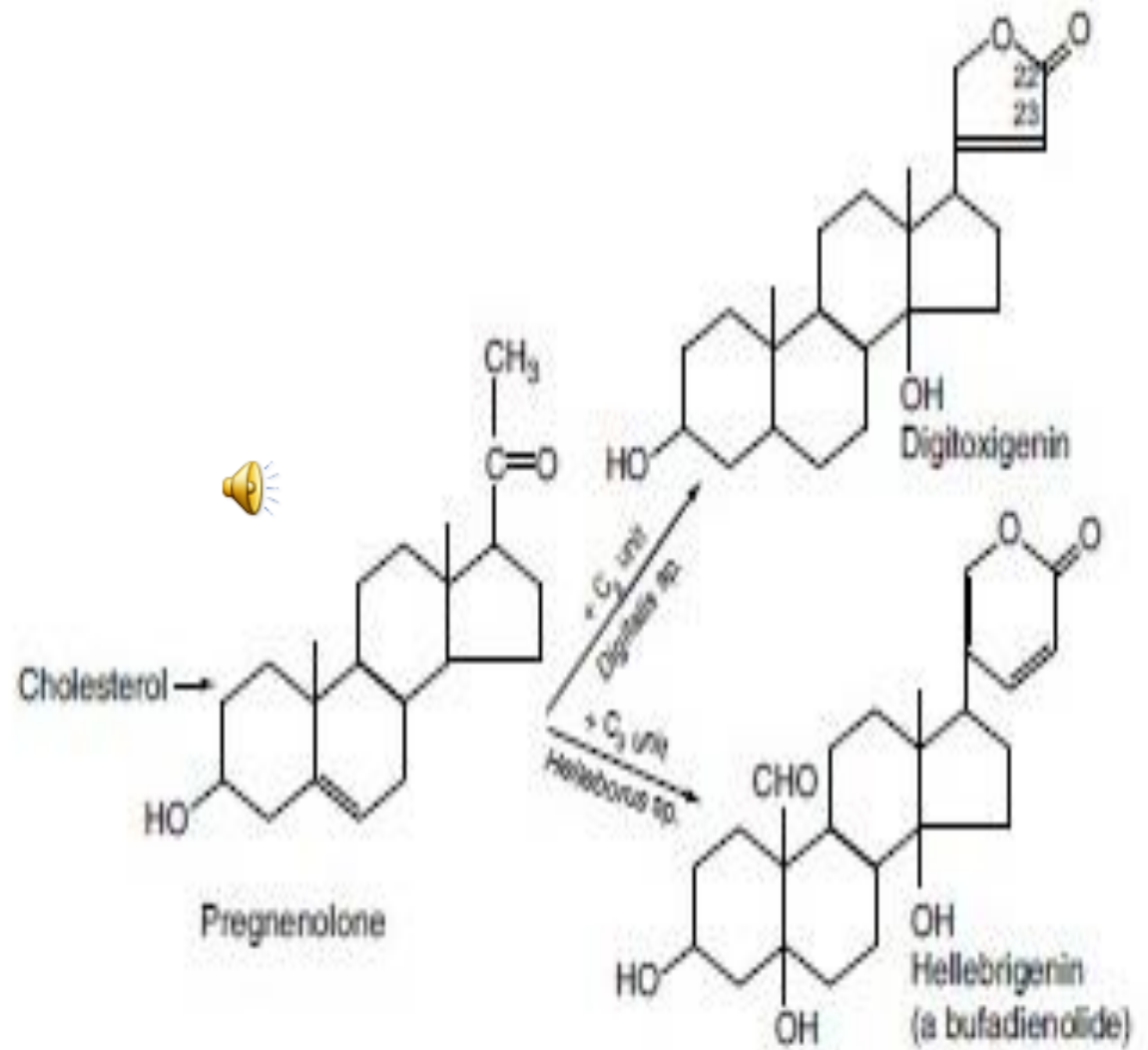


Biogenesis of cardiac glycosides

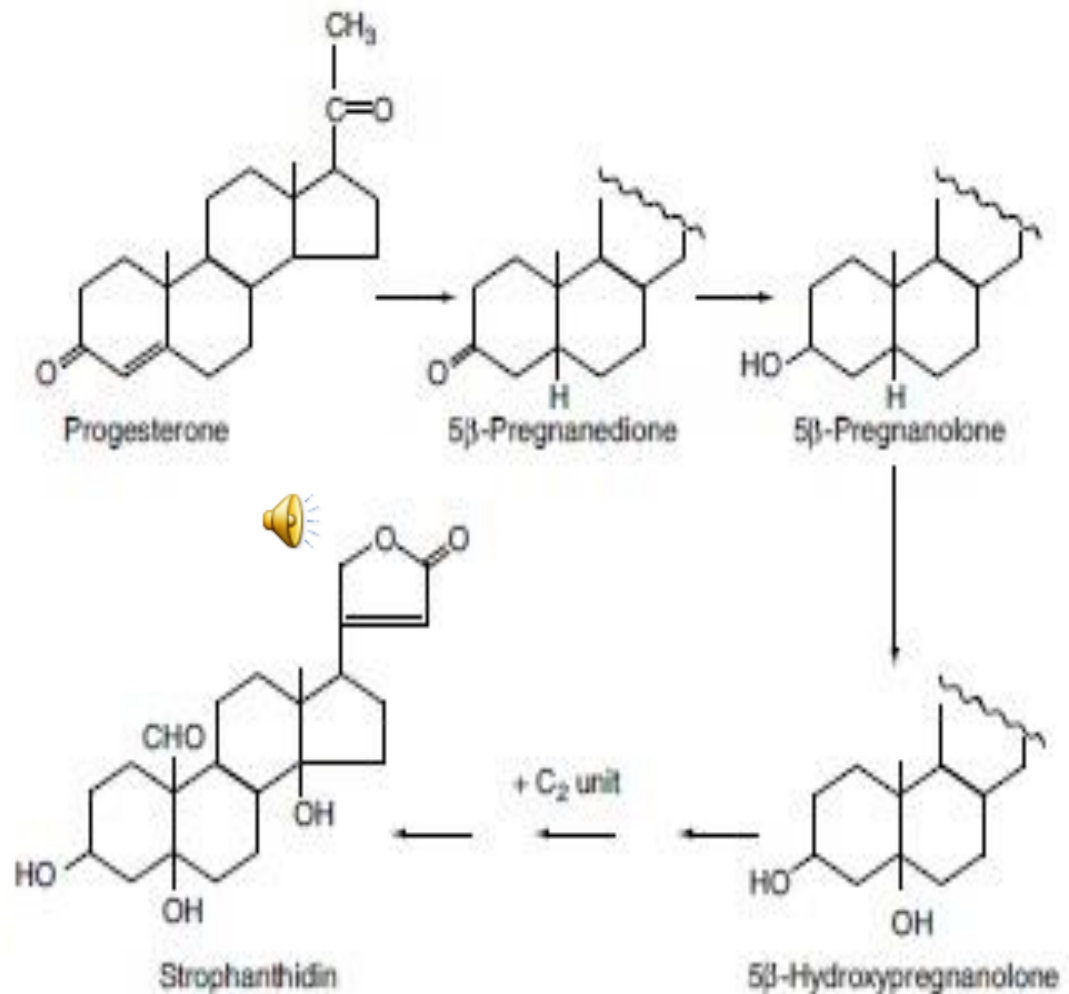
Aglycones of the cardiac glycosides are derived from mevalonic acid but the final molecules arise from a condensation of a C_{21} steroid with a C_2 unit (the source of C-22 and C-23). Bufadienolides are condensation products of a C_{21} steroid and a C_3 unit

Progesterone, which is formed with cardiac glycosides, in *Digitalis lanata* as a result of feeding pregnenolone, is itself a precursor of the cardiac glycosides. 

Biogenetic studies involving the side-chain indicate that glucose is the most effective precursor of digitoxose and of the sugar side-chain of the *Nerium oleander* glycosides. Some ten enzymes have now been shown to be involved in the sugar side-chain biosynthesis in *Digitalis* species.



Formation of aglycones of cardiac glycosides from a C_{21} steroid.



