Pyrrolizidine and Piperidine Alkaloids

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Occurrence

- In 288 species, 40 genera, about 60 medicinal plants (WHO, 1988).
- *Asteraceae, Boraginaceae, Fabaceae, Apocynaceae, Euforbiaceae, Poaceae, Ranunculaceae, Scrofulariaceae*

General structure of the alkaloids

Vast majority of these alkaloids are **esters** of **aminoalcohols** and of one or two aliphatic carboxylic acids.
Pyrrolizidine alkaloids

Aminoalcohols (necins):
- They are derivatives of pyrrolizidine.
- The configuration at C8 varies, and is most often H-8α.
- The ring is not always unsaturated at C-1, but it is always substituted by a hydroxymethyl group at this position.
- A second hydroxyl group is possible at C-7, and in rare cases, a third hydroxyl group at C-2, or at C-6.
- In some cases, oxidation at C-8 leads to the opening of the bicyclic structure (otonecin).
Pyrrolizidine alkaloids

**The acids** (necic acids) are C5, C7, C8 or C10 aliphatic acids,

- *sometimes simple*: angelic or tiglic acids with five carbon,
- *most often specific* to this type of alkaloid:
  - C7 hydroxyisopropylbutanoic monocarboxylic acids (lasiocarpic, trachelanthic, viridifloric acids)
  - C8 dicarboxylic acids (monocrotalic acid)
  - C10 dicarboxylic acids (senecic, jacobinecic, retronecic acids)
Pyrrolizidine alkaloids

Alkaloids:

Mono- or diesters of monocarboxylic acids (characteristic of the Boraginaceae):

- C-9 OH is esterified by a hydroxyisopropylisobutanoic acid (lycopsamine, intermedine)
- C-7 OH is esterified by either angelic or tiglic acid (in case of diesters only)
Pyrrolizidine alkaloids

Macrocyclic diesters (mainly in the Asteraceae):
The pyrrolizidines that are 7,9-diols may be esterified by a dicarboxylic acid, which leads to a macrocycle (senecionine, symphitine).
Biosynthesis of pyrrolizidine alkaloids

The NAD\(^+\) dependent condensation of two molecules of putrescine (or putrescine + spermidine) yields a symmetrical intermediate, namely homospermidine. The latter is subsequently cyclized according to a classic sequence: 1, 2, 1, 3.
Pyrrolizidine alkaloids

Toxicity
These alkaloids are cytostatics, some of them mutagenic and can cause hepatic tumors.

A. for Animals:
• Consumption of feedstuff contaminated by these toxic plants. Effective treatment do not exits.
• The toxicity is chiefly hepatic: swelling of the hepatocytes, centrolobular necrosis, caryomegaly, thrombosis of the hepatic vein, increase in bilirubinaemia↑, and liver failure.
• Symptoms depends on alkaloid structure, type of intoxication and the animal species.

B. for Humans
Mainly chronic intoxication. Eg.: consumption of grains contaminated by the seeds of *Crotalaria retusa* L. (in Afghanistan, India in the seventies).

*Crotalaria retusa* L. traditionally used for the flu or pulmonary ailments in the Antilles.

Structure and toxicity:
To be toxic the alkaloid must be dehydrogenated at C-1 and C-2, and at least monoesterified.

Toxicity: Monoesters < acyclic diesters, < macrocyclic diesters.
Pyrrolizidine alkaloids

Pyrrole derivatives resulting from the microsomal oxidation of the pyrrolizidines in the liver, react as alkylating agents with biological nucleophiles such as nucleic and protein macromolecules.
Experiments in rats

- **several alkaloids** (retrorsine, senkirkine, monocrotaline, lasiocarpine, symphitine) and a number of plants (*Tussilago farfara* L., *Symphytum officinale* L., *Petasites japonicus* Maxim) induced **hepatic tumors** when administered orally on a regular basis.

- The **mutagenic** and **teratogenic properties** of several alkaloids in this group have also been shown experimentally.

Exceptions

- **Platiphylline** is not toxic and can be considered as an **antispasmodic** and a **mydriatic**.

