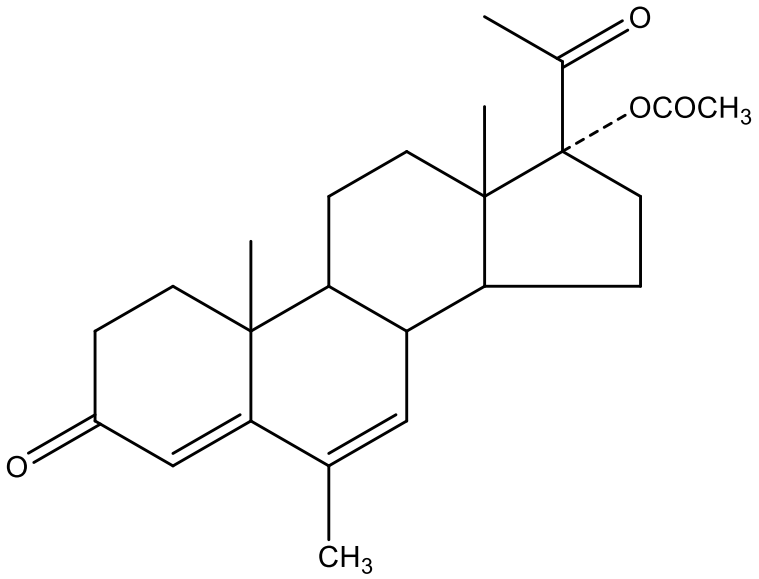
17α-hydroxy-6α-methyl pregn-4-en-3,20-dion acetate

- Parenteral ➔ 50 times active than Progesteron
- 6 Methyl ➔ this methyl group prevents metabolic reduction of 3-oxo and Δ^4
- and activity increases

- Ester➔ Duration of activity is prolonged.

- Menstruel disorders, abortus, uterine cancer oral or i.m. are used.

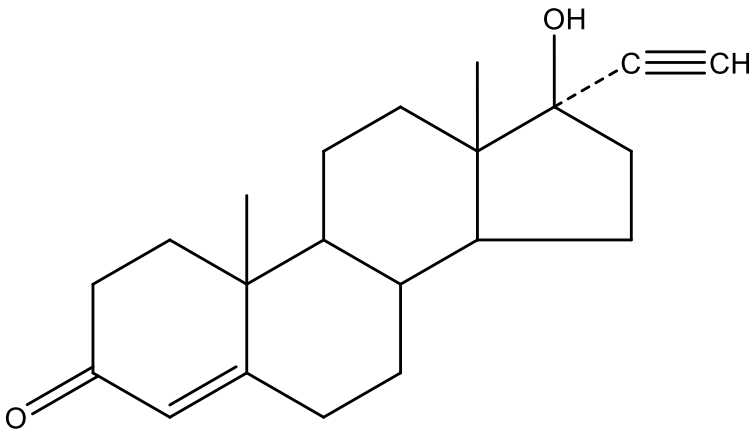
Megestrol acetate Borea®



17-α-hydroxy-6β-methyl-pregn-4,6-dien-3,20-dion acetate

It is used against breast and endometrium cancers by orally.

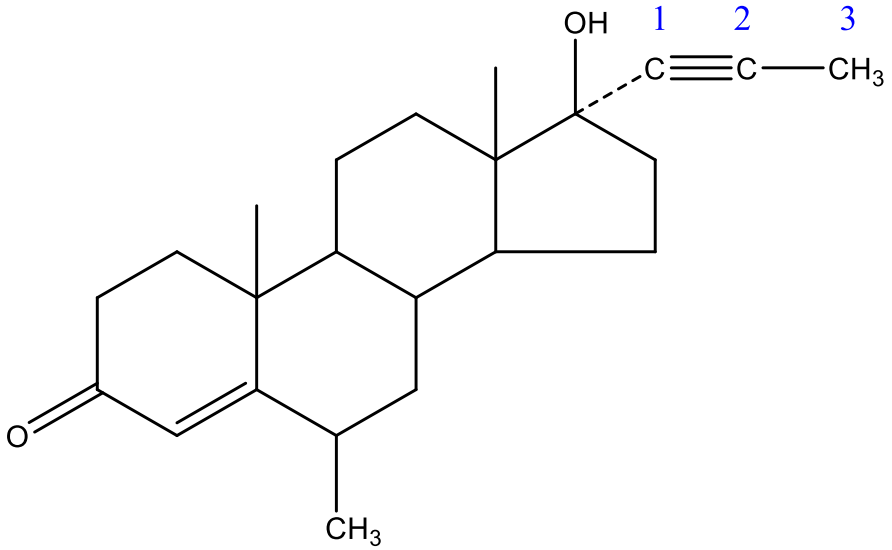
Ethisterone



17-α-ethinyl-17β-hydroxyandrost-4-en-3-one

- Activity is 10 times lower than progesterone in s.c.
- It is an orally preferred compound.