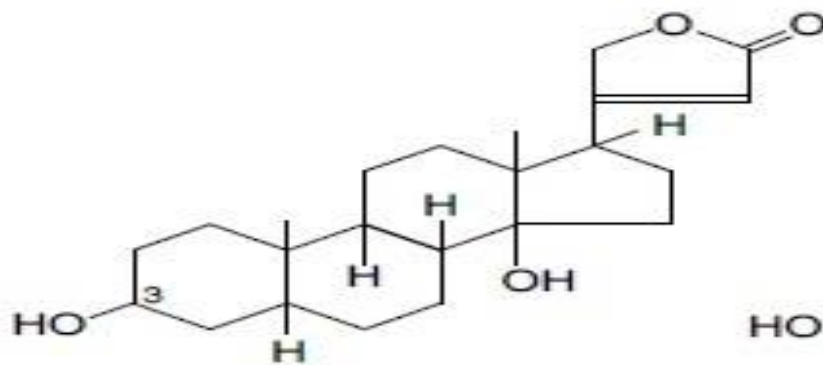
Suggested intermediates in the metabolism of progesterone to cardiac glycosides.

a key enzyme in the biosynthesis of cardiac glycosides is progesterone 5β-reductase.

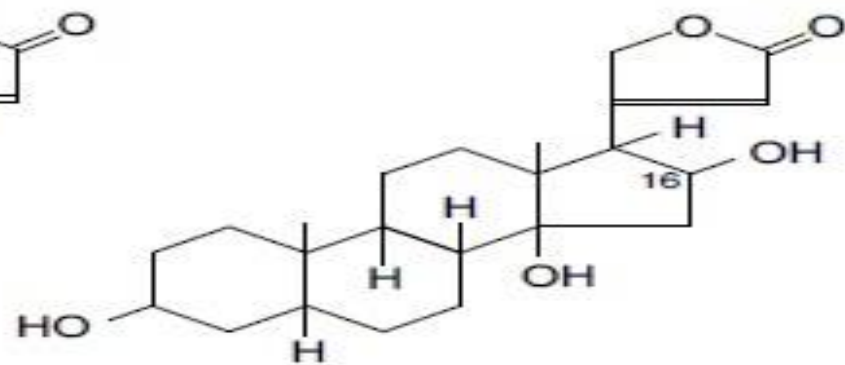
DIGITALIS LEAF

Digitalis (*Purple Foxglove Leaves*) consists of the dried leaves of *Digitalis purpurea* L. (Scrophulariaceae).

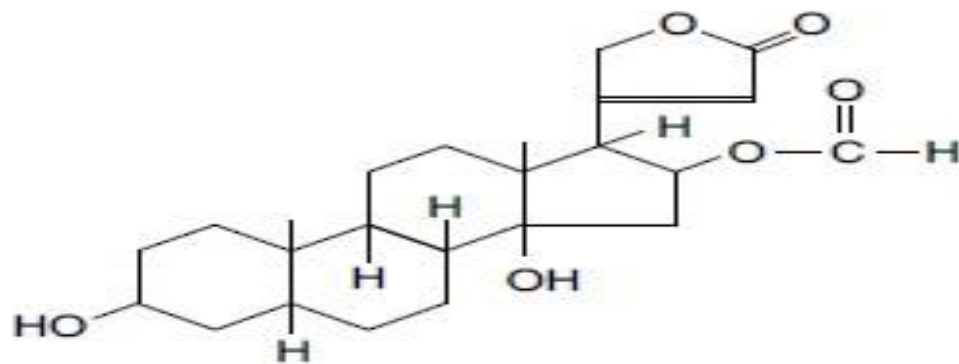
The primary (tetra) glycosides (purpurea glycoside A, purpurea glycoside B and glucogitaloxin) all possess at C-3 of the genin a linear chain of three digitoxose sugar moieties terminated by glucose. Purpurea glycosides A and B, first characterized by A. Stoll in 1938, constitute the principal active constituents of the fresh leaves. On drying, enzyme degradation takes place with the loss of the terminal glucose to give digitoxin, gitoxin and gitaloxin, respectively. Digitoxin and gitoxin are therefore the main active components of the dried drug. Poor storage conditions will lead to further hydrolysis and complete loss of activity. The gitaloxigenin series with its formyl group at C-16 is less stable than the other two series and was not discovered until 1956; the glycosides of this series are claimed to have similar or greater activities than those of the digitoxigenin group. The aglycones digitoxigenin and gitoxigenin are produced by acid hydrolysis of the respective glycosides but they are not found in quantity in the fresh or dried leaves. *Digitalis purpurea* leaves also contain anthraquinone derivatives,



Digitoxigenin



Gitoxigenin



Gitaloxigenin

Aglycones of *Digitalis purpurea* cardioactive glycosides.

