



Pharmacognosy and Phytochemistry

Alkaloids-Part 3

B. Pharm. Semester-1

Course Code: 0510221; Session: 2022-2023

Dr. BALAKUMAR CHANDRASEKARAN

**Professor-Faculty of Pharmacy
Philadelphia University-Jordan**

Learning Outcomes

At the end of this lesson, students will be able to explain

- **Piperidine-pyridine alkaloids and their Biosynthesis**
- **Piperidine alkaloids: Pelletierine, Lobeline, Piperine, Coniine and Arecoline**
- **Pyridine alkaloids: Nicotine, Trigonelline and Epibatidine**

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the alkaloids as major phytoconstituents.

Piperidine-pyridine alkaloids

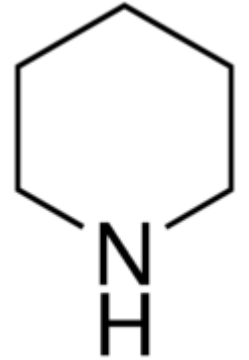
I. Piperidine alkaloids

A. Lysine derived Piperidine alkaloids

Examples: Pelletierine (psudopelletierine and anaferine),
Lobeline and piperine

B. Acetate or Nicotinic acid derived Piperidine alkaloids

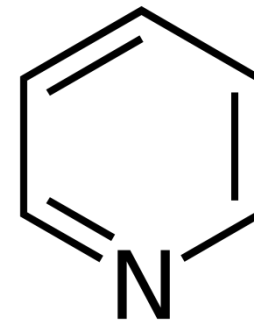
Examples: Coniine and Arecoline



Pka ~ 10

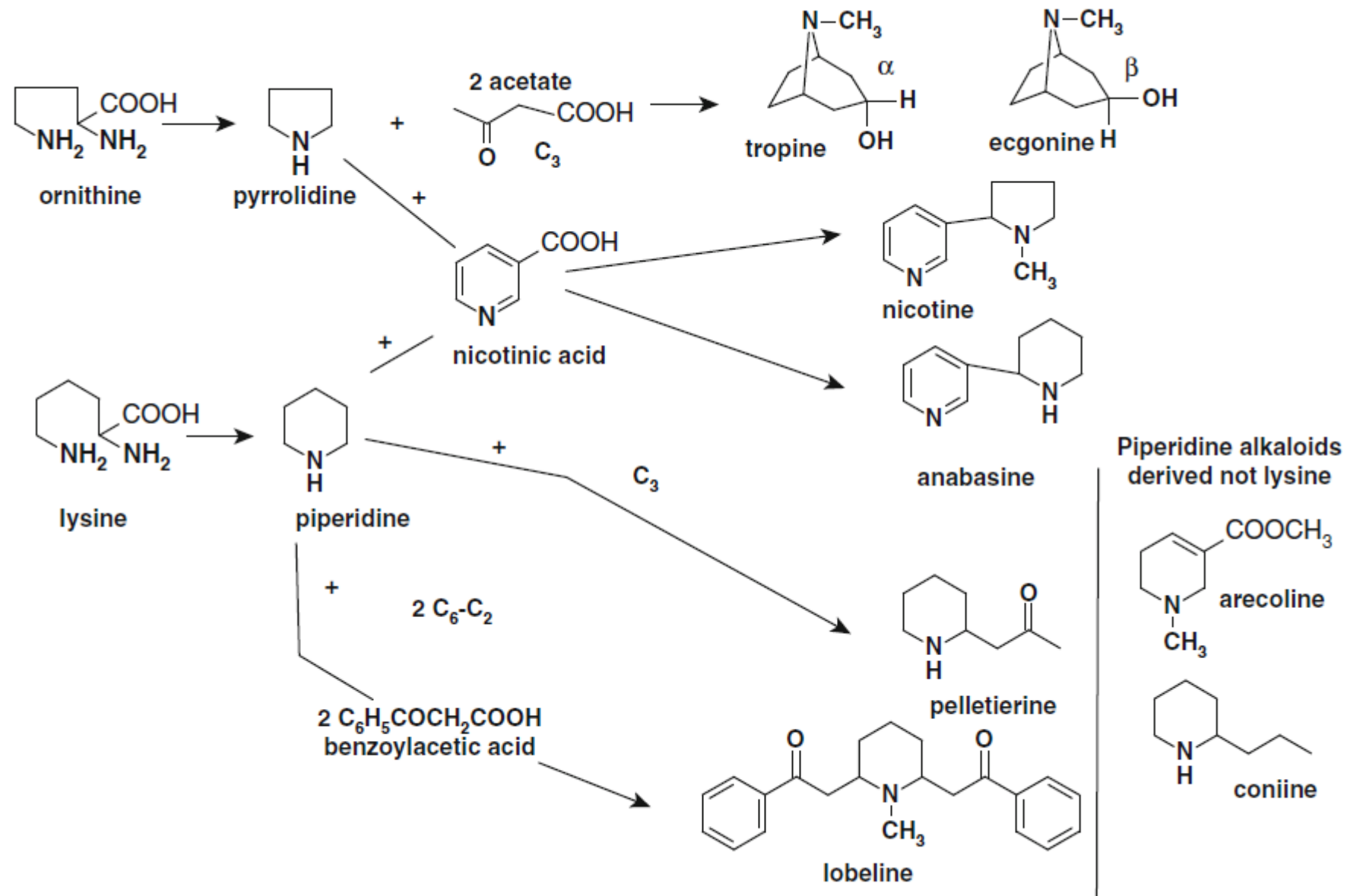
II. Pyridine alkaloids

