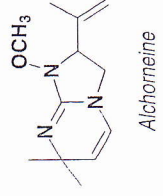
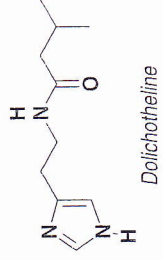
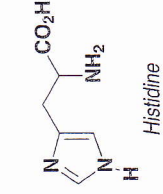


Alkaloids Derived from Histidine

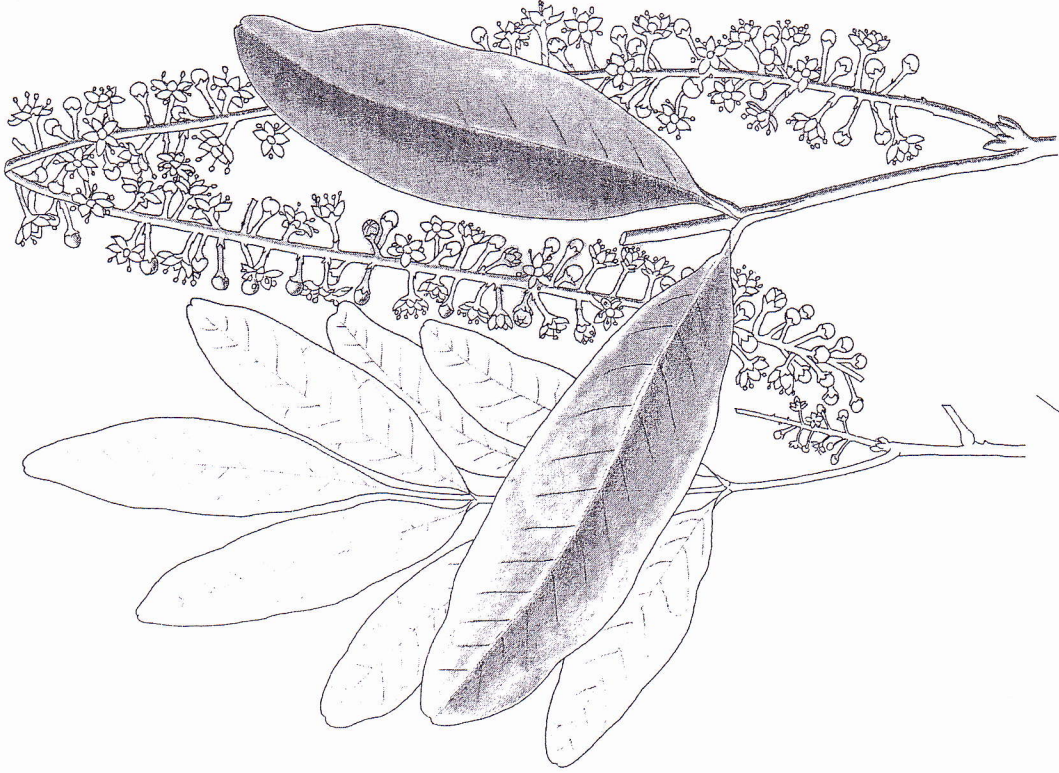
Imidazole Alkaloids

Although histidine and histamine are ubiquitous, alkaloids that possess an imidazole nucleus are very rare. They are found in some Rutaceae: leaves of the *Pilocarpus* of South America, seeds of *Casimiroa edulis* Llave & Lex. (a species with edible fruit from Mexico), and also in some Cactaceae (*Dolichotetele*), and in some Fabaceae. In some cases the imidazole ring is probably formed by a different mechanism, for example in the case of alchormeine (*A. floribunda* Muell. Arg., Euphorbiaceae) which may be considered a "hemiterpenoid" alkaloid.



- **JABORANDI,**
Pilocarpus microphyllus Stapf., Rutaceae

The 9th edition of the French Pharmacopoeia gave a description of the *Maranham jaborandi* and specified that "*P. jaborandi* and *P. pennatifolius* are also found in commerce [and] less rich in alkaloids". In 1982, Kaastra indicated: "the sources of the alkaloid are *P. microphyllus* and the related species *P. trachylophus*".



PILOCARPUS PENNATIFOLIUS Lamour.

Chemical structures are reproduced from: The Laboratory of Organic Chemistry, University of Groningen, The Netherlands.

season, but even so, their regeneration is insufficient to protect the exploited species from extinction. The leaves are then dried in the sun and sorted into commercial categories. For about 10 years, irrigated cultures have been developed in the state of Maranhão, which contributes 95% of the Brazilian production. The simultaneous cultivation of *Pilocarpus* and *Tagetes* (or *Sesamum*) is said to be an efficient means of controlling the nematodes that are the main threat to *Pilocarpus* cultures. The leaves are harvested mechanically, dried, and shipped to extraction facilities in Parnaíba, where pilocarpine salts are produced.

