



Glycosides

Biosynthetic pathways of natural drugs

According to the biosynthetic pathways, the natural compounds are classified into :

1. Active compounds derived from shikimic acid pathway
2. Active compounds derived from acetate – mevalonic acid pathway
3. Mixed pathway derived from both shikimate & mevalonate.

Glycosides

Definition:

Organic natural compounds present in a lot of plants and some animals, these compounds upon hydrolysis give one or more sugars (glycone) and a non sugar moiety (aglycone) or called genin.

The most frequently occurring sugar is β -D-glucose; however, rhamnose, digitoxose, cymarose and other sugars may also occur.

When the sugar formed is glucose, the compound may also called glucoside.



Some glycosides contain more than one saccharide group, possibly as di or trisaccharides.

Upon proper conditions of hydrolysis, one or more of the saccharide groups can be removed from such compounds resulting in glycosides of simpler structures.



Chemically glycosides are acetals in which the hydroxyl of the sugar is condensed with the hydroxyl group of the non-sugar moiety, and the secondary hydroxyl is condensed within the sugar molecule itself to form an oxide ring.

More simply, glycosides may be considered sugar ethers.

Both alpha and beta glycosides are possible, depending on the stereoconfiguration of the glycosidic linkage. However, only beta forms occur in plants and most natural enzymes hydrolyze only beta forms of glycosides.



All glycosides are hydrolyzed by boiling with mineral acids; however, they vary in the ease with which this hydrolysis occurs.

Mostly glycoside is easily hydrolyzed by an enzyme that occurs in the same plant tissue, but in different cells from those that contain the glycoside.

Injury to the tissues, germination process and other physiological activities of the cells bring the enzyme in contact with the glycoside resulting in hydrolysis.



Many enzymes have been found in plants which hydrolyze only single glycoside; however, 2 enzymes namely **emulsin** and **myrosin** hydrolyze a considerable number of glycosides.

Function of glycosides in plants

- 1. Waste product**
- 2. Detoxification**
- 3. Regulate osmosis**
- 4. Role in the metabolism**
- 5. Defense function**
- 6. Sugar reserve**

Types of glycosides

The most distributed type is O- Glycoside

In addition

N- Glycosides: RNA

S- Glycosides

C-Glycoside

physio-chemical properties of glycosides (in general)

- Colorless, solid, amorphous, nonvolatile (flavonoid-yellow, anthraquinone-red or orange).
- Give positive reaction with Molisch's and Fehling's solution test (after hydrolysis).
- They are soluble in water, alcohol, acetone, insoluble in ether.
- Glycosides are readily hydrolyzed by mineral acids

Classification of glycosides

The classification of glycosides is a difficult matter, if classification is based on the sugar moiety, a number of rare sugars are involved whose structures are not very well known, and if classification is based on the aglycone moiety, groups from all classes of plant constituents will appear. The therapeutic classification is excellent from the pharmaceutic viewpoint, but omits many glycosides of pharmacognostic interest.

Classification of glycosides depending on the chemical structure of the non sugar moiety:

- 1. Cardioactive glycosides (steroidal glycosides)**
- 2. Anthraquinone glycosides**
- 3. Saponine glycosides**
- 4. Flavonoid glycosides**
- 5. Lactone glycosides**
- 6. Alcohol glycosides**
- 7. Aldehyde glycosides**
- 8. Isothiocynate glycosides**
- 9. Cynophore glycosides**
- 10. Phenol glycosides**

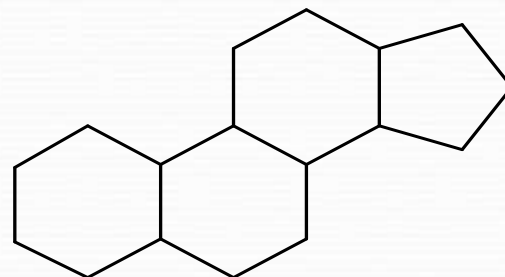
(Cardiac glycosides) : .1

A considerable number of plants scattered throughout the plant kingdom contain C_{23} or C_{24} steroidal glycosides which exert on the failing heart a slowing and strengthening effect. In Western medicine it is the glycosides of various *Digitalis* species that are extensively employed.

These glycosides have a powerful action on cardiac muscles. they increase tone, excitability & contractility of heart muscle.