- **Others**, such as **indicine-N-oxide**, are **anticancer agents** in experimental conditions, but can not be used in humans.
Borage, Boraginis herba, *Borago officinalis* L. Boraginaceae

This annual plant is indigenous to the Near East and is currently cultivated to produce seeds containing unsaturated fatty acids.

It is easy to identify by its leaves covered with rough hairs, its bright blue flowers, with hairy sepals, and its connivent stamens and black filaments with a horn-shaped appendix.

**Constituents**

**Stem and leaves:** mucilage, small quantities of pyrrolyzidine alkaloids: lycopsamine, intermedine, amabiline, supinine.

**Flowers:** alkaloids as an unsaturated derivative, namely thesinine.

- There has been no pharmacological study of this drug.
- It is reputed to be a “sudorific” emollient, and diuretic.
- **Traditionally used**
  - to treat acute benign bronchial diseases.
  - to enhance the renal elimination of water.
Common Confrey, *Symphytum officinale* L., Boraginaceae

- A large **perennial plant** (0.5-1 m) with
- voluminous and fleshy rhizome,
- large leaves decurrent on a great part of their length, and
- white, pinkish, or purplish flowers, grouped in scorpioid cymes.
- It is very common in all of Europe.
- Several cytotypes exist (2n= 24, 48, 40).
Symphyti radix, Constituents

Root

- Fructanes, mucilage, allantoin (0.6-0.8 %),
- rozmarinic acid, litospermic acid,
- pyrrolizidine alkaloids (0.02-0.07%): lycopsamine, intermedine and their acetylated derivatives, symphytine and echimidine.

Leaves. Pyrrolizidine alkaloids (0.003-0.2% !)

Allantoin (5-ureidohydantoin)

intermedine

symphytine
Symphyti radix

Effects
Helps tissue regeneration (allantoin, polysaccharides), antiinflammatory, antioedemic.

Uses
• The root is an ingredient of herbal remedies.
• Indications must be limited to local use: emollient, itch-relieving, and trophic protective (cracks, abrasions, chaps).
• It can be applied only to unbroken skin, and for maximum 4-6 weeks in a year.

Toxicity
• When administered orally to rats for a long period of time, the roots and leaves of comfrey induce hepatic tumors in nearly half of the populations, and so does symphytine.
• The percutaneous absorption of the alkaloids has been studied in animals, is small, and the risk seems negligible.
Coltsfoot, *Tussilago farfara* L., Asteraceae

- Coltsfoot is a small perennial plant very common in Europe and in Northern Asia.
- In very early spring, it produces capitulum of yellow flowers on a scaly stalk.
- Rosettes of cordate and coriaceous leaves that are pubescent on the lower side appear later.
Farfarae folium et flos

Constituents

- pyrrolizidine alkaloids (few ppm):
  - senkirkine!, and artefacts of the extraction with MeOH: tussilagine, isotussilagine,
  - the oriental and North American drugs contain, in addition, senecionine, which is more toxic alkaloid (importance of geographical origin),
- acidic mucilage (~6%), triterpenes, flavonoids, carotenoids,
- tussilagon, a sesquiterpenoid ester in the floral buds
Farfarae folium et flos

Actions
• *Farfarae folium.* Antitussive, antiinflammatory.
• *Tussilagone* (sesquiterpenoid ester)
  – respiratory stimulant (ventilation and arterial blood pressure ↑),
  – inhibit PAF-acether, a mediator whose role in inflammation and respiratory difficulties is known.

Uses
• Coltsfoot (infusions, nebulisates) continues to be used in phytotherapy (tracheitis, chronic bronchopneumopathy). It is widely self-administered (cough teas).
• The oriental medicine use it to treat asthma, bronchitis, and other respiratory ailments.
• **Precautions:** It can be used max. **for 4-6 weeks in a year.**

Toxicity
• Senkirkine: cocarcinogenic, can induce hepatic tumors.
• Contraindications: Pregnancy and lactation.
European ragworth, *Senecio jacobaea* L., Asteraceae

- **A perennial plant**, widespread in neglected meadows and along country roads.
- It is characterized by **very divided leaves** which hug the stem with two jagged little wings.
- The **yellow flowers** are grouped in a corymb of radiate capitulums.

