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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 C₁₇ β

Mechanism of Action:

- Bind estrogen receptors (ER α , ER β) → 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:

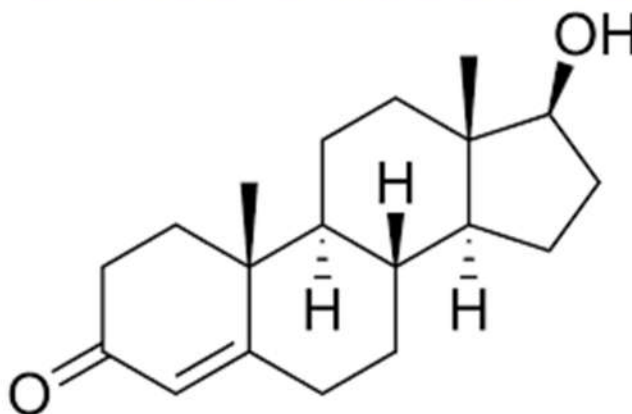
- Weight gain, mood changes
- Irregular bleeding
- Thromboembolic risk (synthetic progestins)

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: 17 β -hydroxyandrost-4-en-3-one
- Molecular formula: C₁₉H₂₈O₂
- Molecular weight: 288.42 g/mol
- Chemical class: Androgenic steroid; 17 β -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

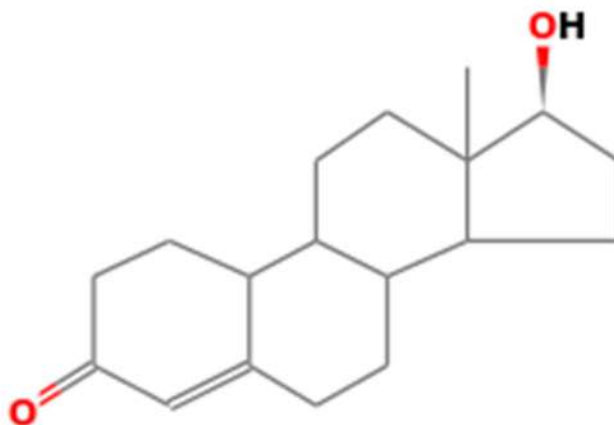
- Therapeutic Uses:
 1. Hypogonadism in males (primary or secondary)
 2. Delayed puberty in boys
 3. Androgen replacement therapy in transgender males
 4. Anemia due to chronic disease (off-label)
 5. Muscle wasting disorders (e.g., HIV-associated)

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 (17 β -hydroxyestr-4-en-3-one)
- Molecular formula: C₁₈H₂₆O₂
- 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 17 β -hydroxyl → Nandrolone decanoate or phenylpropionate
- Purification: Crystallization yields injectable-grade nandrolone

Uses

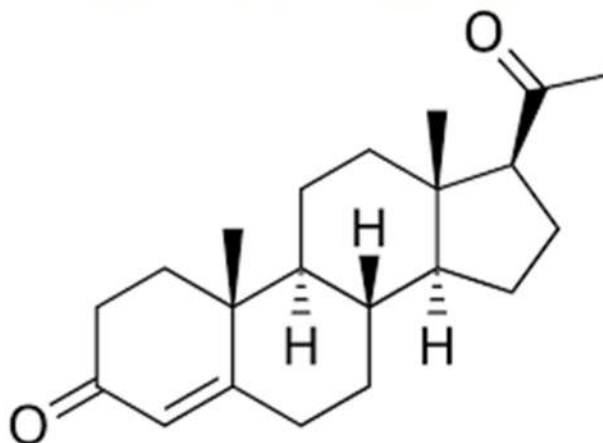
- **Therapeutic Uses:**
 1. **Anemia** (stimulates erythropoiesis)
 2. **Osteoporosis** (increases bone density)
 3. **Cachexia and muscle wasting** (chronic illness, HIV, cancer)
 4. **Chronic debilitating conditions** with weight loss

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 (P450_{sc}) 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

