ALKALOIDS

One of the most important secondary metabolites from the pharmacological point view

- structural diversity
- therapeutic usage
- number of structures

Alkaloids are prevalently products of higher plants secondary metabolism.

Lower number of alkaloids is produced by cyanobacteria, fungi and some amphibians.

Designation „alkaloid" was added to pharmacist W. Meissner (1819) and was used because of expression of their alkalic nature, although some of them are of neutral character (colchicine).

ALKALOIDS

Significant physiological effect of alkaloids was a stimulus for their early research and discoveries, in which lots of pharmacists have been involved. This research was leading to isolation and characterization of typical examples

- morphine (Sertürner, 1806)
- strychnine (Pelletier and Caventou, 1818)
- quinine (Pelletier a Caventou 1820)
- coniine (Giesecke, 1872)
- nicotine (Posselt a Reimann, 1828)
- atropine (Hesse, 1831)
- codeine (Robiquet, 1832)
- papaverine (Merck, 1848)

Physiologic effect of alkaloids is often observed in their extreme toxicity. But, in many sublethal doses, alkaloids posses therapeutically advantageous pharmacological properties and are used as valuable therapeutics.

ALKALOIDS

The plant usually produces more alkaloids (major and minor)

- often the same basic structure (skeleton), different in various substituents
- in such as group we can presume common precursors
  - Exceptions: for example Chinae cortex – bark of cinchona, here can be found two different types of alkaloids: with quinoline and indol core
- alkaloids are mostly stored in tissues showing active growth, and then in sheaths of vascular bundles and in lactifers
- alkaloids are often stored in form of hydrophilic salts with organic acids in vacuoles (for example tartric acid, citric acid, oxalate, malate, aconitic acid, chelidonic acid, meconic acid)
- alkaloids can be also found as insoluble substances bound with tannins
- The place of alkaloid storage is not always the same as place of biosynthesis.
  - For example: Nicotine is produced in roots and it is transported to leaves when it is accumulated.

ALKALOIDS

- The natural function of alkaloid production has not been recognized until present.
  - In toxicity or bitter taste of majority of alkaloids was observed the calculated defense of alkaloid plants against „predators".
  - But this is contradictory to that fact that there is much bigger majority of plants which do not use protection from alkaloid content.
  - Some insect species are specialized on certain plant with alkaloid content (*Atropa*, *Cinchona*) and cause several damage to their cultures.
- Selective toxicity of quinine is principle of its therapeutic usage. For human relatively not poisonous, for *Protozoans* toxic in very low dosage
- In opposite: for human are toxic berries and leaves of *Atropa*, and are without problem consumed by pheasants and rabbits (which are to hyosciamine practically insusceptible
- Hypothesis: alkaloids could mediate interspecies competition (allelopathy) or blastokolin effect similarly to coumarins
- Biosynthesis of alkaloids is energy-demanding, needs highly specific enzymes. This gives evidence of certain role of these compounds, which is not clear until now. In respect to their structural diversity, also the functional diversity could be large.

ALKALOIDS

- Bases of alkaloids are lipophilic, poorly soluble in water, mostly crystalline colorless compounds.
- With acid form colorless crystalline salts (exceptions: yellow berberine, chelidonine and cotarnine) of bitter taste.
- If optically active, than prevalently levorotary
- Precipitation reactions important for their proof:
  - with solution of potassium bismuth iodide (Dragendorff) and solution of potassium mercury iodide (Mayer) produce precipitate, formation of poorly soluble salts with dihydrotetrachloroplatinic acid , picric acid and ammonium reineckate solution
- Colored reactions
  - with concentrated mineral acids or their mixtures
- Several alkaloids can be found in liquid form of base (nicotine, coniine, sparteine), easily can be isolated from raw plant material by using hydrodistillation.
- Different solubility of alkaloid bases and their corresponding salts allows their relatively easy purification.

ALKALOIDS

Occurrence

- alkaloids are present in 10-15 % of vascular plants
- rarely found in lower plants (*Claviceps* – ergot alkaloids), gymnosperms (*Coniferae* – conifers), or monocotyledonous (Liliaceae)

- occurre especially in some dicotyledonous plants, prevalently in families
  - *Apocynaceae*
  - *Solanaceae*
  - *Fabaceae*
  - *Rutaceae*
  - *Papaveraceae*
  - *Ranunculaceae*
  - *Rubiaceae*
  - *Loganiaceae*

- rarely distributed in big or bigger group of plants.

ALKALOIDS

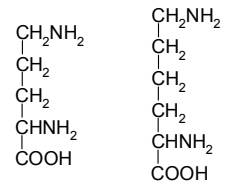
- number of alkaloids isolated till present is around 8000 and constantly grows
- in last tens of years increases the importance of partial and total synthesis, especially when there is need to obtain from practical reasons (biological assays, therapeutic usage)

BASIC BUILDING BLOCKS OF ALKALOIDS

Based on current knowledge it is possible to declare, that basic building blocks of alkaloids produced by plants are

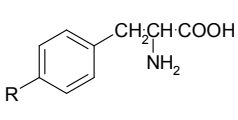
- aliphatic aminoacids
  - ornithine and lysine
- aromatic aminoacids
  - phenylalanine, tyrosine, tryptophan and histidine
- several alkaloids are produced
  - nicotinic acid and anthranilic acid, which are products of secondary metabolic processes
- Several other aminoacids can be used for biosynthesis of alkaloids
  - glycine, cysteine, methionine, asparagic acid and proline.

BASIC BUILDING BLOCKS OF ALKALOIDS

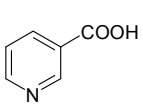


ornithine

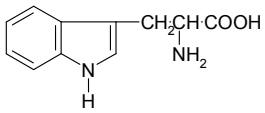
lysine



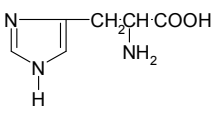
R=H, phenylalanine
R=OH, tyrosine



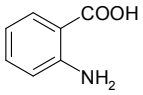
nicotinic acid



tryptophan

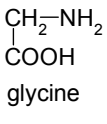


histidine

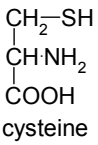


anthranilic acid

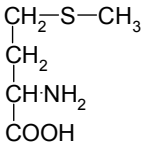
Other compounds joining alkaloid biosynthesis



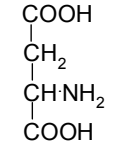
glycine



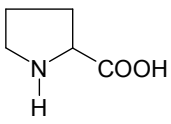
cysteine



methionine



aspartic acid



proline

ALKALOIDS

- basic structure or part of structure of some alkaloids is terpenoid skeleton (hemi-, mono-, di- a triterpenes, such as steroids).
- other group of alkaloids is produced via incorporation of nitrogen into polyketide skeleton, for example coniine.
- many other widely distributed bases of plant origin, for example methyl-, trimethyl-, and further simple alkylamines with open chain, and also cholines and betaines are not classified as alkaloids, but as „biogenic amines"
- other heterocyclic nitrogenous bases, which do not belong to alkaloids are for example thiamine (regarding to its general spread in living organisms and also purine bases, for example caffeine, theobromine and theophyline and group of betalaines.

