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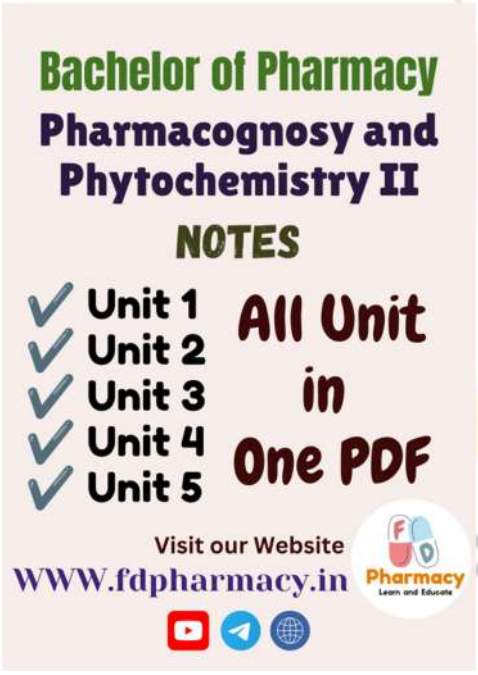
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MEDICINAL CHEMISTRY - II

UNIT 4

TOPIC :

- **Sex hormones :** Testosterone, Nandralone, Progestrones, Oestriol, Oestradiol, Oestrione, Diethylstilbestrol.

Sex Hormones

- Sex hormones are steroid hormones that regulate sexual development, reproduction, and secondary sexual characteristics.
- Produced mainly by the gonads (ovaries and testes), with minor contributions from the adrenal cortex.
- Classified into three major groups:
    1. Androgens – male sex hormones
    2. Estrogens – female sex hormones
    3. Progestins – support pregnancy and menstrual cycle

1. Androgens

- Primary male sex hormones; also present in females in small amounts.
- Source: Testes (Leydig cells), adrenal cortex
- Key hormones: Testosterone, Dihydrotestosterone (DHT), Androstenedione

Chemical Features:

- C17β-hydroxyl, Δ4 double bond, C3-keto group

Mechanism of Action:

- Bind to androgen receptors → modulate gene transcription → protein synthesis → male sexual characteristics

Physiological Effects:

- Development of male genitalia
- Secondary sexual characteristics: deep voice, facial/body hair, muscle mass
- Spermatogenesis
- Libido in both sexes

Therapeutic Uses:

- Hypogonadism
- Delayed puberty
- Certain types of breast cancer (androgen therapy)

Side Effects:

- Virilization in females
- Acne, baldness
- Liver toxicity (with oral synthetic androgens)

2. Estrogens

- Primary female sex hormones; also present in males in small amounts.
- Source: Ovaries (granulosa cells), placenta, adrenal cortex, testes (small)
- Key hormones: Estradiol, Estrone, Estriol

Chemical Features:

- Aromatic A-ring, hydroxyl at C3, hydroxyl at C17β

Mechanism of Action:

- Bind estrogen receptors (ERα, ERβ) → regulate transcription of target genes

Physiological Effects:

- Development of female genitalia and breasts
- Regulation of menstrual cycle
- Maintain bone density
- Promote fat distribution (hips, thighs, buttocks)

Therapeutic Uses:

- Hormone replacement therapy (HRT)
- Contraception (combined with progestins)
- Osteoporosis prevention
- Treatment of estrogen-deficient states

Side Effects:

- Thrombosis, nausea, breast tenderness
- Risk of endometrial or breast cancer with prolonged use

3. Progestins

- Support pregnancy and menstrual cycle regulation
- Source: Corpus luteum (ovary), placenta, adrenal cortex
- Key hormones: Progesterone, Medroxyprogesterone, Norethisterone

Chemical Features:

- C3-keto, C20-keto, Δ4 double bond

Mechanism of Action:

- Bind to progesterone receptors → regulate gene expression in reproductive tissues

Physiological Effects:

- Prepares endometrium for implantation
- Maintains pregnancy
- Suppresses ovulation
- Regulates menstrual cycle

Therapeutic Uses:

- Contraception (alone or with estrogen)
- Amenorrhea
- Dysfunctional uterine bleeding
- Hormone replacement therapy

Side Effects:

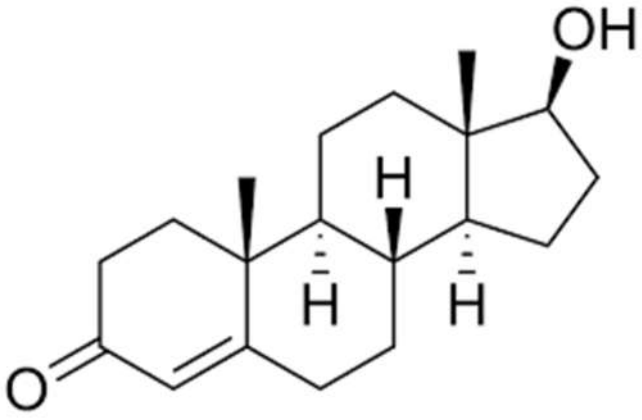
- Weight gain, mood changes
- Irregular bleeding
- Thromboembolic risk (synthetic progestins)

Testosterone

- Testosterone is the primary male sex hormone (androgen) responsible for the development of male reproductive tissues and secondary sexual characteristics.
- It is synthesized naturally in the Leydig cells of the testes and in smaller amounts in the ovaries and adrenal glands.
- Clinically, testosterone is used for androgen replacement therapy, delayed puberty, hypogonadism, and sometimes for anemia and muscle wasting disorders.
- Available in various formulations: oral, injectable, transdermal, and topical preparations.

Chemical Structure

- Chemical name: 17β-hydroxyandrost-4-en-3-one
- Molecular formula: $C_{19}H_{28}O_2$
- Molecular weight: 288.42 g/mol
- Chemical class: Androgenic steroid; 17β-hydroxy steroid
- Structural



Mechanism of Action

- Target: Androgen receptor (AR) in target tissues

Stepwise Mechanism:

1. Testosterone diffuses into target cells and binds the cytoplasmic androgen receptor.
2. Hormone-receptor complex translocates to the nucleus.

3. Binds to androgen response elements (AREs) on DNA → modulates gene transcription.
4. Physiological effects:
    - Development of male reproductive organs (testes, prostate)
    - Secondary sexual characteristics (facial hair, deep voice)
    - Anabolic effects: increased muscle mass and bone density
    - Spermatogenesis via stimulation of Sertoli cells (after conversion to DHT)

- Metabolism: Testosterone can be converted to:
    - Dihydrotestosterone (DHT) by 5α-reductase → more potent androgen
    - Estradiol by aromatase → mediates estrogenic effects

Synthesis

- Natural biosynthesis:
    1. Cholesterol → pregnenolone → 17α-hydroxypregnenolone → dehydroepiandrosterone (DHEA)
    2. DHEA → androstenedione → Testosterone
- Chemical synthesis (pharmaceutical):
    - Starts from cholesterol or diosgenin (from plants)
    - Multi-step steroidal transformations to introduce 3-keto group, 4-5 double bond, and 17β-hydroxyl
    - Purification yields testosterone suitable for medical use

Uses

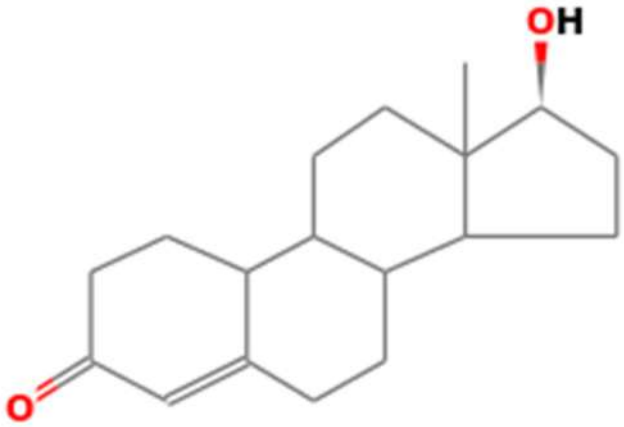
- Therapeutic Uses:
    1. Hypogonadism in males (primary or secondary)
    2. Delayed puberty in boys
    3. Androgen replacement therapy in transgender males
    4. Anemia due to chronic disease (off-label)
    5. Muscle wasting disorders (e.g., HIV-associated)

