

Iceland   
Liechtenstein  
Norway grants

“Working together for a green,  
competitive and inclusive Europe”

# GREENCAM for tomorrow



# Chapter 8-1 The alkaloids

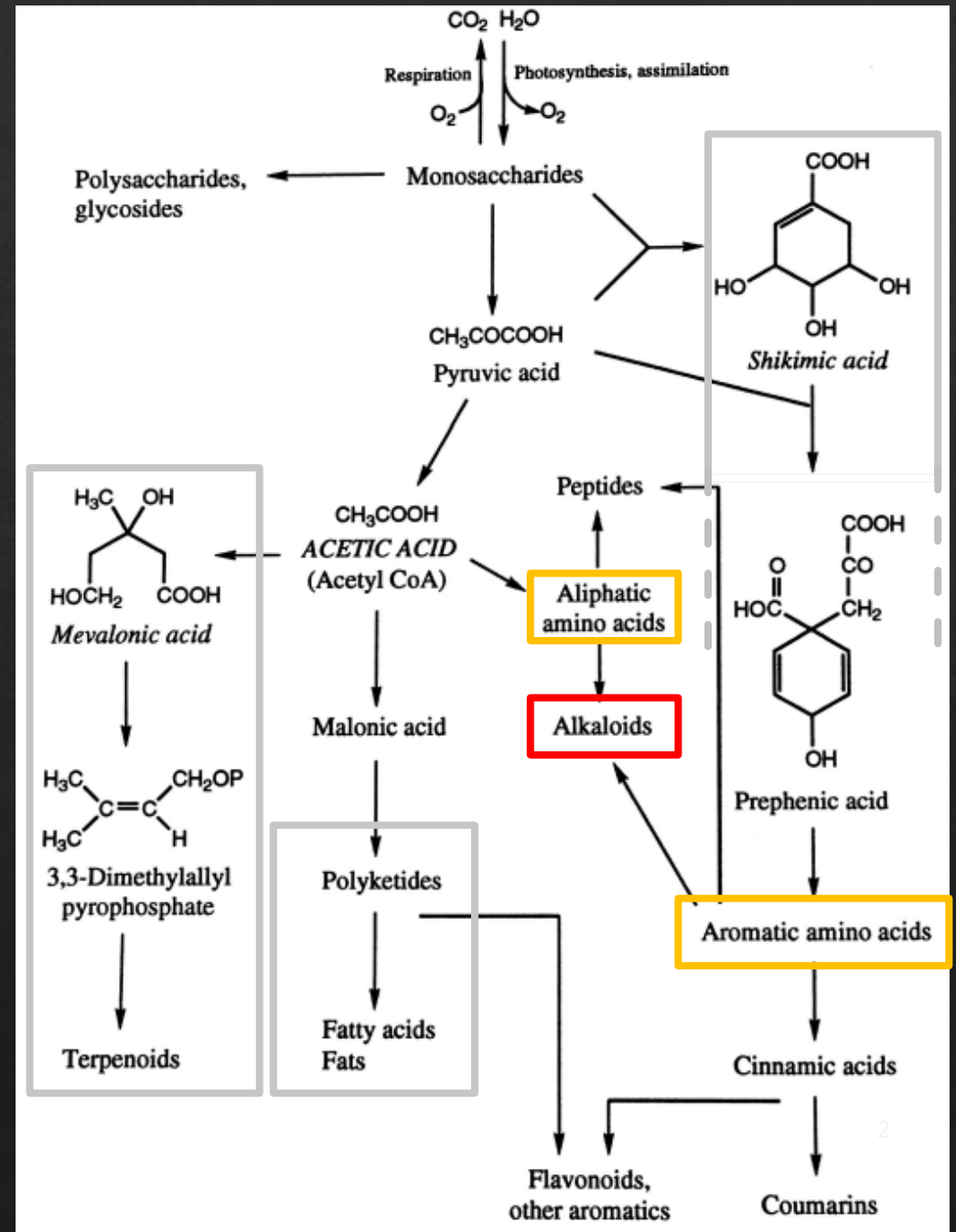
Elisabeth Jacobsen and Lucas Boquin, NTNU

Spring 2022

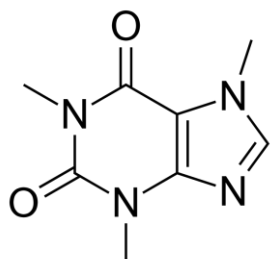
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# What are alkaloids?

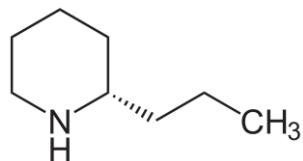
- ◆ An alkaloid is a cyclic organic compound that contains nitrogen in a negative oxidation state and is of limited presence among living organisms. It doesn't include simple amides.
- ◆ It is almost always derived from an amino acid combined with building blocks from the shikimic acid, polyketide, or mevalonic acid pathways.



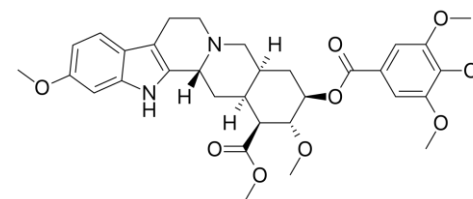
# What are alkaloids?



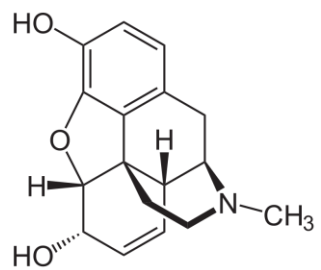
Caffeine (*Coffea*)



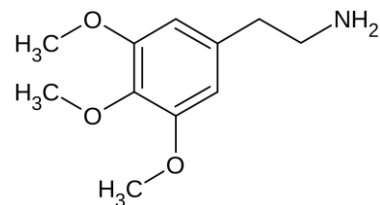
Coniine (*Conium maculatum*)



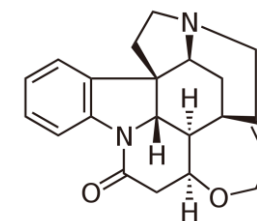
Reserpine (*Conium maculatum*)



Morphine (*Papaver somniferum*)



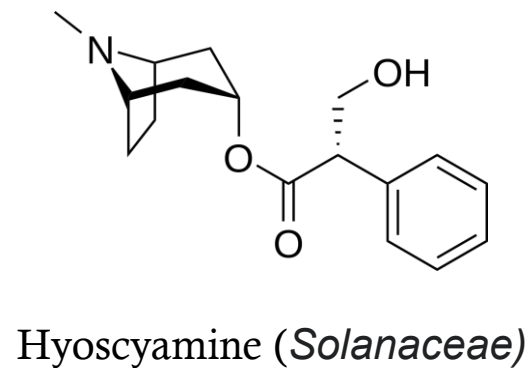
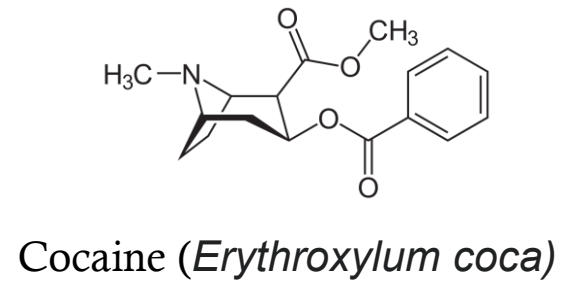
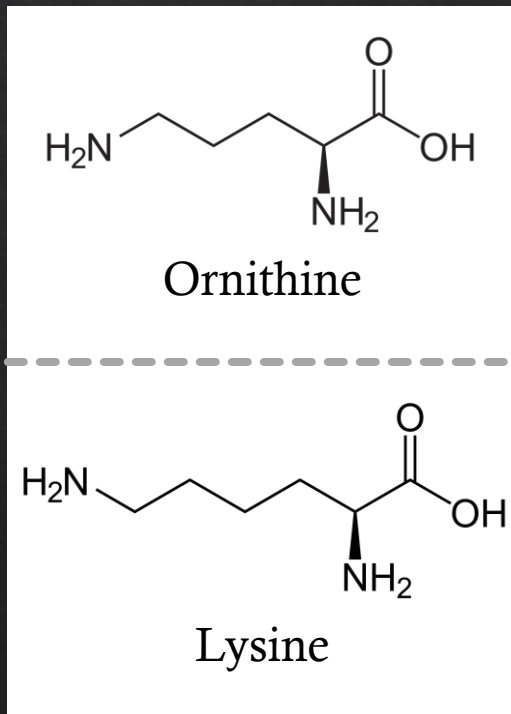
Mescaline (*Lophophora williamsii*)



Strychnine (*Strychnos nux-vomica*)



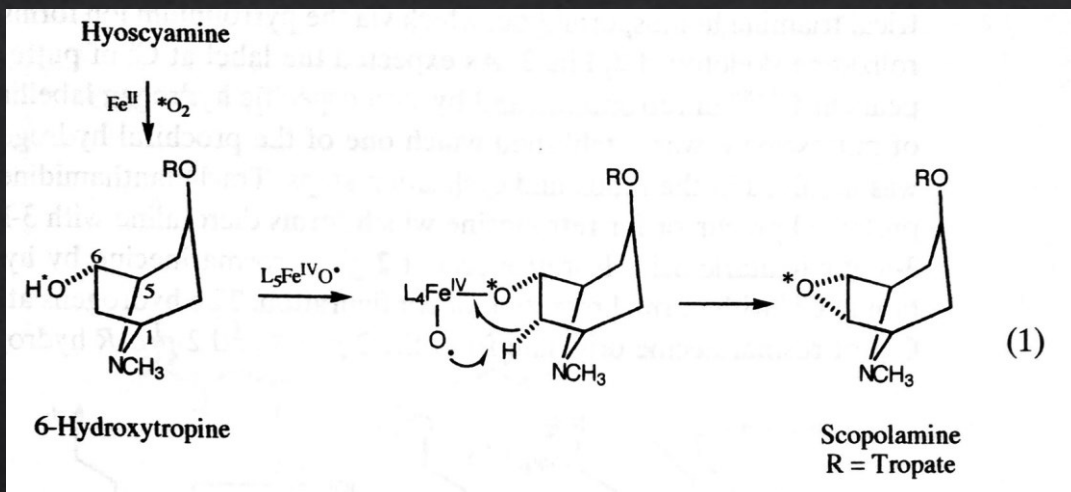
# The pyrrolidine and piperidine alkaloids



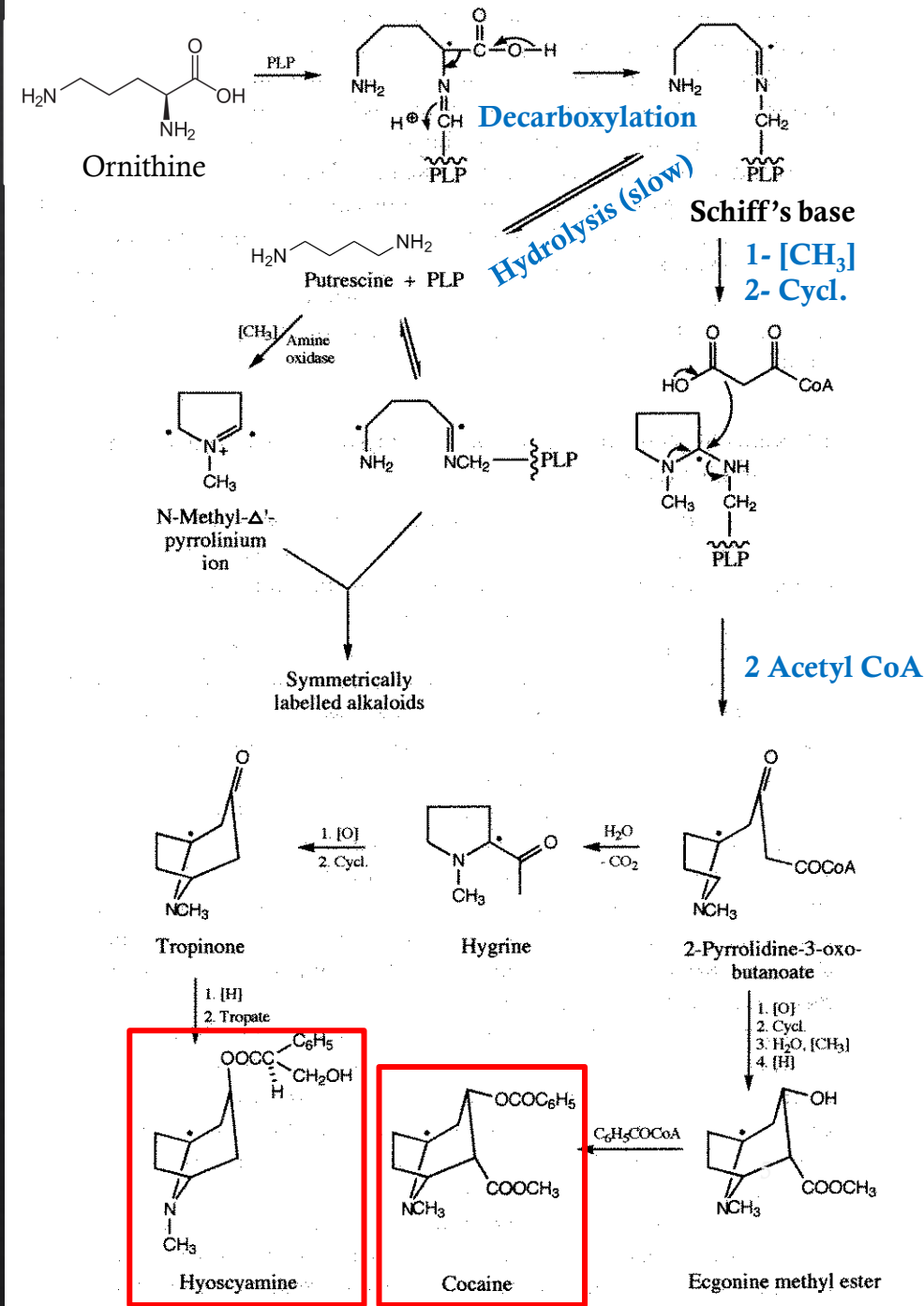


# The pyrrolidine and piperidine alkaloids

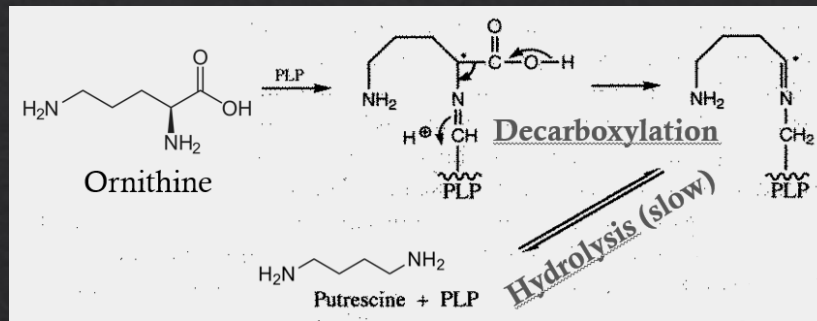
- Putrescine is accepted by the plant as a precursor, but the asymmetric incorporation of ornithine shows that putrescine isn't on the main pathway.



- To form scopolamine, an epoxide is added on the hyoscyamine structure via an unusual pathway involving a non-heme iron catalyst and molecular oxygen.



