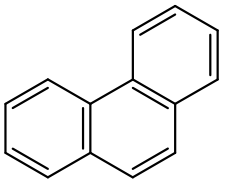
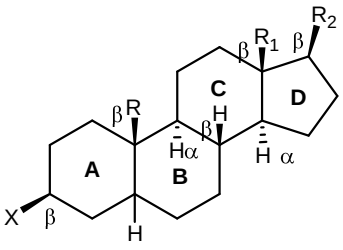
№47. STEROIDS – STRUCTURE, CONFORMATION, REPRESENTATIVES

Structure. Steroids are complex polycyclic molecules found in all plants and animals. They are nonsaponifiable lipids because they do not undergo base catalyzed hydrolysis as the fats, oils, and waxes do. A steroid is a terpenoid lipid characterized by a carbon skeleton with four fused rings, generally arranged in a 6-6-6-5 fashion. The skeleton or steroid nucleus is called also cyclopentanoperhydrophenanthere or sterane. Steranes are a class of four-cyclic compounds derived from steroids or sterols via diagenetic and catagenetic (both – geological) degradation and saturation. They are sometimes used as biomarkers for the presence of eukaryotic cells.

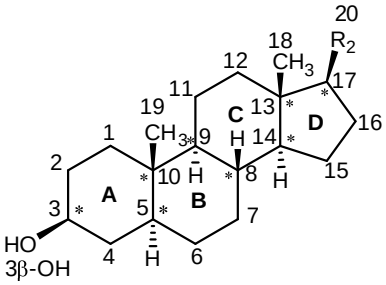


phenanthrene

cyclopentanoperhydrophenanthrene, sterane, steroid nucleus



α– or β-steroid skeleton

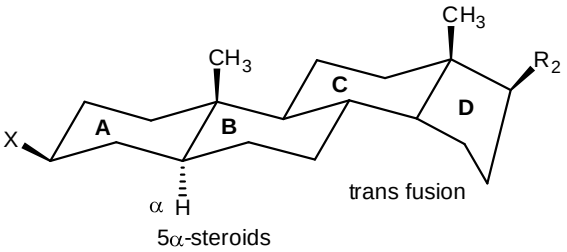


5α-sterol

A **steroid structure** is usually projected onto paper as shown above and the four rings are assigned the first four letters of the alphabet (A, B, C, and D), beginning with the ring at the lower left. The carbon atoms are numbered in a specific for steroids way beginning with A ring and ending with the angular (axial, β-) substituents. Steroids vary by the functional groups (oxygenated or aliphatic) attached to these rings and the oxidation state (presence of double bonds) of the rings.

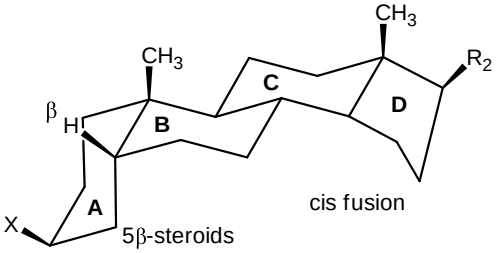
- most often the substituents are at C-3, C-10, C-13, and C-17 position
- at carbon C-3: X=OH, OR or =O (ketone)
- at carbon C-10: R=CH_3 or H
- at carbon C-13: always R_1=CH_3
- at carbon C-17: Vast variety of alkyl saturated or unsaturated groups is possible. They can contain OH, CO or COOH groups
- the skeleton can incorporate one or more double bonds often at C-5/C-6 and C-7/C-8 in ring **B** or ring **A** may be aromatic nucleus or has double bond at C-4/C-5