ALKALOIDS CLASSIFICATION

- true, derived from aminoacids, atom of nitrogen pasted in form of heterocycle (morphine, quinine, hyoscyamine, strychnine and others)
- protoalkaloids, derived from aminoacids, atom of nitrogen is not part of heterocycle, can be simple basic amines (ephedrine, meskaline, cathinone, psilocybine)
- pseudoalkaloids, posses the character of true alkaloids but are not derived from aminoacids
  - mostly of isoprenoid origin and are classified also as terpenoid alkaloids, for example diterpenoid alkaloid aconitine
  - or can be of acetate origin, for example coniine

BIOSYNTHESIS OF ALKALOIDS

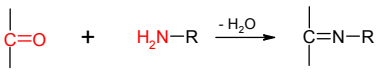
Most important reactions involved in alkaloid biosynthesis are:

- formation of Schiff bases, when primary amino group condens with carbonyl group of aldehyde to produce substance with azomethine residue (–CH=N–) to form aldimine.
- Mannich condensation, when compounds with active hydrogen condense with formaldehyde in presence of NH_3, aliphatic primary or secondary amine and system C-C-N is produced
- aldol type condensations between compounds containing imino groups

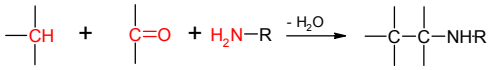
A panel of other reaction is involved in alkaloid biosynthesis, such as oxidation, reduction, metathesis and others. For example in group of benzylisoquinoline alkaloids it is oxidative phenolic coupling, biosynthesis of big group of indole alkaloids involves connection of tryptophan skeleton with C9-10 fragment of terpenoid origin.

BIOSYNTHESIS OF ALKALOIDS

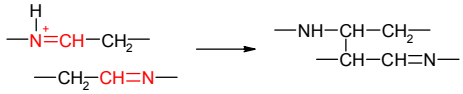
a) Formation of Schiff bases



b) Mannich condenzation (after formation of Schiff base)

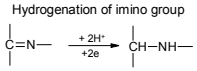


c) Condenzation of aldol type compounds between substances with iminogroups

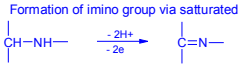


BIOSYNTHESIS OF ALKALOIDS

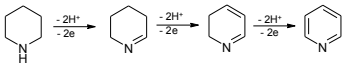
Hydrogenation of imino group



Formation of imino group via satturated amines dehydrogenation

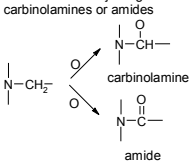


Dehydrogenation leading to formation of aromatic ring

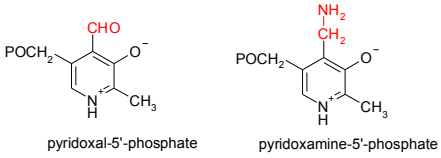


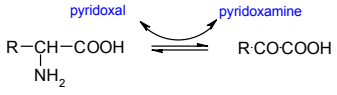
Isomerization of double bond of imino group to α,β-unsaturated amino group

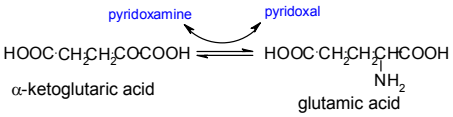
Oxidation of C adjoining with N to produce carbinolamines or amides

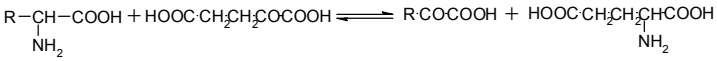


METABOLISM OF AMINOACIDS IN RELATION TO ALKALOID BIOSYNTHESIS

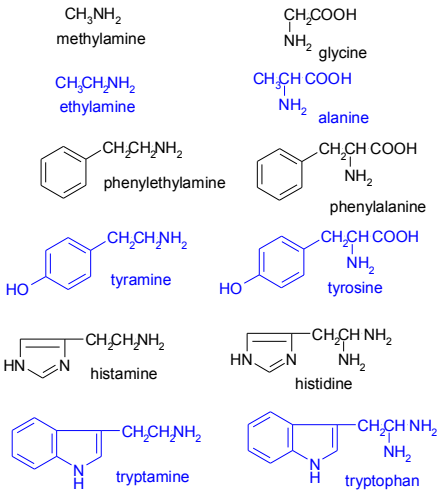






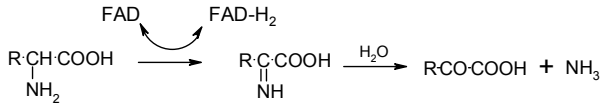


AMINES AND CORRESPONDING AMINOACIDS

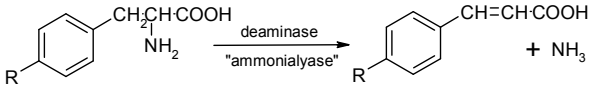


OXIDATIVE AND NON-OXIDATIVE TRANSFORMATION OF AMINOACID

Oxidative transformation of aminoacidi to α-ketoacid depending on FAD

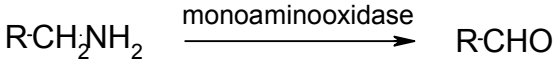


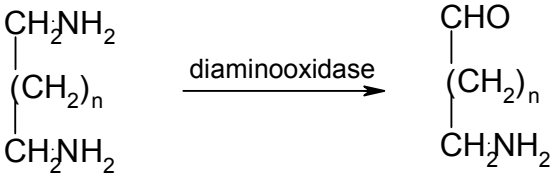
Non-oxidative deamination of aromatic aminoacids