# The pyrrolidine and piperidine alkaloids



- ◇ Condensation of two molecules of putrescine leads to pyrrolizidine alkaloids.
- ◇ They are produced by plants as a defense mechanism against insect herbivores. Many insects build up those alkaloids in their bodies, and use them to produce useful compounds (such as pheromones in queen butterfly)

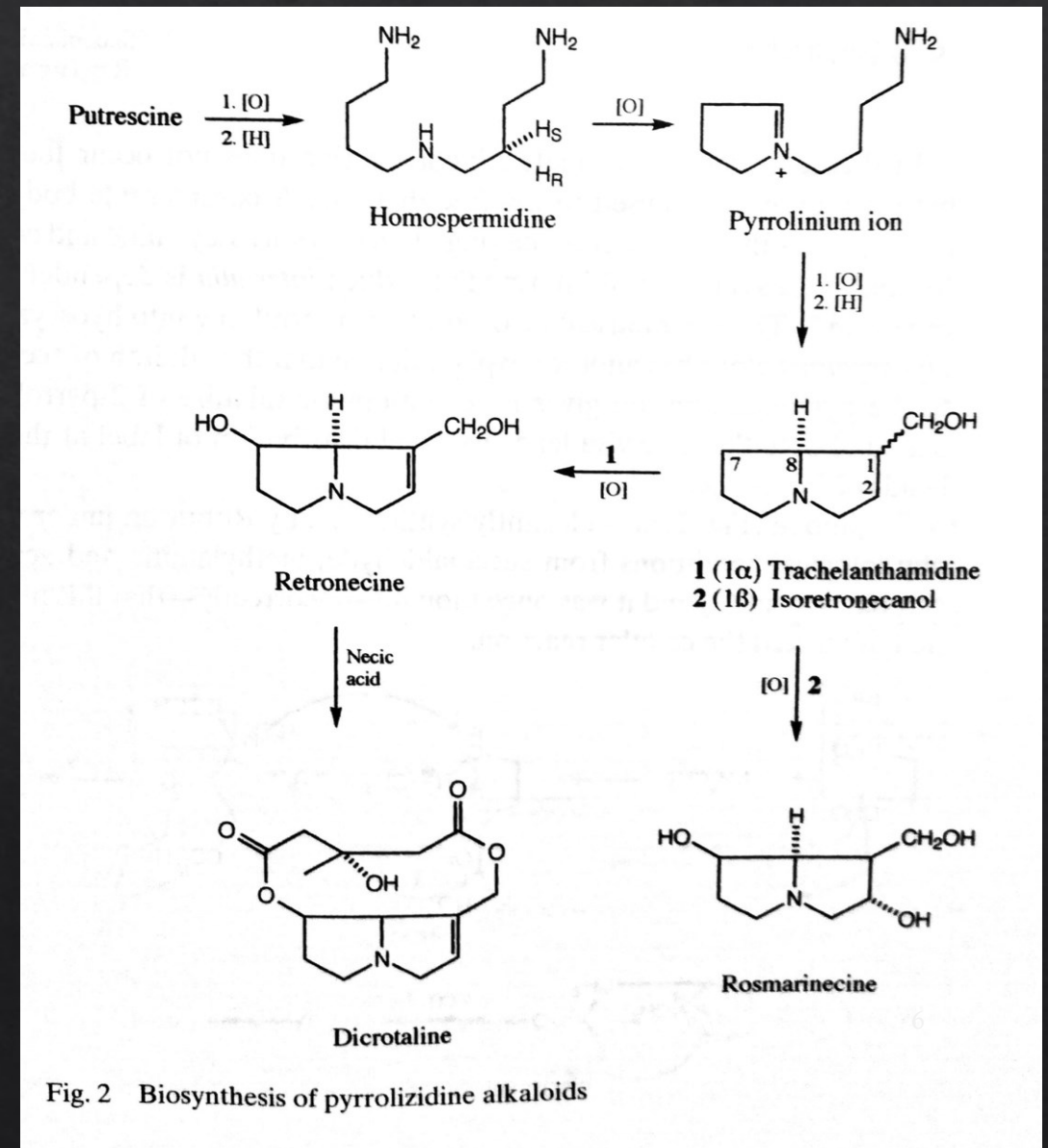
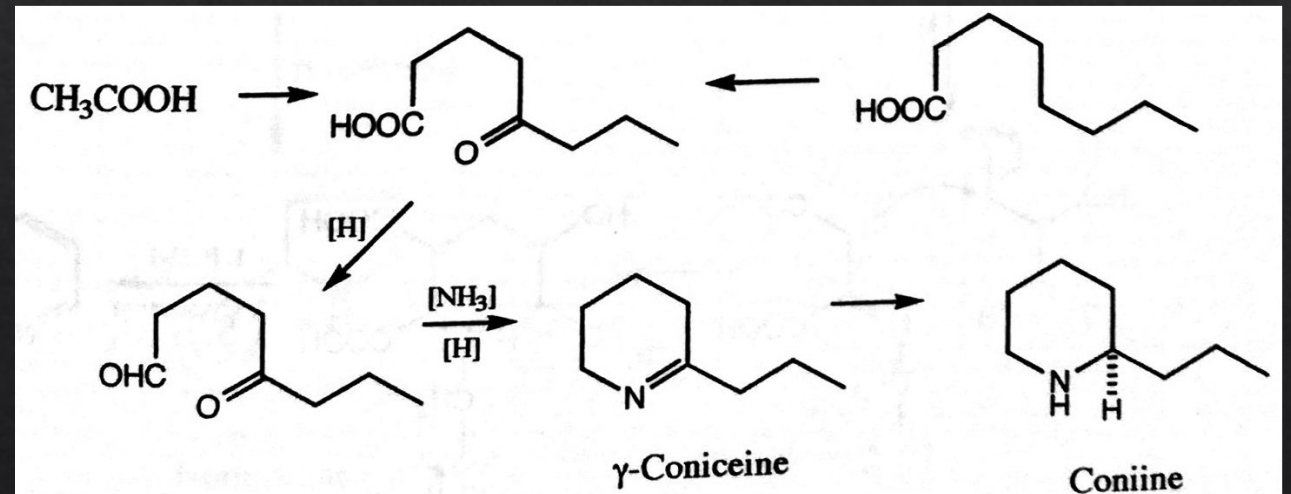
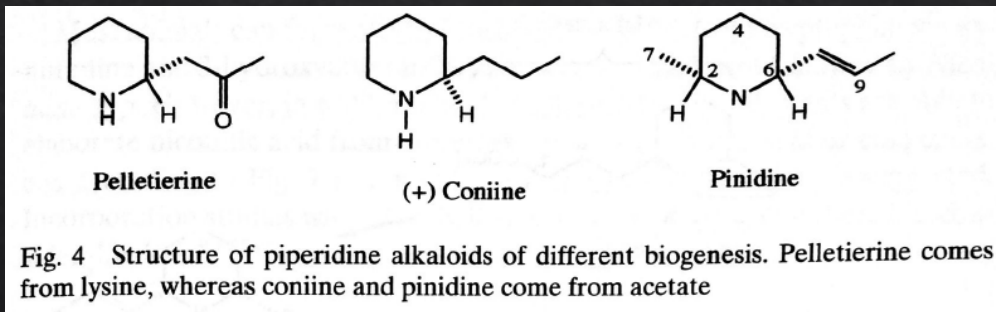


Fig. 2 Biosynthesis of pyrrolizidine alkaloids

# The pyrrolidine and piperidine alkaloids

- ◆ Pelletierine, a vermifuge, is biosynthesized from lysine, in a pathway similar to the one leading to cocaine.
- ◆ Other alkaloids similar in structure follow a completely different path:

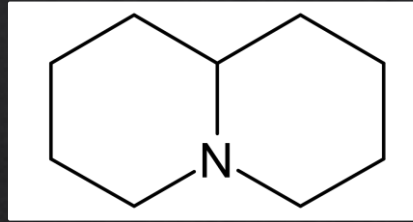


Here, the nitrogen atom doesn't come from an amino acid, but directly from ammonia



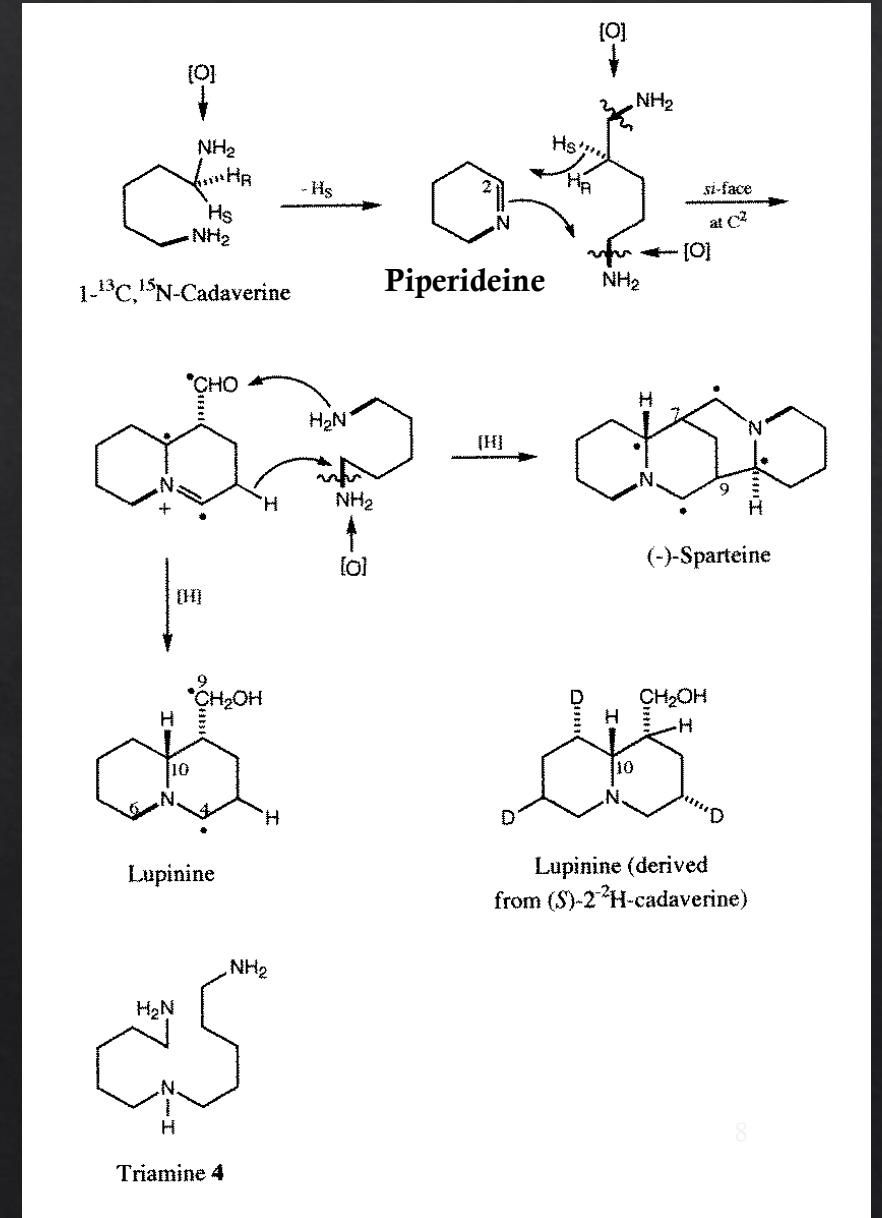
# The pyrrolidine and piperidine alkaloids

- Quinolizidine alkaloids are formed from cadaverine (coming from lysine) and piperidine.

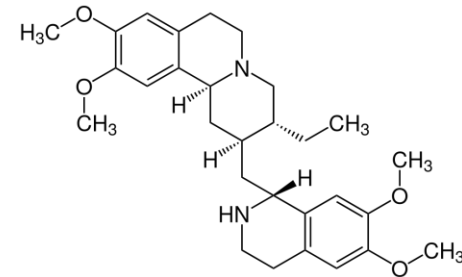
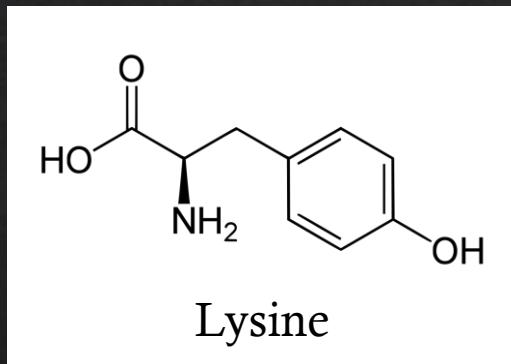


Quinolizidine

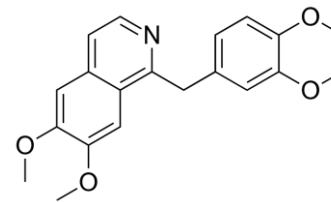
- Sparteine is an antiarrhythmic agent found in *Cytisus scoparius*.



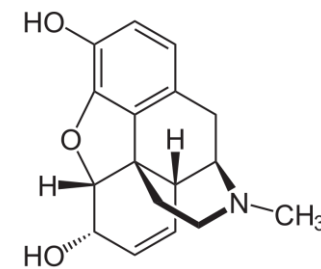
# Alkaloids derived from tyrosine



Emetine (*Carapichea ipecacuanha*)



Papaverine



Morphine



(*Papaver somniferum*)





# Alkaloids derived from tyrosine

- ◆ The rather complicated aliphatic part of emetine comes from the monoterpene loganine.
- ◆ Secologanin on the scheme comes from the oxidative fission of loganine.