Aglycone and sugar components of digitalis leaves.

Sugar components (attached at C-3)	Aglycone		
	Digitoxigenin	Gitoxigenin	Gitalexigenin
Glucose-(digitoxose) ₃ -	Purpurea glycoside A	Purpurea glycoside B	Glucogitaloxin
(Digitoxose) ₃ -	Digitoxin	Gitoxin	Gitalexin
Glucose-digitalose-	Glucodoroside H	Digitalinum verum	Glucoverodoxin
Digitalose-	Odoroside H	Strospeside	Verodoxin

Acetylated side-chain glycosides of *Digitalis purpurea*.

Glycoside	Aglycone	Sugar moieties
Acetyl glucogitoroside	Gitoxigenin	Glucose-acetyldigitoxose-
Acetyl digitalinum verum	Gitoxigenin	Glucose-acetyldigitalose-
Purlanoside A	Digitoxigenin	Glucose-(digitoxose) ₂ -acetyldigitoxose-
Purlanoside B	Gitoxigenin	Glucose-(digitoxose) ₂ -acetyldigitoxose-

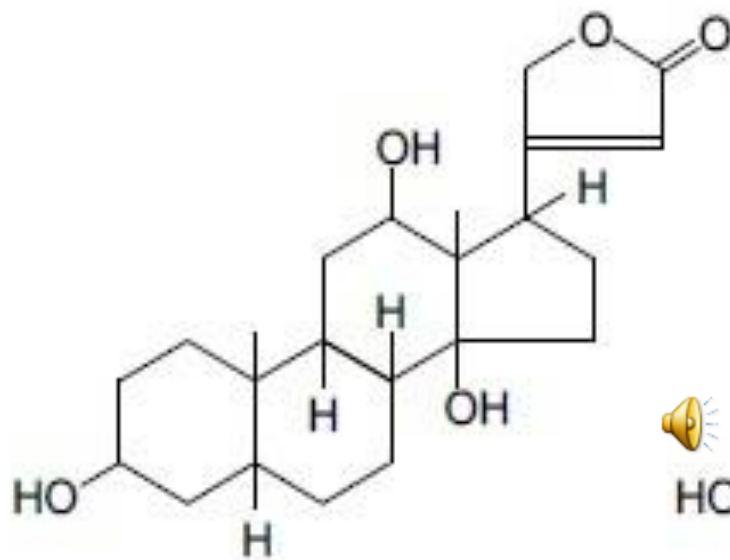
DIGITALIS LANATA LEAF

The plant, *Digitalis lanata* (Scrophulariaceae), the leaves of which are used as a source of the glycosides digoxin and lanatoside C, is a perennial or biennial herb about 1 m high, indigenous to central and south-eastern Europe. It is also cultivated in Holland, Ecuador and the USA.

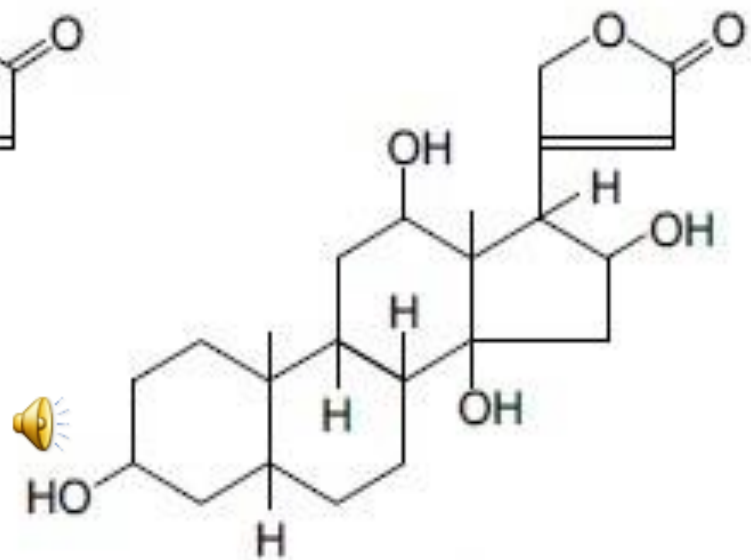
Constituents. First isolated by S^oll in 1933, the primary glycosides resemble those of *D. purpurea* but are acetylated at the digitoxose moiety next to the terminal glucose. This confers crystalline properties on the compounds, making them more amenable to isolation. Partial hydrolysis of the glycosides occurs during the drying and storage of leaves, and deacetylation will produce products the same as in *D. purpurea*. In addition to the above series of glycosides, two others, involving digoxigenin and diginatinin are found in the leaves.

