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Series

The Alkaloids. *Chemistry and Pharmacology*, 1950 —>, (became *The Alkaloids - Chemistry and Physiology* in 1983 [vol. 21 —>] then *The Alkaloids - Chemistry and Biology* [vol. 51 —>]). Initially edited by Manske, R.H.F. (1-17), then by Manske, R.H.F. and Rodrigo, R.G.A. (18-20), Brossi, A. (21-36 then 38-40), Brossi, A. and Suffness, M. (37), Brossi, A. and Cordell, G.A. (41, 45), Cordell, G.A. (42-44, 46—>), Academic Press, London (the latest volume is vol. 52 [1999]).

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See also

Alkaloids, The Royal Society of Chemistry, London, 13 volumes from 1972 to 1983; since 1984, the series has been merged with: *Natural Products Reports* (volume 16 in 1999).

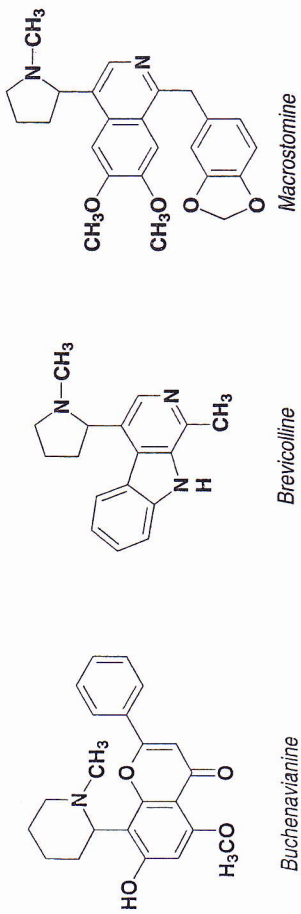
Alkaloids Derived from Ornithine and Lysine

Introduction

Two amino acids with four or five carbon atoms—ornithine and lysine—are at the origin of many alkaloids whose structure may be simple (pyrrolidines, such as hygrine from coca leaves, piperidines such as pelletierine from the pomegranate tree) or more complex. Structural complexity, in this group, translates into the formation, from several molecules of the amino acid, of polycyclic edifices: pyrrolizidines, indolizidines, quinolizidines (bi-, tri-, tetra-, and pentacyclic). The complexity may also arise from the participation of other precursors: acetate (tropanes, homotropanes, elaeocarpine), phenylalanine (phenanthroindolizidine, phenanthroquinolizidine), tryptophan (elaecarpine), phenylalanine (phenanthroindolizidine, anabasine), or phenylpropanoic acid (alkaloids of the Lythraceae).

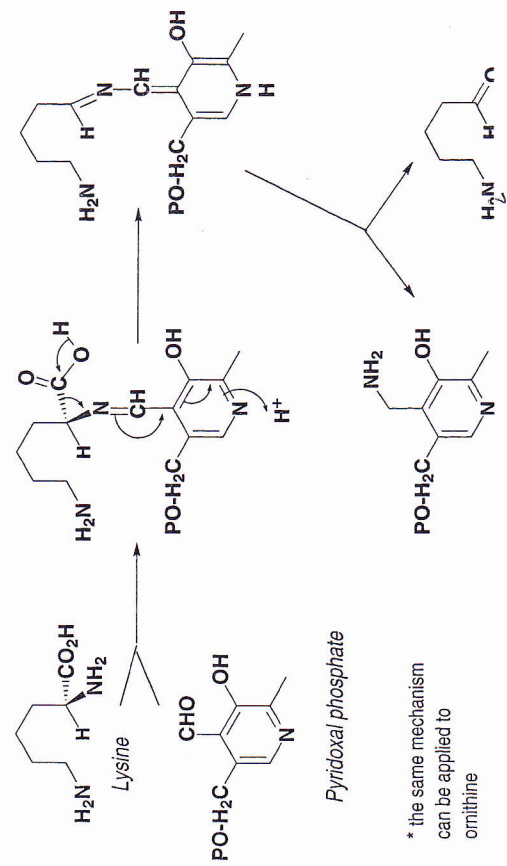
Also known are compounds in which a ring arising from ornithine (pyrrolidine) or lysine (piperidine) is combined with complex structures of the flavone type* (buchenavianine of *Buchenavia* sp. Eichl., Combretaceae, or ficine from *Ficus pantoniana* King., Moraceae), benzylisoquinoline (macrostomine from *Papaver macrostomum* Boiss. & E. Huet, Papaveraceae), or harmans (brevicolline from a Cyperaceae of the genus *Carex*).