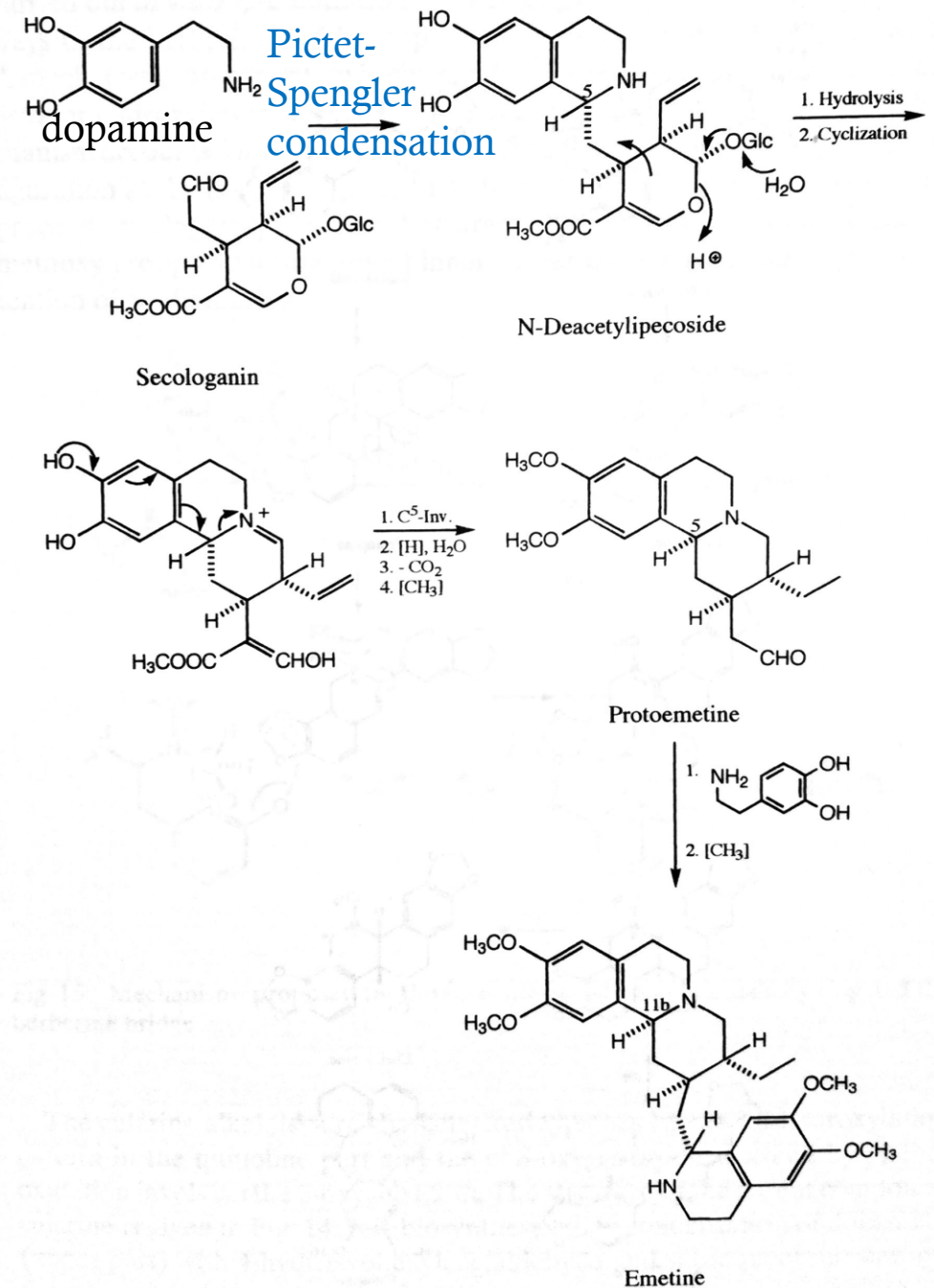
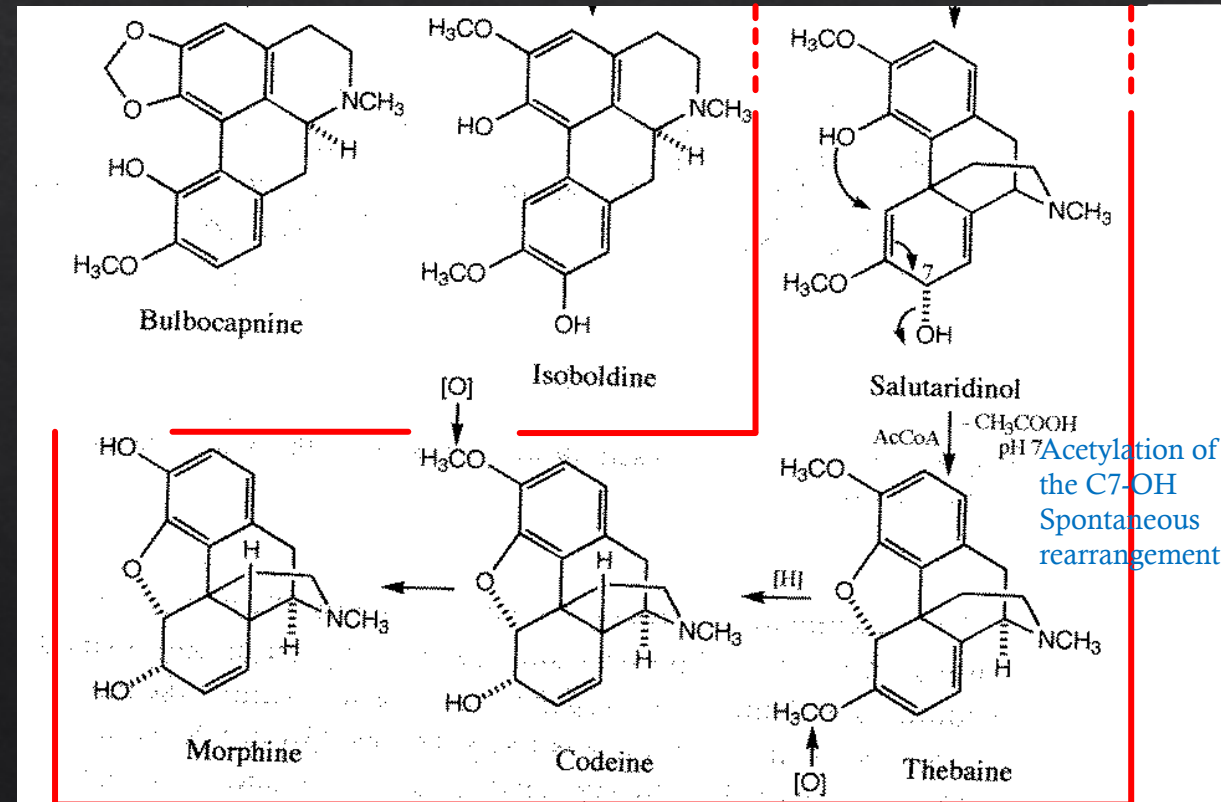
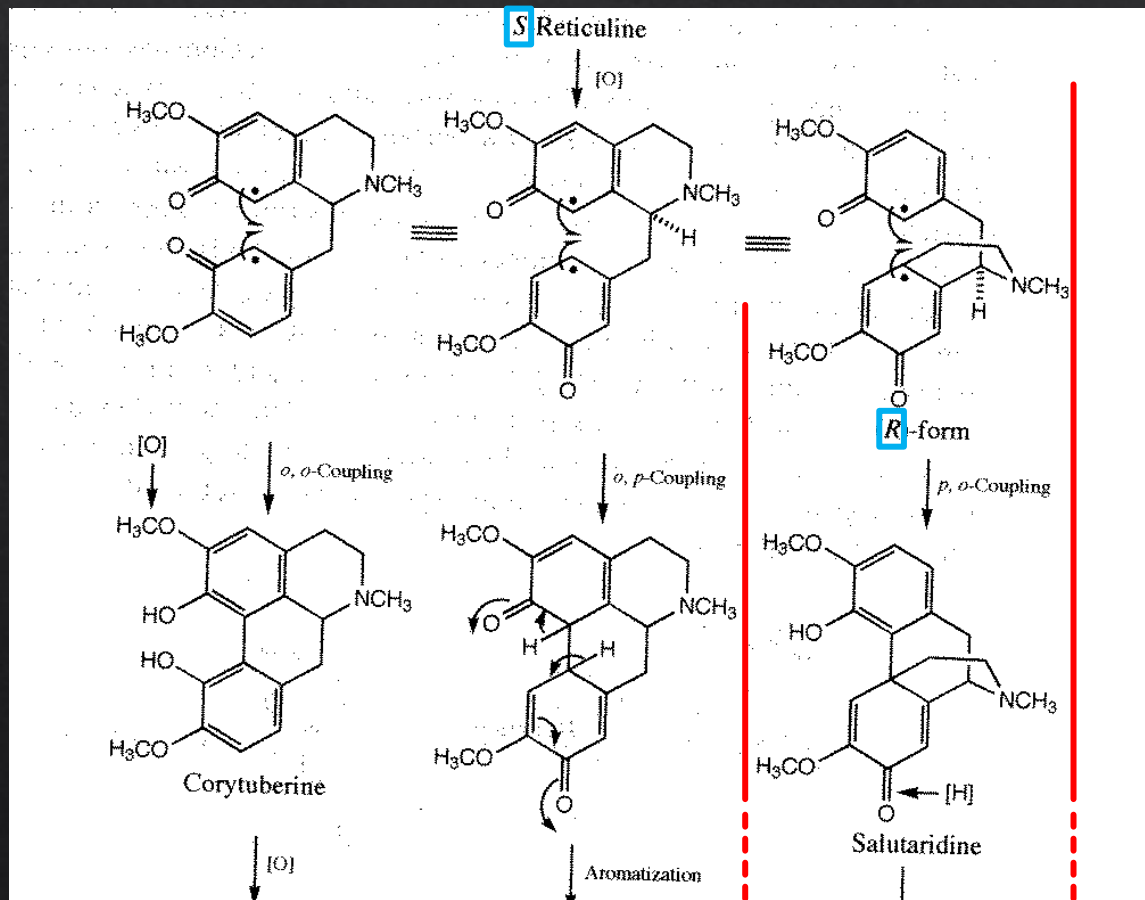


Fig. 13 Biosynthesis of emetine

# Alkaloids derived from tyrosine

◇ Morphine is biosynthesized from reticuline, which we saw two slides ago.



◇ The enzyme systems capable of converting codeine into morphine are also present in mammalian tissues





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# Chapter 8-2

# The Alkaloids

Elisabeth Jacobsen and Susanne Hansen Troøyen, NTNU

Spring 2022

# Alkaloids derived from tryptophan

- ◊ «The indole alkaloids»
- ◊ Primarily from three plant families:



*Apocynaceae*



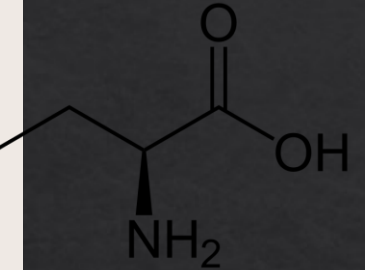
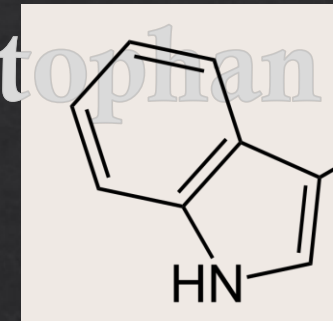
*Loganiaceae*



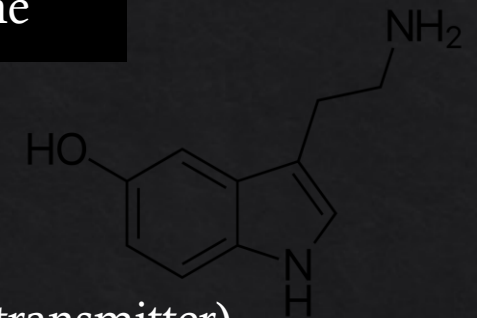
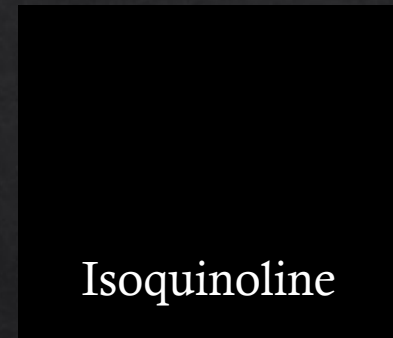
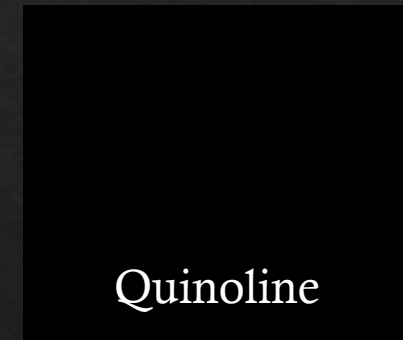
*Rubiaceae*

- ◊ Neurophysiological action
- ◊ Sometimes the indole nucleus is modified

Indole



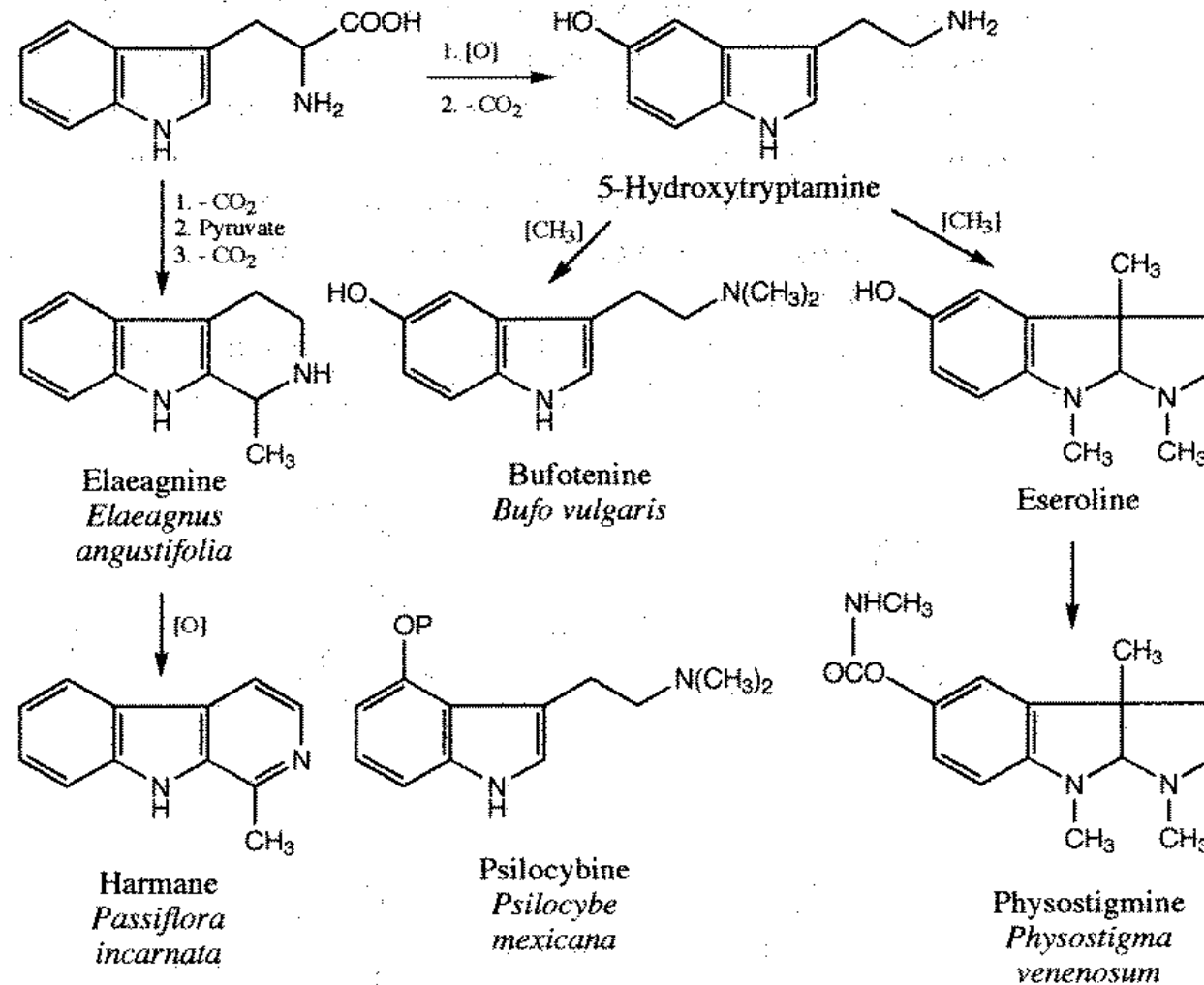
Tryptophan



Serotonin (neurotransmitter)

# Alkaloids derived from tryptophan

Biosynthesis of some simple tryptophan alkaloids:

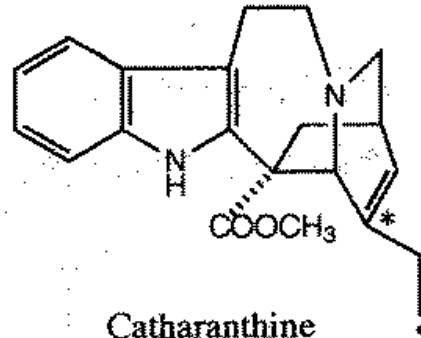




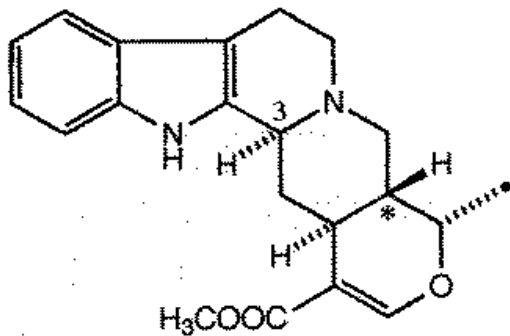


# Alkaloids derived from tryptophan

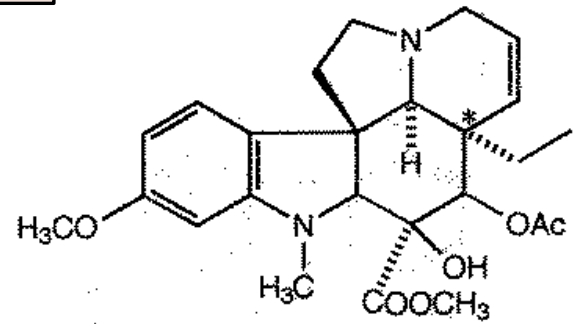
Where does the aliphatic part of more complex indole alkaloids come from?