**Constituents.** Pyrrolizidine alkaloids, esters of retronecine: seneciphylline, senecionine, jacobine, jacozone, and closely related products.

**Intoxications.** Mainly in horses, who lose their appetite, and develop jaundice, edema, ascites, and finally, an encephalopathy, which includes gait anomalies.

Accidents occur following the repeated ingestion of preserved fodder. (Often fatal, but quite rare intoxication in Europe).
Common groundsel, *Senecio vulgaris* L., Asteraceae

**Constituents**

Pyrrolizidine alkaloids (0.05-0.1%): seneciphylline, *senecionine*, retrorsine, spartioidine, usaramine, integerrimine.

**Uses**

*Senecionis herba*. It is presented, without any pharmacological evidence, as capable of improving venous circulation. As such – despite the presence of toxic pyrrolizidine diesters – it still finds some uses (compound herb teas, extracts).
Quinolizidine Alkaloids
Scotch Broom, *Cytisus scoparius* (L) Link., Fabaceae

This plant also known as *Sarothamus scoparius* (L.) Wimmer ex Koch is a bushy shrub (50-150 cm) fond of siliceous soils and very common in all of Europe.

It is characterized by erect, angular, and glabrous branches,

at the apex of which are inserted simple and sessile leaves, whereas at their base the leaves are petiolate and trifoliate.

The flower’s zygomorphous corolla with vexillar prefloration is typical of the Fabaceae. It has a short, bilabiate, and scarious calyx, and a coiled style.

The fruit is a hairy and flattened pod which turns black when ripe.
Sarothamni scoparrii herba

Constituents

• **Quinolizidine alkaloids**: (-) sparteine (0.5-1%), lupanine, 17-oxosparteine, 4-hydroxylupanine, 13-hydroxylupanine.

• **Sparteine** (chief alkaloid in the branches, 60%), a tetracyclic alkaloid without oxigen atoms and with two *trans*-fused *cis*-quinolizidine nuclei (6R,7S,9S,11S isomer).

• **Flavonoids**: isoflavones (genistein) and flavones C-glycosides (*scoparozide*).

• **Amines**: (especially in the flowers, up to 2%) tyramine, dopamine, epinine.

(-) Sparteine
**Sarothamni scoparii herba**

**Pharmacological Action**

*Spartein* is a mild ganglioplegic, which blocks conduction and prevents the depolarization of the post-synaptic membrane.

- In the **heart**, after a transient phase of ganglionic excitation,
- it shields the myocardium from central neurovegetative regulation, and
- decreases excitability, conductibility, and the frequency and amplitude of the contractions.
- It is **oxytocic**: it causes a moderate increase in the tone and strength of the contractions of the uterus.

**Uses**

- The **branches** are used to **extract sparteine**.
- Proprietary products based on **sparteine sulphate** are indicated
  - for sinusal tachycardia of neurotonic origin and cardiac erethism as well as
  - in obstetrics, as an oxytocic during labor.
- Phytopharmaceuticals based on **broom flowers** may be (traditionally) used
  - to enhance renal and digestive elimination functions and
  - to enhance the renal excretion of water (watching out for possible drug interactions with MAO inhibitors).
PIPERIDINE ALKALOIDS
Indian Tobacco, *Lobelia inflata* L., Campanulaceae

Indian tobacco grows wild in the Appalachian Mountains, **North America**.

It is a small **annual herb** (20-50 cm) with erect and ramnified stems.

The **leaves** are sessile and the blades have a **dentate margin**.

The **flowers** are pale **blue** with foliaceous bracts, and are gathered in **terminal racemes**; their inflated calyces become vesiculose after the floration.