Examples: Nicotine, Trigonellin
and Epibatidine



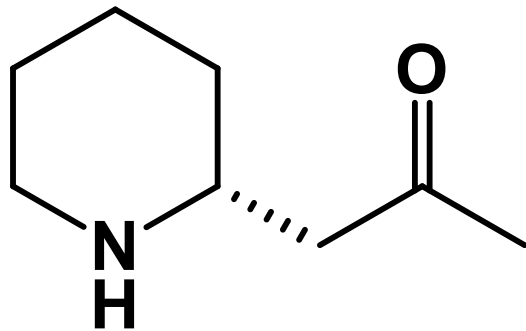
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Piperidine-pyridine alkaloids: Biosynthesis



Piperidine alkaloids: 1. Pelletierine

- It is found in pomegranate tree bark, *Punica granatum*, (الرمان Punicaceae).
- The official drug is the tannate salt of this alkaloid.
- It is used as a vermifugal as it is toxic to tape worms as anthelmintic.
- They contain about 0.5-0.9% of volatile liquid alkaloids, the chief of which are pelletierine and pseudopelletierine, together with about 22% of tannin.
- They cause paralysis of the "tapeworm".

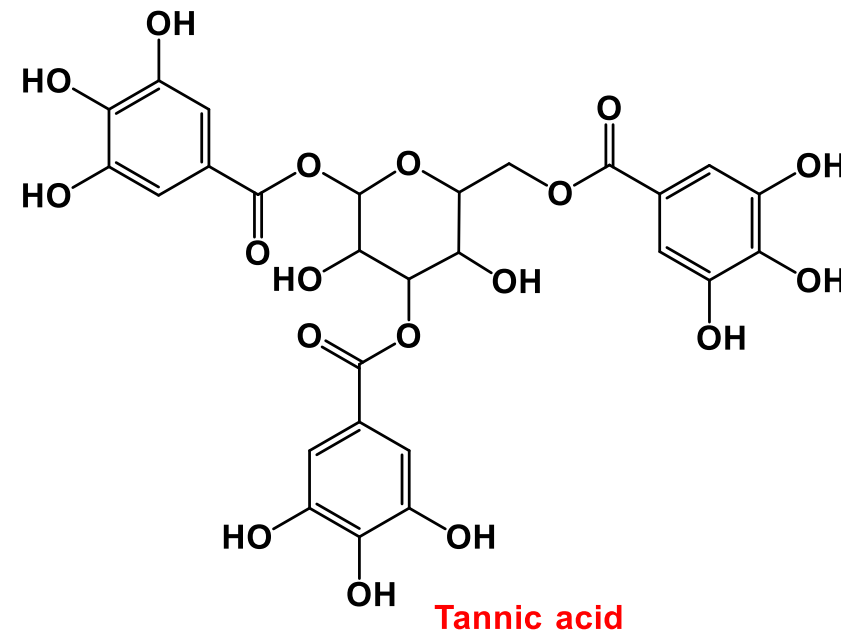
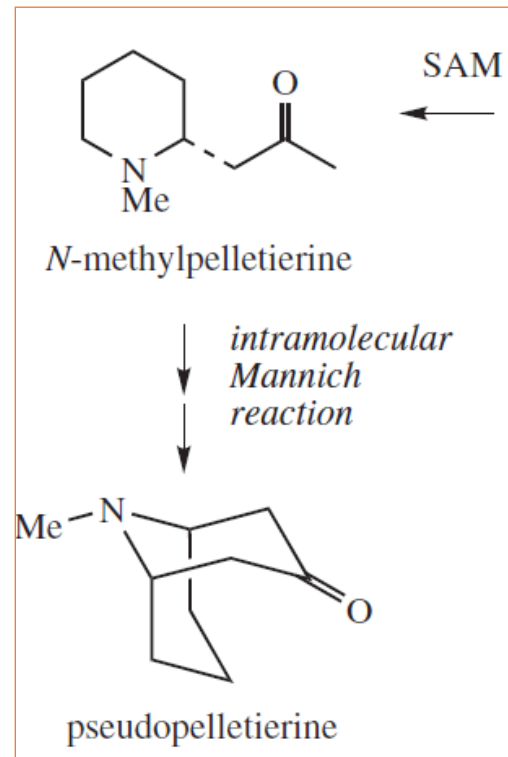
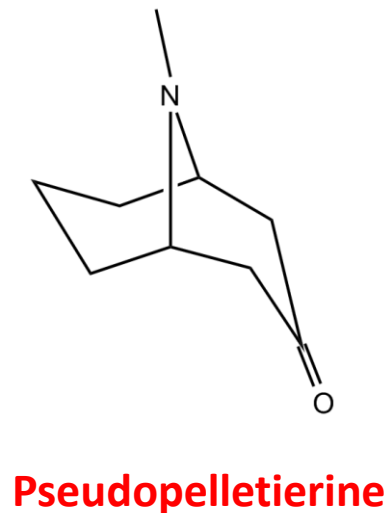


PELLETIERINE



Piperidine alkaloids: 1. Pelletierine

- It will relax its grip on the wall of the intestine thus allowing the parasites to be easily expelled by a second herbal drug (a cathartic).
- A fraction of the drug could be absorbed from the intestine and induce harmful effects.