Catharanthine  
*Iboga type*



Ajmalicine  
*Corynanthe type*



Vindoline  
*Aspidosperma type*

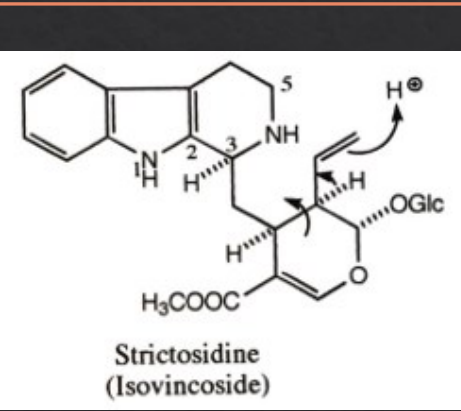
Monoterpene hypothesis:

Mevalonate (in the form of geranyl phosphate) is incorporated to give a variety of indole alkaloids

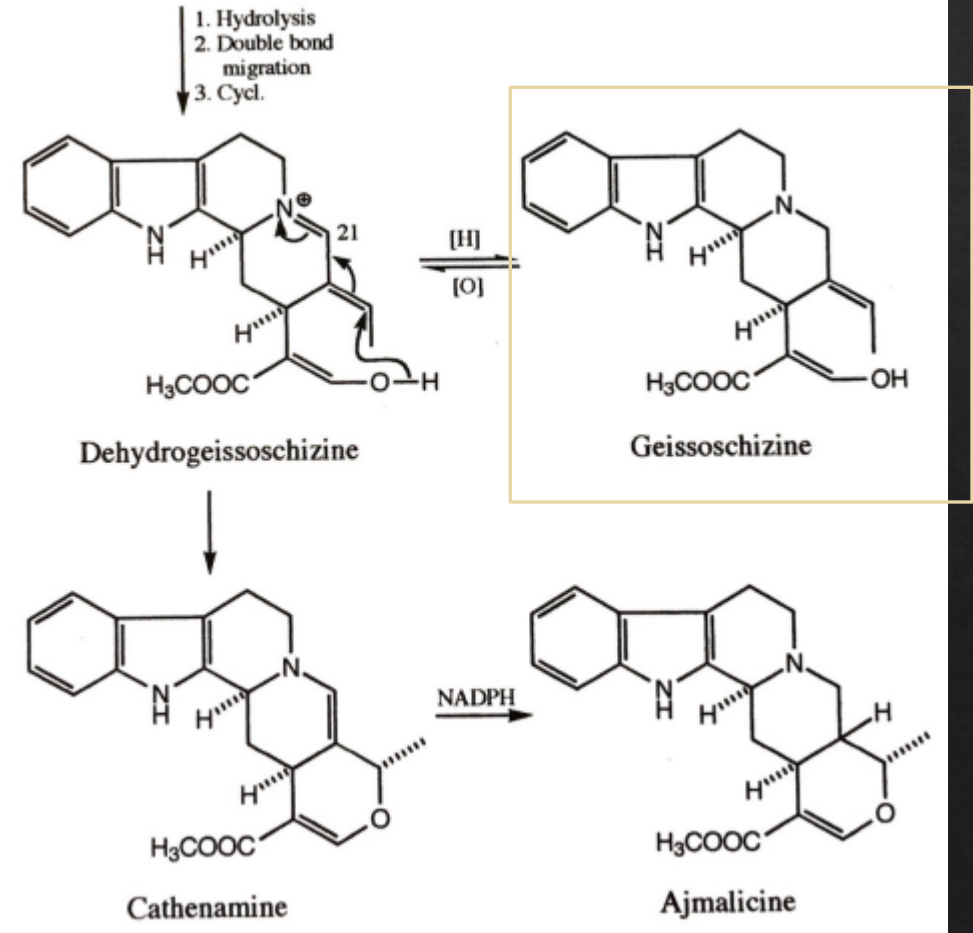
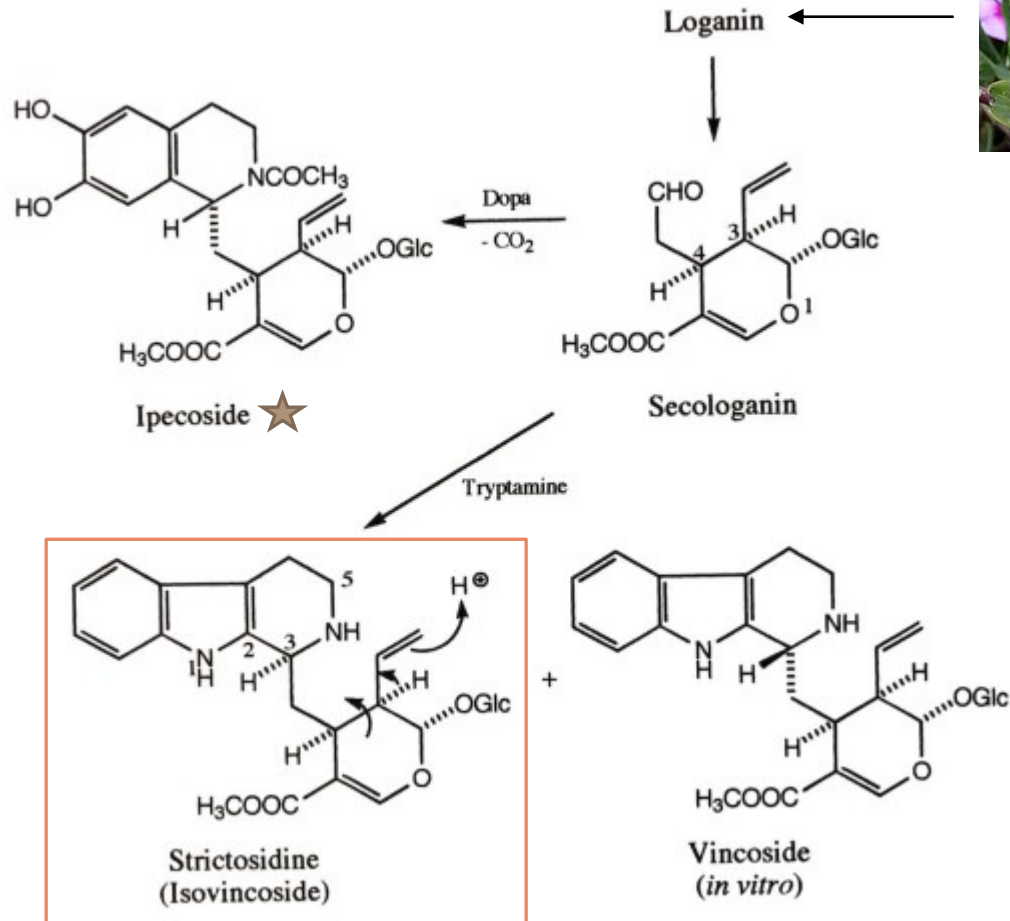
Proved by incorporating <sup>13</sup>C labelled geranyl phosphate

# Alkaloids derived from tryptophan

*Catharanthus roseus*



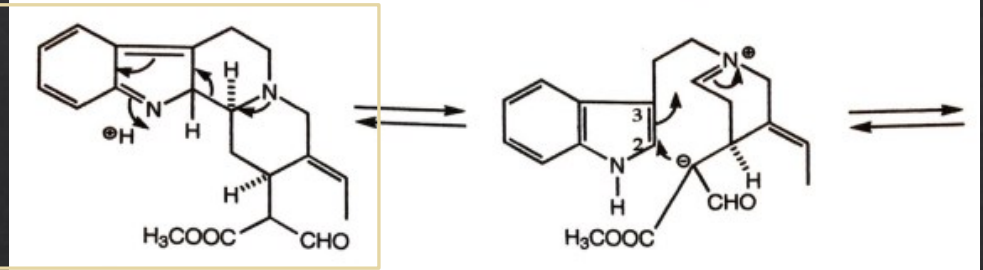
Strictosidine is a «universal intermediate» in the biosynthesis of indole alkaloids



antihypertensive drug

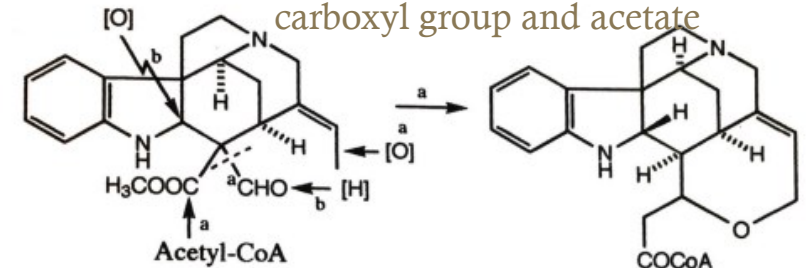
# Alkaloids derived from tryptophan

◆ Geissoschizine is also an important intermediate

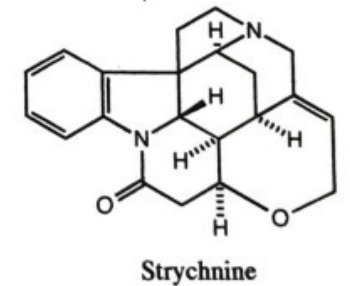


(Geissoschizine, tautomeric form)

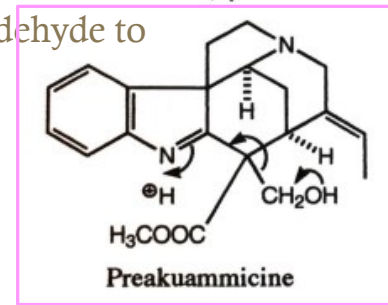
Condensation between carboxyl group and acetate



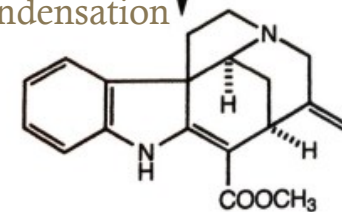
Reduction and cyclization



Oxidation gives double bond  
Reduction of aldehyde to alcohol



Retroaldol condensation  $-CH_2O$



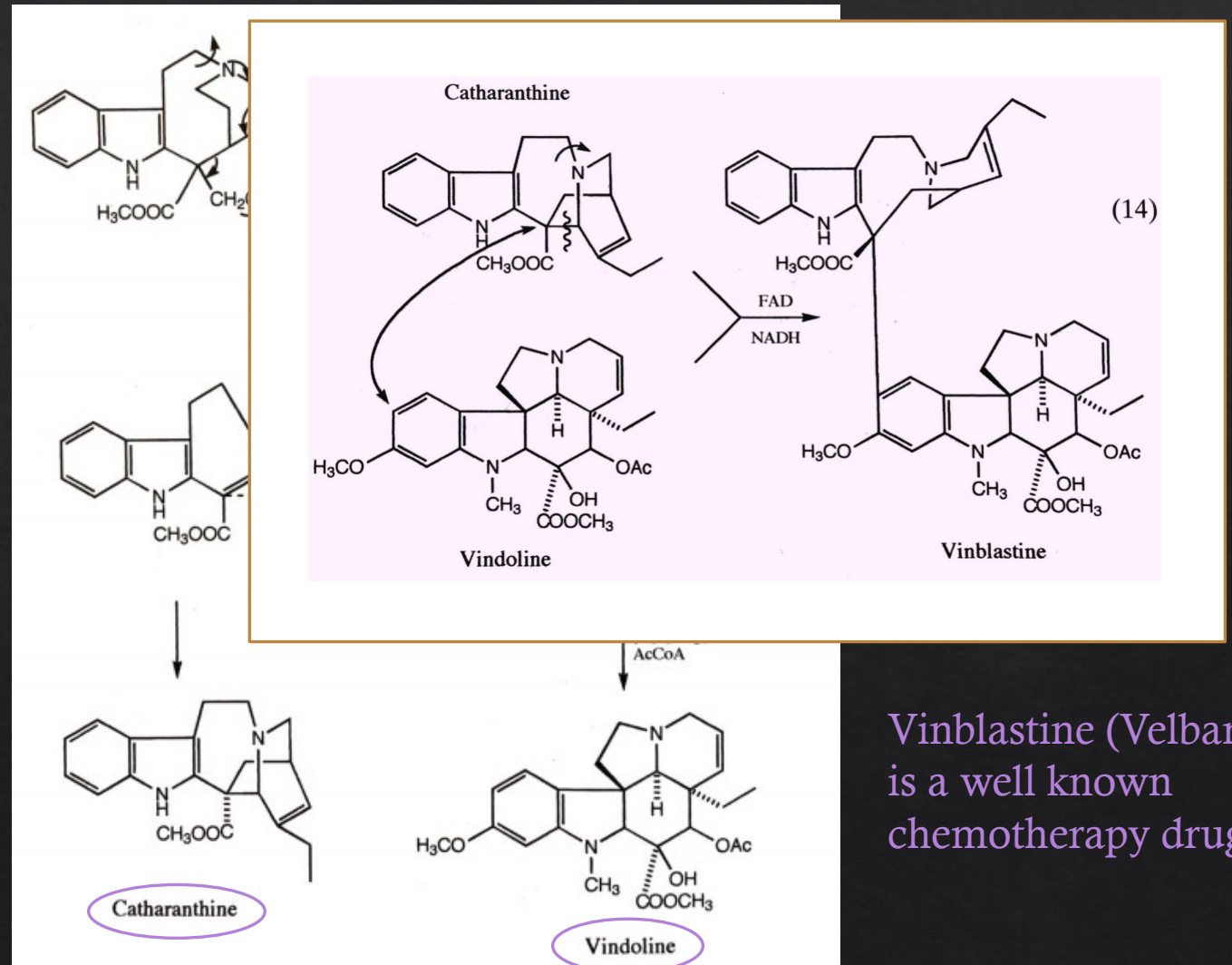
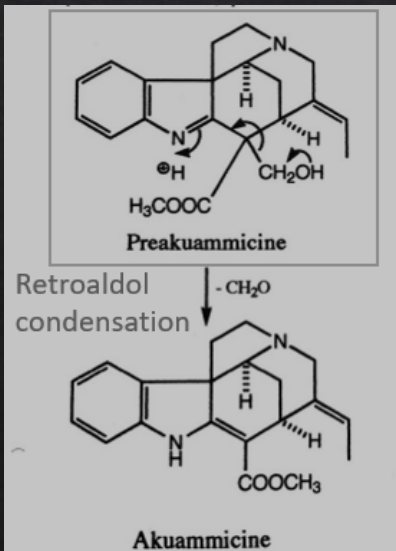
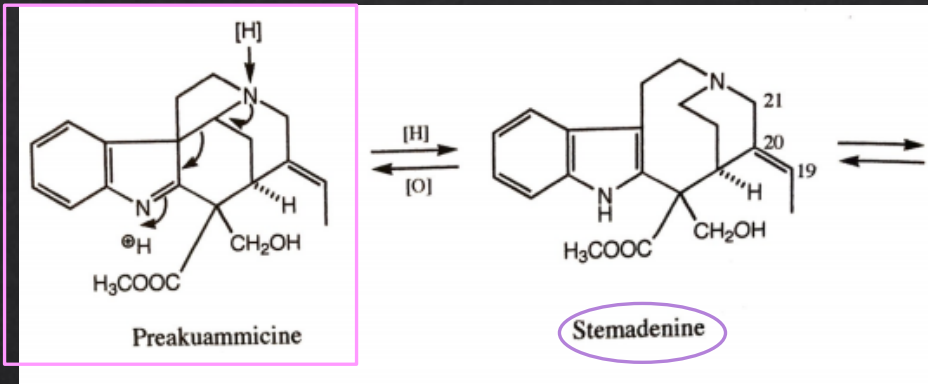
Akuammicine