* Structures of the same type are formed when nicotinic acid is involved, for example, the pyridine-type chromones of a medicinal plant from western Africa, *Schumanniohyton magnificum* (K. Schumann) Harms (Rubiaceae).

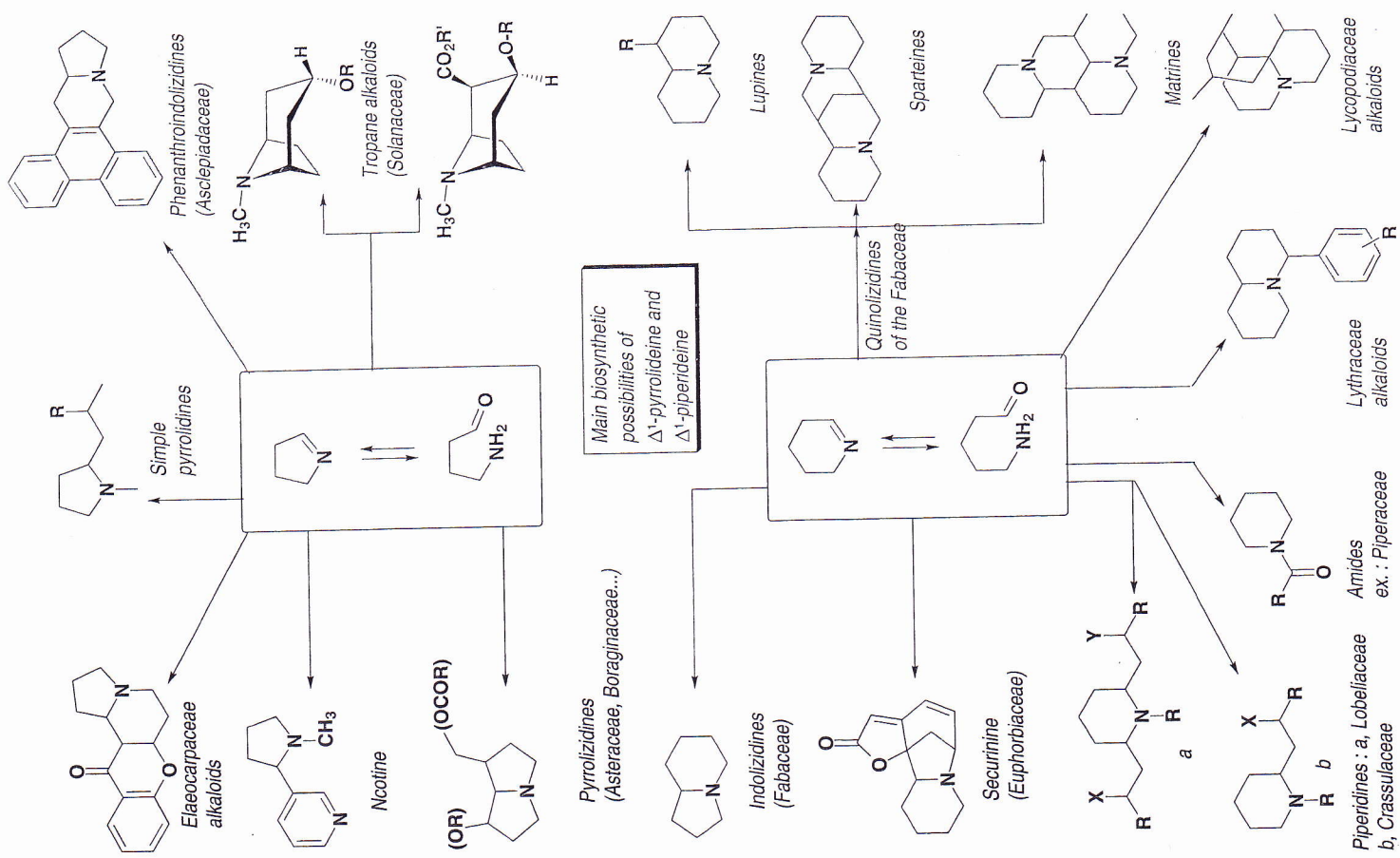


Experiments with ^{15}N -labeled amino acids show that it is the terminal nitrogen atom (δ or ϵ) which is incorporated; tritium labeling shows that as a general rule, the proton at C-2 is retained, which excludes the possibility that α -ketoacids (2-oxo-5-aminopentanoic or 2-oxo-6-aminohexanoic) are the precursors of the rings: it is more likely that aldehydes (4-aminobutanal and 5-aminopentanal), in equilibrium with the cyclic forms (Δ^1 -pyrrolidine and Δ^1 -piperidine), are the true precursors of the pyrrolidine- and piperidine-type structures.

