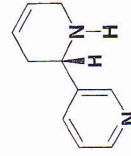




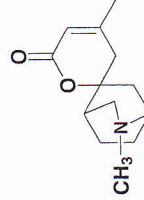
NICOTIANA TABACUM L.

Alkaloids Derived from Nicotinic Acid

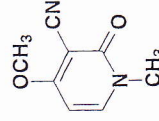
In plants, it is the condensation of aspartic acid and glyceraldehyde which leads, via quinolinic acid, to nicotinic acid, the precursor of alkaloids such as the piperidines of the areca or betel nut, nicotine, anatabine and its analogs in tobaccos, pyridone of the castor bean, but also anibine or dioscorine, and nicotinic acid, a constituent of the polyol esters found in some Celastraceae.



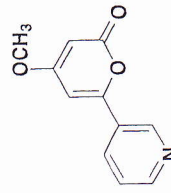
Anatabine



Dioscorine



Ricinine



Anibine

• TOBACCOS, *Nicotiana* spp., Solanaceae

The tobaccos, *N. tabacum* L., *N. rustica* L., and their multiple cultivars, are grown for the production of leaves for smoking. They are toxic plants which contain alkaloids, chiefly represented by nicotine, which is used in phytotherapy, and was introduced relatively recently in smoking cessation programs.

Although tobacco is economically and socially of tremendous importance, we shall mention only a few key points here. The history of tobaccos, their commercial production (aeronomy, processing, preparation, marketing), their toxicity, their

impact on public health, and the regulations that are applied to them have been the subject of many popular and scientific publications, which the interested reader may find useful.

In 1492, tobacco was already smoked, snuffed, and chewed in America; it was also used as a medicinal plant, and during magic and religious practices. In Europe, it was initially used as a medication; it was first planted in France by André Thévet* in 1556; it was recommended to the Queen of France, Catherine de Médicis, by Jean Nicot; it found success and its use spread rapidly: it was snuffed, chewed, and, beginning in the seventeenth century, smoked. The fact that some physicians denounced tobacco (already, even though it was as an enema that its decoctions were tested!), the excommunication which struck its use in churches (in 1628, i.e., 364 years before the French law that prohibits smoking in public places), and the implementation of a tax on tobacco (by French minister Richelieu, in 1629) all failed to slow the growth of its use. At first, in France, the privilege of tobacco sales was granted to the "Company of India" by the French political figure Colbert, in exchange for the payment of a tax. But the French government soon understood that it was probably in its best interest to control this product (and its profits! **), so the government took hold of the tobacco monopoly in 1674; this first French government monopoly on tobacco was a distant ancestor of today's *Société d'Exploitation Industrielle des Tabacs et Allumettes* (= SEITA).

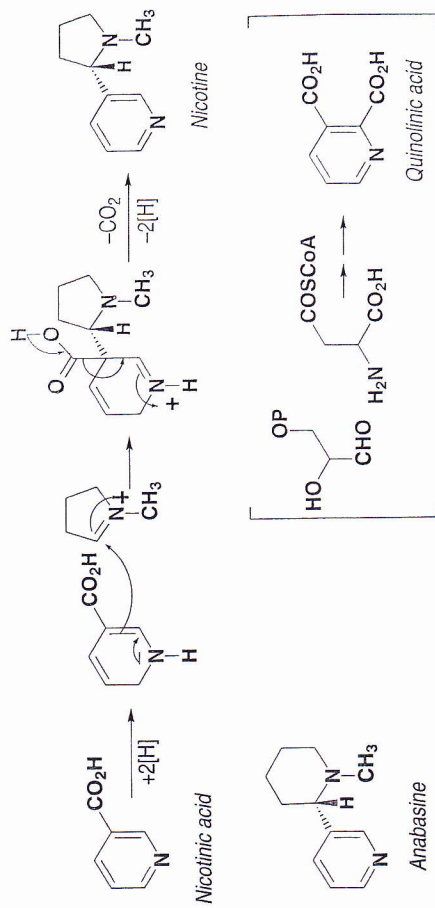
The Plant. The cultivated species are mostly *N. tabacum* varieties. This tobacco, also known as common tobacco, is an annual plant reaching 2 m in height, characterized by very large (50-70 x 30-45 cm), alternate, sessile or sheathing leaves, and by panicles of flowers with a tubulous flared corolla, ranging in color from pinkish to ruby red.