(Toxic)





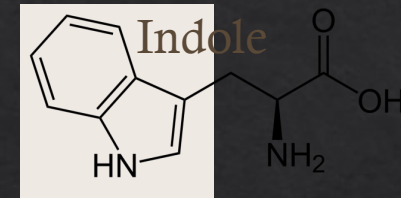
# Alkaloids derived from tryptophan



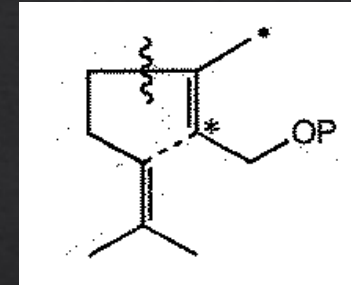
Vinblastine (Velban) is a well known chemotherapy drug

# Summary of tryptophan (indole) alkaloids

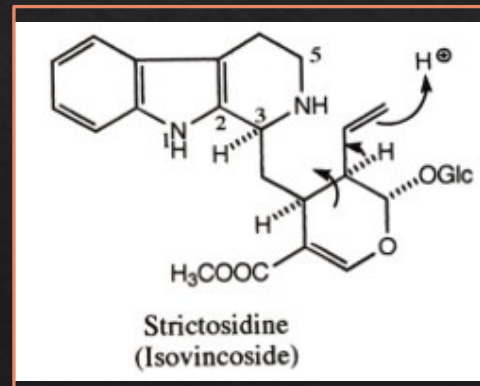
- ◇ Indole part comes from tryptophan
- ◇ Rest comes from mevalonic acid as geranyl phosphate
- ◇ Important intermediates:
  - ◇ Strictosidine
  - ◇ Geissoschizine
  - ◇ Prekuammicine



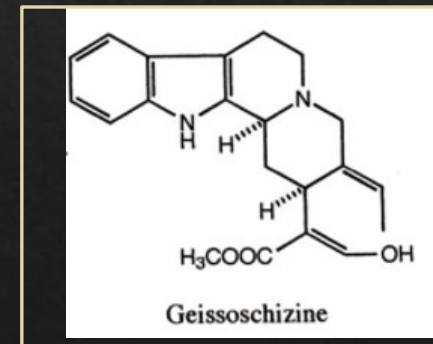
Tryptophan



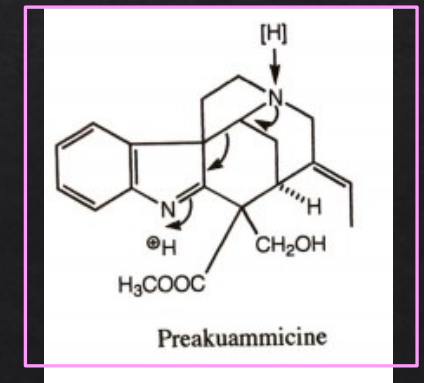
Geranyl phosphate



Strictosidine  
(Isovincoside)

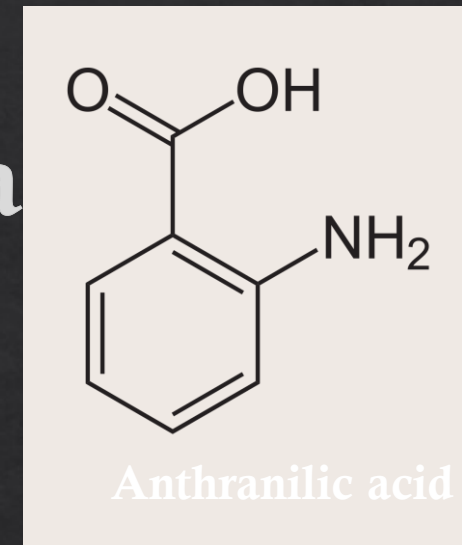


Geissoschizine

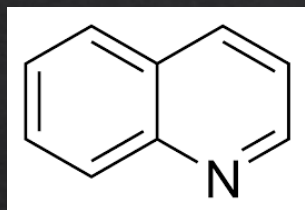


Prekuammicine

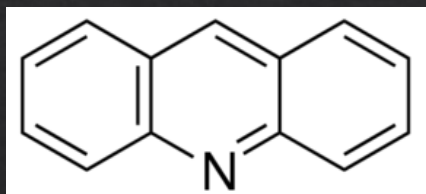
# Alkaloids derived from anthranilic acid



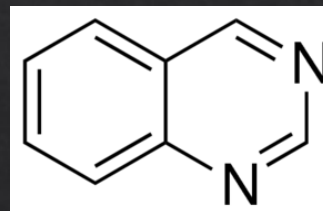
- ◆ Quinoline, acridine and quinazoline skeletons



Quinoline



Acridine



Quinazoline

- ◆ Anthranilic acid comes from shikimic acid, and is a precursor to tryptophan



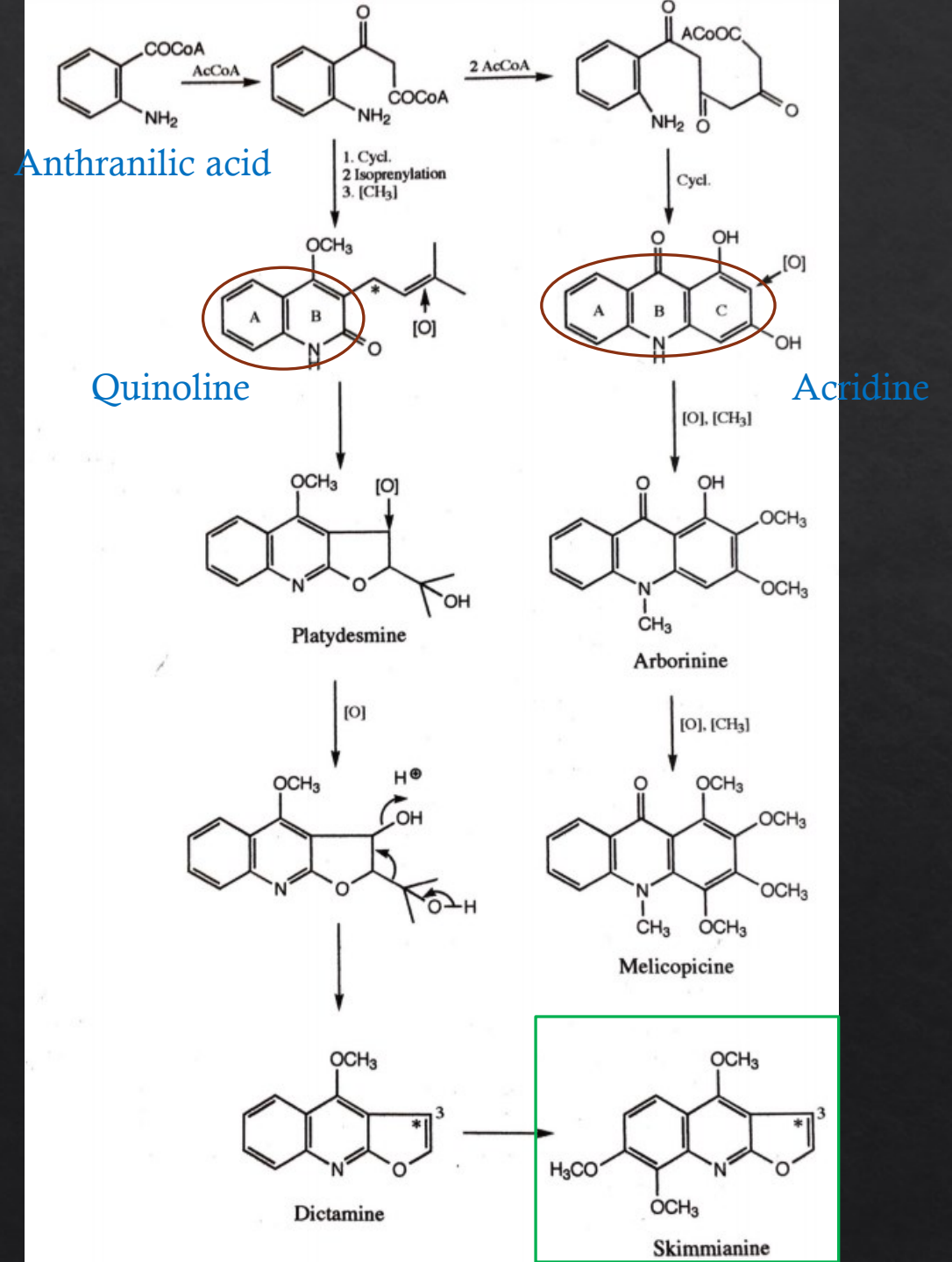
Often found in the *Rutaceae* (rue) family



# Alkaloids derived from anthranilic acid

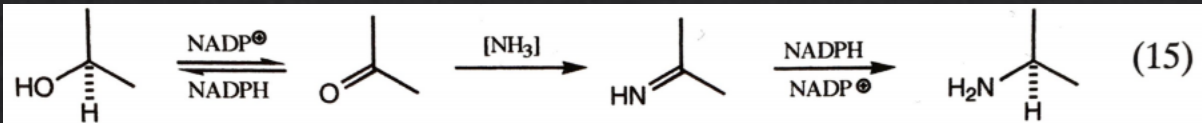
## The skimmianine alkaloids

1. Activation of the anthranilic acid with acetyl CoA
2. Chain elongation with acetyl or malonyl CoA.
3. Cyclization gives quinoline and acridine skeletons
4. Further derivatization



# Terpene derived alkaloids

## ◇ Amination of terpenes/terpenoids



Redox process (oxidation, amination, reduction)



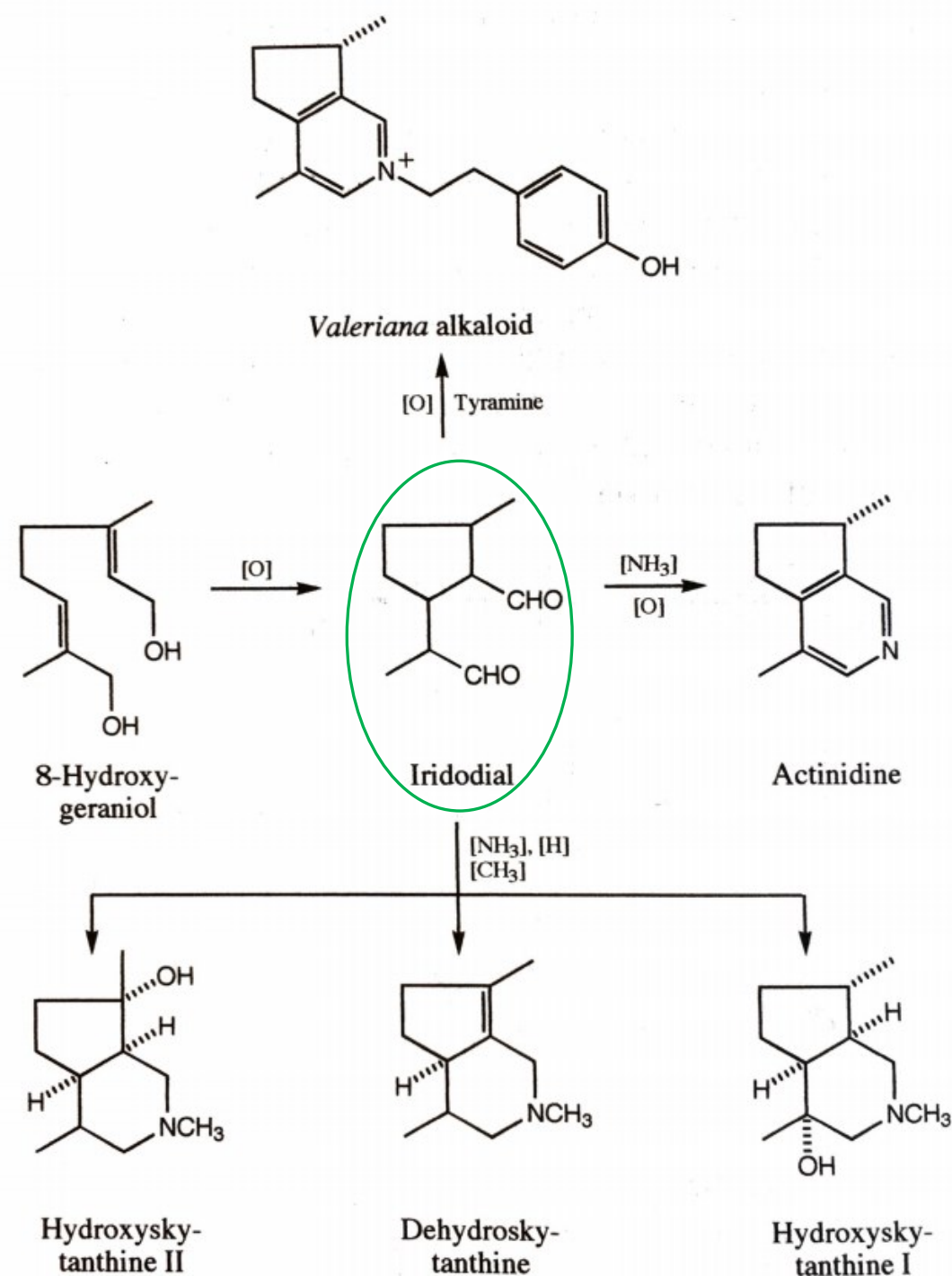
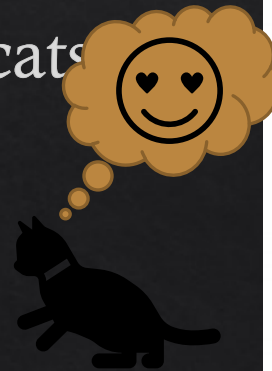
Substitution



Addition

# Terpene derived

- ◆ Many monoterpene alkaloids are derived from iridoids of varying oxidation levels
- ◆ *Valeriana officinalis* and *Actinidia polygama* attract cats because they contain specific monoterpenoids and alkaloids
- ◆ Actinidine affects the EEG of cats

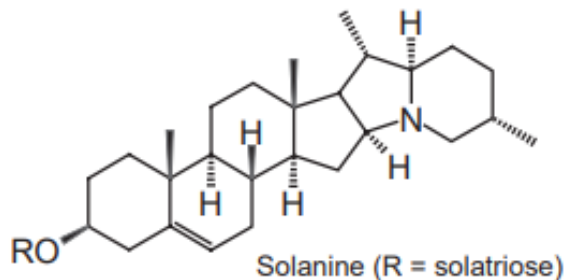




# Terpene derived alkaloids

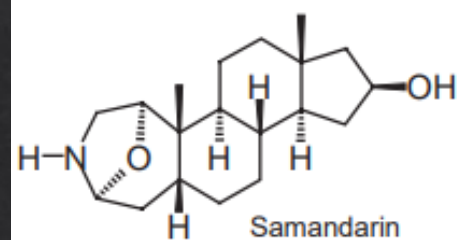
## STEROID ALKALOIDS

- Metabolites of *Solanaceae*, *Liliaceae* and *Buxaceae* families



Found in nightshades  
Very toxic  
Used in pesticides, asthma treatment and for common cold

«Symptoms include nausea, diarrhoea, vomiting, stomach cramps, burning of the throat, headaches and dizziness. Other adverse reactions, in more severe cases, include hallucinations, loss of sensation, paralysis, fever, jaundice, dilated pupils and hypothermia. Solanine overdose can be fatal.»