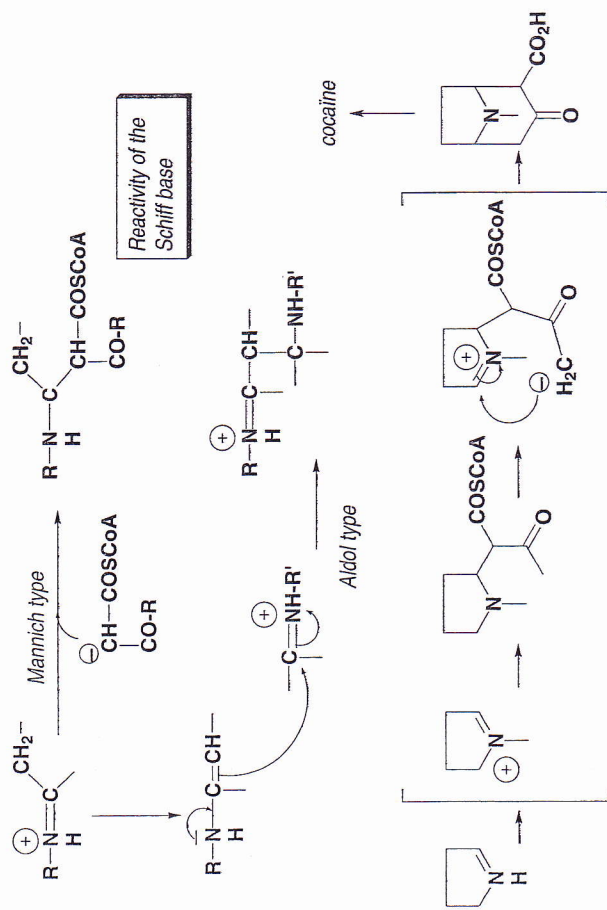
To account for the results of several labeling experiments, a global scheme has been proposed; it emphasizes the major role of enzymes whose coenzyme is pyridoxal phosphate. The latter forms an intermediate Schiff base whose hydrolysis to a diamine (putrescine or cadaverine) is less rapid than its cyclization, which explains why the incorporation of the precursor is very often asymmetrical. It is not uncommon, however, for the initial labeling (in the 6-position of lysine or in the 5-position of ornithine) to be evenly distributed (at the 2- and 6-position of piperidine, and at the 2- and 5-position of pyrrolidine, respectively), which proves that in certain plants, diamines, namely cadaverine and putrescine, are biosynthetic intermediates (see, among others, the origin of tropane alkaloids, p. 809, and the references on p. 831).



* the same mechanism can be applied to ornithine



Subsequently, the mechanisms that are likely to lead to the more complex structures can be envisioned through simple chemical reactions (formation of Schiff bases, Mannich condensation, aldol condensation). The *N*-methyl groups that are often found are generally provided by *S*-adenosylmethionine.



The pharmacological and therapeutic interest of the alkaloids derived from ornithine and lysine is very uneven. Some are currently used in therapy (atropine, scopolamine), while others are now of limited use (sparteine) or only of historical interest (lobeline, arecoline). Many ought to be known only because of their toxicity: pyrrolizidine alkaloids from Boraginaceae and Asteraceae that are often gifted with medicinal virtues, quinolizidine alkaloids of Fabaceae that are common in our environment because of their ornamental character, not forgetting nicotine in tobacco. A small number have an interesting potential, for example, some indolizidines (castanospermine) which are efficacious against retroviruses, or huperzine, which has been tested in the context of Alzheimer's disease.

Thus, we shall limit our coverage to these few examples, and we shall follow a chemical classification. The figure on page 803 gathers the most common alkaloid structural types that are related to ornithine and lysine.

Tropane Alkaloids

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Tropane alkaloids have in common a nitrogen-containing bicyclic structural element, namely azabicyclo[3,2,1]octane: they are 8-methyl-8-azabicyclo[3,2,1]octanes.

Approximately 200 alkaloids are known in this group, and they are distributed in a small number of Angiosperm families: Solanaceae (they are found in about twenty genera, e.g., *Anthocercis*, *Atropa*, *Brugmansia*, *Datura*, *Mandragora*, *Physalis*,