The commercial drug consists of 50-60 % stems which are angular, hollow, covered with rough hairs and mixed with broken leaves.
Lobeliae herba

Constituents

- 0,2-0,5 % alkaloids (> 50): piperidines [(-) lobeline (chief constituent), *meso*-lobelanine, *meso*-lobelanidine, lobinine] and piperideines.
- chelidonic acid, lobelic acid.
- Infandint (fitoszterin)
Biosynthesis of lobelia alkaloids

Biosynthetically, these alkaloids may be formed by a double Mannich reaction between two molecules of phenylalanine (via cinnamic acid and benzoylacetate-coenzyme A) and one $\Delta^1$-piperidium cation arising from lysine via cadaverine.
Lobeliae herba, Pharmacological activity

Lobeline

- It is a respiratory stimulant which enhances and accelerates the respiratory movements by
  - improving the reactivity of the brain stem centers to carbon dioxide and also,
  - acting by a reflex mechanism involving the carotid chemoreceptors.
- Secondarily, it is a ganglionic stimulant and a β-adrenergic bronchodilator.
- It showed positive effects in the treatment of multidrug-resistant tumor cells in vitro.
- Furthermore, lobeline can be modified to lobelane which decreased methamphetamine self-administration in rats.
- It therefore opens a perspective in methamphetamine dependency treatment.
- The North American Indians smoked lobelia rather like tobacco (Nicotiana tabacum; Solanaceae).
- Lobeline stimulates nicotinic acetylcholine receptor sites in a similar way to nicotine, but with a weaker effect.
Lobeliae herba, Uses

Lobeline

- Formerly used (IM or SC) for resuscitation after asphyxia, particularly to treat apnea in new borns,
- lobeline is no longer used because of its substantial side effects and poor therapeutic index.
- Several studies show that lobeline (in smoking cessation preparations) is ineffective in helping people to quit smoking.

Galenicals

- prepared from indian tobacco (extract and tincture) are ingredients of a few specialized medications designed for the symptomatic treatment of various bronchopulmonary ailments.
PIPERINE AMIDS: PIPERACEAE
Black Pepper, *Piperis nigri fructus, Piper nigrum L.*, Piperaceae

- Pepper is one of the most acient spices.
- It is a **perennial plant originally from** the south-west of **India** (Malabar Coast), and now **cultivated** in India, Indonesia, Malaysia, Sri Lanka, and South America (Brazil).
- Black pepper is a **flovering vine** with ligneous volubile stem affixed to their support by secondary brances.
- The leaves have an **oval acute blade** and are alternate.
- The **sessile flowers** have no perianth and are grouped by 20 to 20 units into dangling spikes.
- The fruit is a **berry** of 4-8 mm in diameter, which turns from green to **red as ripens**.
Piperis nigri fructus

Different kinds of pepper are well recognized.

- **Green pepper**: the *whole fresh berries*, generally *conserved* in acidic aqueous solution (or frozen, or pasteurized). Highly aromatic.

- **White pepper**: the *fruits* collected at full maturity, dried after removing fruit pericarp and the external layer of mesocarp.

- **Black pepper**: collected immediately *after the first berries turn red*, dried than separated from the stalks. The *dried fruits* are *spherical* (3-6 mm) and particularly *hard*. Their surface is *brownish black* and *extremely wrinkled*. 
Piperis nigri fructus

- The pepper **odor** is due to 1 to 3.5 % of an **essential oil** rich in terpenoid hydrocarbons, and
- the pungent taste to **amides** (5-10 %).
  - The chief constituent is **piperine**, an amide of piperidine and of piperic acid.
  - The other **amides** are **piperidines** (piperanine, piperettine), **pyrrolidines** (piperyline) or **isobutylamines**; **The acid** which is part of their structure **has a side chain of variable length** (5 to 10 carbon atoms).
- **Piperine** is a **CNS depressant** and an **anticonvulsant** in rats. Some of its synthetic derivatives have been **used in china as anti-epileptics**.
PIPERIDINE ALKALOIDS NOT FROM THE METABOLISM OF LYSINE
Poison Hemlock, Conii fructus, *Conium maculatum* L., Apiaceae

