

CHAPTER VI

PIPERIDINE ALKALOIDS

Piperidine is one of the basic constituents in pepper (Piper nigrum Linn. of Piperaceae), tobacco (Nicotiana tabacum Linn. of Solanaceae), and Petrosimonia monandra (Pall.) Bge., Chenopodiaceae; 1.33% as well as in Psilocaulon absimile N.E.Br., Aizoaceae; 4.5%. N-Methylpiperidine constitutes 1% of the green parts of Girgensohnia diptera Bge., Chenopodiaceae, where it is associated with the alkaloid dipterine⁽¹⁷⁸⁾. The piperidine nucleus also occurs throughout the lobelia, poison hemlock, adenocarpus, cassia, and pomegranate alkaloids. In addition, it is present in a fused state in many other alkaloids such as coca, solanaceous, lupine and even morphine groups. Much of the work in the piperidine series has been aimed at the synthesis of these alkaloidal products, or the preparation of synthetic substances with similar properties. A very large number of compounds have been made for testing as local anaesthetics, the structures of which were patterned after cocaine and contained the piperidine nucleus. Compounds patterned after the belladonna alkaloids have been made and tested as mydriatics. Since the discovery of Demerol, there have been several studies of piperidine compounds as simpler models of the morphine structures⁽¹⁷⁹⁾.

The numbering in the piperidine system is the same as that in the pyridine types⁽¹⁷⁹⁾.

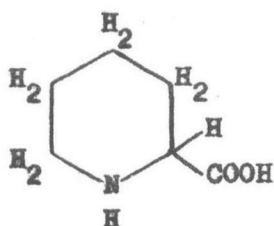


Numbering systems in the piperidine ring.

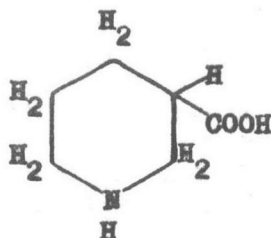
The radical ($C_5H_{10}N$) is known as the piperidyl radical. A compound such as $C_5H_{10}NCH_3$, in which the substituent is on the nitrogen atom, can be named 1-piperidylmethane or piperidinomethane. The "-ine" ending is reserved for piperidine derivatives substituted on the nitrogen atom. The names of piperidine derivatives are often derived from those of the corresponding pyridine compound simply by inserting "-pe-" after the first syllable; accordingly, 2-methylpiperidine may be referred to as 2-pipecoline⁽¹⁷⁹⁾.

1. The Chemical Nature of the Piperidine Alkaloids

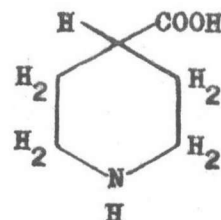
The chemistry of piperidine is primarily that of a secondary amine. Since the six-membered ring in piperidine is saturated, there exist all the possibilities of optical and geometrical isomers that are found in the cyclohexane series. Because the piperidine ring is not completely symmetrical, the position of the groups on the ring is also important in determining the number of such isomers. Accordingly, pipecolinic acid possesses an asymmetric carbon atom and exist in d- and l-forms. Both of these have been obtained. The same consideration applies for the isomeric nipecotinic acid, but the isonipecotinic acid molecule contains a plane of symmetry⁽¹⁷⁹⁾.



Pipecolinic acid

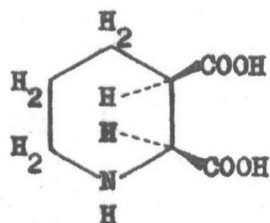
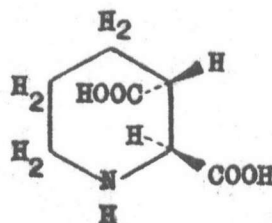


Nipecotinic acid



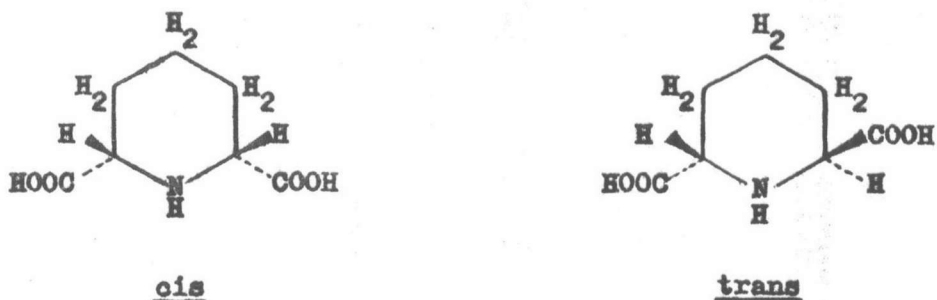
Isonipecotinic acid

In the case of piperidine-2,3-dicarboxylic acid (hexahydroquinolinic acid), not only are there two asymmetric carbon atoms, but the ring also allows the existence of cis and trans isomers. It therefore exists in two stereochemical modifications, both of which have been resolved.