Piperidine alkaloids: 2. Lobeline

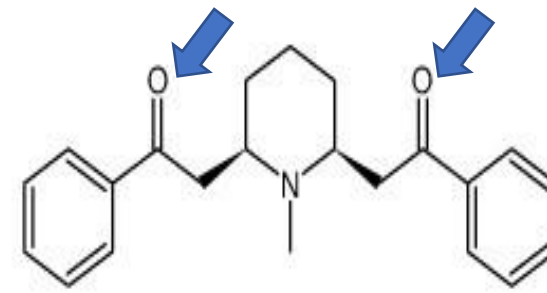
- The herb *Lobelia inflata* (Indian tobacco). Family **Campanulaceae** { **bellflower family** } contains many alkaloids.
- The most important is **lobeline** which is optically active.
- By **reduction** it yields **lobelanidine**, while **oxidation** will yield **lobelanine**.
- Lobeline HCl is exceptionally soluble in **chloroform**.
- **Biosynthetic origin:**
- Botanical source: *Lobelia inflata* – *Campanulaceae*

Pharmacological actions: Lobeline is quite similar in action to nicotine, but less active. It is stimulant to the respiratory center, although of short duration and somewhat unreliable. The extract has been incorporated in Galanical preparations as expectorant. This activity cannot attributed to lobeline as it is unstable.

Piperidine alkaloids:

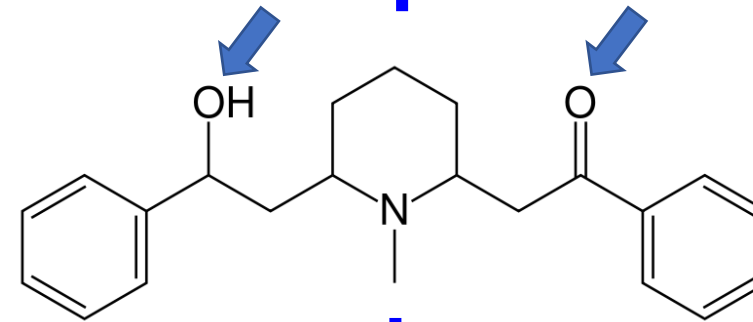
2. Lobeline-Chemistry

Lobelanine



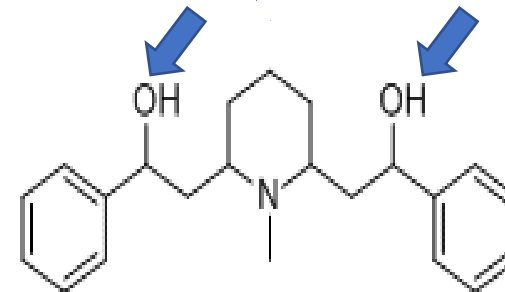
Oxidation

Lobeline



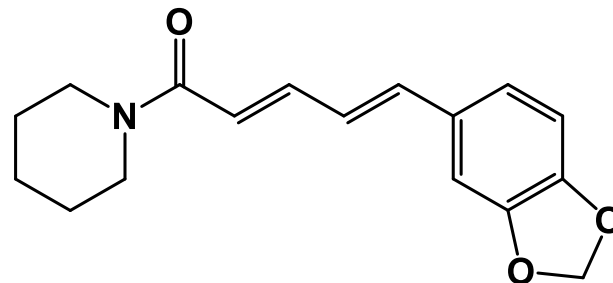
Reduction

Lobelanidine

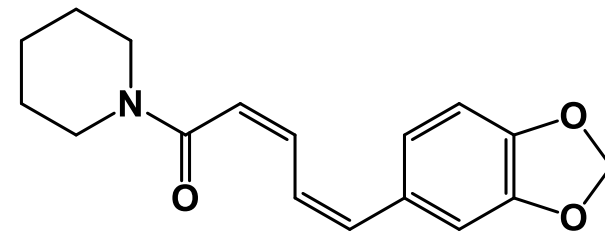


Piperidine alkaloids: 3. Piperine

- ❖ The pungent taste and irritant properties of pepper (*Pepper nigrum*) are due to the alkaloid piperine.
- ❖ The peppery odor is due to 1–3.5 % of an essential oil rich in terpenoid hydrocarbons.
- ❖ The pungency of pepper is ascribed to piperidine amides (5–10 %). The chief constituent is piperine (amide of piperidine and piperic acid) and its geometric isomer chavicine.



Piperine



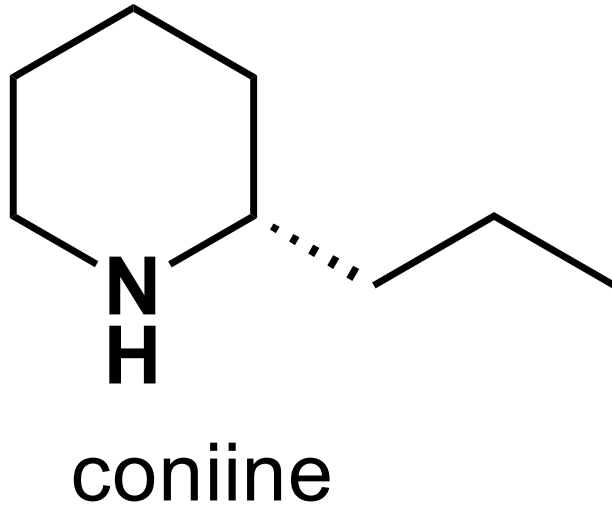
chavicine

Piperidine alkaloids: 3. Piperine-Uses

- Piperine is involved to increase the absorption of other nutrients in the body, helping to fight colon cancer, having an anti-depressant effect while enhancing the cognitive functions of the brain.
- Piperine and its synthetic derivatives can stimulate pigmentation in the skin especially when combined with UV-R treatment.
- Piperine blocks the formation of new fat cells by interfering the activity of genes that control the generation of fat cells.