R = H, OH

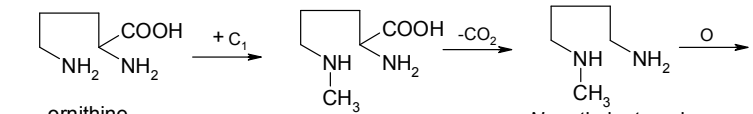
OXIDATION OF AMINES





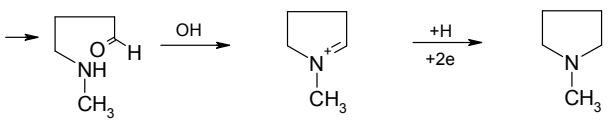
n = 2, putrescine
n = 3, cadaverine

ALKALOIDS DERIVED FROM ORNITHINE



ornithine

N-methylputrescine

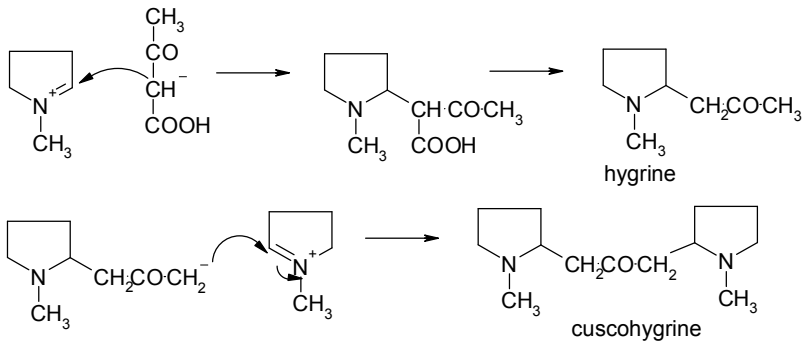


4-methylaminobutanal

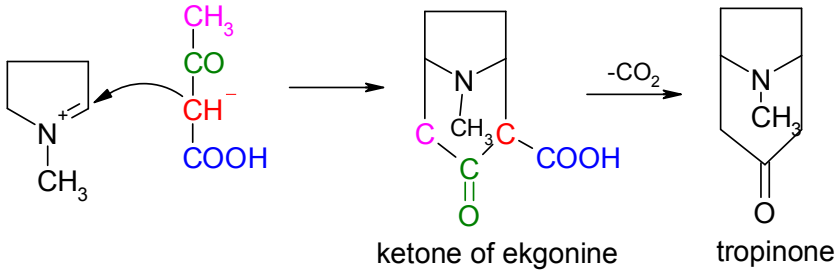
N-methyl-1-pyrroline

N-methylpyrrolidine

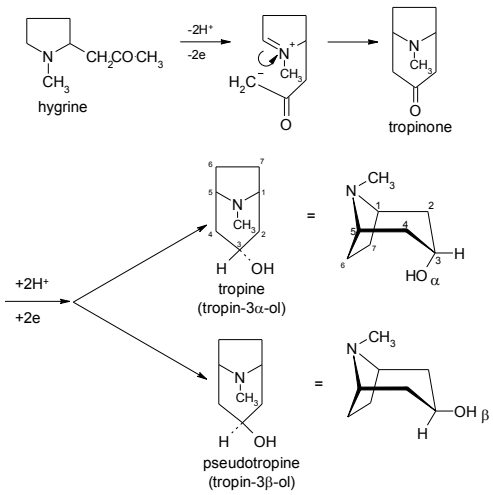
ALKALOIDS DERIVED FROM ORNITHINE



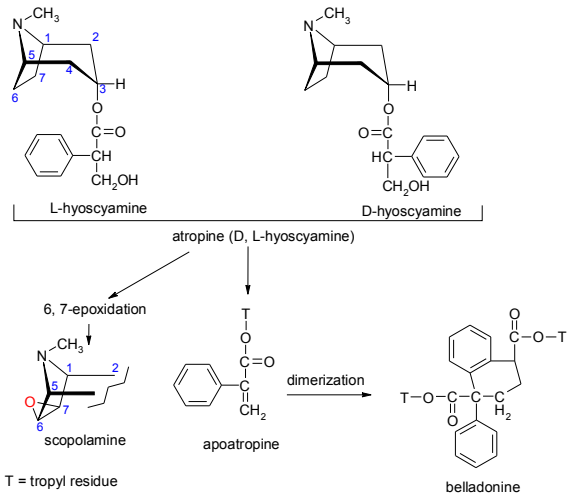
TROPANE ALKALOIDS



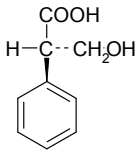
TROPANE ALKALOIDS



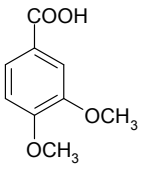
REACTIONS OF TROPANE CORE



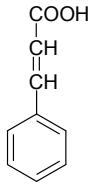
ACIDS ESTERIFIING TROPANOL



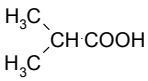
(-)-tropic acid



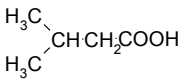
veratric acid



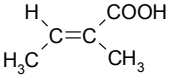
cinnamic acid



isobutyric acid

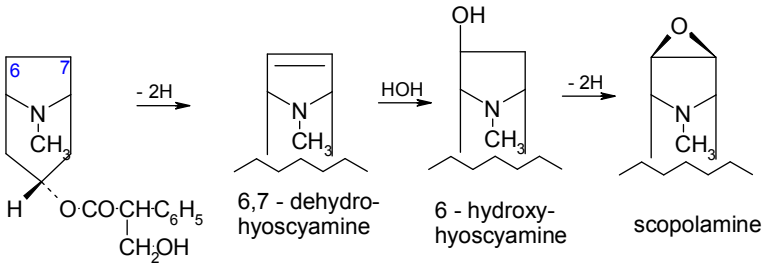


isovaleric acid



tiglic acid

EPOXIDATION OF TROPANE CORE



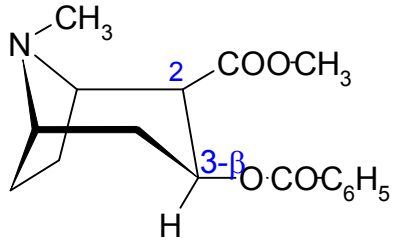
hyoscyamine

6,7 - dehydro-hyoscyamine

6 - hydroxy-hyoscyamine

scopolamine

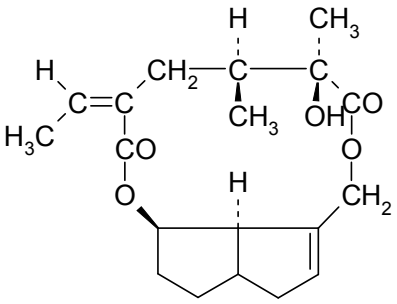
DERIVATIVES OF PSEUDOTROPINE



cocaine

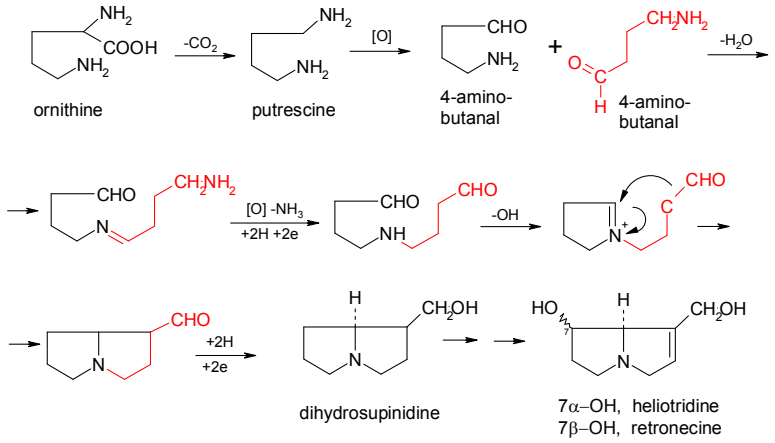
derivative of 2-carboxy-tropan-3-β-ol

PYRROLIZIDINE ALKALOIDS



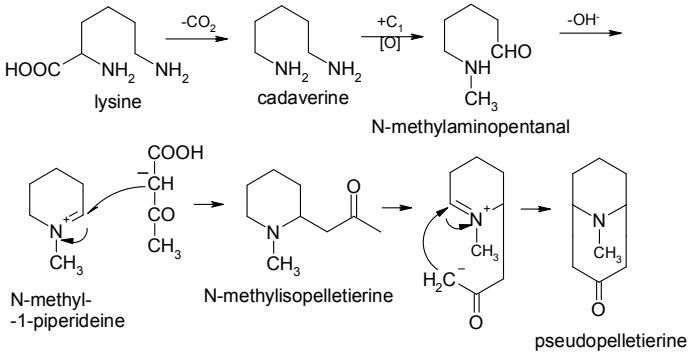
senecionine
(retronecine +
senecic acid,
Asteraceae)