In South America, the term *jaborandi* designates miscellaneous drugs that belong to various families, including various species of Rutaceae of the genus *Pilocarpus*.

- **Maranhão jaborandi**, *P. microphyllus* Stapf. This is a slender shrub with imparipinnate leaves normally comprising seven small folioles (2.5 x 1-2.5 cm). The folioles are sessile (except for the apical one). They have an asymmetric blade with a deep notch at the apex and a prominent vein on the upper side; the blade is almost glabrous. The drug is bitter and aromatic, and chewing it triggers an increase in salivation.

- **Pernambuco jaborandi**, *P. jaborandi* Holmes. The folioles are large (4-12 x 2-4 cm) and their midrib is prominent on the lower side.

- **Paraguay jaborandi**, *P. pennatifolius* Lemaire. The blade of the folioles is grayish-green, not asymmetrical at the base, and has a papery texture; its lower side is either glabrous (var. *pennatifolius*) or else pubescent (var. *pilosus* Kaastra). The veins are only slightly anastomosed at the edge of the blade.

- **Ceara jaborandi**, *P. trachylophus* Holmes. The folioles are smaller than those of *P. jaborandi*, their blade is coriaceous, and covered, especially on the lower side, with curved trichomes.

- **Guadeloupe jaborandi**, *P. racemosus* Vahl. Its subspecies and varieties are characteristic of the Caribbean Islands.

Chemical Composition. The odor of the drug is due to the presence of 0.5% essential oil. The concentration of total alkaloids is nearly 0.7-0.8%; the chief constituent is (3*S*,4*R*)-(+)-pilocarpine. This is a lactone and it is fragile: in aqueous medium, it is readily hydrolyzed to pilocarpic acid and isomerized to isopilocarpine (3*R*,4*R*). The epimerization is very rapid in alkaline conditions, and involves an



enolate that is stabilized by mesomerization. Because of the lability of this compound, an adaptable and rapid method of extraction is required (defatting in acidic conditions, extraction in alkaline conditions, crystallization—difficult—of pilocarpine nitrate). The lability also complicates quality control and limits the storage time of solutions (hydrolysis, as well as epimerization, result in a loss of pharmacological activity).

Pharmacological Activity and Uses. Pilocarpine is a parasymphathomimetic. It induces salivary, gastric, and sweat hypersecretion; it increases intestinal motility, induces bronchoconstriction, and bradycardia.

In the eyes, pilocarpine causes the iris sphincter to contract and causes myosis, which leads to the opening of the space between the iris and the cornea, which in turn is expected to relieve narrow angle glaucoma; the contraction of the ciliary muscle, on the other hand, facilitates the flow of aqueous humor in case of wide angle glaucoma. By decreasing resistance to the outflow of aqueous humor, pilocarpine markedly decreases intraocular pressure.

Jaborandi leaves are used for the extraction of pilocarpine. This compound is used as its nitrate (eye drops at 1, 2, and 3%) or as its hydrochloride (eye drops at 1, 2, 3, and 4%), alone or in combination with phenylephrine. The normal indications are chronic simple (wide angle) glaucoma, acute congestive (narrow angle) glaucoma, and the diagnostic of the causes of mydriasis. Its use in near-sighted patients requires a preliminary examination of the retina (risk of retinal detachment). Side effects include myosis, induced upon instillation of the eye drops, and which can be a problem; transient headaches, and an increase in tear secretion. Because of these side effects, pilocarpine is generally not prescribed as an initial treatment. Combinations of pilocarpine and a beta-blocker (timolol or carteolol) were marketed in the late 1990s. Indicated especially in case of elevated intraocular pressure and chronic wide angle glaucoma, these combinations help some patients who do not respond to the conventional therapy with pilocarpine alone.

Pilocarpine (15 mg/day, *per os*) can be used as a sialagogue to relieve dryness of the mouth (for example, that due to the radiotherapy of mouth and throat cancers).

BIBLIOGRAPHY

- Kaastra, R.C. (1982). A Monograph of the Pilocarpinae (Rutaceae), Flora Neotropica n° 33, The New York Botanical Garden, New York.
- Pinheiro, C.U.B. (1997). *Jaborandi* (*Pilocarpus* sp., Rutaceae): A Wild Species and its Rapid Transformation into a Crop, *Econ. Bot.*, **51**, 49-58.
- Zimmerman, R.P., Mark, R.J., Tran, L.M. and Juillard, G.F. (1997). Concomitant Pilocarpine during Head and Neck Irradiation is Associated with Decreased Posttreatment Xerostomia, *Int. J. Radiation Oncology Biol. Phys.*, **37**, 571-575.