Some cardioactive glycosides of *Digitalis lanata* leaves.

Glycoside	Aglycone	Sugar moieties
Lanatoside A	Digitoxigenin	Glucose-acetyldigitoxose-(digitoxose) ₂ -
Acetyldigitoxin	Digitoxigenin	Acetyldigitoxose-(digitoxose) ₂ -
Digitoxin	Digitoxigenin	(Digitoxose) ₃ -
Glucovatromonoside	Digitoxigenin	Glucose-digitoxose-
Digitoxigenin-O-glucosyl-6-deoxyglucoside	Digitoxigenin	Glucose-glucomethylose-
Glucodigifucoside	Digitoxigenin	Glucose-fucose-
Lanatoside B	Gitoxigenin	Glucose-acetyldigitoxose-(digitoxose) ₂ -
Glucogitoroside	Gitoxigenin	Glucose-digitoxose-
Digitalinum verum	Gitoxigenin	Glucose-digitalose-
Lanatoside C	Digoxigenin	Glucose-acetyldigitoxose-(digitoxose) ₂ -
Acetyldigoxin	Digoxigenin	Acetyldigitoxose-(digitoxose) ₂ -
Deacetyl-lanatoside C	Digoxigenin	Glucose-(digitoxose) ₃ -
Digoxin	Digoxigenin	(Digitoxose) ₃ -
Digoxigenin-glucosyl-bis-digitoxoside	Digoxigenin	Glucose-(digitoxose) ₂ -
Lanatoside D	Diginatigenin	Glucose-acetyldigitoxose-(digitoxose) ₂ -
Lanatoside E	Gitoxigenin	Glucose-acetyldigitoxose-(digitoxose) ₂ -
Glucolanadoxin	Gitoxigenin	Glucose-digitoxose-
Glucoverodoxin	Gitoxigenin	Glucose-digitalose-



Digoxigenin



Diginitagenin

Aglycones of *Digitalis lanata* cardioactive glycosides.

Uses The leaves are used almost exclusively for the preparation of the lanatosides and digoxin. Over the past decades digoxin has become the most widely used drug in the treatment of congestive heart failure. In long-term treatments patients require about 1 mg day^{-1} and the world-wide use of the drug now amounts to several thousand kilograms per year.

Proprietary preparations of the lanatoside complex, lanatoside C and lanatoside A are available in various countries but the glycoside from *D. lanata* most widely used is digoxin. Acting similarly to digitalis leaf, digoxin is more rapidly absorbed from the gastrointestinal tract than are the purpurea glycosides, which renders it of value for rapid digitalization in the treatment of atrial fibrillation and congestive heart failure. Lanatoside C is less well absorbed than digitoxin but it is less cumulative and for rapid digitalization the deacetyl derivative is preferable.

Nerium oleander is an evergreen shrub or small tree of the family Apocynaceae, toxic in all its parts