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—although the composition changes depending on the variety in question—anabasine, normnicotine,

* History has retained the name of J. Nicot, French Ambassador to Portugal (nicotine, *Nicotiana*), but botanists have in part repaired this injustice by creating the genus *Thevetia* (see cardiac glycosides). In any event, it is Christopher Columbus who brought the plant back from his first voyage.

** In France, the SEITA sales were 18.4 billion French francs (over 3 billion U.S. dollars) in 1997 (a 5.9% increase). Consumption: 90.3 billion units (94.8 billion units in 1995). As of January 5, 1998, the French tax on tobacco represented 77.54% of its price (see: <http://www.seita.fr>).



the *N*-oxidized derivatives of nicotine, *N*-acetylnicotines, nicotine, and myosmine; they also include anabasine and anatabine.

Nicotine is a strong volatile base. Its structure comprises a pyrrolidine and a pyridine ring, biosynthesized from putrescine and nicotinic acid, respectively. The formation of anabasine and other piperidine analogs involves lysine. As shown in the above figure, the formation of nicotine proceeds through the condensation of the *N*-methylpyrrolinium cation with a 1,2-dihydropyridine (enamine). The resulting product is decarboxylated, then it undergoes an oxidation which regenerates the pyridine ring.

Pharmacological Activity. The immediate toxicity of tobacco is linked to the presence of nicotine: the responsibility for the genesis of cancer is that of the combustion products, especially the nitrosamines arising from nicotine*. In the long run, nicotine is responsible for the genesis of cardiovascular and pulmonary diseases other than tumors. The lethal dose of nicotine is near 60 mg *per os* for an adult: the rate of elimination of the alkaloid and the tolerance, which develops rapidly, explain why smokers are not subject to acute intoxication, and why only beginners and non-smokers experience discomfort in a smoky environment (tachycardia, nausea). A smoker absorbs, by the pulmonary route, an estimated 1-3 mg of the 6-11 mg of nicotine contained, on average, in a cigarette; smoking a pack per day represents an alkaloid intake of about 20-50 mg.

Nicotine is readily absorbed through the mucosae and through the lungs. By transient stimulation followed by persistent depression of all autonomic ganglia, it acts:

* Is there a trend toward cigarette substitutes? Systems that deliver an aerosol composed of water, glycerin, oxides of carbon, and nicotine are being tested in several countries. On this topic and its inevitable legislative ramifications, see: Warner, K.E., Slade, J. and Sweator, D.T. (1997). The Emerging Market for Long-term Nicotine Maintenance, *JAMA*, 278, 1087-1092.

- on the CNS, which it stimulates up to the point of causing, if the dose is sufficient, tremors and convulsions; 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.

Uses. The only medical use of nicotine is to relieve the corresponding withdrawal symptoms during smoking cessation programs. For some patients, this type of treatment is efficacious, but for others, the long-term results have limited significance. Most of the published long-term clinical trials show that nicotine-based products are not much more efficacious than a placebo. Various authors conclude that these products, which are 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.

In France, two forms of nicotine are currently on the market:

- one form is a chewing gum containing 2 or 4 mg* of nicotine combined to a cationic resin and buffered with a carbonate (to improve the absorption of nicotine base). This formulation allows a slow release of the alkaloid and its perlingual absorption: about 50% of the nicotine is absorbed, in other words chewing a gum containing 4 mg gives a blood nicotine level similar to that which results from smoking one cigarette (hourly average);
- the other form is a transdermal nicotine system (patch). Nicotine patches are available in different sizes (10 to 30 cm²) and release 5-7 to 15-21 mg/24 h of nicotine. The largest patches give a plasma nicotine concentration equivalent to that which results from smoking 10 cigarettes/day on average. Local skin reactions (erythema) are common.

All nicotine-based products are contraindicated in pregnant and breast-feeding women, in children under the age of 15, and in case of recent myocardial infarction, angina, or severe cardiac arrhythmia. These products must be prescribed only as a part of a comprehensive smoking cessation program with strict medical follow-up.

Chronic smokers have developed tolerance, but non-smokers and children have not, therefore transdermal nicotine systems must be kept out of the reach of children, even after use: a used patch can still contain up to 30 mg of nicotine, far more than enough to represent a major risk.

