Steroid; Biosynthesis of Cholesterol

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

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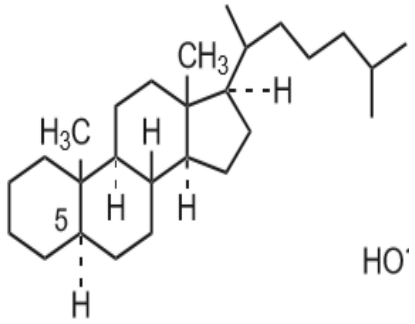
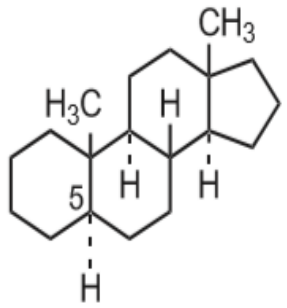
Introduction

- Steroids form a group of structurally related compounds which are widely distributed in animal and plants. Steroids are oxidized derivatives of sterols; they have the sterol nucleus but lack the alkyl chain attached to ring D of cholesterol.
- The major groups of steroids are the male and female sex hormones (estrogens, progestogens and androgens) and corticosteroids.
- Steroids consist of four fused rings (A, B, C, and D). Chemically, these hydrocarbons are cyclopentanoperhydrophenanthrenes; they contain a five membered cyclopentane (D) ring plus the three rings of phenanthrene.

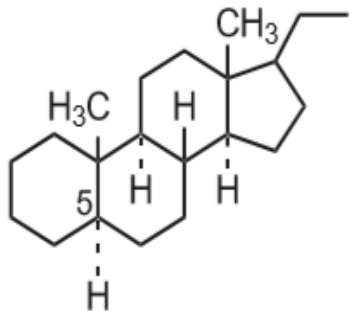
Nearly all steroids are named as derivatives of **Cholestane, Androstane, Pregnane, and Estrane.**