Conformation of steroids. The **conformation** (the stereostructure (3-D) obtained by rotations about one or more σ bonds) in steroids is determined by the way of bending and fusing the rings. The cyclohexane rings are in "chair" conformation which is more stable than "boat" conformation and is preferred. The cyclopentane ring is in "envelope" conformation, typical for **D** ring. There are two ways of fusing the **A / B** rings – trans and cis, depending on the mutual location of C-5 and C-10 substituents. The **B / C** and **C / D** junctions are usually trans in the natural steroids. The stereochemical designation of substituents is based on their position relative to the average plane passing through the rings. When the rings of a steroid are denoted as projections onto the plane of the paper, the formula is normally to be oriented as shown above. An atom or group attached to a ring depicted as in the orientation above is termed **α- (alpha)** if it lies **below the plane** of the paper or **β- (beta)** if it lies **above the plane** of the paper. In formulae, bonds to atoms or groups lying



5α-steroids

trans fusion



5β-steroids

cis fusion

below the plane of the paper (α-) are shown as broken lines(- - - or |||||||), and bonds to atoms or groups lying above the plane of the paper (β-) are shown as solid lines (preferably thickened ▬ or ▬◀).

Very often, the hydroxyl at C-3, the methyl groups at C-10 and C-13, and the aliphatic side chain at C-17 are all β-oriented substituents.

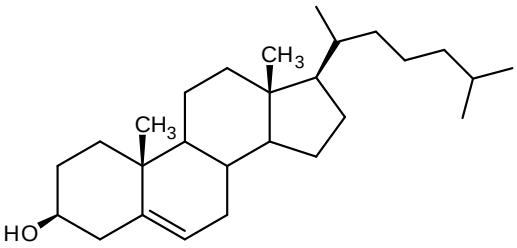
Representatives. The steroid nucleus is found in the structure of sterols, several vitamins, bile acids (as 5β-), hormones, drugs, and poisons. The classification of steroids may be done by taxonomical and functional criteria:

- Animal steroids
  - Insect steroids - ecdysteroids such as ecdysterone
  - Vertebrate steroids
    - Steroid hormones
      - Sex steroids are a subset of sex hormones that produce sex differences or support reproduction. They include androgens, estrogens and progestanes.
      - Corticosteroids include glucocorticoids and mineralocorticoids. Glucocorticoids regulate many aspects of metabolism and immune function, whereas mineralocorticoids help maintain blood volume and control renal excretion of electrolytes. Most medical 'steroid' drugs are corticosteroids.
      - Anabolic steroids are a class of steroids that interact with androgen receptors to increase muscle and bone synthesis. There are natural and synthetic anabolic steroids. In popular language, the word "steroids" usually refers to anabolic steroids.
    - Cholesterol, which modulates the fluidity of cell membranes and is the principal constituent of the plaques implicated in atherosclerosis.
    - Bile acids
- Plant steroids: Phytosterols and brassinosteroids
- Fungus steroids: Ergosterols

Structural classification: It is also possible to classify steroids based upon their chemical composition.

Class	Examples	Number of carbon atoms
Cholstanes	cholesterol	27
Cholanes	cholic acid	24
Pregnanes	progesterone	21
Androstanes	testosterone	19
Estranes	estradiol	18

All steroids are made in cells either from the sterol lanosterol (animals and fungi) or from the sterol cycloarnetol (plants). Both sterols are derived from the cyclization of the triterpene squalene. All sterols (short from **ster**oid alcoh**ol**) have an alcohol function at C-3 and methyl groups at C-10 and C13. Their variety is due to the nature of R_2 substituent at C-20. Sterols have up to 8 chiral centers, and possible double bonds at C-5/C-6 and C-7/C-8. The most abundant sterol is cholesterol whose name comes from combination of the Greek words “chole” (bile) and “stereos” (solid) preceding the characteristic alcohol suffix “ol”. The cholesterol molecule has double bond at C-5 and C_8H_{17} side chain at C-17.



cholesterol

Cholesterol is the most important steroid that makes up a significant part of the membranes of animal cells. For instance, the erythrocyte membrane is about 25% cholesterol by mass. It is found in relatively large amounts in the tissues of central nervous system. Human plasma contains about 50 mg/100 mL free cholesterol and about 170 mg of cholesterol esters with various fatty acids. Cholesterol can be ingested in the diet, recycled within the body through reabsorption of bile in the digestive tract, and produced *de novo* (biosynthesis in the liver, intestines, adrenal glands and reproductive organs). Although cholesterol is essential for life, high levels in circulation are associated with atherosclerosis.