Found in the skin of the fire salamander (*Salamandra salamandra*)

Extremely toxic, causes strong muscle convulsion (shaking) and hyperventilation in vertebrates



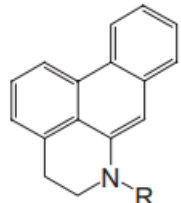
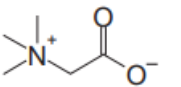
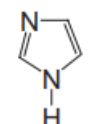
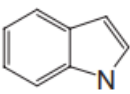
*Solanaceae* (nightshades)

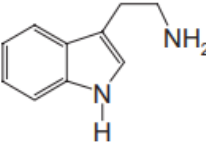
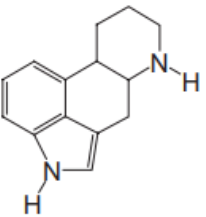


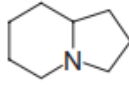
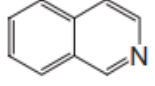
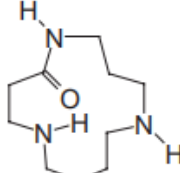
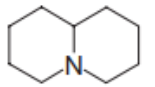
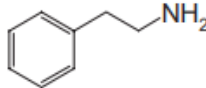
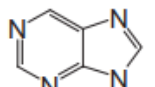
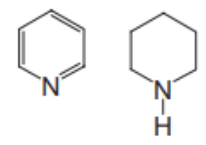
*Liliaceae* (lily family)

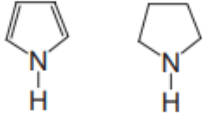
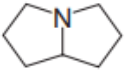
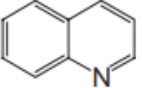
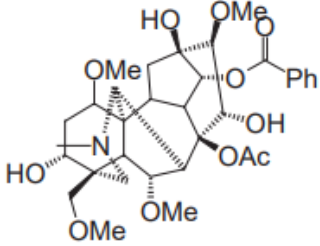
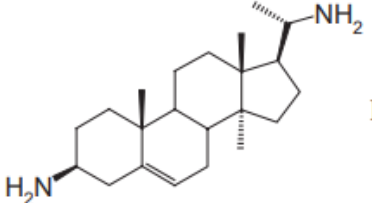
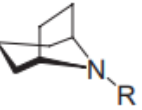


*Buxaceae* (box family)

Class/structural types	Generic structure	Examples
Aporphine (Tyrosine derived)	 <p>Aporphine R = Me Noraporphine R = H</p>	Boldine
Betaines	 <p>Betaine</p>	Choline, muscarine and neurine
Imidazole	 <p>Imidazole</p>	Pilocarpine
Indole (Tryptophan derived)	 <p>Indole</p>	

Tryptamines	 <p>Tryptamine</p>	Moschamine, moschamindole, psilocybin and serotonin
Ergolines	 <p>Ergoline</p>	Ergine, ergotamine and lysergic acid

Class/structural types	Generic structure	Examples
Indolizidine	 <p>Indolizidine</p>	Swainsonine and castanospermine
Isoquinoline (Tyrosine derived)	 <p>Isoquinoline</p>	Codeine, berberine, morphine, papaverine, sanguinarine and thebaine
Macrocyclic spermines and spermidines	 <p>Spermine</p>	Celabenzine
Norlupinane (Lysine derived)	 <p>Norlupinane</p>	Cytisine and lupanine
Phenethylamine (Phenylalanine derived)	 <p>Phenylethylamine</p>	Ephedrine and mescaline
Purine	 <p>Purine</p>	Caffeine, theobromine and theophylline
Pyridine and (Nicotinic acid derived)	 <p>Pyridine Piperidine</p>	Arecoline, coniine, nicotine, piperine, sparteine and trigonelline

Class/structural types	Generic structure	Examples
Pyrrole and pyrrolidine (Ornithine derived)	 Pyrrole      Pyrrolidine	Hygrine, cuscohygrine and nicotine
Pyrrolizidine	 Pyrrolizidine	Echimidine and symphitine
Quinoline (Tryptophan/anthranilic acid derived)	 Quinoline	Cinchonine, brucine, quinine and quinidine
Terpenoidal/steroidal Terpenoidal	 Aconitine	Aconitine
Steroidal	 Steroidal alkaloid	Batrachotoxin, conanine, irehdiamine A, solanine, samandarine and tomatillidine
Tropane (Ornithine derived)	 Tropane R = Me Nortropane R = H	Atropine, cocaine, ecgonine, hyoscyne and scopolamine



Iceland   
Liechtenstein  
Norway grants

“Working together for a green,  
competitive and inclusive Europe”

**GREENCAM for tomorrow**



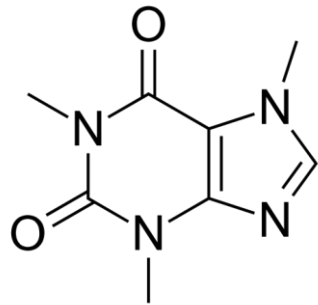
# Chapter 9: N-Heteroaromatics

Elisabeth Jacobsen and Lucas Boquin, NTNU

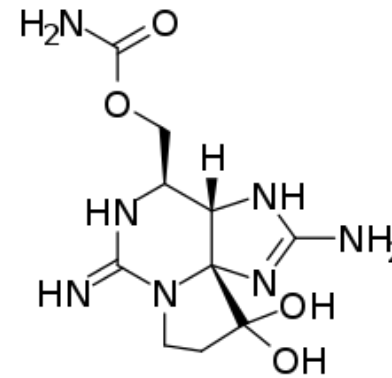
Spring 2022

# N-Heteroaromatics

- ◆ A lot of N-heteroaromatics are essential for life and reproduction, and are part of the primary metabolism.
- ◆ Some N-heteroaromatics are products of the secondary metabolism, such as caffeine, and saxitoxin



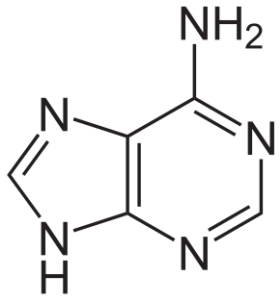
Caffeine



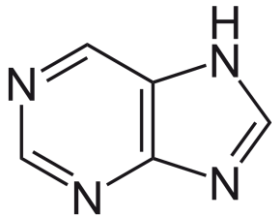
Saxitoxin

Fatally poisonous toxin produced by some algae, and occasionally accumulated in clams and shellfishes

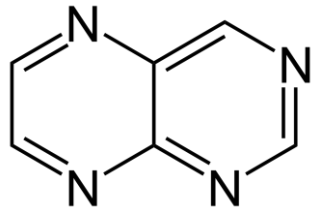
# N-Heteroaromatics



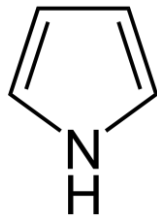
Pyrimidine



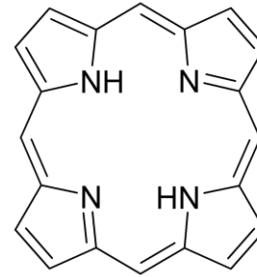
Purine



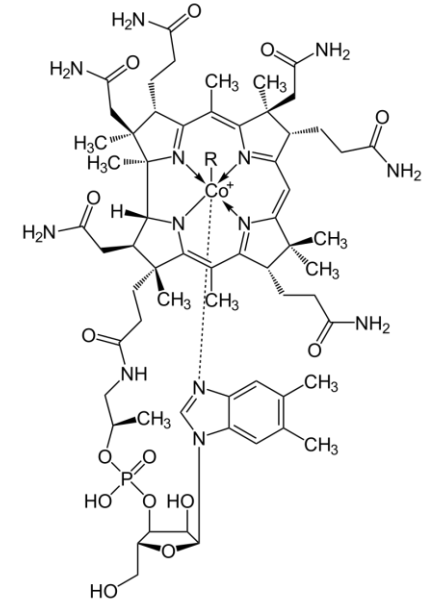
Pteridine



Pyrrole



Porphin



Cobalamin (vitamin B12)

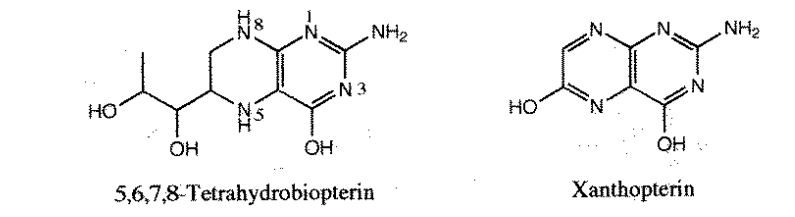
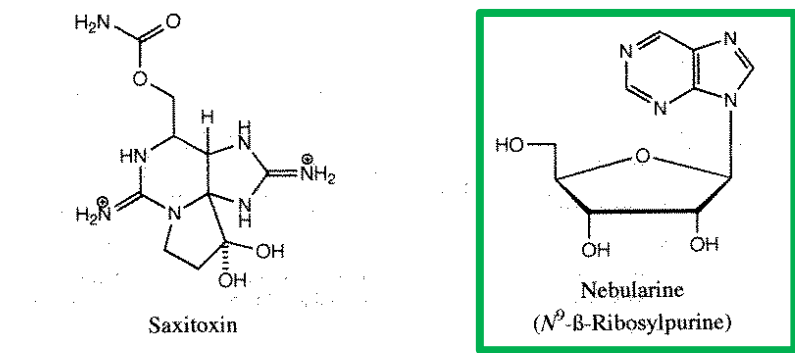
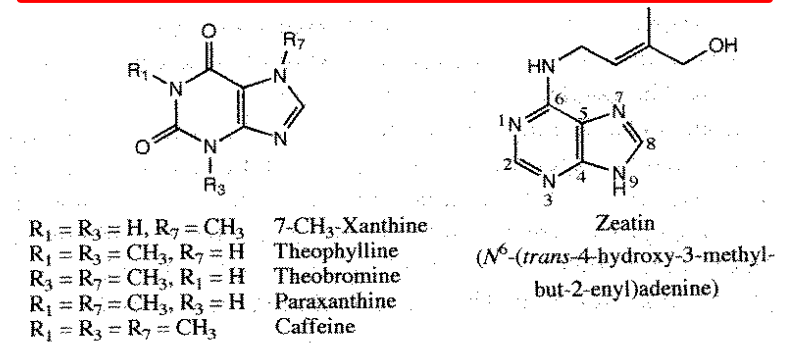
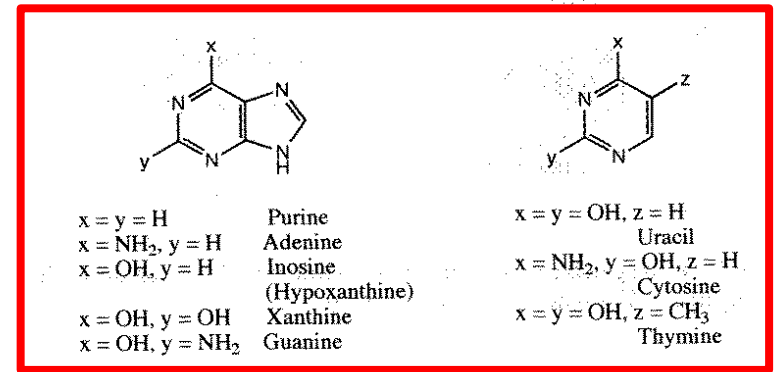


# Pyrimidines, purines and pteridines

- ◆ The major bases in RNA and DNA are purine derivatives (adenine, guanine, cytosine, uracil (only in RNA), thymine (only in DNA)...)
- ◆ The free bases are only present in trace amounts in the cells.
- ◆ In some fungi, nucleosides are produced in larger quantities and have antibiotic properties (such as nebularine)