PYRROLIZIDINE ALKALOIDS



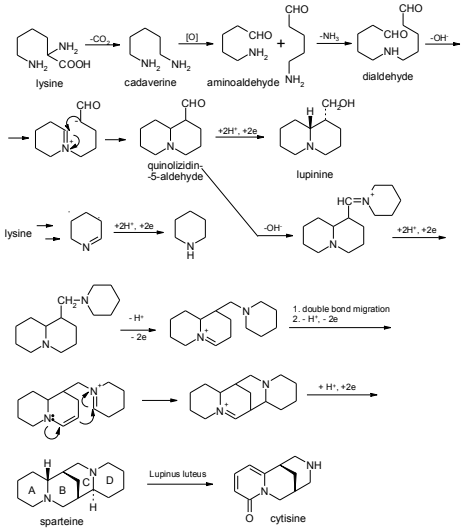
ALKALOIDS DERIVED FROM LYSINE

SIMPLE PIPERIDINE DERIVATIVES

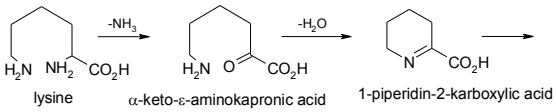


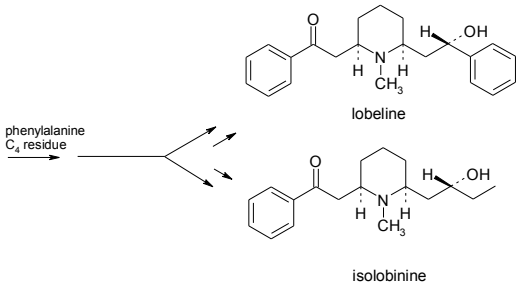
ALKALOIDS DERIVED FROM LYSINE

QUINOLIZIDINE ALKALOIDS



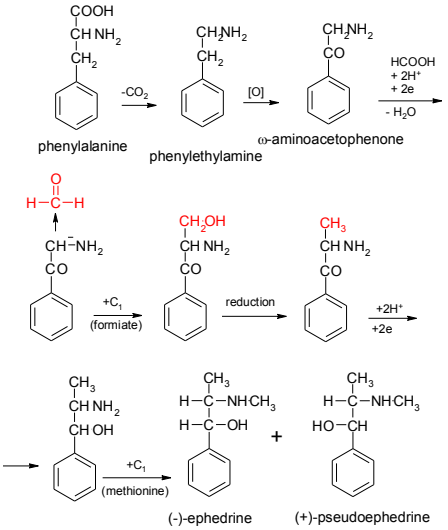
COMPOSED PIPERIDINE ALKALOIDS



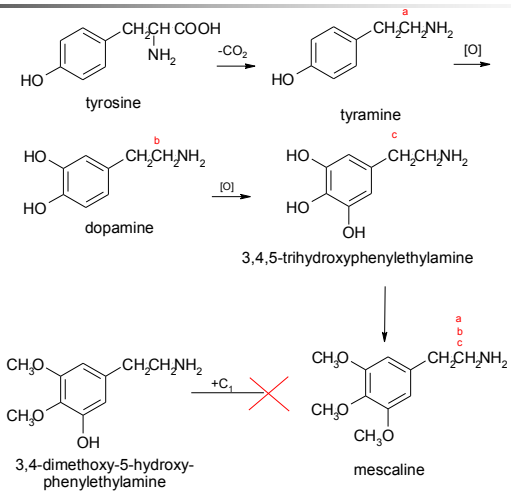


ALKALOIDY DERIVED FROM PHENYLALANINE AND TYROSINE

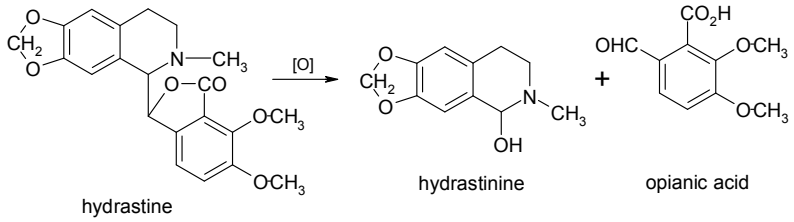
ALKALOIDS OF PHENYLETHYLAMINE TYPE



ALKALOIDS DERIVED FROM TYROSINE