Nandrolone

- Nandrolone is a synthetic anabolic-androgenic steroid (AAS), derived from testosterone by removal of a carbon atom at C19 (hence also called 19-nortestosterone).
- It exhibits strong anabolic effects (muscle growth, bone density) with relatively lower androgenic activity compared to testosterone.
- Used clinically for anemia, osteoporosis, cachexia, and certain wasting conditions.
- Available as esters (e.g., Nandrolone decanoate, Nandrolone phenylpropionate) for prolonged release injectable formulations.

Chemical Structure

- Chemical name: 19-nortestosterone (17β-hydroxyestr-4-en-3-one)
- Molecular formula: $C_{18}H_{26}O_2$
- Molecular weight: 274.4 g/mol
- Chemical class: Anabolic-androgenic steroid; 19-nortestosterone derivative
- Structural



Mechanism of Action

- Target: Androgen receptor (AR) in target tissues

Stepwise Mechanism:

1. Nandrolone diffuses into cells and binds to the cytoplasmic androgen receptor.
2. Hormone-receptor complex translocates to the nucleus.

3. Binds androgen response elements (AREs) → modulates transcription of anabolic genes.
4. Physiological effects:
    - Anabolic: Increases protein synthesis, muscle mass, and bone density
    - Androgenic: Mildly stimulates male secondary sexual characteristics
    - Erythropoiesis: Stimulates red blood cell production (used in anemia)

Overall Effect:
→ Enhanced muscle mass and bone strength with moderate androgenic effects.

Synthesis

- Starting material: Testosterone or diosgenin (plant-derived steroid)
- Key modification:
    - Removal of C19 methyl group → 19-nortestosterone (nandrolone)
    - Introduction of ester at 17β-hydroxyl → Nandrolone decanoate or phenylpropionate
- Purification: Crystallization yields injectable-grade nandrolone

Uses

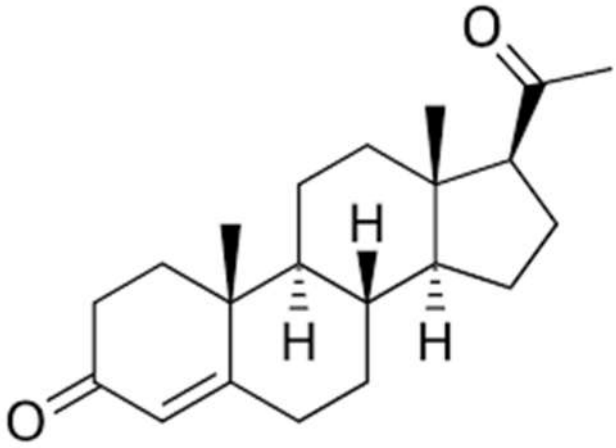
- Therapeutic Uses:
    1. Anemia (stimulates erythropoiesis)
    2. Osteoporosis (increases bone density)
    3. Cachexia and muscle wasting (chronic illness, HIV, cancer)
    4. Chronic debilitating conditions with weight loss

Progesterone

- Progesterone is a natural steroid hormone belonging to the progestogens.
- Produced mainly by the corpus luteum in the ovary, placenta, and adrenal cortex.
- Plays a crucial role in regulating the menstrual cycle, maintaining pregnancy, and preparing the endometrium for implantation.
- Clinically, progesterone is used in hormone replacement therapy, treatment of menstrual disorders, infertility, and prevention of preterm birth.
- Available as oral, injectable, and vaginal formulations.