Some of the functions of cholesterol are:

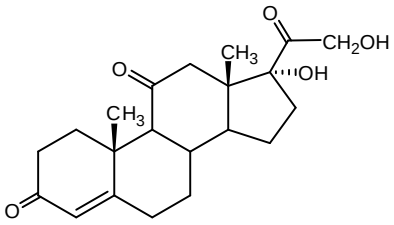
- It is a precursor to the steroid hormones made in human body (estrogen, testosterone, DHEA, progesterone, cortisol, aldosterone);

- Precursor for vitamin D synthesis;
- Important in the production of bile, which aids in fat digestion;
- Important for the metabolism of the fat soluble vitamins (A, D, E, K);
- Maintains the fluidity of cellular membranes.

Since cholesterol is insoluble in blood, it is transported in the circulatory system within lipoproteins, complex (supramolecular) spherical particles which have an exterior composed of amphiphilic proteins and lipids whose outward-facing surfaces are water-soluble and inward-facing surfaces are lipid-soluble. Triglycerides and cholesterol esters are carried internally. Phospholipids and cholesterol, being amphipathic, are transported in the surface monolayer of the lipoprotein particle. Depending on the overall structure of lipoproteins there are two main types of them: **l**ow **d**ensity (LDL) and **h**igh **d**ensity (HDL) **l**ipoproteins. A transmembrane protein organizes the particle and is recognized by target cells. LDL are the major particles that transport cholesterol and triacylglycerols produced by the liver to the tissues. HDL acts as cholesterol scavengers. They remove cholesterol from tissue cell surfaces and carry it back to the liver. The build-up of plague on the artery walls causing restriction of blood flow (atherosclerosis) has been correlated with high LDL and low HDL levels in the blood.

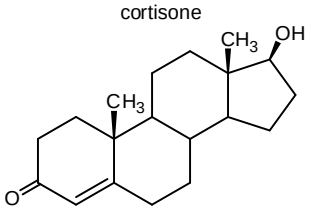
Some other important steroids with their structure and function are:

Cortisone – One of many hormones produced in the adrenal glands. It is important in controlling carbohydrate metabolism and is used therapeutically to relieve symptoms of inflammation, especially in rheumatoid arthritis.



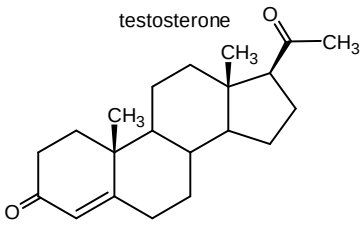
cortisone

Testosterone – the principal male sex hormone that regulates the development of the male reproductive organs (also anabolic steroid). It is primarily secreted in the testes of males and the ovaries of females. In men, testosterone plays a key role in health and well-being as well as in osteoporosis. On average, an adult human male body produces about forty to sixty times more testosterone than an adult female body.



testosterone

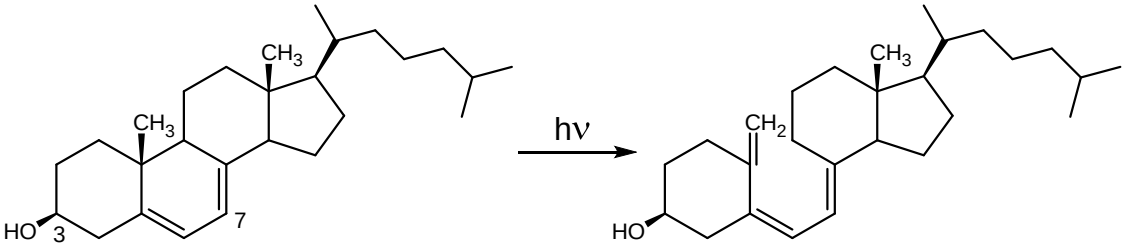
Progesterone – the female sex steroid hormone that is involved in the female menstrual cycle, produced in pregnancy and acts on the uterine lining, preparing it to receive the embryo. Progesterone is produced in the ovaries (specifically after ovulation), the brain, and, during pregnancy, in the placenta.