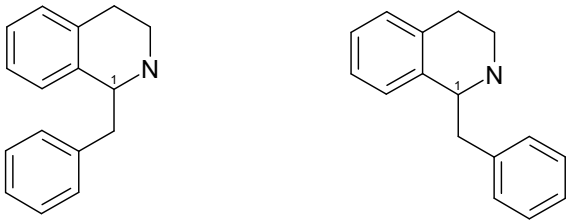


TETRAHYDROISOQUINOLINE ALKALOIDS



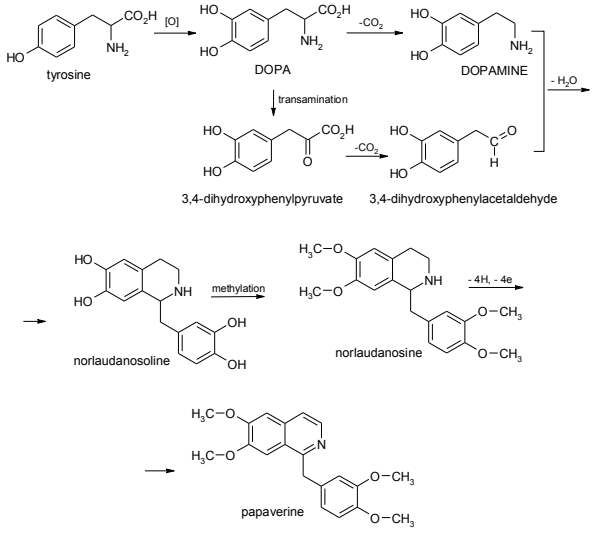
hydrastine hydrastinine opianic acid

BENZYLISOQUINOLINE ALKALOIDS

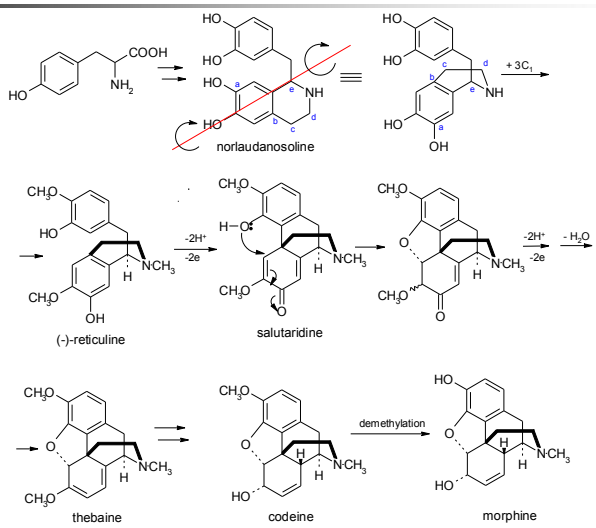


1-benzyltetrahydroisoquinoline

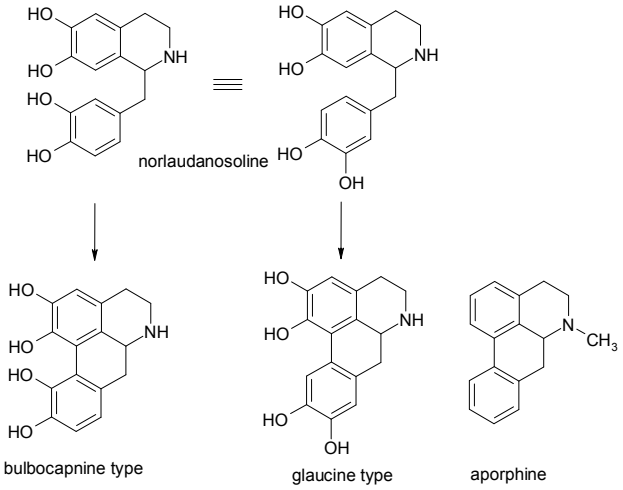
BIOSYNTHESIS OF PAPAVERINE



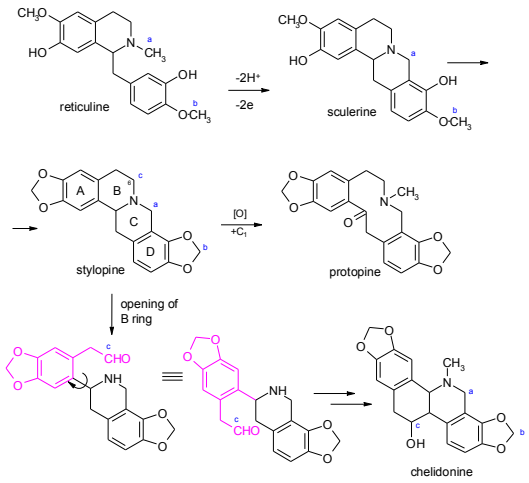
BIOSYNTHESIS OF MORPHINAN ALKALOIDS



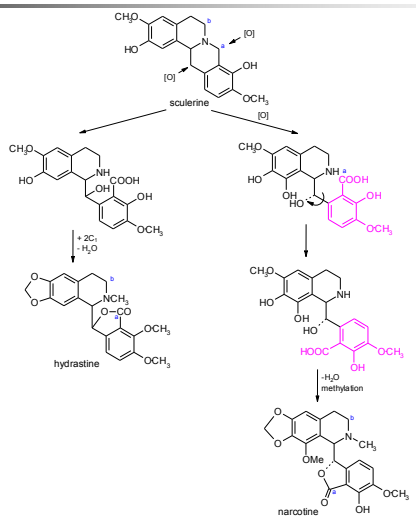
BIOSYNTHESIS OF APORPHINE ALKALOIDS



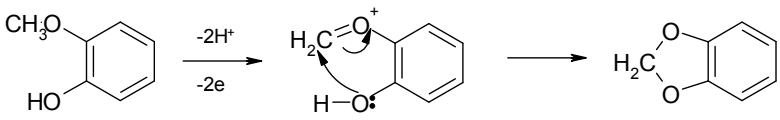
PROTOPINE AND BENZOPHENANTHRIDINE ALKALOIDS