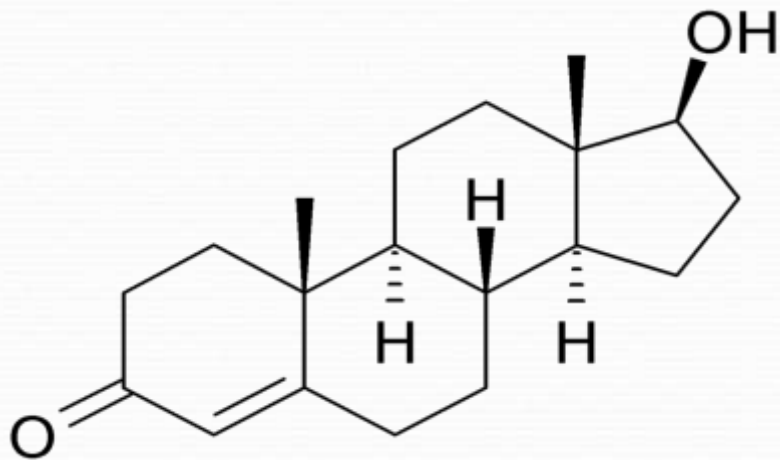
The glycone part consists of one , two, three or more similar or different monosaccharide units

aglycone part has steroidal nucleus

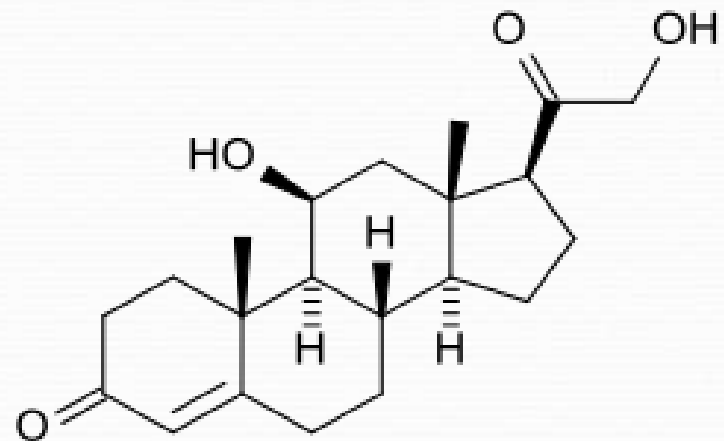


cyclopentaphenanthrene

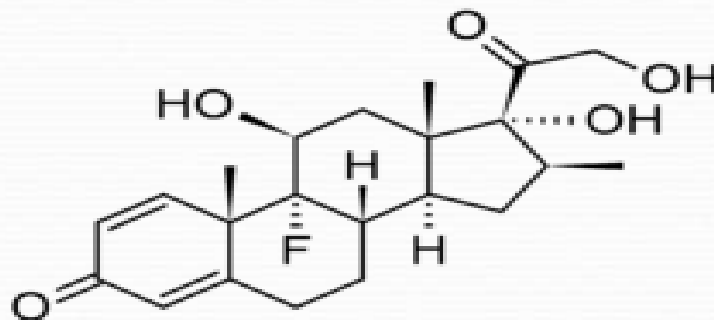
glycone part of C.G always attached at C-3 position of aglycone part



Testosterone



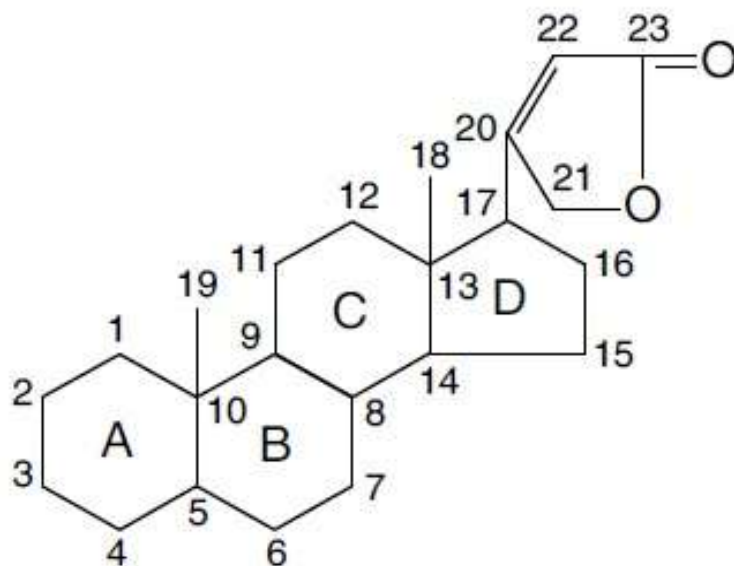
Corticosteroid



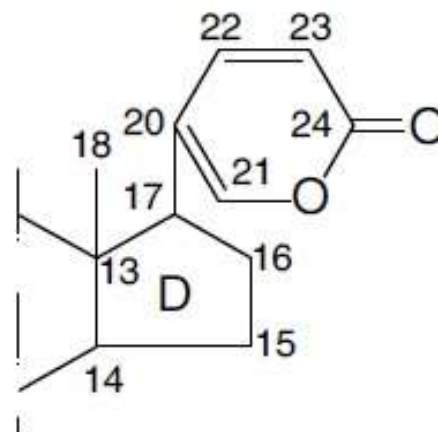
Betamethasone

Structure of glycosides

Two types of genin may be distinguished according to whether there is a five- or six-membered lactone ring. These types are known respectively as cardenolides (e.g. digitoxigenin) and bufanolides or bufadienolides (e.g. scillarenin). The following formulae indicate their structure and ring numbering:

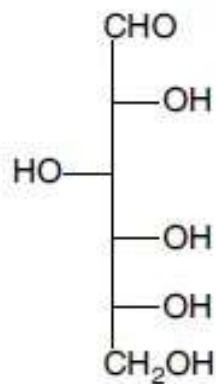


Cardenolide

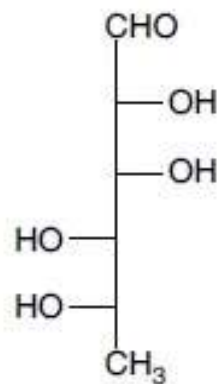


Bufadienolide

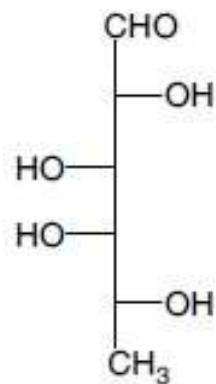
The sugar moieties, attached to the aglycone by a C-3, β -linkage, are composed of up to four sugar units which may include glucose or rhamnose together with other deoxy-sugars whose natural occurrence is, to date, known only in association with cardiac glycosides. A number of the deoxy-sugars are 2,6-dideoxyhexoses (e.g. digitoxose) or their 3-*O*-methyl ethers (e.g. cymarose). In addition to rhamnose and fucose, a number of other 6-deoxyhexose derivatives have more recently been discovered together with 2-*O*-methyl and 2-*O*-acetyl sugars. In the case of fucose, the D-form is known only in cardiac glycosides, whereas the L-form is widely distributed in nature. Cardiac glycosides involving cyclic sugars are known in *Calotropis* spp. and probably occur in other members of the Asclepiadaceae.



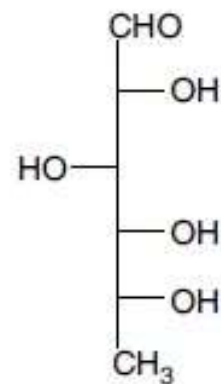
D-Glucose



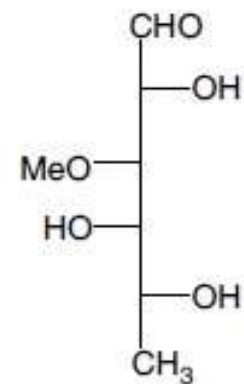
L-Rhamnose



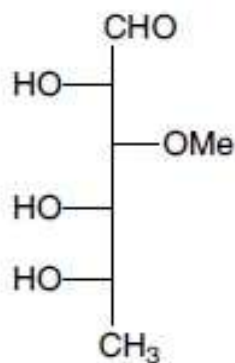
D-Fucose



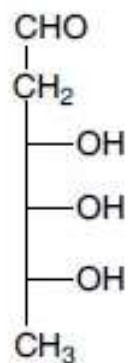
D-Glucomethylose



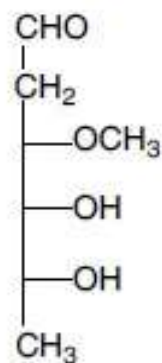
D-Digitalose



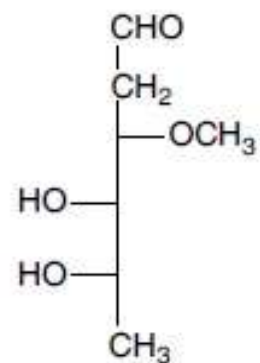
L-Thevetose



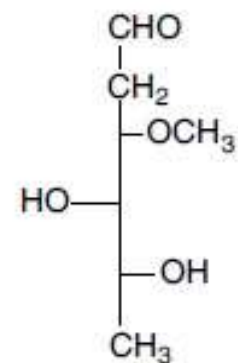
D-Digitoxose



D-Cymarose



L-Oleandrose



D-Sarmentose

Some examples of sugars found in cardiac glycosides (Fischer representation).

To convert steroidal compound to cardio-active drug :-

The steroidal nucleus should contain Alpha & Beta unsaturated lactone ring at Carbone 17 β (this will change steroidal compound to cardio-active drug). The absence of this ring ----- inactive compound(as cardio-drug)

For maximal activity :

The presence of hydroxyl group at C₁₄ position makes the glycoside very active and gives rapid action in the body and the lack of this hydroxyl group greatly reduces the activity.

The ring junctions Cis, Trans, Cis make the nucleus very stable so more active.

A/B ring junction *cis* –

- B/C ring junction *trans*-

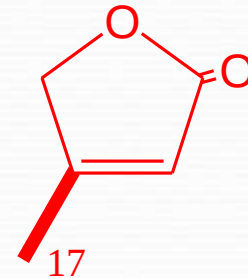
-C/D ring junction *cis*

The sugar part attached to aglycone at C-3 β (this increases absorption and distribution of glycoside in the body, ex. : Glucose, Rhamnose, Digitoxose

According to the type of lactone ring •
Cardiac Glycosides are classified into:

Cardinolides:

The C-23 containing 5-membered lactone ring e.g. *Digitalis* & unsaturated *Strophanthus* .



Bufadienolides: The C-24 containing 6-membered unsaturated lactone ring e.g. *Squill*