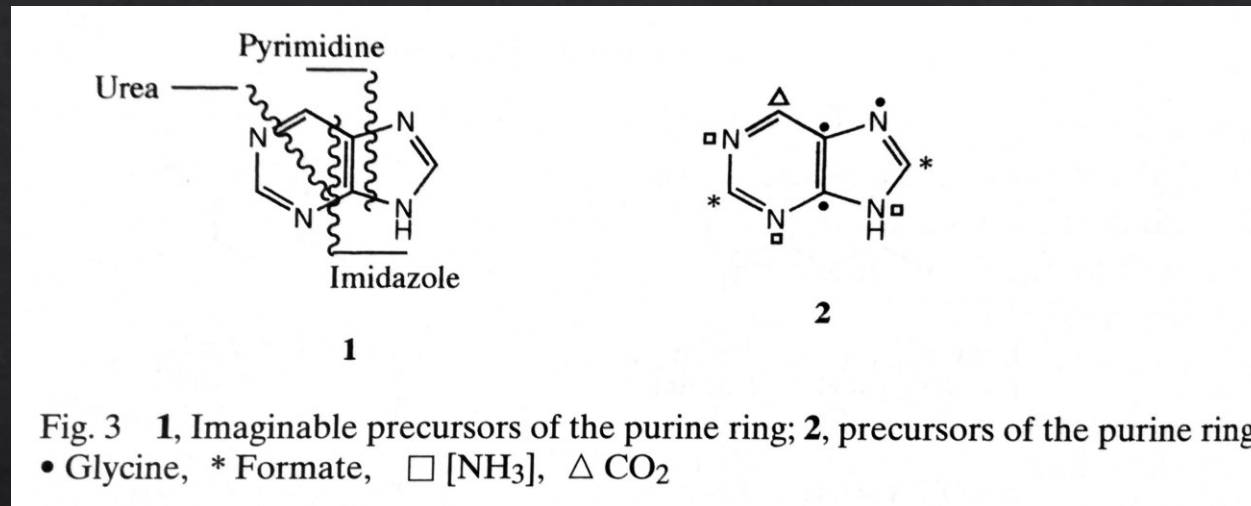


*Clitocybe nebularis*



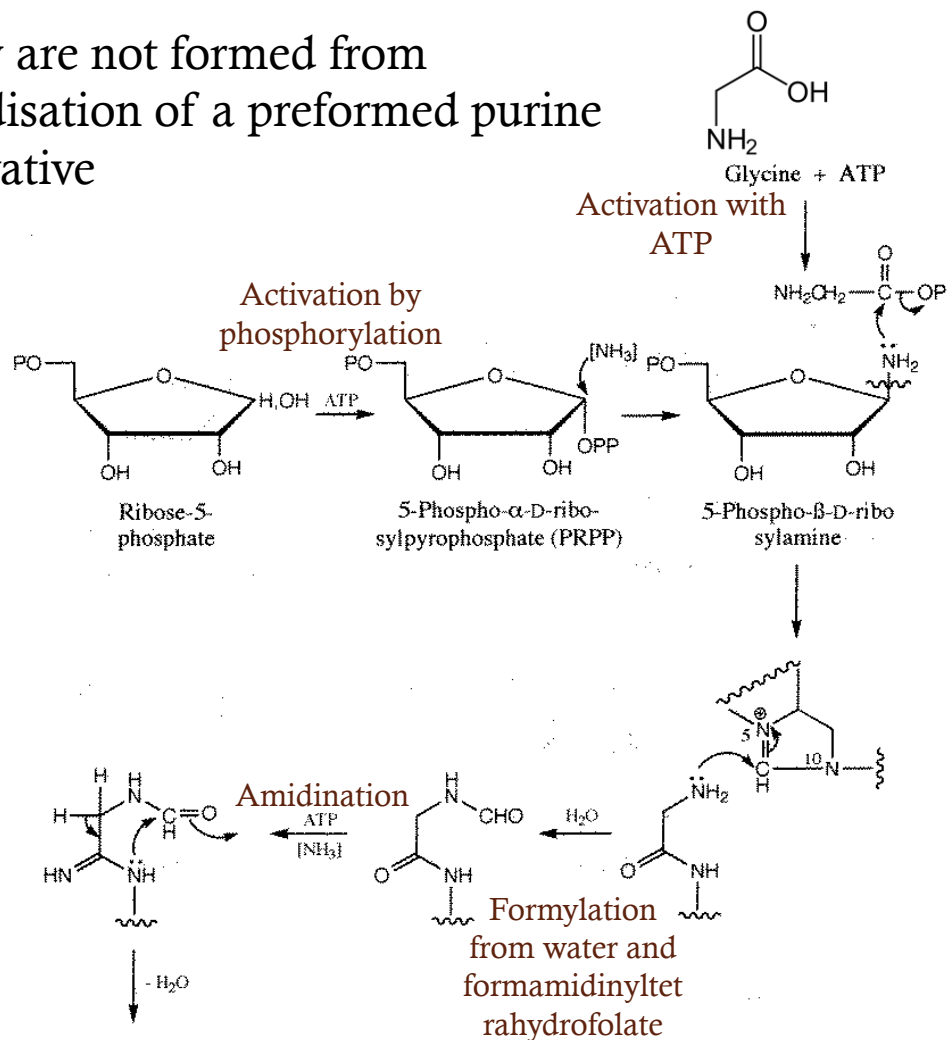
# Biosynthesis of purines

- ◇ This biosynthesis shows, again, that structural information can be misleading when finding the natural synthesis pathway.