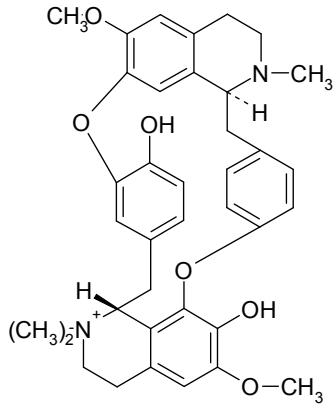
PHTALIDTETRAISOQUINOLINE ALKALOIDS



FORMATION OF METHYLENDIOXY GROUP

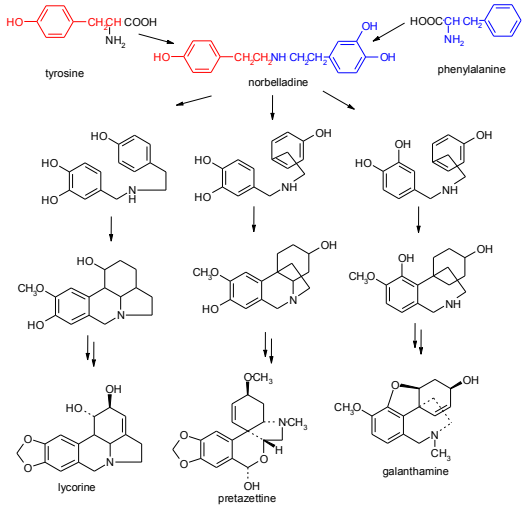


BISBENZYLIQUINOLINE ALKALOIDS

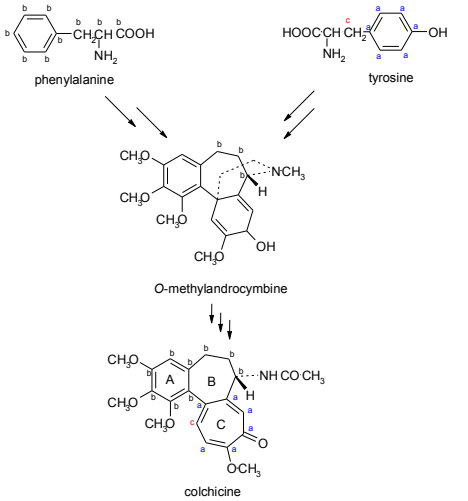


tubocurarine

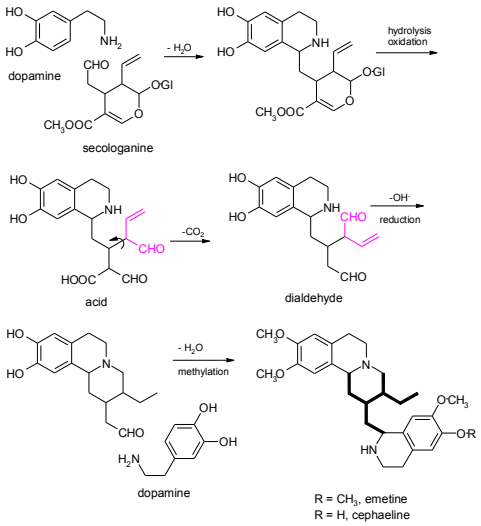
ALKALOIDS OF AMARYLLIDACEAE FAMILY



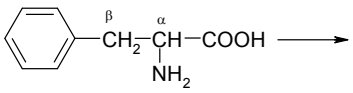
COLCHICINE ALKALOIDS



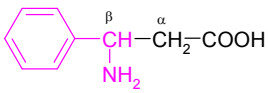
COMPOSITE BENZYLISOQUINOLINE ALKALOIDS



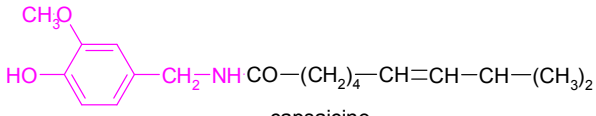
OTHER NITRIGENOUS COMPOUNDS DERIVED FROM PHENYLALANINE



phenylalanine



β-phenyl-β-aminopropionic acid



capsaicine

4-hydroxy-3-methoxybenzylamide of trans-8-methyl-6-nonenic acid

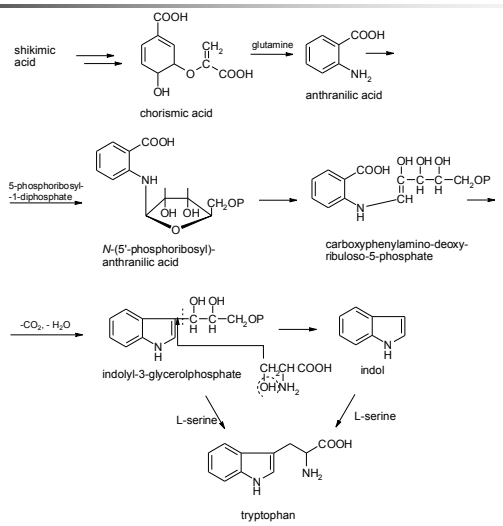
ALKALOIDS DERIVED FROM TRYPTOPHAN „INDOL ALKALOIDS"

RICH AND PHARMACEUTICALLY IMPORTANT SOURCE OF THESE ALKALOIDS ARE MEMBERS OF FAMILIES:

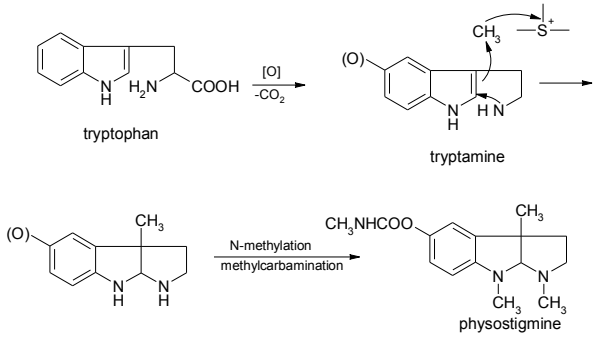
- APOCYNACEAE (Rauwolfia, Catharanthus, Aspidosperma)
- RUBIACEAE (Cinchona)
- LOGANIACEAEA (Strychnos)
- CLAVICIPITACEAE (Claviceps)
- EUPHORBIACEAE

PARTNERSHIP OF HEMITERPENIC OR MONOTERPENIC UNIT

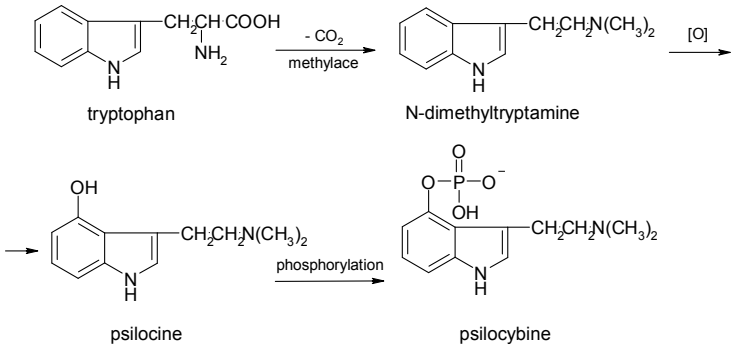
TRYPTOPHAN FORMATION



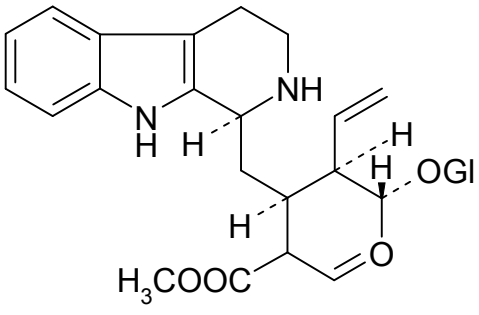
SIMPLE INDOL ALKALOIDS
INDOLYLALKYLAMINES