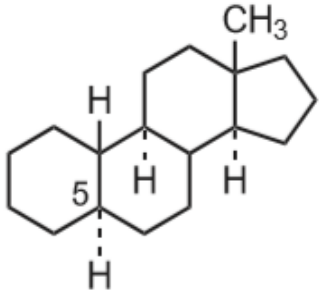
5α-Cholestane



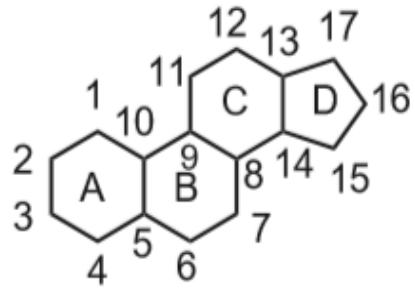
5α-Androstane



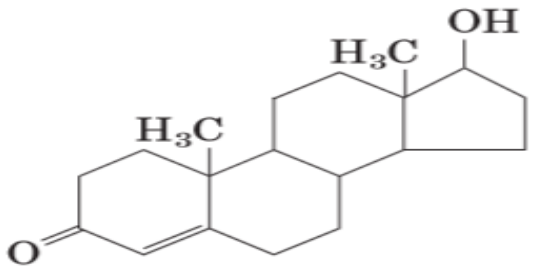
5α-Pregnane



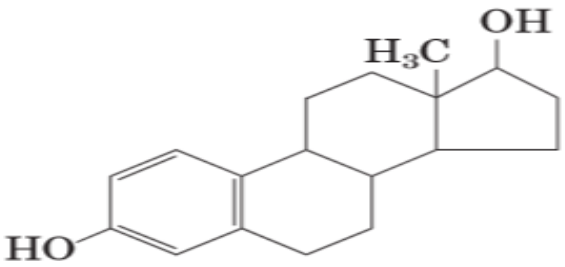
5α-Estrane



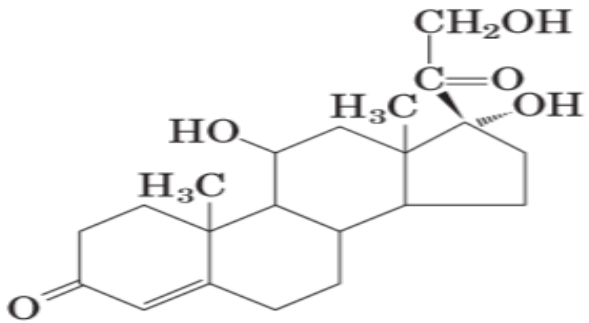
Cyclopentanoperhydrophenanthrene



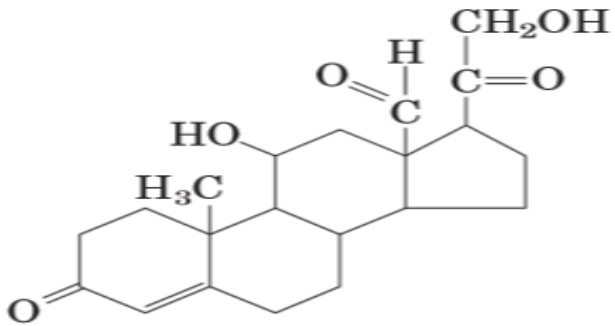
Testosterone



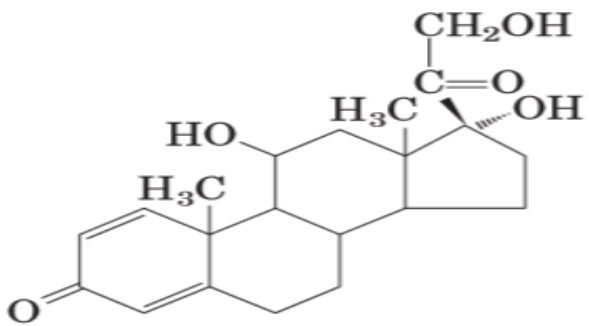
Estradiol



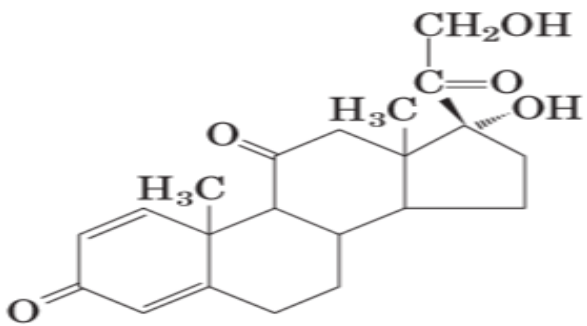
Cortisol



Aldosterone



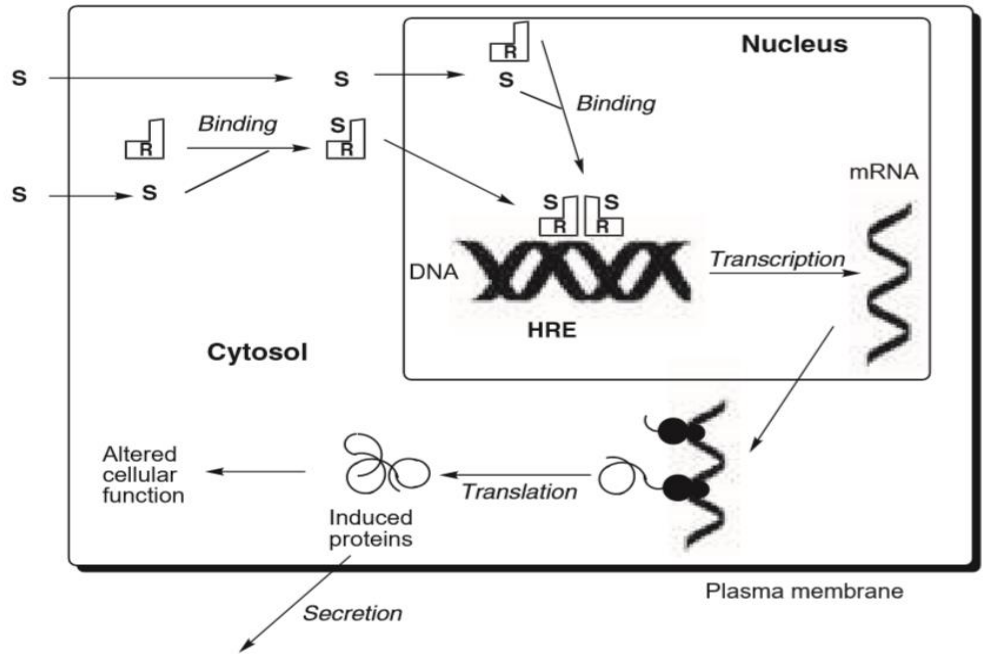
Prednisolone



Prednisone

Mechanism

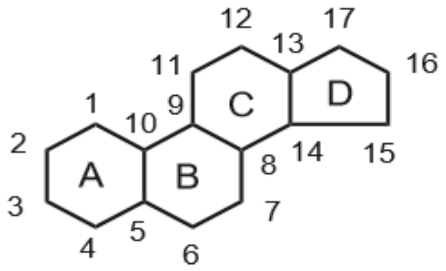
- They play important physiological roles in the human body, Steroid hormones move through the bloodstream (on protein carriers) from their site of production to target tissues, where they enter cells, bind to highly specific receptor proteins in the nucleus, and trigger changes in gene expression and thus metabolism.



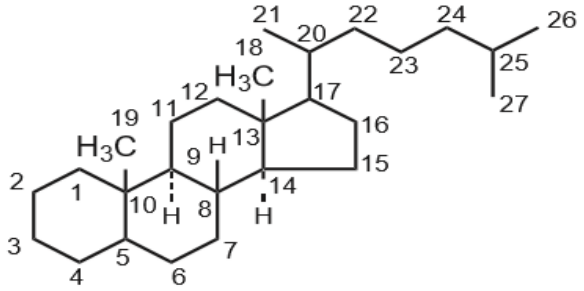
Mechanism of steroid hormone action. S, steroid; R, receptor.

Cholesterol

- Cholesterol primarily is the sterol of the higher animals. It occur free or as fatty esters in all animal cells, particularly in the brain and spinal cord. The main sources of cholesterol are the fish liver oils, brain and spinal cord of cattle.