* Nicotine is toxic and it is a controlled substance on French liste I, i.e., a prescription drug which may not be renewed, except in chewing gums containing not more than 2 mg per unit and not more than 200 mg per box, which are exempt (decree or *Arrêté* of March 5, 1997).

Other Use. Nicotine is traditionally used in phytopharmacy to treat aphid and other insect infestations (nicotine solutions titrated to contain 10-20 g/L nicotine sulfate, concentrated extracts).

Tobacco, a toxic plant. Because nicotine goes through the skin easily—its passage is enhanced by humidity (dew, sweat)—workers who harvest tobacco sometimes experience symptoms: vomiting, headaches, muscle weakness, and potential breathing difficulties. Vomiting is the principal symptom of the onset of intoxication in children who have ingested cigarette butts or other fragments.

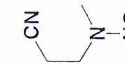
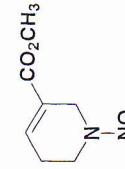
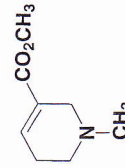
● **BETEL (NUT) PALM,**
Areca catechu L., Palmae

The seed of this palm tree, known as betel nut, is an ingredient of betel, a very popular masticatory in India and in southeast Asia where it is widely cultivated (India, Bangladesh).

The Drug, Origin, Composition, and Properties. 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 the south of China and the Philippines, in Malaysia, and in Indonesia; it is also found in eastern Africa (Tanzania). The seed is a hard ovoid mass (diameter = 2 cm) the color of cinnamon; it can be consumed fresh or after treatment with boiling water, or else after drying with or without preliminary slicing. Sometimes the whole fresh fruit is used (Taiwan).

Chemically, the drug contains 50-60% sugars, 15% lipids, flavan-3-ols and condensed tannins, and 0.2-0.5% alkaloids: arecoline, arecaidine, guvacine (tetrahydro-nicotinic acid), and guvacoline. The whole unripe fruit is particularly rich in phenolics: condensed tannins (9% of the dry weight), hydrolyzable tannins (7%), flavans (8.4%), and simple phenols (5.6%).

Arecoline is a parasymphathomimetic which acts on muscarinic receptors, and at high doses, on nicotinic receptors. This results in multiple actions: vasodilation, hypotension, and reflex tachycardia at low doses, stimulation of intestinal tone and peristalsis, increase in secretions (hypersalivation, sweating), myosis, and bladder contraction. Known and used as a taenicide in oriental medicine, the drug has been used as such, especially in veterinary medicine. Like many other acetyl-



cholinomimetics, arecoline has been tested with more or less success in senile patients suffering from Alzheimer-type dementia.

Traditional Use. Betel chewing probably originated in Malaysia (Penang). It is a very ancient social, religious, and cultural practice. It was documented more than two thousand years ago in China and India, a country where betel is celebrated in Ayurvedic medicine for many therapeutic virtues. 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 a betel leaf (*Piper betle* L., Piperaceae). Depending on the area, tobacco, gambir, or, in India, spices (nutmeg, cardamom, clove [*pan masala*]) are added to the preparation.

Betel has a reputation for being psychoactive, and according to Norton, it is used by 200 million persons worldwide, to whom it brings a sensation of well being and of greater capacity to act. Chewing betel turns the mouth red and the chewers spit frequently, their saliva also colored red by the oxidation products of the polyphenols contained in the drug. In invertebrate chewers, gums and teeth turn red and even black over time.

Betel chewing can induce oral submucous fibrosis of the mouth and oropharynx which, in the late stages, causes swallowing and speech difficulties. There is a correlation between the development of buccal cancers and the regular use of betel, as well as with submucous fibrosis. The later might be linked to the high levels of copper in betel nut. The development of cancer might be linked to the alkalinity, the tannins, and/or the cytotoxic and teratogenic *N*-nitrosamines formed from the alkaloids of the betel nut, particularly 3-(*N*-nitroso-*methylamino*)-*propionaldehyde* (= NMPA), which, in human buccal epithelium cells cultured *in vitro*, causes alterations of the normal cell morphology, growth, and differentiation, and induces DNA damage. Since tobacco consumption is commonly associated with that of betel, it increases the carcinogenic potential of the masticatory.

Various betel nut-based products are available outside of the areas where they originate (e.g., in the United States). There, they are used mostly in communities of immigrants.

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