- A **large biennial herb** indigenous to Europe and naturalized in North and South America.
- This plant can be differentiated from most other members of the Umbelliferae /Apiaceae by its **tall** (1-2m), smooth, **purple-spotted stems**.
- The sheathing leaves have a **tripinnatisect blade** with acute lobes.
- The umbel has an involucre and involucels consisting of two to six short curved bracts.
- When crushed the whole plant releases an unpleasant „**mouse” odor.”
Poison hemlock, Constituents

- The **chief alkaloids** found in the plant are **coniine** (volatile alkaloid that can be distillated), γ-coniceine, conhydride, *N*-methylconiine, *N*-methylconhydride, pseudoconhydride, and conhydrinone.
- The **ripe fruit** can contain more than **1.5 % alkaloids** located in the epicarp and endocarp, and **mostly** represented by **coniine**.
- In the **vegetative parts**, **coniceine** is the chief constituent, especially at the beginning of the growth phase (furthermore, it is six to eight times **more toxic**).
Poison hemlock, Biosynthesis of the Alkaloids

These alkaloids are elaborated from a polyacetalte unit which incorporates a nitrogen atom:

- In case of coniceine, there is a transamination between alanine and 5-keto-octanal formed from capric acid.
- Subsequent transformations are imine formation giving the heterocyclic ring of \( \gamma \)-coniceine, reduction to coniine, then methylation to \( N \)-methylconiine.

\[
\begin{align*}
\text{HO}_2\text{C} & \rightarrow \text{OHC} \\
\text{O} & \rightarrow \text{O} \\
\text{5-keto-oxanal} & \\
\end{align*}
\]
Poison hemlock

The fruit of hemlock was used for two millennia for its antineuralgic properties, but have no medicinal use now.

Toxicity

- **Coniine** blocks neurotransmission in ganglions and neuromuscular junctions.
- All parts of the plant are poisonous due to the alkaloid content.
- The ancient Greeks are said to have executed condemned prisoners, including Socrates, using poison hemlock.
- **Symptoms of the intoxication**: decrease in mobility and sensitivity, progressive paralysis of the muscles, progressive cooling of the extremities, dizziness and mydriasis. The **gradual muscular paralysis** is followed by **convulsions** and **death from respiratory paralysis**.
- Human intoxication by poison hemlock, which is sometimes confused with chervil, require rushing the victims to a hospital emergency room.
- **All animals can be intoxicated** by the plant, but their susceptibility varies with the species. Poison hemlock can induce **congenital malformations** in pregnant females.
ALKALOIDS DERIVED FROM NICOTINIC ACID
Tobaccos, *Nicotiana tabacum* L., *N. rustica* L., Solanaceae

- These tobaccos and their multiple cultivars are grown for the **production of leaves for smoking**.

*N. tabacum* is an **annual plant** reaching 2m in height.

- Characterized by **very large** (50-70 x 30-45 cm) alternate, sessile or sheathing **leaves**, and
- **panicles of flowers with a tubulous flared corolla**, ranging in color from pinkish to ruby red.
Nicotianae folium

Chemical Composition

- Green tobacco leaves are rich in sugars (40%; starch, pectin, cellulose, soluble sugars), proteins and organic acids (15-20%).
- The **alkaloid concentration** varies greatly depending on the cultivation practices and the variety (2-10%, more than 15% in some cultivars of *N. rustica*).
- The chief alkaloid is *(S)-(−)-nicotine*.
- The other alkaloids are very close structurally and are anabasine, nornicotine, the *N*-oxidized derivatives of nicotine, *N*-acylnornicotines, nicotirine, and myosmine; they also include anabaseine and anatabine.
- Nicotine is a strong volatile base.
Biosynthesis of Nicotine

The formation of nicotine proceeds through the condensation of the $N$-methylpyrroloinum cation with a 1,2-dihydropyridine (enamine). The resulting product undergoes oxidation which regenerates the pyridine ring.
The formation of anabasine and other piperididine analogs involves nicotinic acid and lysine.
Nicotianae folium, Pharmacological activity

- The immediate toxicity of tobacco is linked to the presence of nicotine.
- Combustion products, especially the nitrosamins are responsible for the genesis of cancer.
- In the long run, nicotine is responsible for the genesis of cardiovascular and pulmonary diseases other than tumors.