Piperidine alkaloids: 4. Coniine

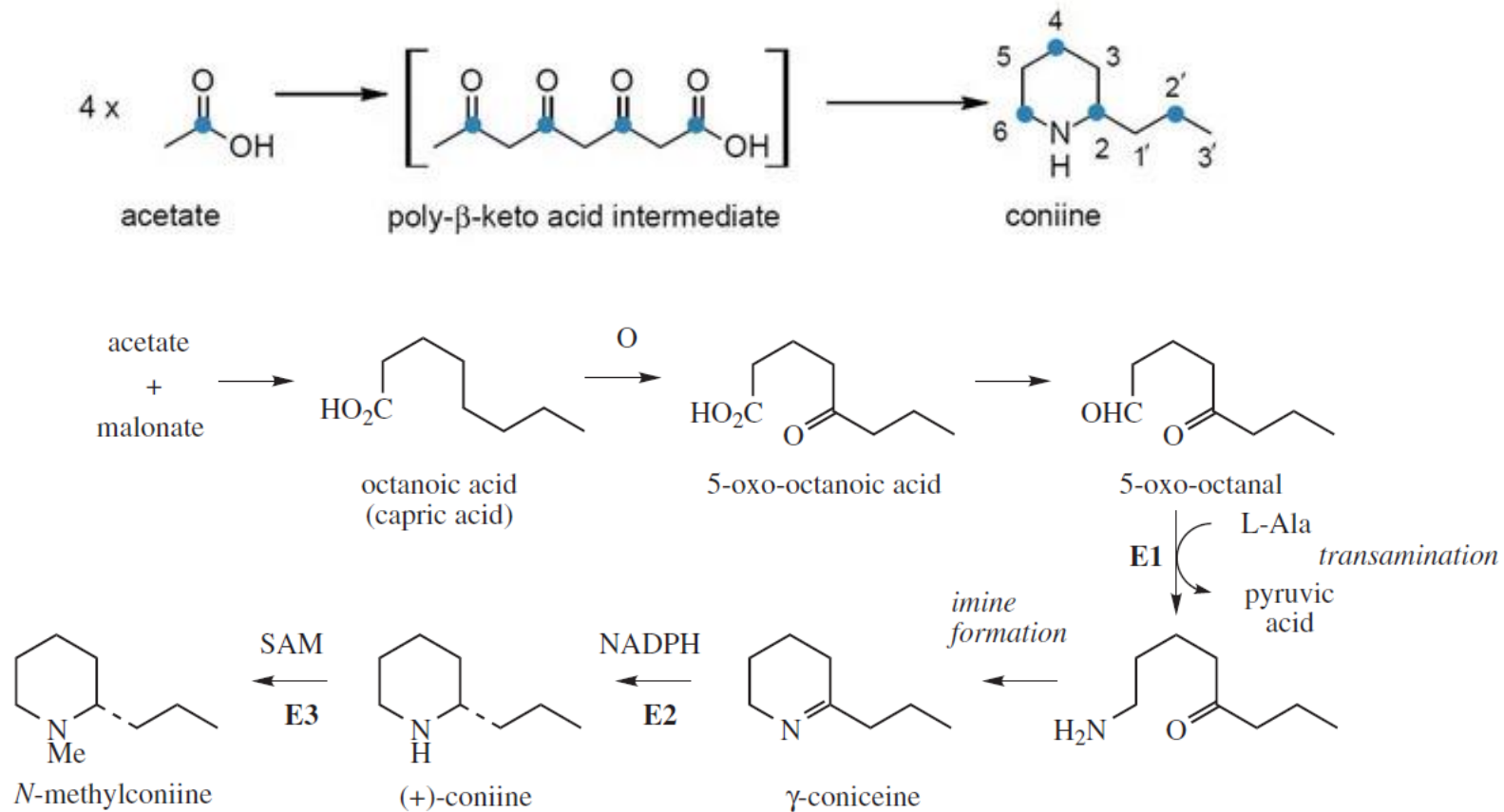
- The unripe fruit of *Conium maculatum* (Hemlock) الشوكران الأبقع
- It contains 0.9% of alkaloids, and up to 0.2% coniine and are very toxic.
- The most important is coniine, an oil.