cistrans

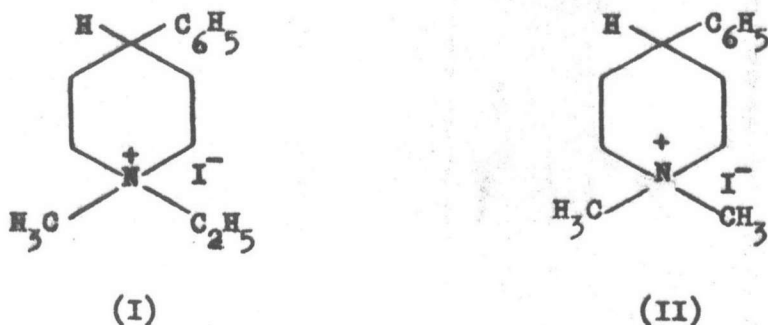
Piperidine-2,3-dicarboxylic acids

A similar argument applies to the isomeric piperidine-3,4-dicarboxylic acid, but piperidine-2,6-dicarboxylic acid contains two identical asymmetric centres and therefore exists in cis and trans forms, only the latter of which may be resolved, since the cis form is a meso modification⁽¹⁷⁹⁾.



Piperidine-2,6-dicarboxylic acids

Another interesting example is the cis and trans isomerism of a quaternary compound such as (I) and the lack of such isomerism in (II) in which the two alkyl groups on the nitrogen atom are identical. The stereochemical considerations for the quaternary nitrogen atom are therefore the same as for the carbon atom⁽¹⁷⁹⁾.



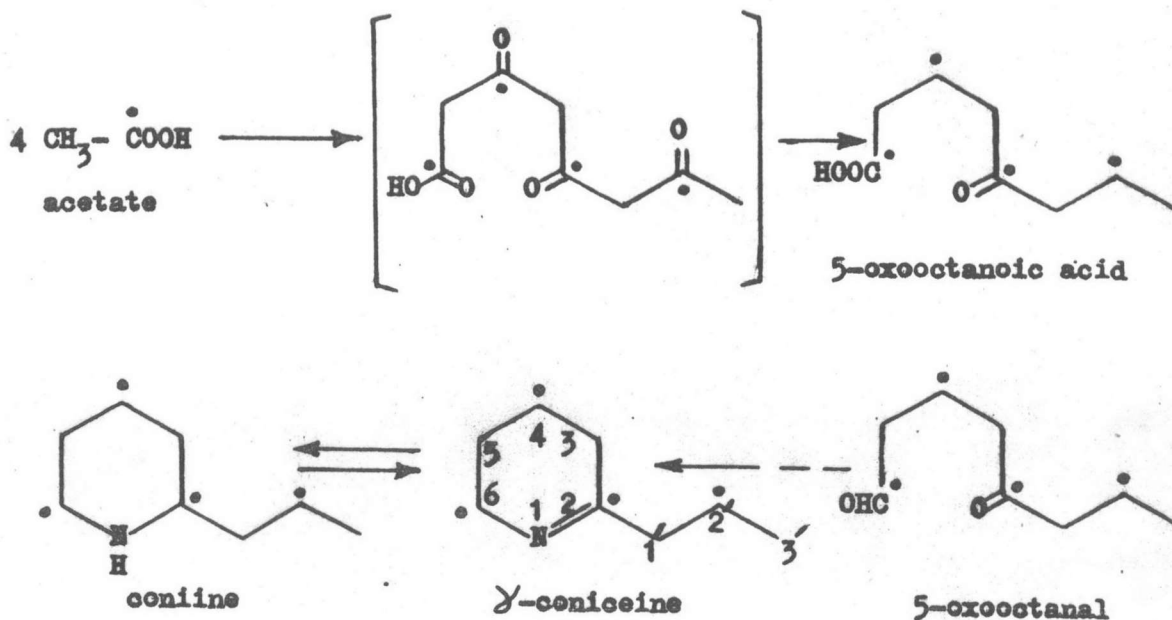
2. Biogenesis of Piperidine Alkaloids

Piperidine alkaloids have more than one biosynthetic route. The piperidine ring arises by at least two biosynthetic routes. One derived from the acetate hypothesis e.g. conine, pinidine and the other from lysine.