- Cholesterol structurally corresponds to **cholestane**. The structure shown indicates stereo chemical features at different chiral centers. It may be chemically named as 5-cholesten-3β-ol.



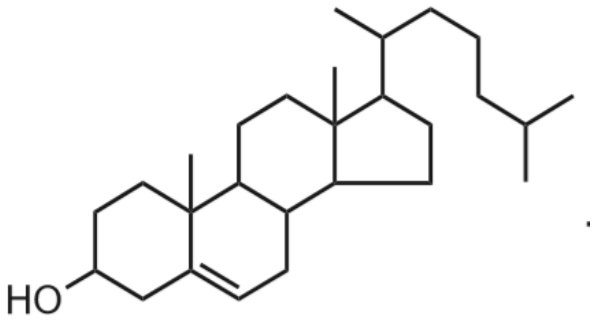
Steroid template



Cholestane template

- In biological system Cholesterol plays an important role. The sterol is required for the production of bile acids, needed in the absorption of fats from the intestine.

- Cholesterol is essential for the synthesis of steroid hormone. Moreover, Cholesterol is a vital element in the membrane of cells. Like proteins it is a basic building block of all cells.



Cholesterol

Biosynthesis of Cholesterol

Cholesterol synthesis takes place in all tissues of the body to varying degrees; however the liver makes most of it. Steroid hormones in animals are biosynthesized from Cholesterol. Biosynthesis begins with activation of acetate by co-enzyme-A.

A. Synthesis of 3-hydroxy-3-methyl Glutaryl Co-A (HMG Co-A)

- Frist, two acetyl Co-A molecules condense to form Acetoacetyl Co-A. Next a third molecule of acetyl Co-A is added producing HNG Co-A in presence of HMG Co-A synthase.