Its fruits are similar to anise seeds

Piperidine alkaloids: 4. Coniine: Biosynthesis

Acetate pathway/Capric acid

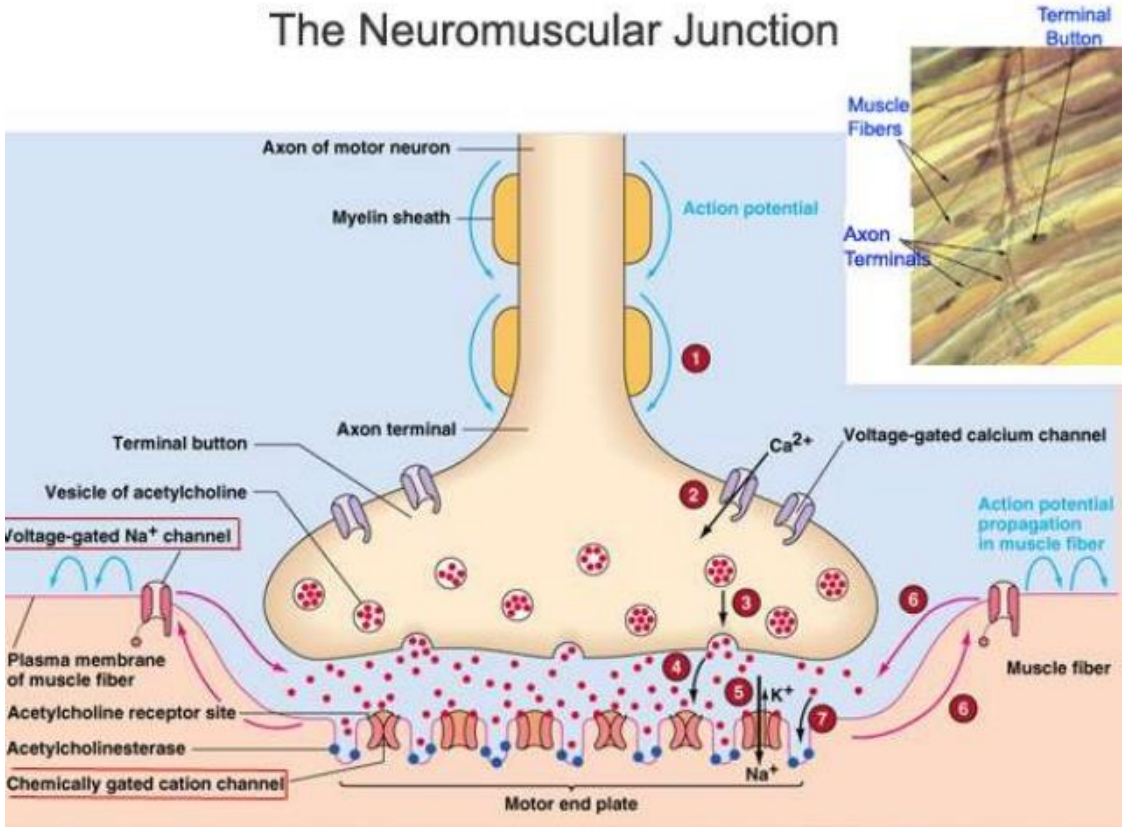
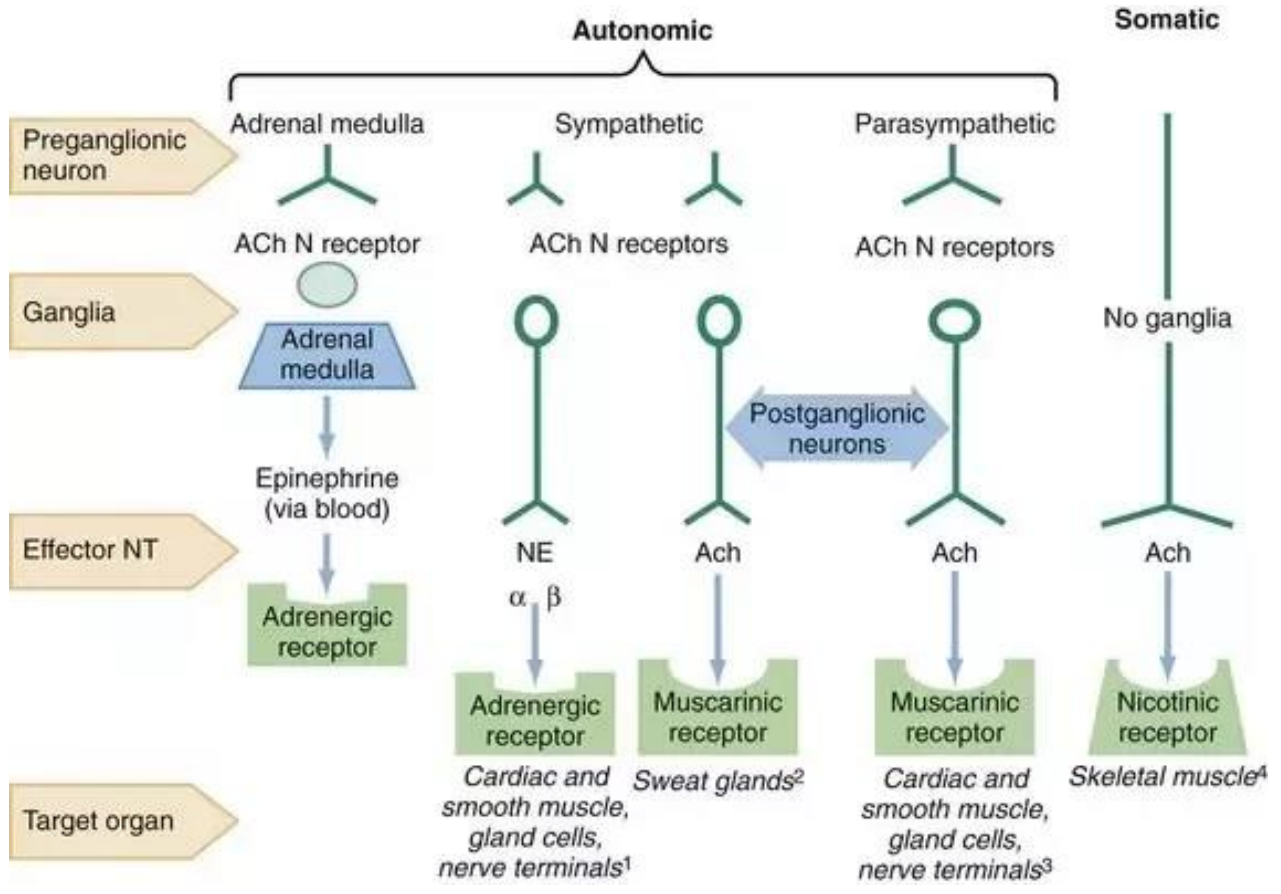