SIMPLE INDOL ALKALOIDS
INDOLYLALKYLAMINES

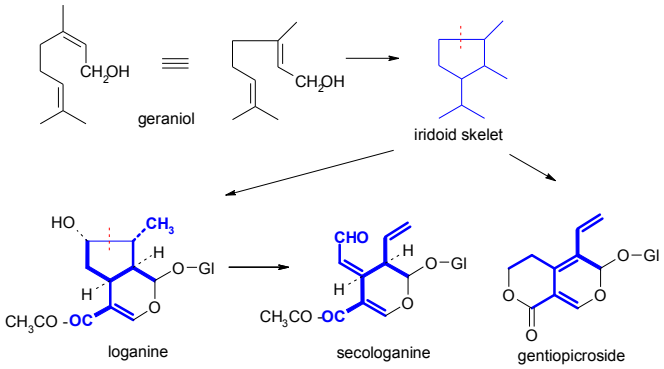


COMPOSITE INDOL ALKALOIDS

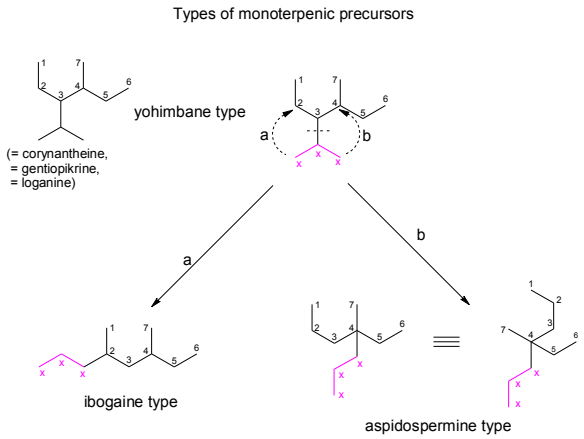


strictosidine

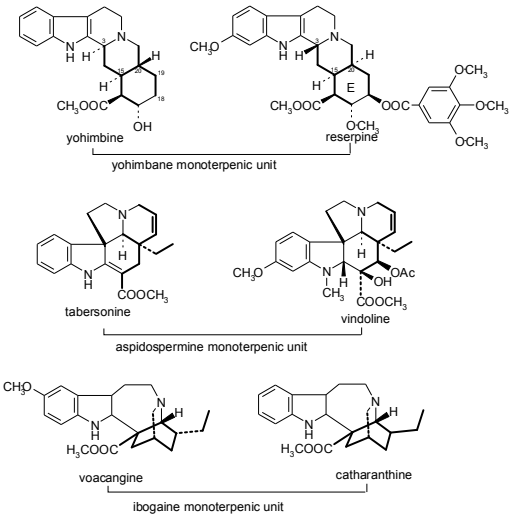
MONOTERPENIC PRECURSORS



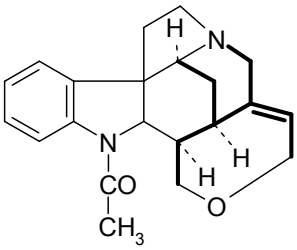
CLASSIFICATION ACCORDING TO MONOTERPENIC UNIT



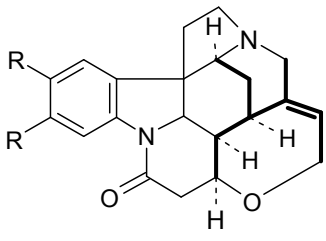
EXAMPLES



ALKALOIDS OF *STRYCHNOS NUX VOMICA*

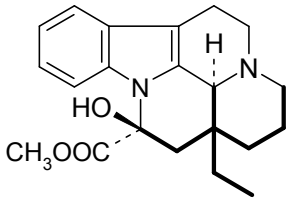


spermostrychnine

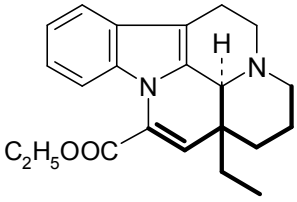


R = H, strychnine
R = OCH_3, brucine

ALKALOIDS OF *VINCA MINOR*



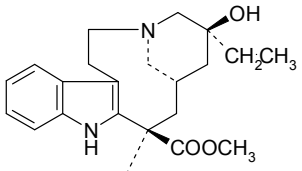
vincamine



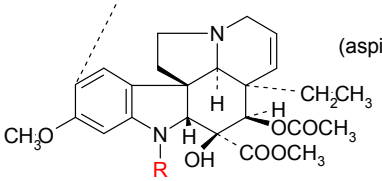
ethyl-apovincaminate

BISINDOL ALKALOIDS

CATHARANTHUS ROSEUS



catharanthine
(velbanamine)
(ibogaine type)

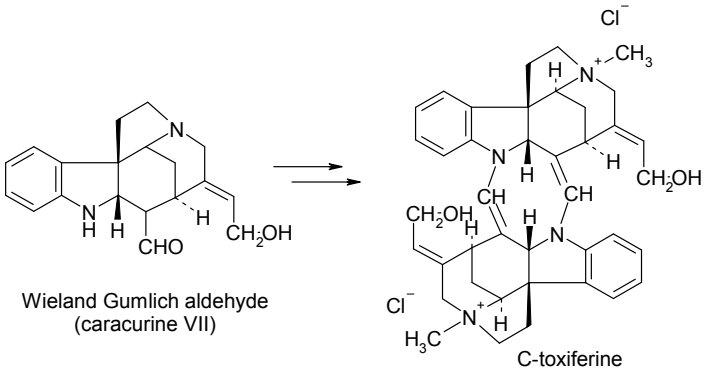


vindoline
(aspidospermine type)

R = CH_3, vincaleucoblastine
R = CHO, leucocristine

BISINDOL ALKALOIDS

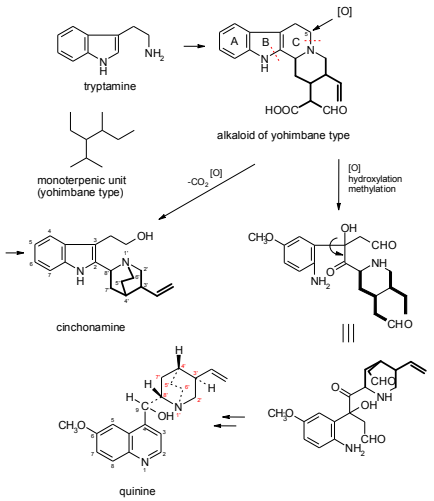
STRYCHNOS TOXIFERA



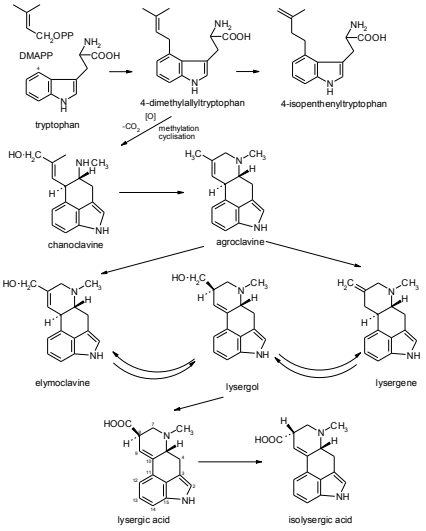
Wieland Gumlich aldehyde
(caracurine VII)