B. Synthesis of Mevalonic acid (Mevalonate)

- The next step is catalyzed by HMG Co-A reductase and is the rate limiting step in Cholesterol biosynthesis. It occurs in the endoplasmic reticulum uses two molecules of NADPH as the reducing agent and releases Co-A, making the reaction irreversible.

C. Synthesis of Cholesterol

1. Mevalonic acid is converted to 5-pyrophospho mevalonate in two steps, each of which transfers a phosphate group from ATP.
2. A five carbon isoprene unit isopentyl pyrophosphate (IPP) is formed by the decarboxylation of 5-pyro phosphomevalonate. The reaction requires ATP.

3. IPP is isomerized to 3,3-dimethyl ally pyrophosphate (DPP).
4. IPP and DPP condense to form geranyl pyrophosphate (GPP).
5. A second molecule of IPP then condenses with GPP to form farnesyl pyrophosphate (FPP).

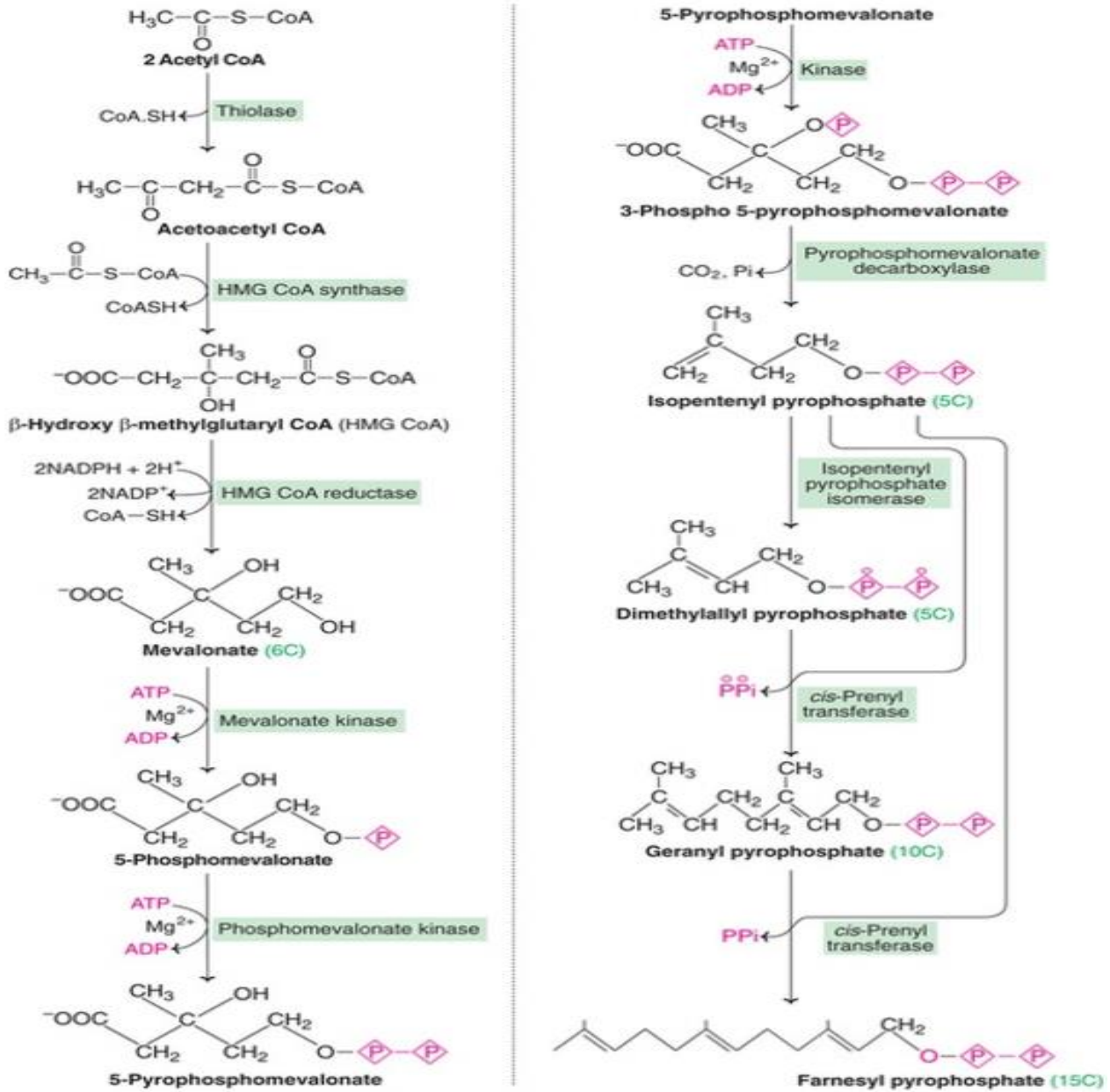
6. Two molecule of the 15-carbon farnesyl pyrophosphate combine releasing pyrophosphate, and are reduced, forming the 30-carbon compound squalene.