Piperidine alkaloids: 4. Coniine

- It is toxic to humans and all classes of livestock ; **موتاشي** less than 0.2g is fatal [6-8 leaves can kill a human being].
- It is teratogenic, and it produces crooked calf disease.
- Coniine paralyzes muscles by blocking the nicotinic receptor on the post-synaptic membrane of the neuromuscular junction causing a flaccid paralysis **مترهل**. This action is similar to that of curare.



Autonomic Nervous System

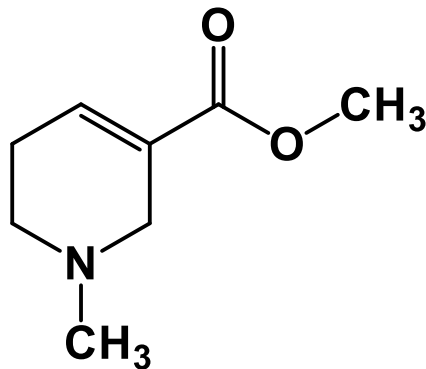


Piperidine alkaloids: 4. Coniine: Toxicity

- ❖ Symptoms of paralysis occur within a half hour, and death happens in few hours. The cause of death is **lack of oxygen to the brain and heart** as a consequence-**respiratory paralysis**.
- ❖ As the central nervous system is not affected, the person remains conscious and aware until respiratory paralysis results in cessation of breathing.
- ❖ The muscular paralysis is an ascending flaccid paralysis as the lower limbs are affected first.
- ❖ The person may have a **hypoxic convulsion** just prior to death, but this is greatly disguised (hidden) by the muscular paralysis and the person may just weakly shudder (shiver, shake).
- ❖ A poisoned person will recover if artificial ventilation (breathing) is maintained until the toxin is removed from the receptor.

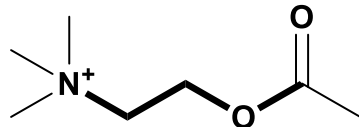
Piperidine alkaloids: 5. Arecoline

- ❖ Botanical sources: found in the betel nuts (seeds) of *Areca catechu* - a type of palms that grows in India and Malaysia.
- ❖ الفصيلة النخلية *Areaceae*.
- ❖ Chewed in India for the of
- ❖ Arecoline is an odorless oily liquid and gives stimulant effect
- ❖ Research results indicate that arecoline could induce neuronal apoptotic death by attenuating antioxidant defense and enhancing oxidative stress.
- ❖ It has been used as **vermicide** to eradicate worms in veterinary practice.

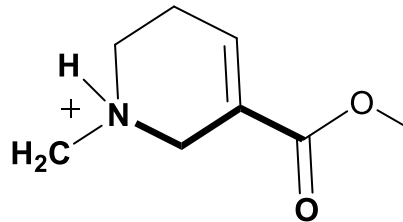


Piperidine alkaloids: 5. Arecoline

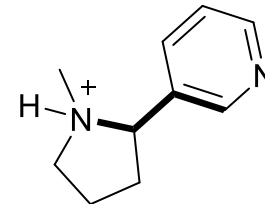
- ❖ In the Indian subcontinent, large quantities of betel nuts are consumed by farm workers to get CNS stimulant properties to alleviate fatigue.
- ❖ The nuts are red (due to the presence of tannins), which causes staining of the teeth (It causes redness of mouth, teeth and saliva, when use for long time cause buccal cancer)
- ❖ These nuts are addictive, the active stimulant component being the piperidine alkaloid arecoline.
- ❖ Like nicotine, arecoline binds to the muscarinic Acetylcholine receptors (mAChR) and has a stimulant effect on the CNS.