Dimethisteron

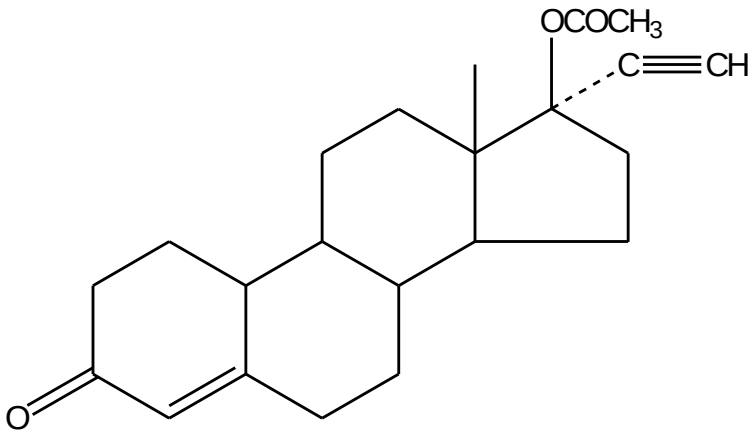


17-β-hydroxy-6β-methyl-17α-(propin-1-yl)-androst-4-en-3-one

- 12 times active than ethisteron by orally.
- It is used as oral contraseptive.

2. Androgenic Progestagens

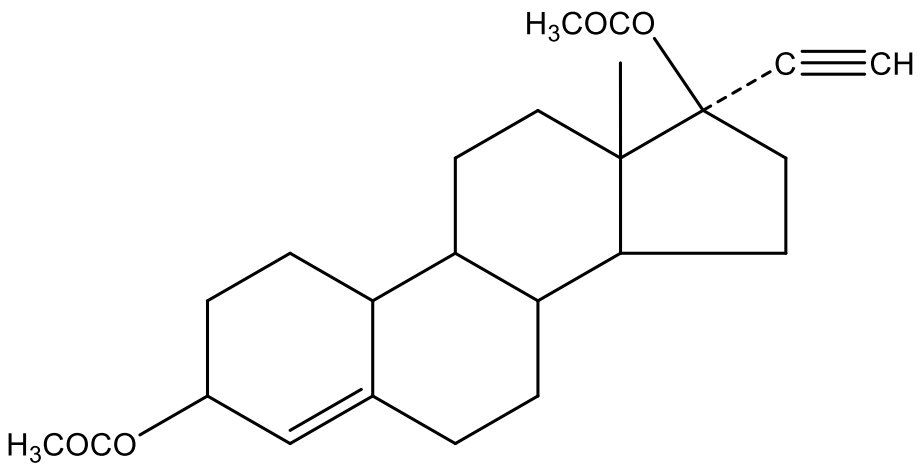
Norethisteron/ Norethisteron acetate Primolut-N®



17α-Ethynl-17β-hydroxyostr-4-en-3-on acetate

- It is used in its own or as an acetate ester.
- Parenteral and orally active,
- Against menstruel disorders and oral contraseptives.

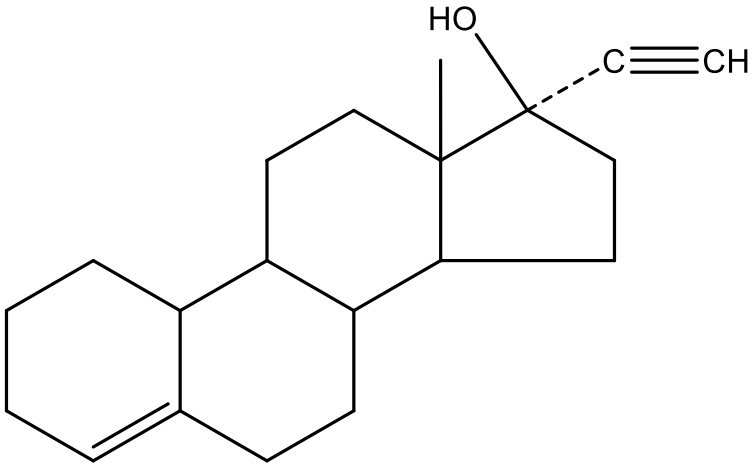
Etinodiol Diasetat Femulen®



17α-etinil-3β,17β-dihidroksiöstr-4-en-3,17 diasetat

- Used as an oral progestagen. It also uses in oral contraceptives.

