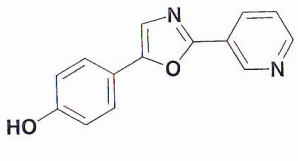
Alkaloids Derived from Phenylalanine and Tyrosine

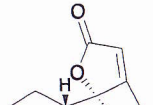
GENERALITIES

A very large number of alkaloid structures arise from the metabolism of aromatic amino acids (phenylalanine, tyrosine), and at first approximation, these are always isoquinoline alkaloids. In fact, we shall not consider here structures such as those of halfordinol or annuloline, which are oxazoles arising from the internal cyclization of cinnamamides such as withasomnine, a rare pyrazole derivative, or the diketopiperazines, which are mycotoxins.

Alkaloids elaborated from several amino acids are preferentially and arbitrarily considered derivatives of these other precursors: examples are the phenanthroindolizidines of the *Tylophora** and other Asclepiadaceae formed from ornithine, or securinine and its derivatives, in the metabolism of which lysine and Δ^1-piperideine are involved.

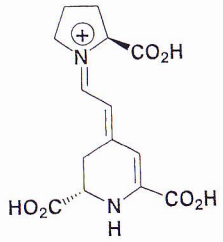


Halfordinol



Withasomnine

Securinine



Indicaxanthine

* Phenanthroindolizidines have amebicide properties and are active against *Candida*. Tylophorine, which is extracted from a plant traditionally used in India (*Tylophora asthmatica* Wight. and Arn., Asclepiadaceae) has been tried for the treatment of asthma but turned out to be toxic. Alkaloids of the same type occur in *Vincetoxicum* spp.

The betalains are also substances biosynthetically elaborated from phenylalanine and tyrosine, but they are not generally considered alkaloids, therefore we shall not cover them in this chapter.

For the sake of convenience, we shall include here, like most classical authors, certain aromatic amines such as ephedrine and mescaline: they do not strictly fit the definition of alkaloids, but they are generally considered as such. Moreover, they often occur in drugs which do contain true alkaloids, and they are their precursors (e.g., peyote).

The alkaloids derived from phenylalanine and tyrosine which will retain our attention are compounds in which the basic structural nucleus is an isoquinoline, or far more often, a 1,2,3,4-tetrahydroisoquinoline.

Biosynthetically, these structures arise from the reaction of the product of decarboxylation of the amino acid (phenylethylamine, tyramine) or of one of its homologs (dopamine) with another molecule, most often a second molecule of amino acid which has been deaminated (aldehyde or equivalent, i.e., an α-ketoacid). In rare cases, an isoprene unit may be involved, for example in Rubiaceae (*Psychotria*).

We shall distinguish, besides the phenethylamines, five main groups of alkaloids as a function of the nature of the precursor(s) which react(s) with the aromatic amino acid to form the final structure.

1. Simple Tetrahydroisoquinoline* Alkaloids

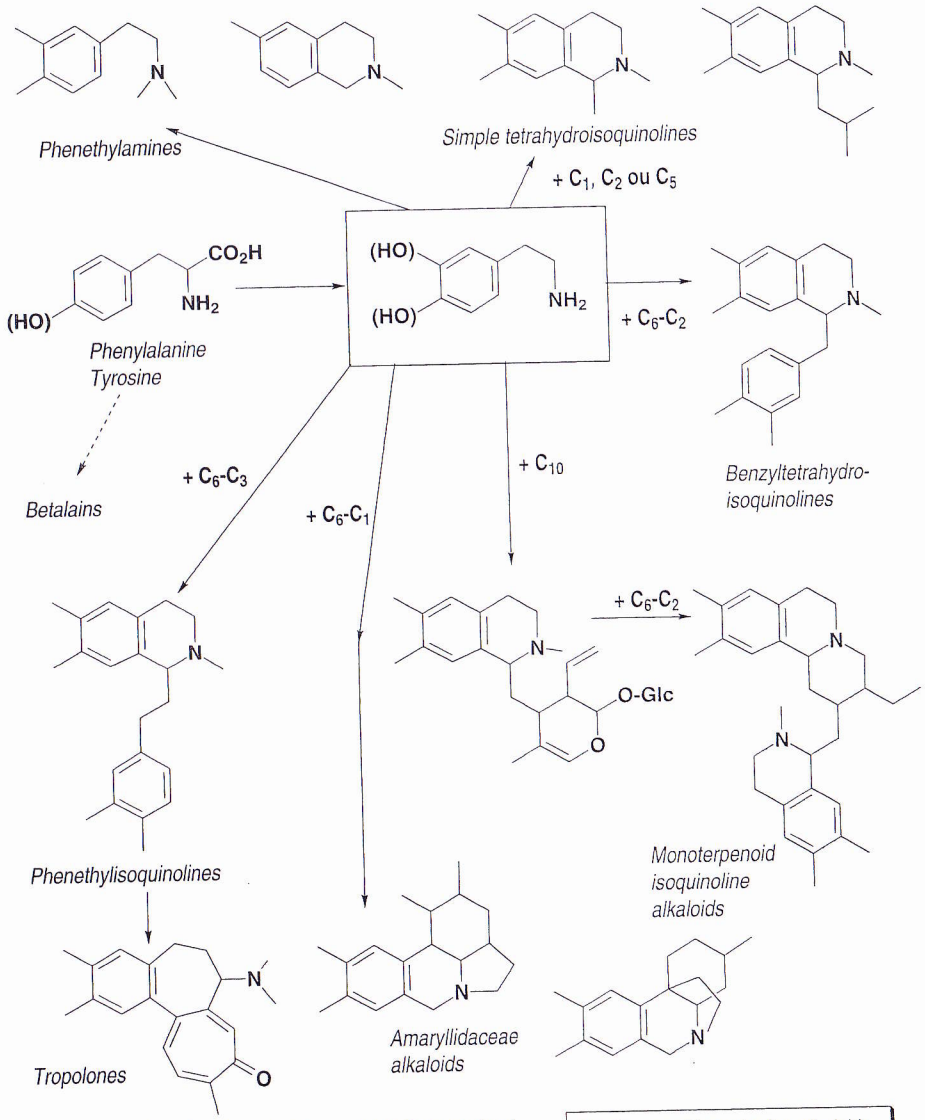
In this case, pyruvic acid or leucine reacts with the arylalkylamine to form a 1-alkyltetrahydroisoquinoline. The reaction with formaldehyde (or its equivalent) leads to a tetrahydroisoquinoline. These compounds are relatively rare, and are found in the Caryophyllales: Cactaceae (*Lophocereus, Pachycereus, Lophophora, Dolichotele*, and others), Chenopodiaceae (*Salsola*), but also in some of the Fabaceae (*Desmodium, Mucuna*). They are also found in most of the species known to elaborate benzylisoquinolines: whether these are isoquinolones or tetrahydroisoquinolines, it is likely that in the majority of cases, they are formed by oxidation of the benzyltetrahydroisoquinolines.