acetylcholine



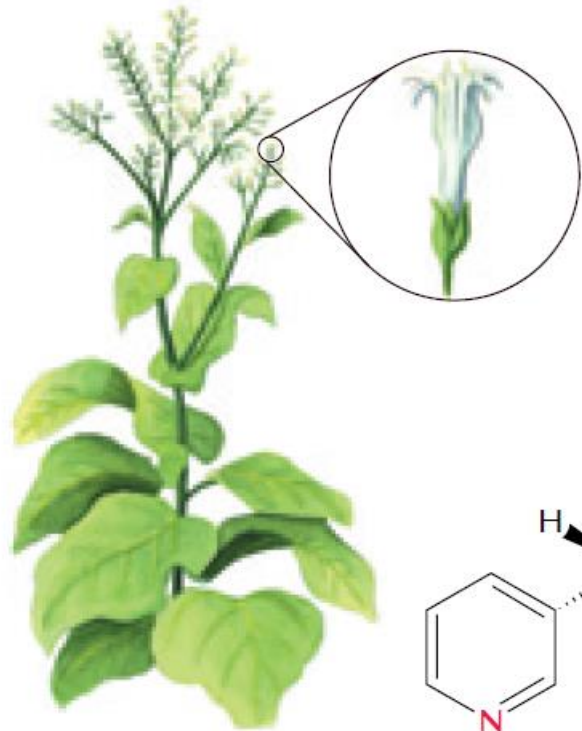
Arecoline



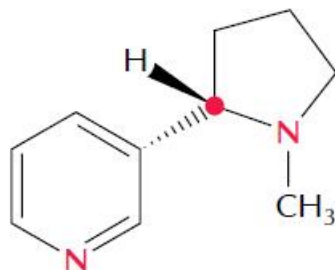
Nicotine

Pyridine alkaloids: 1. Nicotine

- ❖ Botanical source: leaves *Nicotiana tabacum* (Solanaceae).
- ❖ Nicotine is a toxic compound, 0.6 to 9 % of (–)nicotine present in leaves.
- ❖ Yellowish, oxidized by light and gives brown color. It is volatile nature.

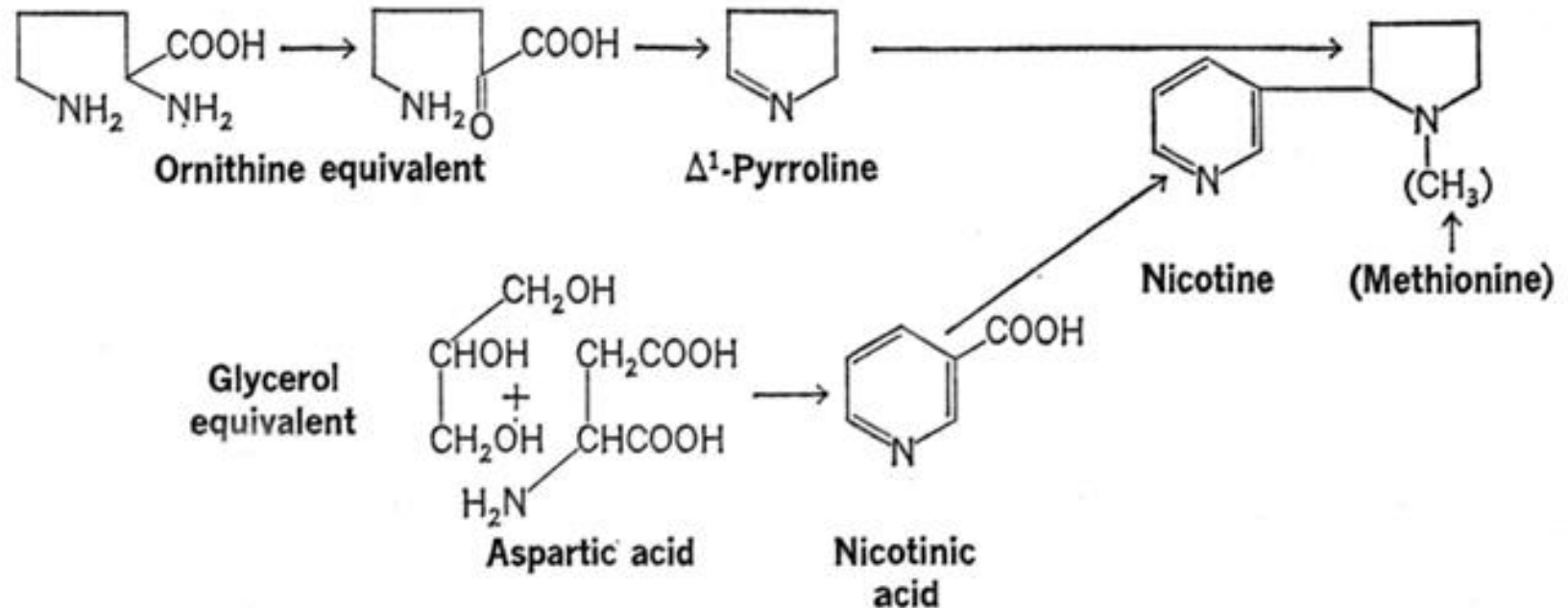


Nicotiana tabacum



Nicotine

Biosynthesis of Nicotine

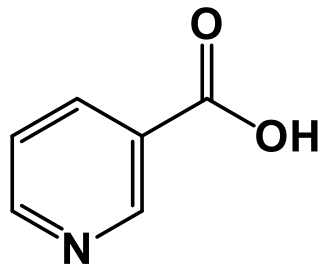


Pyridine alkaloids: 1. Nicotine: Pharmacological activity and uses

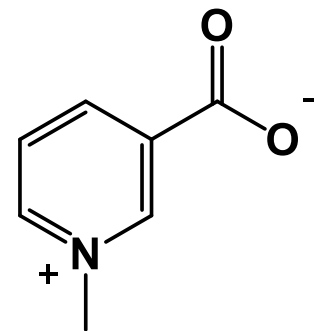
- ❖ Nicotine binds with nicotinic receptor (start by stimulation then inhibition).
- ❖ Nicotine is highly hydrophobic, so it can cross blood brain barrier.
- ❖ In low doses, such as those inhaled in smoking, nicotine causes hypertension, respiratory stimulation, stimulation of secretion from several glands and stimulation of CNS.
- ❖ The lethal dose (50-100 mg) corresponds to 5-cigarette content of nicotine, but it is destroyed by heat or distributed into the air.
- ❖ Toxic doses cause death as a result of respiratory arrest.
- ❖ Nicotine Chewing gum: It is a fast-acting form of replacement in which nicotine is taken in through the mucous membrane of the mouth.
- ❖ It comes in 2 mg and 4 mg strengths.
- ❖ Food and drink can affect the nicotine absorption, so don't eat or drink for at least 15 minutes before and during gum use.