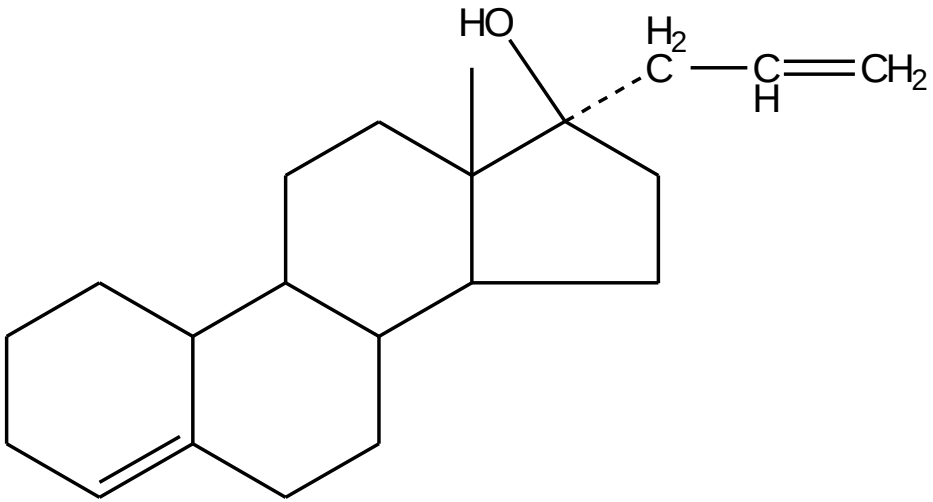
Linestrenol (Linesterol) Orgametril®



17α-ethynl-17β-hydroxyostr-4-en

- It is orally active.
- It is used as oral contraseptive.

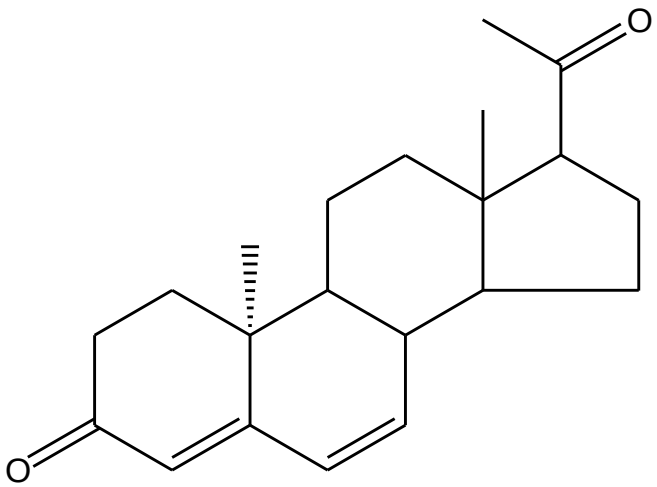
Allylestrenol



17α-allil-17β-hidroksi-östr-4-en

- Orally active.
- It is used against abortion and premature birth and progestagen deficiency.

Didrojesteron Duphaston®



9β-10α-pregna-4,6-dien-3,20-dion

- It is Retro type
- It is used orally for progestagen
- therapy.

PROGESTAGEN ANTAGONISTS

Contraseptives

Progesteron antagonists

Binds to the Progesteron

Receptors and inhibit

Progesteron activity.

Mifepriston

Inhibition of progesteron synthesis

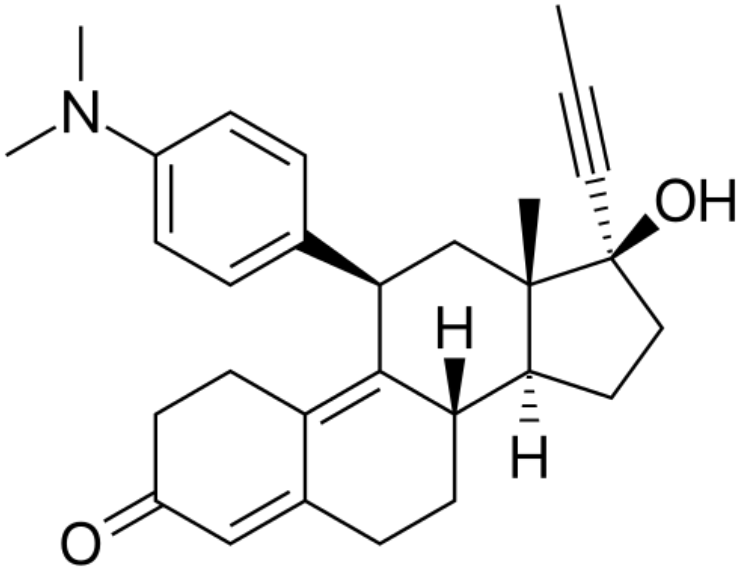
These agents inhibit 3β-hydroxy steroid dehydrogenase enzyme and progestreon synthesis are blocked.

These agents are not used too much, since these agents inhibits other hormones synthesis as well.

trilostan,epostan

(adrenocorticoid antagonist)

Mifepriston



- Prevents ovulation formation in follicular phase.
- Causes bleeding in the luteal phase.
- At the beginning of pregnancy causes abortion.

17β-hydroxy-11β-[4(dimethylamino)phenyl]-17α-(1-propynil)-estra -4,9-dien-3-on

Oral Contraceptives

- Used for contraceptives.

- They contain estrogen and progestagen hormone suitable for oral use. They act on hypothalamus and inhibit ovulation.

Abortifacient drugs

Mifepristone is a drug that can be used safely in the first period of pregnancy.

Prostaglandins are used for this purpose at the last term of pregnancy..

Prostaglandins ➔ increases uterine contractility and causes abortus.

- Prostaglandin E**2** (DINOPROSTON)
- Prostaglandin F**2α** (DINOPROST)