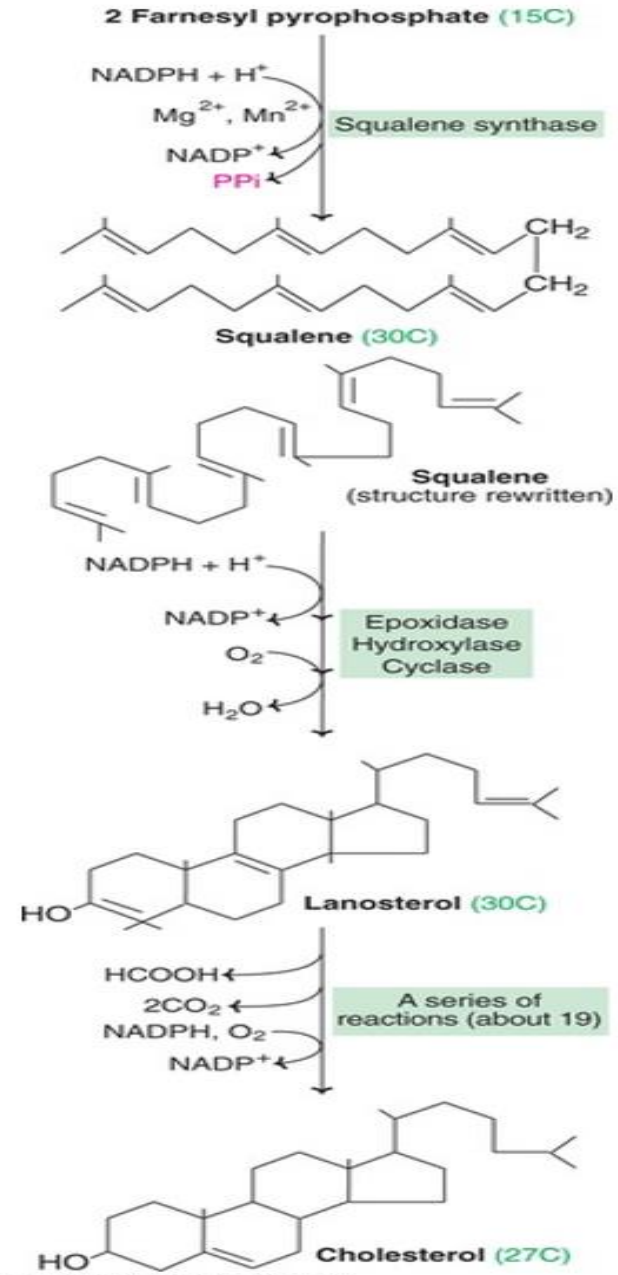
7. Squalene is converted to lanosterol by a sequence of reactions that use molecular oxygen and NADPH. The hydroxylation of squalene triggers the cyclization of the structure to lanosterol.

8. The conversion of lanosterol to Cholesterol.

9. The Cholesterol then converted into various steroid hormones.

Biosynthesis of Cholesterol





Biosynthesis of cholesterol.

Thank You