Chemical Structure

- Chemical name: Pregn-4-ene-3,20-dione
- Molecular formula: $C_{21}H_{30}O_2$
- Molecular weight: 314.46 g/mol
- Chemical class: Pregnane steroid; 21-carbon progestogen
- Structural



Mechanism of Action

- Target: Progesterone receptors (PR-A and PR-B) in target tissues (uterus, mammary glands, hypothalamus)

Stepwise Mechanism:

1. Progesterone diffuses into target cells and binds intracellular progesterone receptors.

2. Hormone-receptor complex translocates to the nucleus.
3. Binds progesterone response elements (PREs) → modulates gene transcription.
4. Physiological effects:
    - Converts proliferative endometrium to secretory endometrium → implantation support
    - Maintains pregnancy by inhibiting uterine contractions
    - Regulates menstrual cycle and inhibits ovulation (via hypothalamic-pituitary axis)
    - Stimulates mammary gland development for lactation

Synthesis

- Natural biosynthesis:
    1. Cholesterol → pregnenolone → progesterone
    2. Enzymes: cholesterol side-chain cleavage enzyme (P450scc) and 3β-hydroxysteroid dehydrogenase
- Pharmaceutical synthesis:
    - Starting from plant sterols like diosgenin (from yam)
    - Multi-step chemical transformation to introduce 3-keto, 4-5 double bond, and 20-keto group
    - Purification yields pharmaceutical-grade progesterone

Uses

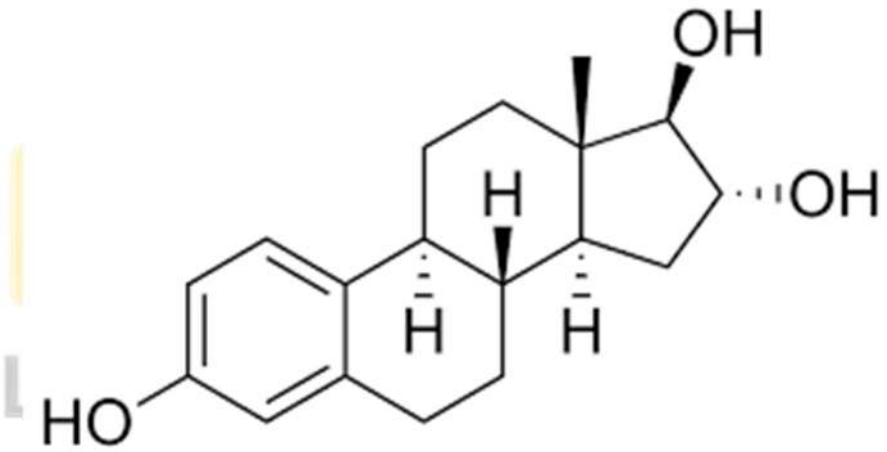
- Therapeutic Uses:
    1. Hormone replacement therapy (HRT) in menopause
    2. Treatment of menstrual disorders: amenorrhea, dysfunctional uterine bleeding
    3. Assisted reproduction and infertility: supports luteal phase
    4. Prevention of preterm birth in at-risk pregnancies
    5. Contraception: in combination with estrogens (oral, injectable, or implant)

Oestriol

- Oestriol (Estriol, E3) is a natural estrogen primarily produced by the placenta during pregnancy, with minor production in the ovaries and liver.
- It is considered a weak estrogen compared to estradiol (E2) and estrone (E1).
- Clinically, oestriol is used in postmenopausal therapy, urogenital atrophy, and hormone replacement therapy.
- It is available in oral, vaginal, and topical formulations.

Chemical Structure

- Chemical name: Estra-1,3,5(10)-triene-3,16α,17β-triol
- Molecular formula: $C_{18}H_{24}O_3$
- Molecular weight: 288.39 g/mol
- Chemical class: Estrogen; steroidal hormone
- Structural



Mechanism of Action

- Target: Estrogen receptors (ERα and ERβ) in target tissues

Stepwise Mechanism:

1. Oestriol diffuses into cells and binds to nuclear estrogen receptors.
2. Hormone-receptor complex translocates to the nucleus.