* Naphthylisoquinoline alkaloids are excluded here. These alkaloids occur in Ancistrocladaceae and Dionchophyllaceae, and they are biosynthesized from acetate *via* a poly-β-keto-ester. Certain naphthylisoquinolines, namely the michellamines A-F (atropisomeric dimers), completely inhibit the cell-killing effect of the HIV-1 and HIV-2 toward human lymphoid cells *in vitro*. These alkaloids and the compounds that are thought to be their monomeric precursors (the korupensamines C-E) are extracted from a vine collected in Cameroon (*Ancistrocladus korupensis* D. Thomas & Gereau). The michellamines act by inhibiting reverse transcriptase and at a later step, by inhibiting the formation of the syncytium. See: McMahon, J.B., Currens, M.J., Gulakowski, R.J., Buckheit, R.W., Lackman-Smith, C., Hallock, Y.F. and Boyd, M.R. (1995). Michellamine B, a Novel Plant Alkaloid, Inhibits Human Immunodeficiency Virus-induced Cell Killing by at Least Two Distinct Mechanisms, *Antimicrob. Agents Chemother.*, **39**, 484-488.

2. Benzyltetrahydroisoquinoline Alkaloids

(see figures on pp. 894-895)

Characterized by a C_6C_2-N-C_2C_6 nucleus, this is the most important subgroup from the standpoint of size (over 2,000 compounds have been described), and also structural variety and pharmacological potential. The basic nucleus arises from the reaction of the arylalkylamine with a second amino acid, tyrosine. The different



For the sake of clarity, the substituents have been omitted purposely (H ou CH_3 on the nitrogen atom; OH, OCH_3, O-CH...O or H on the aromatic carbon atoms).

Chief types of isoquinoline alkaloids

alkaloids in this group are characteristic of a certain number of families of the orders Magnoliales (according to Cronquist), Laurales, or Papaverales (Annonaceae, Magnoliaceae, Lauraceae, Monimiaceae, Papaveraceae, Fumariaceae). They also occur in several families of the Ranunculales (Berberidaceae, Menispermaceae, Ranunculaceae), and more sporadically in other families (Euphorbiaceae, Fabaceae).

3. Phenethylisoquinoline Alkaloids

As before, a second molecule of aromatic amino acid participates in the elaboration of a C_6C_2-N-C_3C_6 nucleus, but this time it is a phenylpropanoic acid (e.g., cinnamic acid). Homologous to the previous alkaloids—phenethylisoquinolines, bisphenethylisoquinolines, homoaporphines, homomorphinandienones, homoerythrinanes, dibenz[d,f]azecines—or rearranged to tropolones (e.g., *Colchicum* alkaloids), these compounds are fairly specific to the Liliaceae (*Androcymbium, Bulbocodium* [*Colchicum*], *Gloriosa, Kreysigia, Schelhammera*).

4. Alkaloids of the Amaryllidaceae

Again, two aromatic amino acids are required for the formation of the alkaloids, but one of the two loses one carbon atom to form a C_6C_2-N-C_1C_6 nucleus, which only occurs in members of this botanical family (e.g., *Clivia, Crinum, Galanthus, Haemanthus, Leucojum, Sprekelia, Sternbergia*).

5. Monoterpenoid Isoquinoline Alkaloids

These compounds incorporate a monoterpenoid unit, secologanin, according to a mechanism resembling the one which leads to monoterpenoid indole alkaloids; in fact, they occur in certain species of Rubiaceae, a family otherwise known to elaborate, from this seco-iridoid, a variety of alkaloidal structures (see the chapter on indole alkaloids).

The figure on the previous page summarizes the different pathways for the formation of alkaloids from phenylalanine and tyrosine.

Phenethylamines

1. INTRODUCTION

Phenethylamines occur in many plants. Some are species specific (ephedrine, mescaline, cathinone) and have marked pharmacological properties, others are common products of the metabolism of aromatic amino acids such as tyramine or phenylethylamine. Although the concentration of these decarboxylation products in edible or medicinal plants is too low to induce harmful effects, it is sometimes sufficient to play a role in the onset of an attack of migraine. The effects of these amines, particularly tyramine, can become serious in patients treated with MAO inhibitors: tyramine is no longer metabolized in the intestine and liver, and a risk of hypertensive crisis ensues. Therefore, it is necessary to monitor the consumption of certain drugs by these patients (e.g., broom flowers), as well as certain vegetables (avocado, cabbage, cucumber, spinach) and certain other foods (cheese).