Nicotine is readily absorbed through the mucosas and through the lungs.

By transient stimulation followed by persistent depression of all automatic ganglia, it acts:
- on the CNS, which it stimulates up to the point of causing, if the dose is sufficient, tremors and convulsion; it also stimulates the respiratory and vomiting centers (at high doses, respiratory paralysis occurs);
- on the smooth muscle of the intestine, by increasing tone and motor activity;
- on the neuromuscular junction; the initial phase of the stimulation is brief and soon followed by a blockade phase;
- on the cardiovascular system, by inducing, through a complex mechanism, a vasoconstriction and an increase in arterial blood pressure.

- Nicotine absorption can alter the activity of certain drugs: it induces enzymes, therefore the blood levels of drug decrease.
Nicotianae folium

Uses
The only medicinal use of nicotine is to relieve the corresponding symptoms during smoking cessation programs.

Nicotine based products: chewing gum (2-4 mg nicotine), transdermal nicotine system (patch) releasing 5-7 to 15-21 mg/24h of nicotine.

These products (being considered to be highly toxic) can be useful as adjuncts in highly dependent patients, but they are no substitutes for a strong motivation to quit smoking and long-term psychological support.
Betel (Nut) Palm, Arecae semen, nuces, *Areca catechu* L., Palmae

- The betel palm is a **palm tree** with a slender stipe ending with a bunch of feathered leaves.
- The **fruit** is a fibrous **drupe**, red when ripe, and it contains only one seed.
- The tree is **widely cultivated**, from India and Sri Lanka to south of China and the Philippines, in Malaysia and in Indonesia; it is also found in Africa (Tanzania).
Arecae semen, nuces

- Areca nut (betel-nut), the seed of *Areca catechu*, is a hard ovoid mass (2 cm in diameter) the color of cinnamon.
- Constituents: 50-60 % sugars, 15 % lipids, 15 % condensed tannins, and 0,2-0,5 % alkaloids.
- Alkaloids: *Arecoline*, arecaidine, guvacine (tetrahydronicotinic acid), and guvacoline.
Arecoline, Biosynthetic Origine

Though arecoline is a piperidine derivative, *its precursor* is not an amino acid but *tetrahydronicotinic acid*. Therefore, it is a *pseudoalkaloid* of pyridine nucleotide origin.

![Chemical structure of arecoline and its biosynthetic pathway](image)
Arecae semen

Effects

• Arecoline is a **parasympathomimetic** which acts on the **muscarinic receptors**, and at high doses, on the nicotinic receptors.

• This results in **multiple actions**:
  – vasodilation, hypotension, and
  – reflex of tachycardia at low doses,
  – stimulation of intestinal tone and peristalsis,
  – increase in secretions (hypersalivation and sweating),
  – myosis, and
  – bladder contraction.

• The mechanism of the **psychostimulant effects** of the drug has not been explained.

Traditional use

• The drug has been used as a **taenicide** in humans and also in veterinary medicine.

• Betel is widely used as a **masticatory** in all of southeast Asia; its consumption is a very ancient social, religious, and cultural practice.
Betel masticatory

• The masticatory known as betel is a concoction at times complex:
  • the cut up betel nut, mixed with lime (charred shells or corals, vegetable ashes), is rolled in betel leaf; depending on the area, spices (nutmeg, cardamom, clove), tobacco, gambír, or saffron are added to the preparation.
  • It is chewed for its stimulant effect, and subsequent feeling of well-being and mild intoxication.
  • The chewers spit frequently, and their saliva is colored red due to the oxidation of polyphenols contained in the drug.
  • Betel is suspected of inducing buccal cancers due to the cytotoxic and teratogenic N-nitrosamines formed from the alkaloids of the betel nut, particularly 3-(N-nitrosomethylamino)-propionaldehyde (=NMPA).
Thank you for your attention!