progesterone

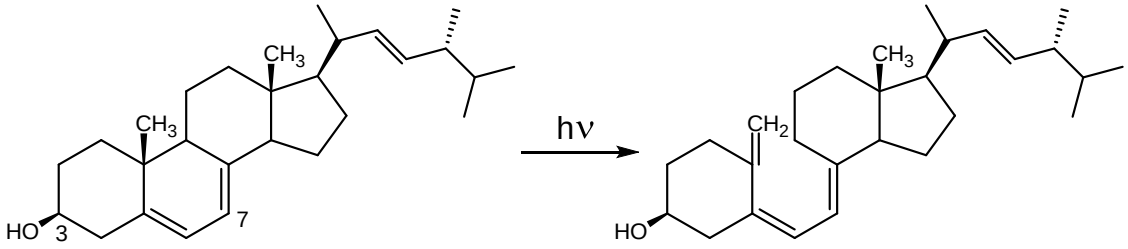
Anabolic steroids, or **anabolic-androgenic steroids**, are a class of steroid hormones related to the hormone testosterone. They increase protein synthesis within cells, which results in the buildup of cellular tissue (anabolism), especially in muscles. Anabolic steroids also have androgenic and virilizing properties, including the development and maintenance of masculine characteristics such as the growth of the vocal cords and body hair. Ergogenic uses of anabolic steroids in sports and bodybuilding is controversial, because of their adverse effects and the potential to gain an advantage conventionally considered "cheating." Their use is considered doping and banned by all major sporting bodies.

Vitamin D family. Structurally very closely related to cholesterol steroid is its C-7 dehydro derivative. It is formed by an enzymic oxidation of cholesterol and has a conjugated diene unit in its **B** ring. 7-Dehydro-cholesterol is present in the tissues of the skin where it is transformed into **vitamin D_3** by sunlight – a photochemical reaction induced by light absorption.



7-dehydrocholesterol vitamin D_3

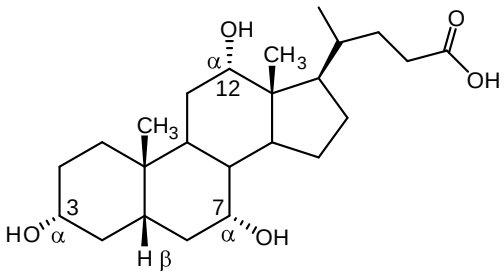
Vitamin D_3 (cholecalciferol) is a key compound in the process of absorption of Ca^{2+} by the intestine. Low levels of vitamin D_3 lead to Ca^{2+} concentrations in the body that are insufficient to support proper bone growth, resulting in the disease called rickets. The Greek derived word "rachitis" (meaning "inflammation of the spine") was later adopted as the scientific term for rickets which can be prevented by sufficient amount of ultraviolet B light in sunlight each day and adequate supplies of calcium and phosphorus in the diet. Though fish liver oil is a good source of vitamin D_3, it is not very palatable. Synthetic vitamin D_3, prepared from cholesterol, is often added to milk and other foods to ensure that children receive enough of the vitamin for their bones to develop properly.



ergosterol vitamin D_2

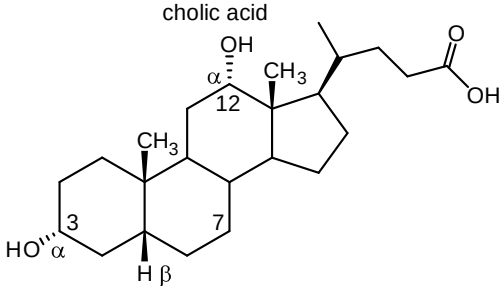
Irradiation of the steroid hormone ergosterol with UV light breaks open **B** ring in the steroid nucleus, producing **vitamin D_2** (ergocalciferol). It is analogous to vitamin D_3 and is also essential in preventing rickets, a disease of calcium metabolism.