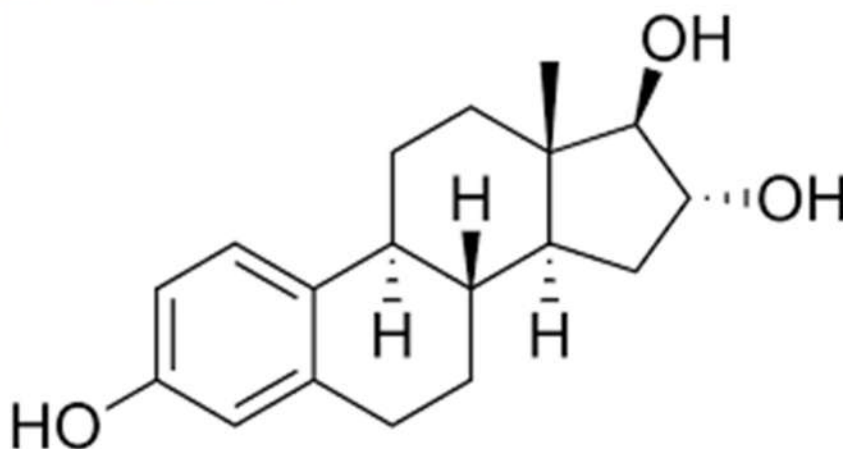
- Therapeutic Uses:
 1. Hormone replacement therapy (HRT) in menopause
 2. Treatment of menstrual disorders: amenorrhea, dysfunctional uterine bleeding
 3. Assisted reproduction and infertility: supports luteal phase
 4. Prevention of preterm birth in at-risk pregnancies
 5. Contraception: in combination 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-3,16 α ,17 β -triol
- Molecular formula: C₁₈H₂₄O₃
- Molecular weight: 288.39 g/mol
- Chemical class: Estrogen; steroidal hormone
- Structural



Mechanism of Action

- Target: Estrogen receptors (ER α and ER β) 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 (ERs) 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 $C_{16\alpha}$ and $C_{17\beta}$ and aromatize A-ring
 - Purification yields pharmaceutical-grade oestriol

Uses

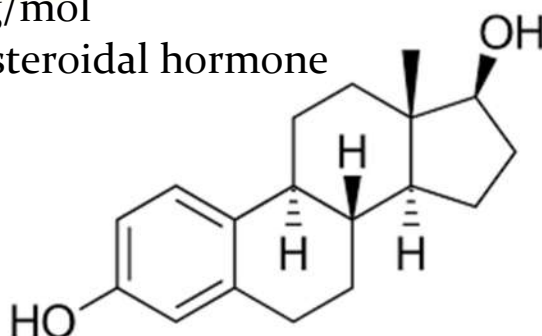
- Therapeutic Uses:
 1. Postmenopausal therapy: Relief of hot flashes, vaginal dryness, and atrophy
 2. Treatment of urogenital atrophy: Vaginal creams, suppositories, or rings
 3. Hormone replacement therapy (HRT) in combination with progestogens
 4. Prevention of urinary tract infections associated 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-3,17 β -diol
- Molecular formula: C₁₈H₂₄O₂
- Molecular weight: 272.38 g/mol
- Chemical class: Estrogen; steroidal hormone
- Structural



Mechanism of Action

- Target: Estrogen receptors (ER α and ER β) 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 → 17 α -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 C₁₇ β
 - Purification yields pharmaceutical-grade oestradiol

Uses

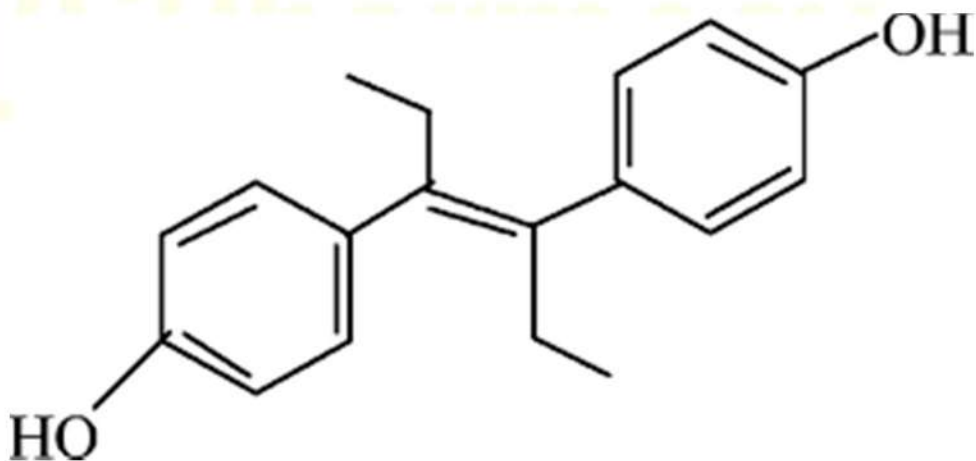
- Therapeutic Uses:
 1. Hormone replacement therapy (HRT) in postmenopausal women
 2. Contraception: Combined with progestogens in oral contraceptives
 3. Treatment of estrogen deficiency: Hypogonadism, premature ovarian failure
 4. Menopausal symptom relief: Hot flashes, vaginal atrophy, osteoporosis 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 ($ER\alpha$ and $ER\beta$) 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)