3. Binds estrogen response elements (EREs) on DNA → modulates gene transcription.
4. Physiological effects:
    - Stimulates uterine and vaginal epithelium growth
    - Maintains urogenital tissues and vaginal lubrication
    - Increases blood flow and elasticity of vaginal tissues
    - Weak effects on secondary sexual characteristics compared to estradiol

Synthesis

- Natural biosynthesis:
    1. Cholesterol → pregnenolone → 17α-hydroxyprogesterone → dehydroepiandrosterone (DHEA) → estriol
    2. Mainly produced in placenta during pregnancy from DHEA sulfate
- Pharmaceutical synthesis:
    - Starts from plant sterols like diosgenin or stigmasterol
    - Multi-step chemical transformations introduce hydroxyl groups at C16α and C17β and aromatize A-ring
    - Purification yields pharmaceutical-grade oestriol

Uses

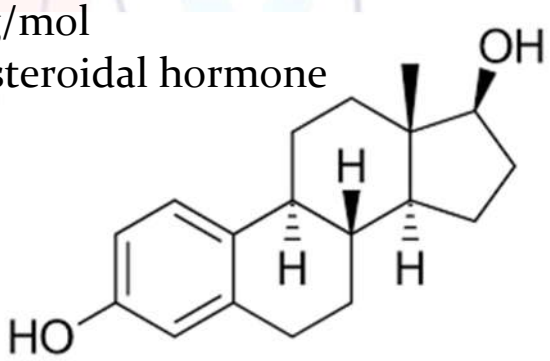
- Therapeutic Uses:
    1. Postmenopausal therapy: Relief of hot flashes, vaginal dryness, and atrophy
    2. Treatment of urogenital atrophy: Vaginal creams, suppositories, or rings
    3. Hormone replacement therapy (HRT) in combination with progestogens
    4. Prevention of urinary tract infections associated with estrogen deficiency

Oestradiol

- Oestradiol (Estradiol, E2) is the most potent natural estrogen in humans.
- Primarily produced by the ovaries (granulosa cells) and, in smaller amounts, by the placenta and adrenal glands.
- It is essential for female reproductive development, regulation of menstrual cycle, and maintenance of secondary sexual characteristics.
- Clinically, oestradiol is used in hormone replacement therapy (HRT), contraception, menopausal symptom relief, and certain estrogen-deficient conditions.
- Available in oral, transdermal, injectable, and topical formulations.

Chemical Structure

- Chemical name: Estra-1,3,5(10)-triene-3,17β-diol
- Molecular formula: $C_{18}H_{24}O_2$
- Molecular weight: 272.38 g/mol
- Chemical class: Estrogen; steroidal hormone
- Structural



Mechanism of Action

- Target: Estrogen receptors (ERα and ERβ) in target tissues

Stepwise Mechanism:

1. Oestradiol diffuses into cells and binds nuclear estrogen receptors.
2. Hormone-receptor complex translocates to the nucleus.
3. Binds estrogen response elements (EREs) on DNA → modulates gene transcription.
4. Physiological effects:
    - Promotes development of female reproductive organs (uterus, vagina, fallopian tubes)

- Maintains secondary sexual characteristics (breast development, fat distribution)
- Regulates menstrual cycle and ovulation
- Bone: Stimulates bone formation and inhibits resorption
- Cardiovascular: Improves lipid profile and endothelial function

Synthesis

- Natural biosynthesis:
  1. Cholesterol → pregnenolone → 17α-hydroxypregnenolone → dehydroepiandrosterone (DHEA) → androstenedione → estrone → oestradiol
  2. Aromatase enzyme converts androstenedione/testosterone to estrogens
- Pharmaceutical synthesis:
  - Starts from plant sterols like diosgenin
  - Multi-step chemical transformations introduce aromatic A-ring and hydroxyl groups at C3 and C17β
  - Purification yields pharmaceutical-grade oestradiol