BILE ACIDS

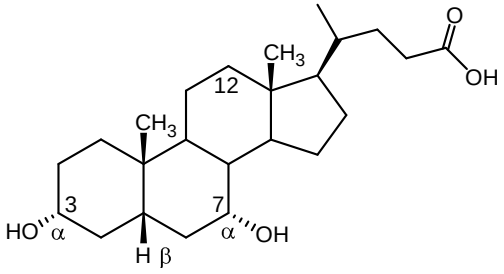


cis **A**/**B** ring fusion

cholic acid



deoxycholic acid



chenodeoxycholic acid

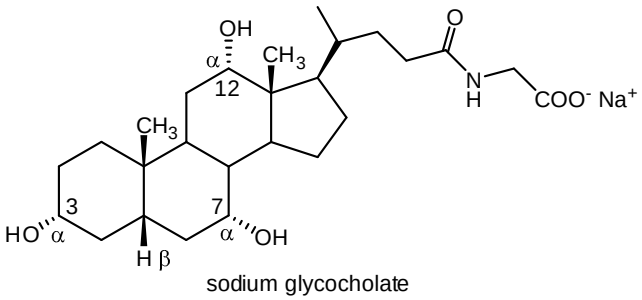
Bile acids. A significant fraction of the body cholesterol is used to form bile acids. They are dihydroxylated and trihydroxylated derivatives of cholesterol which also have undergone oxidative removal of three carbon atom from the C-17 side C_8H_{17} chain to give a skeleton with 24 carbon atoms. Noteworthy is the *cis* **A** / **B** fusion in all major bile acids. They have all hydroxy groups in α- orientation and the two methyl groups - in β- orientation, which renders the molecule with polar and nonpolar face.

The two major bile acids are **cholic acid**, and **chenodeoxycholic acid**. They, their glycine and taurine conjugates, and their 7-α-dehydroxylated derivatives (deoxycholic acid and lithocholic acid) are all found in human intestinal bile. They are conjugated (via formation of an amide bond) with taurine (2-aminoethane sulfonic acid) or the amino acid glycine, or with a sulfate or a glucuronide, and are then stored in the gallbladder. The term *bile acid* refers to the unconjugated form whereas the correspondine amides are called *bile salts*.

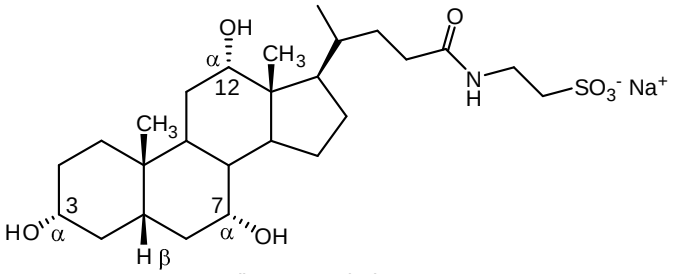
Bile acids' main function is to facilitate the formation of micelles, which promote dietary fat processing. Upon eating a meal, the contents of the gallbladder are secreted into the intestine, where bile acids serve the purpose of emulsifying dietary fats. Bile acids serve multiple other functions, which include: eliminating cholesterol from the body; driving the flow of bile to eliminate catabolites from the liver; emulsifying lipids and

fat soluble vitamins in the intestine; and aiding in the reduction of the bacteria flora found in the small intestine and biliary tract. About 90% of excreted bile acids are reabsorbed (by active transport in the ileum) and recycled.

BILE SALTS



sodium glycocholate



sodium taurocholate

Bile salt refers to the conjugated form of a bile acid with glycine or taurine, e.g. glycocholate and taurocholate are bile salts. They exist in physiological conditions in ionized form, hence – salts. Bile salts are more efficient at emulsifying fats because at intestinal pH, bile salts are more ionized than bile acids.