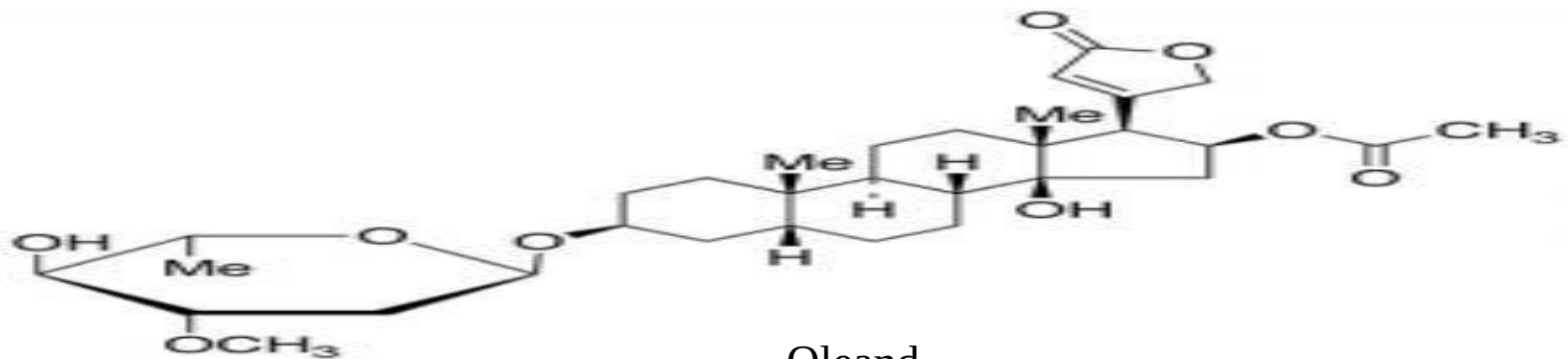


The oleander glycosides

Nerium oleander, the oleander plant, and related species contain glycosides having a similar action to that of digitalis. Of Mediterranean origin, this evergreen flowering tree is widely cultivated in Japan and other countries as a garden and roadside ornamental.

The principal constituents of the leaves are oleandrin and digitalinum verum. Oleandrin is the monoside, comprising oleandrogenin (16-acetylgitoxigenin) and L-oleandrose.

The leaves also contain gitoxigenin and digitoxigenin glycosides. A new glycoside, neridiginoside, has recently been obtained



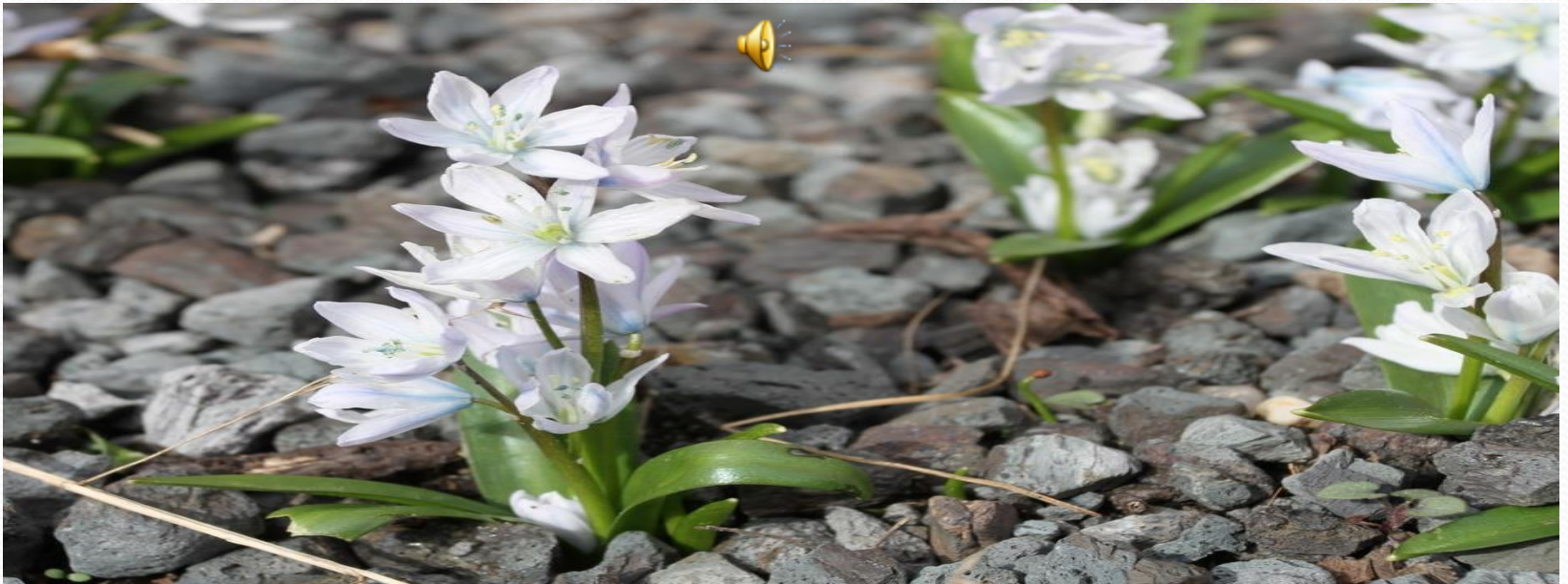
Oleand
rin

BUFADIENOLIDES

The bufadienolides are less widely distributed in nature than are the cardenolides; they are found in some Liliaceae and Ranunculaceae, and in the toad venoms the genins are partly free and partly combined with suberyl arginine. Therapeutically they find little use as cardioactive drugs because of their low therapeutic index and their production of side-effects. However squill (q.v.) has a time-honoured place as an expectorant and has been widely used in the treatment of cough.