C-toxiferine

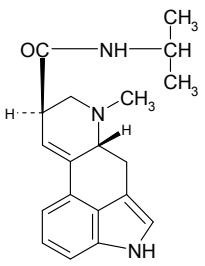
MONOTERPENIC ALKALOIDS OF QUININE TYPE



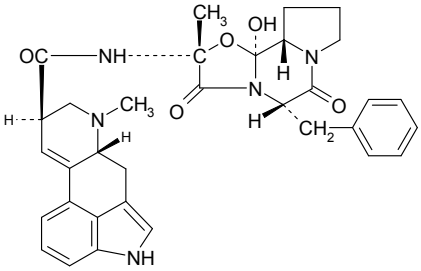
HEMITERPENIC ALKALOIDS – ERGOT



ERGOT ALKALOIDS

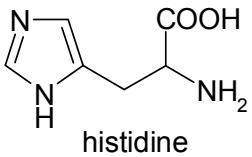


ergometrine

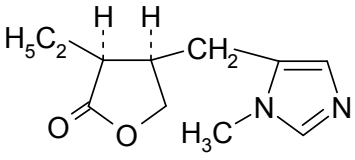


ergotamine

ALKALOIDS DERIVED FROM HISTIDINE

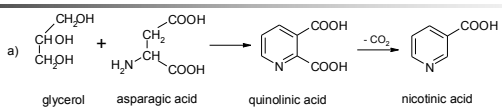


histidine

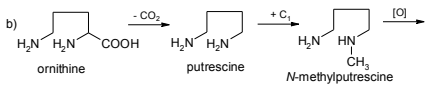


pilocarpine

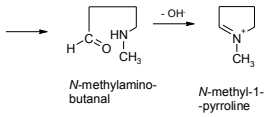
ALKALOIDS DERIVED FROM NICOTINIC ACID



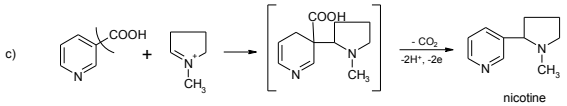
glycerol asparagic acid quinolinic acid nicotinic acid



ornithine putrescine *N*-methylputrescine

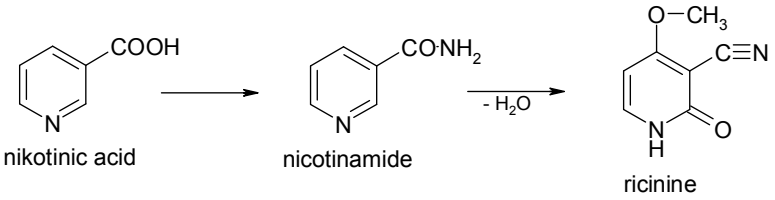


N-methylamino-butanal *N*-methyl-1--pyrroline

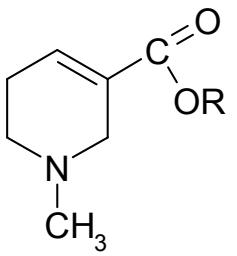


nicotine

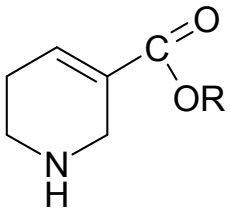
ALKALOIDS OF *RICINUS* SPECIES



ARECA ALKALOIDS

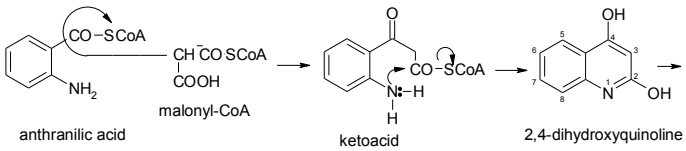


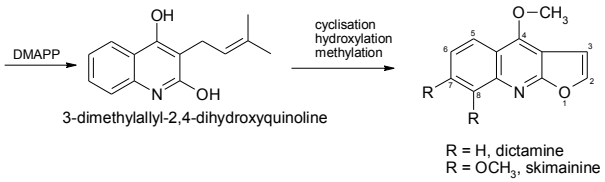
R = CH_3, arecoline
R = H, arecaidine



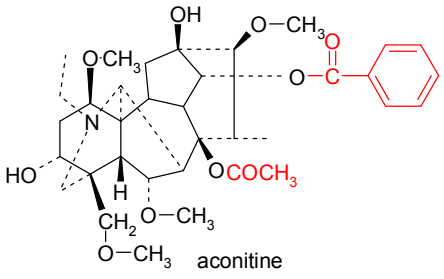
R = CH_3, guvacoline
R = H, guvacine

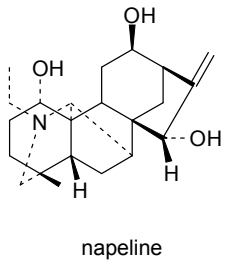
ALKALOIDS DERIVED FROM ANTHRANILIC ACID



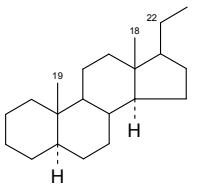


TERPENIC ALKALOIDS

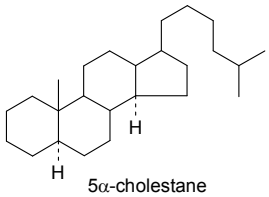




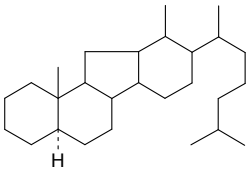
STEROIDAL ALKALOIDS



5α-pregnane

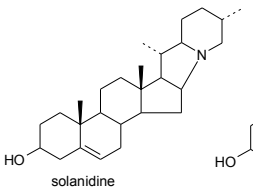


5α-cholestane

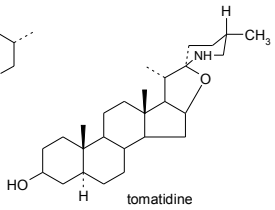


C-nor-D-homo-5α-cholestane

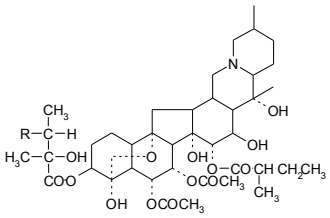
STEROIDAL ALKALOIDS



solanidine

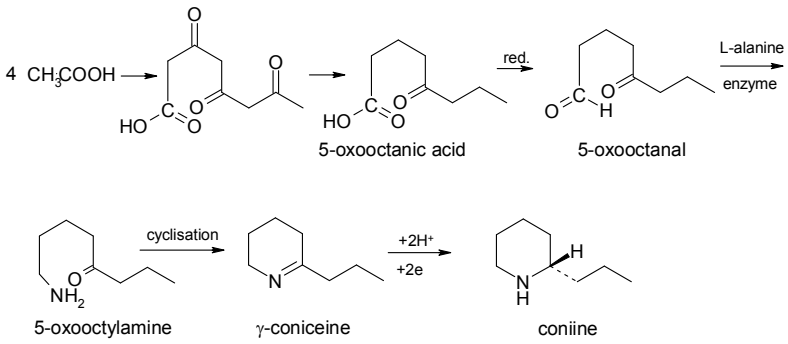


tomatidine



R = H, protoveratrine A
R = OH, protoveratrine B

ALKALOIDS OF *CONIUM MACULATUM*



DERIVATIVES OF PURINE