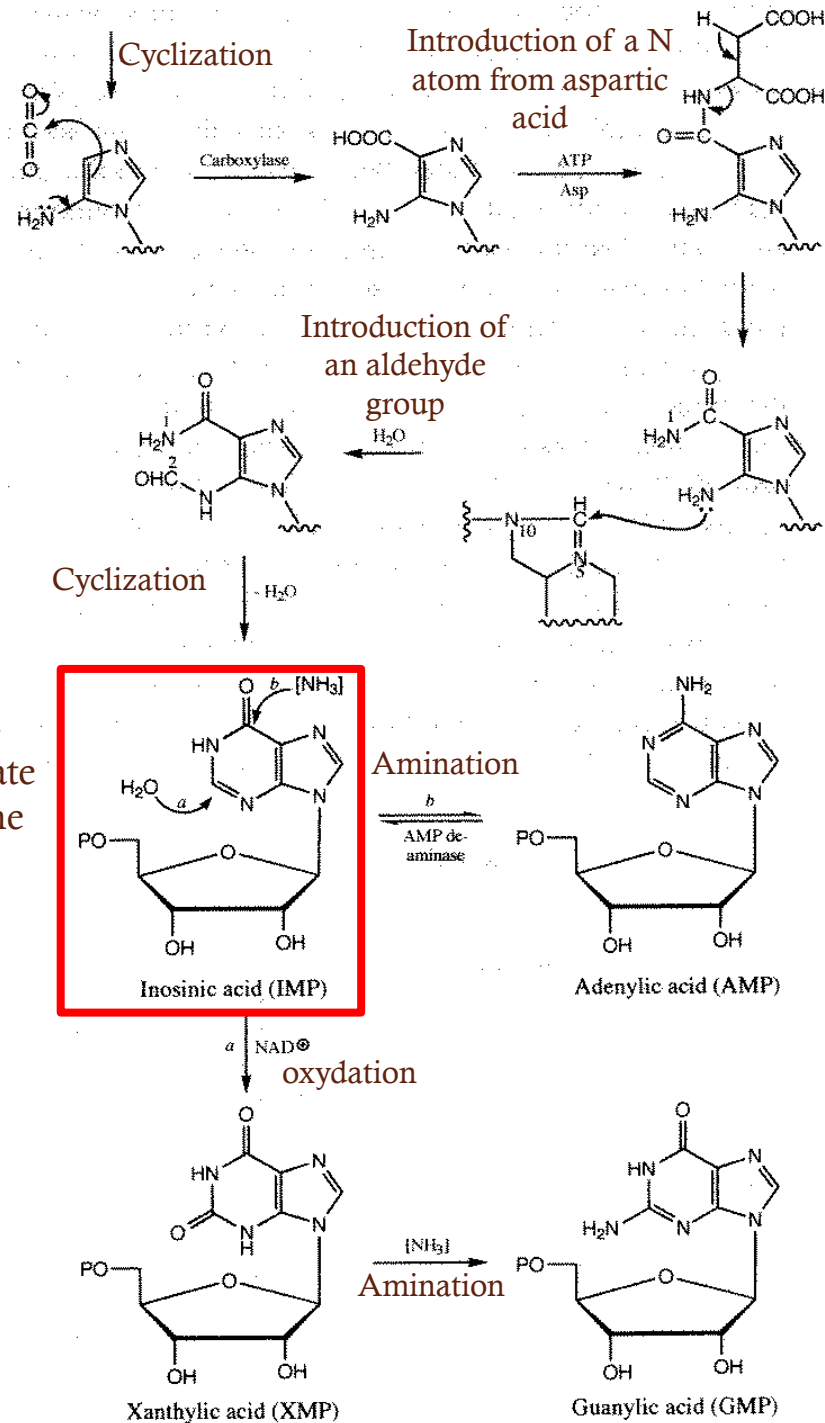


# Biosynthesis of purine nucleotides

They are not formed from ribodisation of a preformed purine derivative

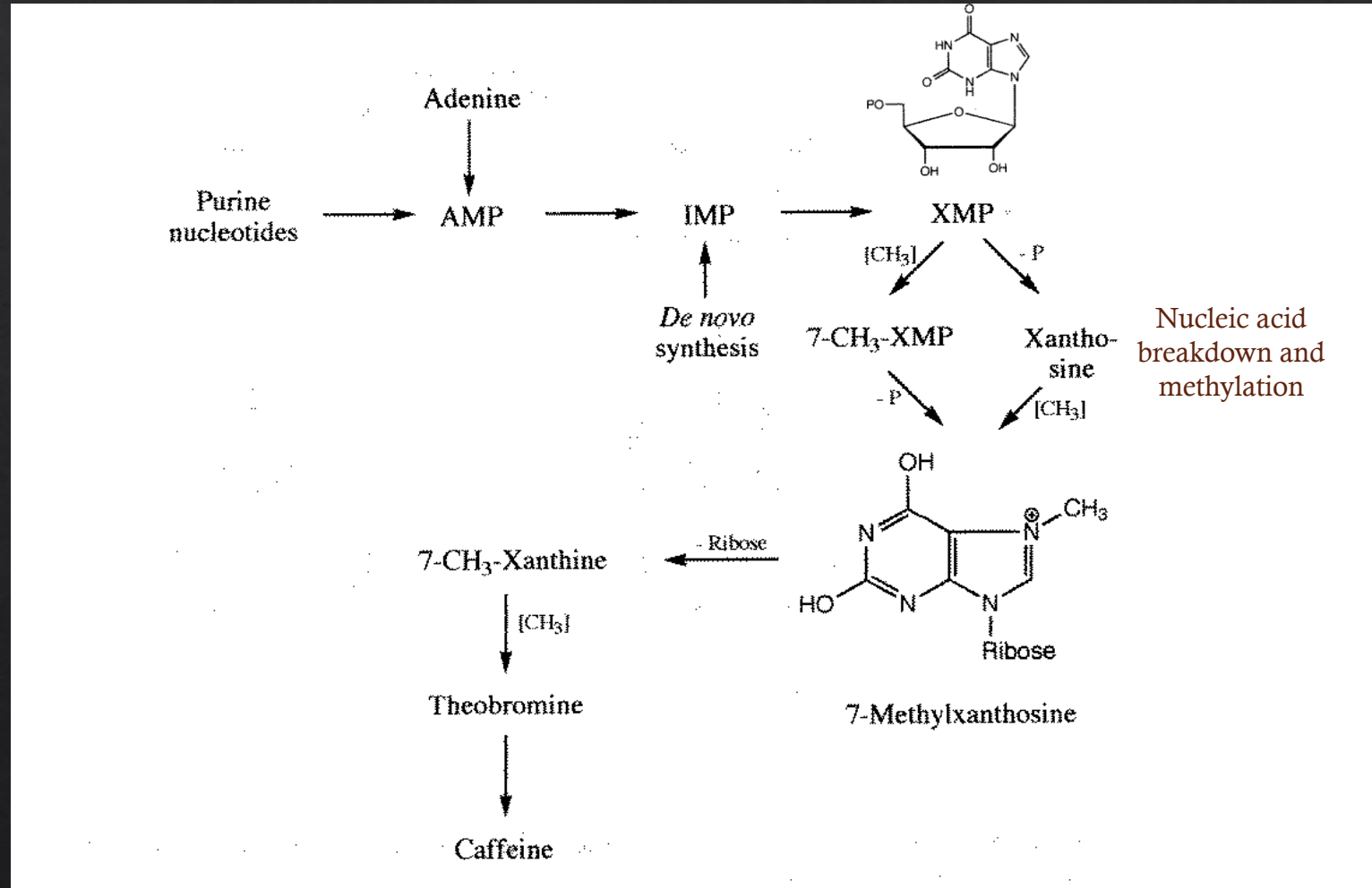


Key intermediate for other purine nucleotides



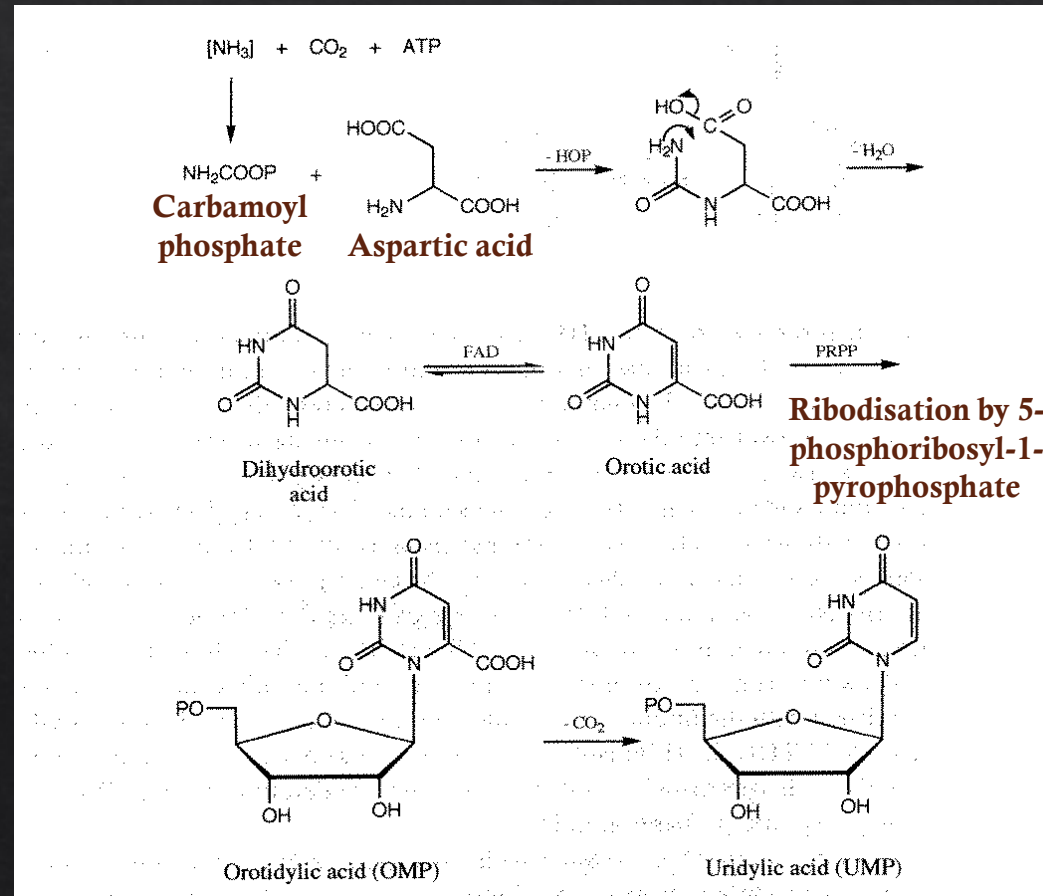


# Biosynthesis of purine alkaloids



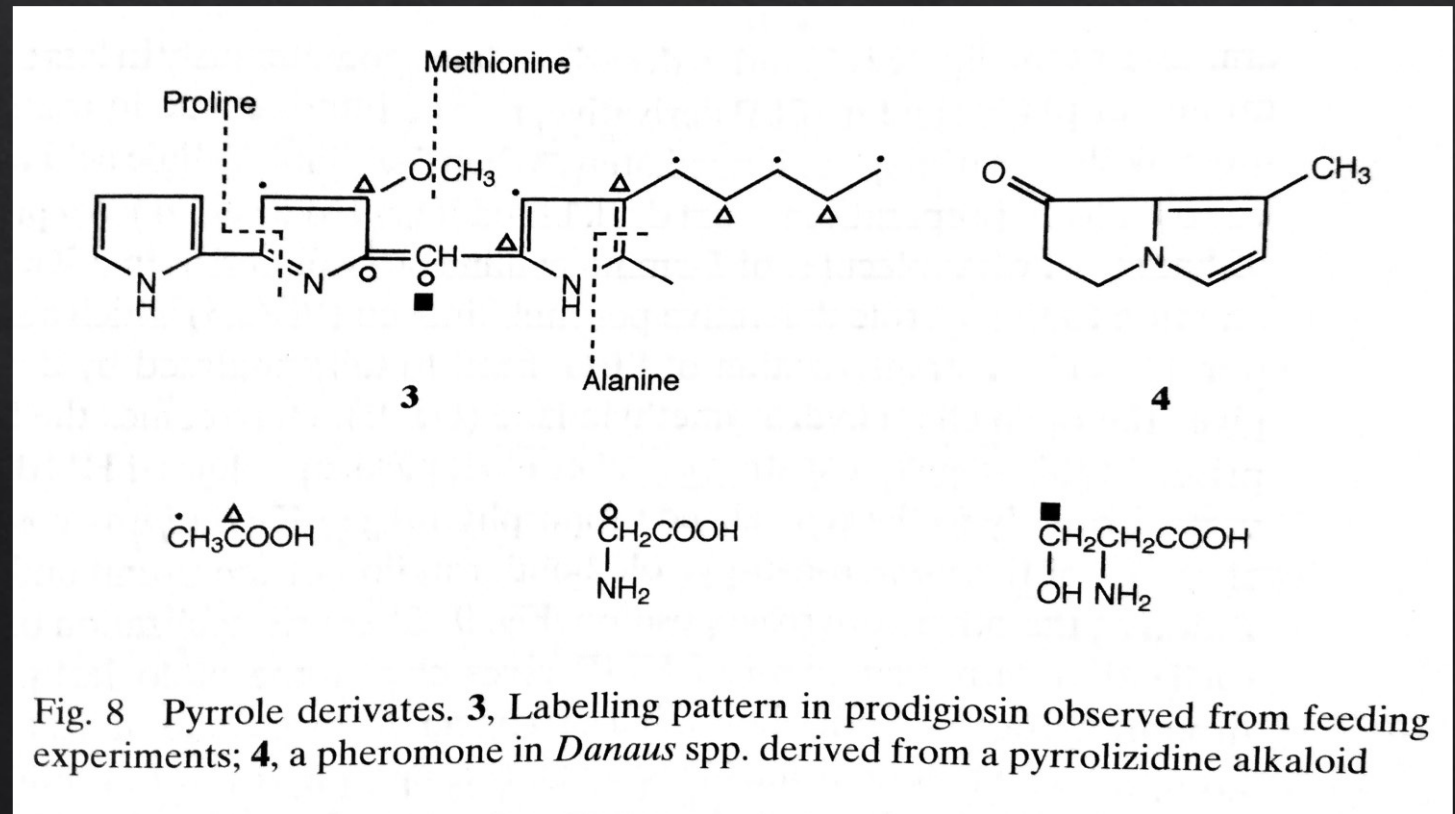
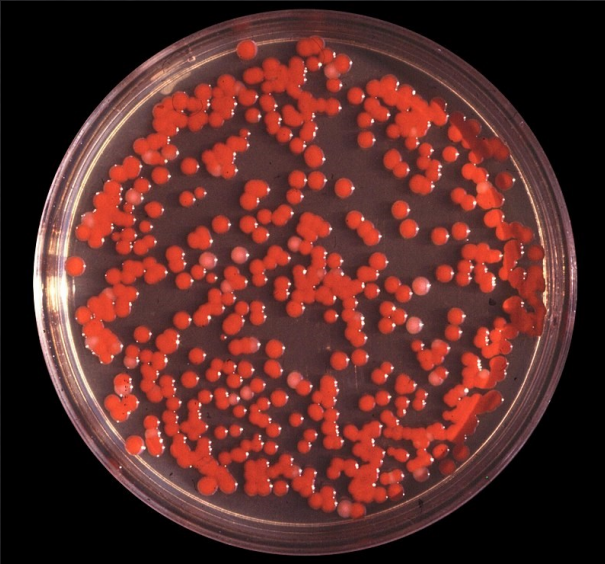
# Biosynthesis of pyrimidine nucleotides

- Pyrimidine nucleotides are formed from ribodisation of a preformed pyrimidine derivative, and has a simpler biosynthesis.



# Pyrroles and porphyrins

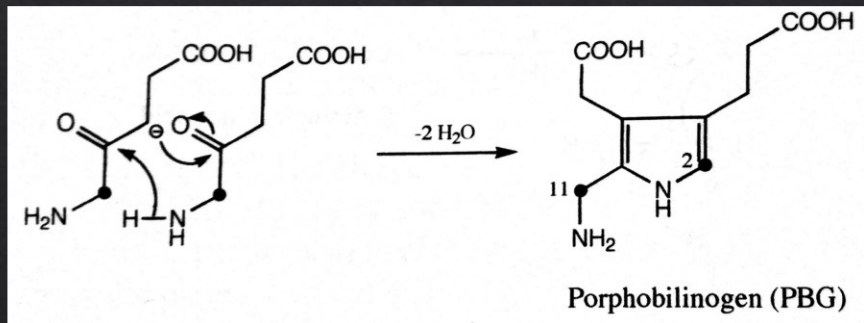
- ◇ Pyrrole derivatives are rare in nature. An example is prodigiosin, produced by the bacteria *Serratia marcescens*.



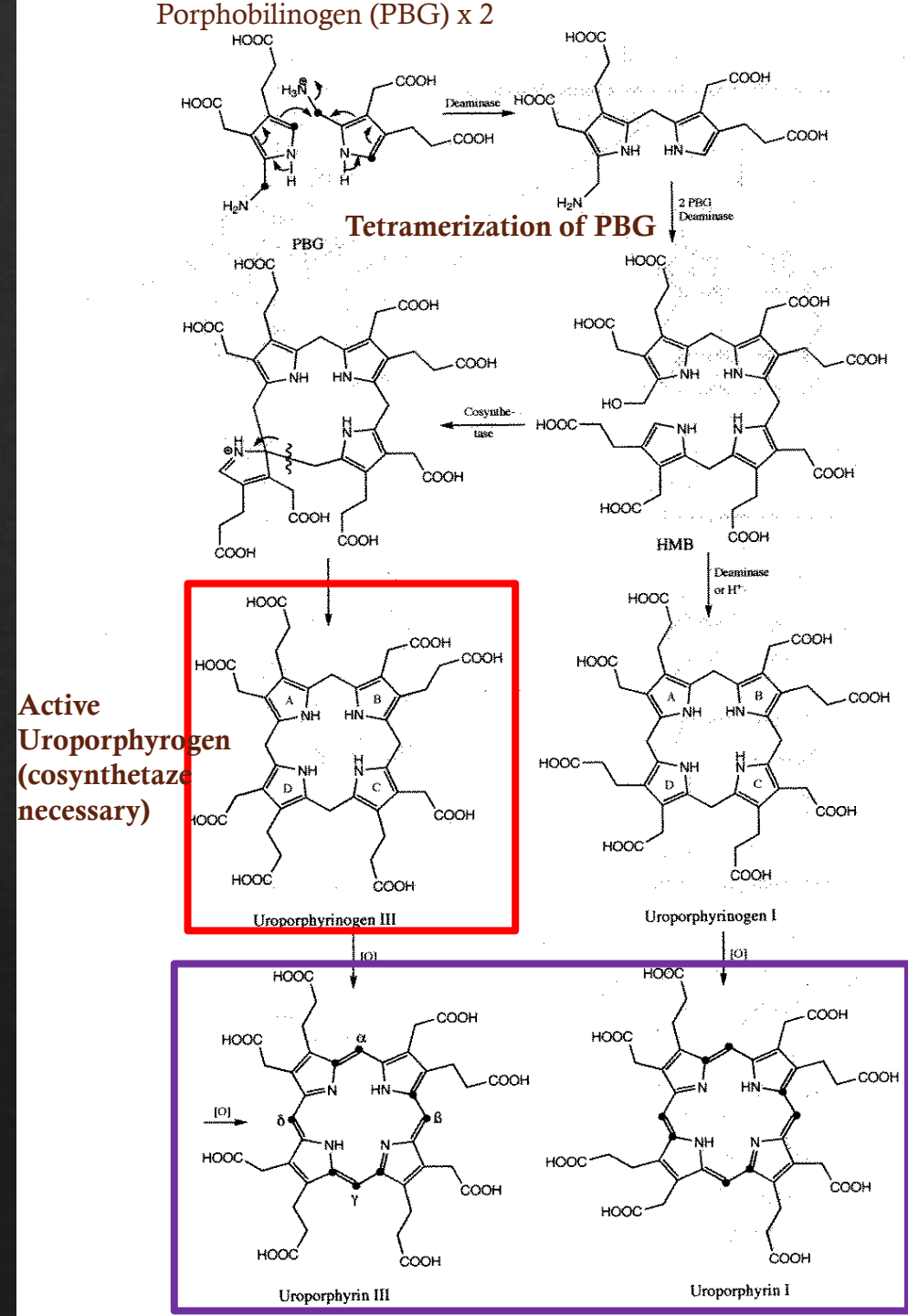


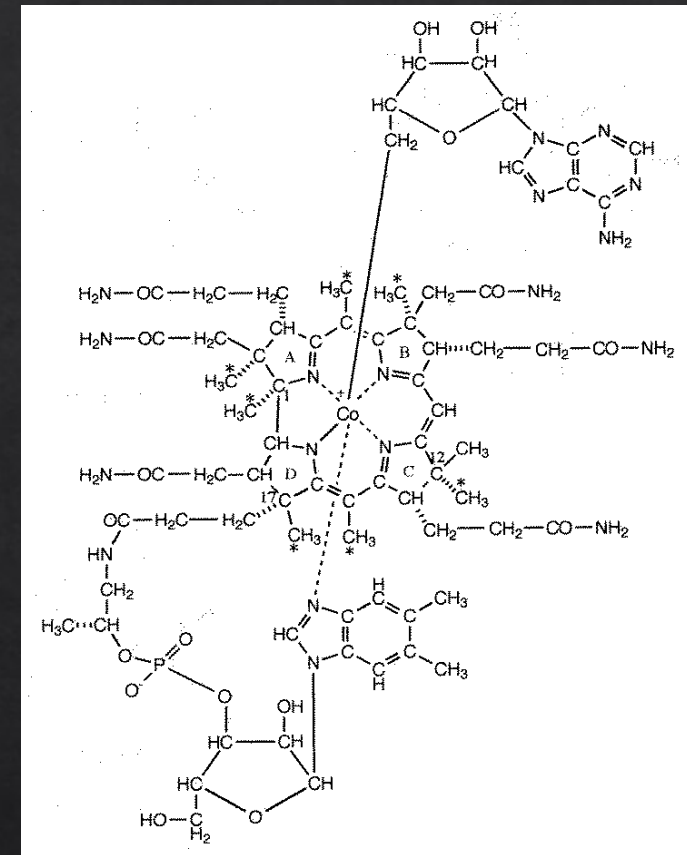
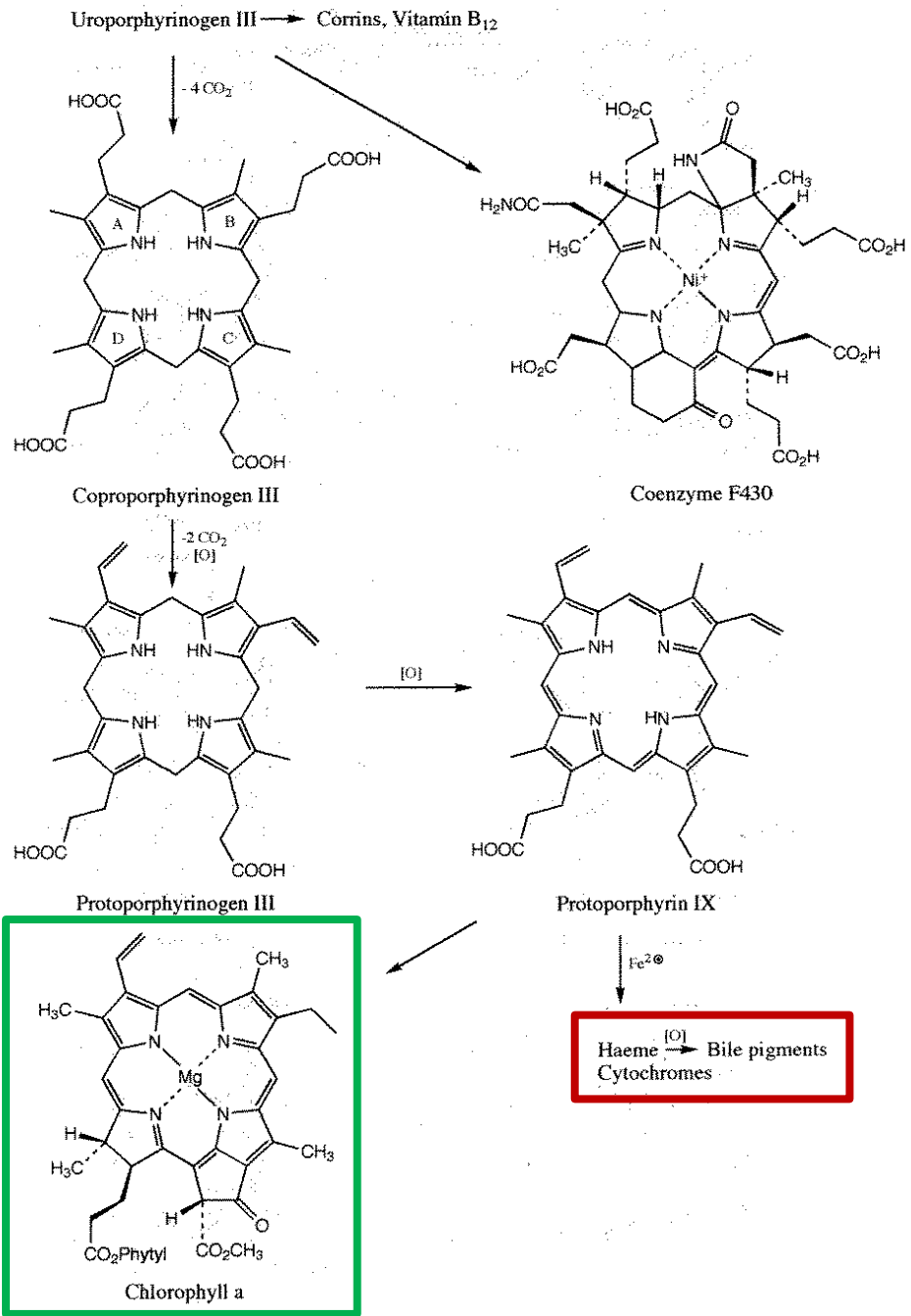
# Biosynthesis of uroporphyrin

- ◆ Porphobilinogen are synthesized from the dimerization of 5-aminolevulinic acid, which comes from succinyl CoA and glycine.



- ◆ Cosynthetase is needed to complete the biosynthesis of uroporphyrin. Otherwise, it leads to its inactive version.
- ◆ Uroporphyrin I and III are strongly colored compound (conjugated 18-pi-systems).





Cobalamin (vitamin B12)

The structure was elucidated in 1946 using X-ray crystallography.