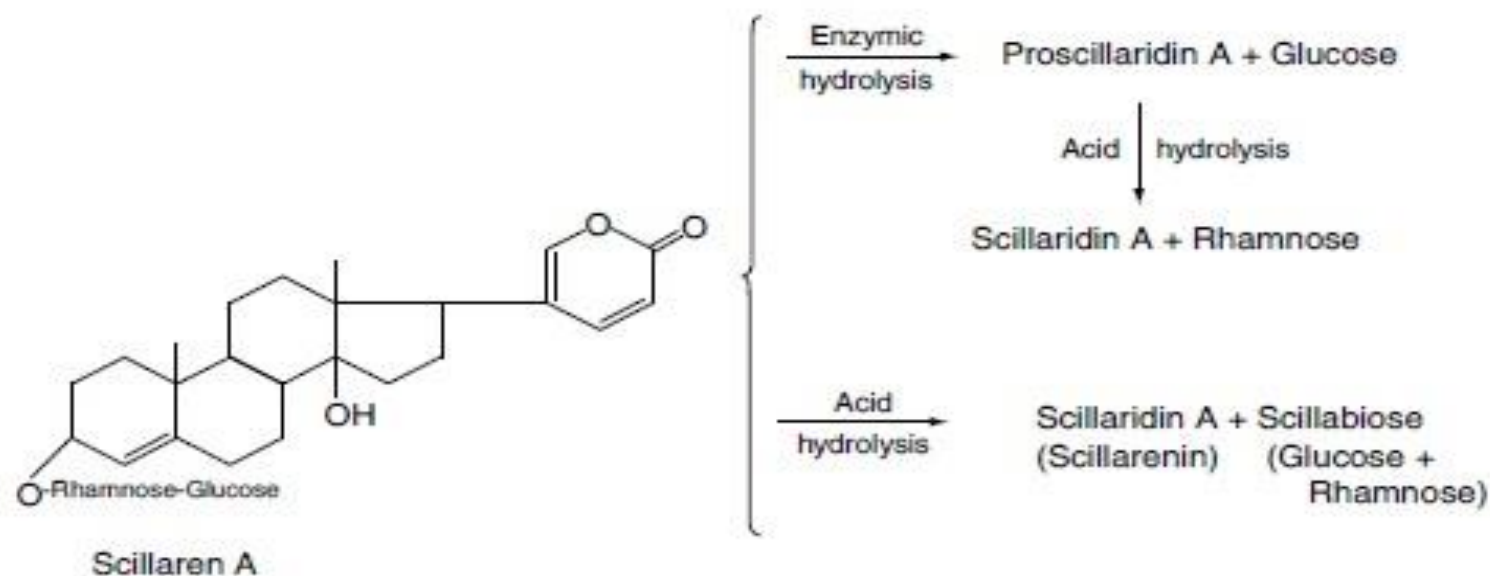
Squill

There are two types of Squill : white consists of the cut & dried bulb of *Urginea maritima* F. *Liliaceae* , it is used as expectorant, but it also possesses emetic , Cardiotoxic and diuretic action.



Constituents. Pure glycosides were not isolated until in 1923 Stoll separated a crystalline glycoside, scillaren A, and an amorphous mixture of glycosides, scillaren B. Scillaren A, the most important constituent of squill, is readily hydrolysed by an enzyme scillarenase or by acids

Many flavonoids have been detected in extracts of the bulb of *U. maritima*; they include quercetin derivatives and kaempferol polyglycosides together with C-glycosides such as vitexin and isovitexin.



Red Squill

This rodenticide is a cardiac glycoside derived from the plant *Urginea maritima*. It is of limited current use, because , red squill is very toxic so it is used as rodenticide