Pyridine alkaloids: 2. Trigonelline

- ❖ Trigonelline is a zwitter ion formed by the methylation of the nitrogen atom of niacin (vitamin B₃).
- ❖ Trigonelline occurs in many plants, isolated from fenugreek seeds and coffee. (Higher levels of trigonelline is found in arabica coffee)
- ❖ Trigonelline (*N*-methyl nicotinic acid) is present in green seeds to an extent of 0.25–1%; during roasting, this is extensively converted into nicotinic acid (vitamin B₃)
- ❖ It inhibits AChE *in vitro*, and it improves memory retention *in vivo*.



nicotinic acid
Vitamine B3 or Niacin



Trigonelline

Pyridine alkaloids: 3. Epibatidine

- ❖ Epibatidine is a **chlorinated alkaloid** that is secreted by the Ecuadoran frog *Epipedobates anthonyi* and poison dart frogs from the Ameerega genus.
- ❖ It was discovered by John W. Daly in 1974, but its structure was not fully elucidated until 1992.
- ❖ They discovered, through tests on mice, that the frog's poison provided pain relief 200 times higher than that of morphine.
- ❖ Epibatidine binds to nicotinic acetylcholine receptors rather than to opiate receptors, and is therefore not addictive. However, epibatidine shows severe side effects.

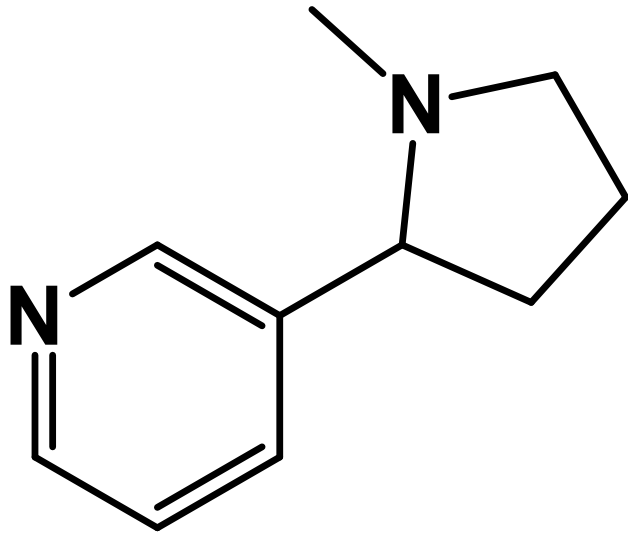
Pyridine alkaloids: 3. Epibatidine

- ❖ Epibatidine is toxic, interacts with nicotinic (high affinity) and muscarinic acetylcholine receptors.
- ❖ These receptors are involved in the transmission of painful sensations, and in movement, among other functions.
- ❖ Epibatidine then causes numbness, and, eventually, paralysis. Doses are lethal when the paralysis causes respiratory arrest.

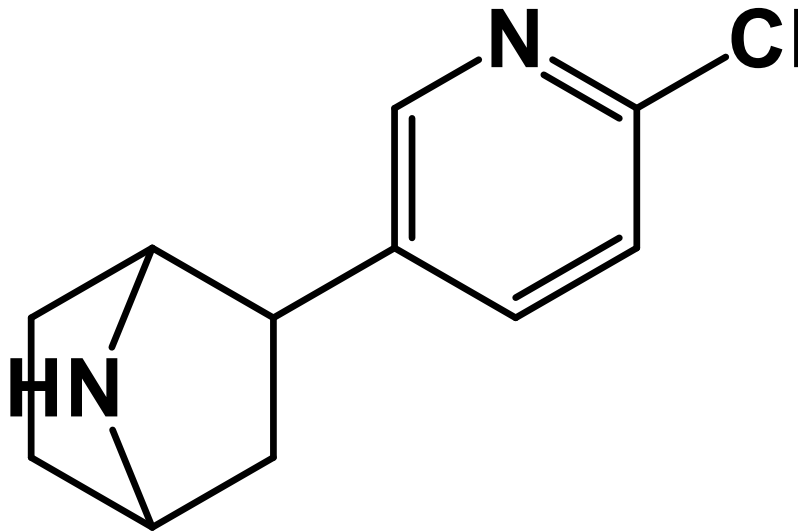


Pyridine alkaloids: 3. Epibatidine

Epibatidine has antinociceptive effect through the nAChRs, but at close dose of analgesia it can increase the arterial blood pressure (sympathetic effect) and with higher doses can cause paralysis (muscular nAChRs activation).



nicotine



Epibatidine

REFERENCES

Textbooks:

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2. **Textbook of Pharmacognosy and Phytochemistry 2nd Edition, 2019, Authors: B. Shah, A. N. Kalia, Publisher: Elsevier, ISBN: 978-978-9386217738.**
3. **Medicinal Natural Products: A Biosynthetic Approach, 2nd Edition, 2002, Author: Paul M Dewick, Publisher: John Wiley and Sons Ltd, ISBN: 0471496405.**

Supplementary book:

Fundamentals of Pharmacognosy and Phytotherapy. A Guide for Health Care Professionals by Carol A. Newal, Linda A. Anderson and J. David Phillipson. (2010). the Pharmaceutical Press, London, UK; ISBN: 0 85369-474-5.