Uses

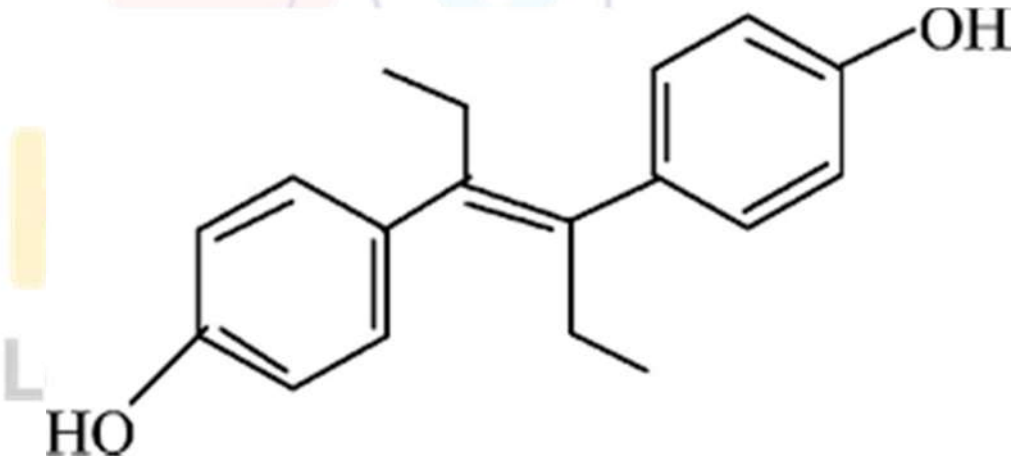
- Therapeutic Uses:
  1. Hormone replacement therapy (HRT) in postmenopausal women
  2. Contraception: Combined with progestogens in oral contraceptives
  3. Treatment of estrogen deficiency: Hypogonadism, premature ovarian failure
  4. Menopausal symptom relief: Hot flashes, vaginal atrophy, osteoporosis prevention
  5. Transgender hormone therapy for feminization

Diethylstilbestrol (DES)

- Diethylstilbestrol (DES) is a synthetic nonsteroidal estrogen.
- Developed in the 1930s, it is structurally unrelated to steroid hormones but mimics estrogenic activity.
- Historically used for pregnancy complications, menopausal symptoms, and certain cancers, but its use in pregnancy was discontinued due to teratogenic effects.
- DES has a potent estrogenic effect and longer half-life compared to natural estrogens.

Chemical Structure

- Chemical name: 4,4'-(1,2-diethyl-1,2-ethenediyl)diphenol
- Molecular formula: $C_{18}H_{20}O_2$
- Molecular weight: 268.35 g/mol
- Chemical class: Nonsteroidal synthetic estrogen; stilbene derivative
- Structural



Mechanism of Action

- Target: Estrogen receptors (ERα and ERβ) in target tissues

Stepwise Mechanism:

1. DES diffuses into target cells and binds nuclear estrogen receptors.
2. Hormone-receptor complex translocates to the nucleus.

3. Binds estrogen response elements (EREs) → modulates gene transcription.
4. Physiological effects:
    - Stimulates uterine growth, endometrial proliferation
    - Maintains secondary sexual characteristics
    - Promotes protein synthesis and anabolic effects

Synthesis

1. Starting materials: Phenol derivatives and acetaldehyde
2. Condensation reaction: Two equivalents of phenol react with acetaldehyde in the presence of an acid catalyst to form diethylstilbestrol
3. Purification: Crystallization yields pure DES suitable for pharmaceutical use

Uses

- Therapeutic Uses (historical, largely discontinued):
    1. Prevention of miscarriages and pregnancy complications (no longer recommended)
    2. Menopausal symptom relief
    3. Hypogonadism and estrogen deficiency
    4. Treatment of prostate and breast cancer (in some cases)