2.1 Biosynthesis of Piperidine Alkaloids Derived from Acetate

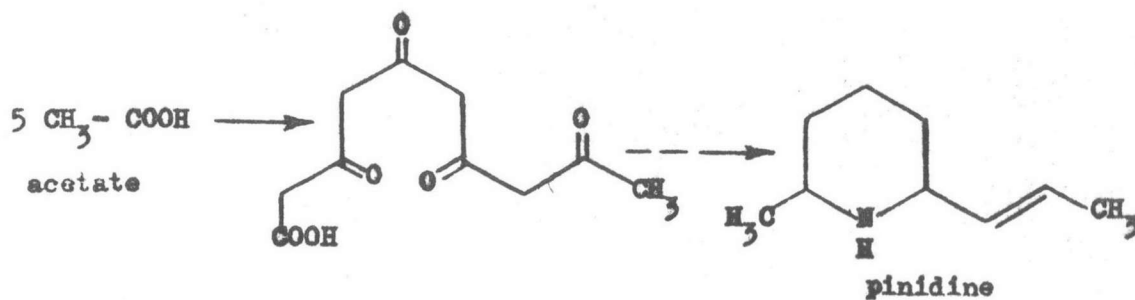
Formation of Poison Hemlock Alkaloids and Pinidine

Alkaloids of the conine type have been found up until now in a few higher plants, besides Conium maculatum Linn., the poison hemlock. In contrast to the Solanaceae, the aerial parts of poison hemlock are the main sites of alkaloid synthesis. The Conium alkaloids probably originate from four molecules of acetate via an intermediate polyketide. After feeding acetate-1-¹⁴C, carbon atom 2, 4, 6, and 2' of γ -coniceine and conine were radioactive as shown below. 5-Oxo-octanoic acid and 5-oxo-octanal are the intermediate precursors of γ -coniceine. γ -Coniceine is easily converted to D-conine and vice versa⁽¹⁸⁰⁾. The natural D-isomer is much more efficiently converted than L-conine⁽¹⁸¹⁾.

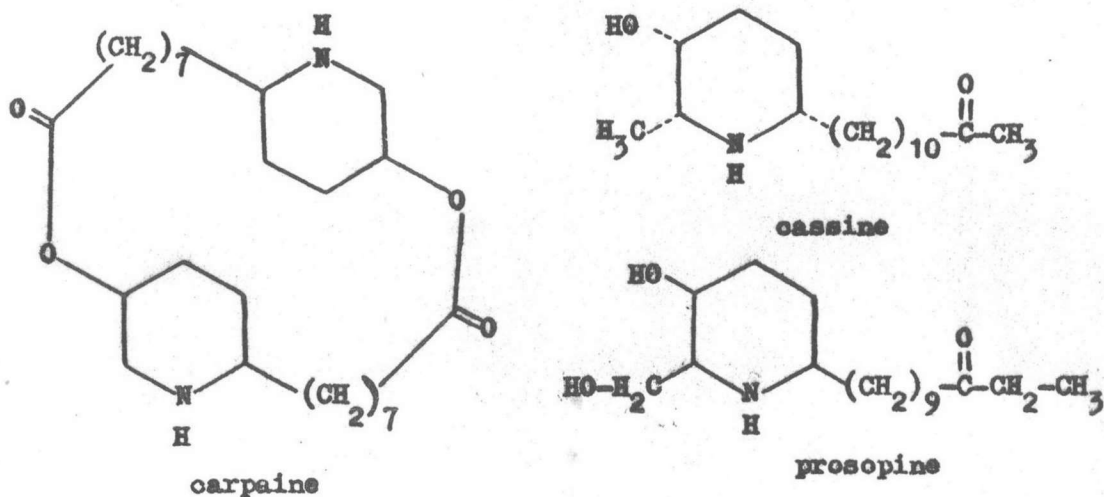


Biosynthesis of γ -coniceine and conine

Pinidine is found in various species of pine, including Pinus jeffreyi Balfour. The pinidine isolated after feeding $[1-^{14}\text{C}]$ acetate to P. jeffreyi Balfour was degraded to reveal essentially all the activity located at the four position expected of a linear combination of five acetate units. The biosynthetic pathway to pinidine is similar to that of the poison hemlock alkaloid conine as shown below⁽¹⁸²⁾.



In the case of the piperidine alkaloids, carpaine, cassine, and prosopine as shown below, which have been isolated from species of Carica, Azima, Cassia, and Prosopis, synthesis via the polyketides is postulated. No proof has, as yet, been put forward⁽¹⁸⁰⁾.



The structural formulae of some piperidine alkaloids

2.2 Biogenesis of Piperidine Alkaloids Derived from Lysine

Five of the carbon atoms of L-lysine (I) (C-2 to C-6) are incorporated into the piperidine ring of these base in a manner which does not allow carbon 2 and 6 of lysine to become equivalent, i.e. no symmetrical intermediates are permissible⁽¹⁸³⁾.

An eminently reasonable hypothesis which fits all the evidence is shown in Fig. X, p. 67. For those alkaloids derived from lysine without the intervention of a symmetrical intermediate, cadaverine formed by decarboxylation of lysine must remain enzyme-bound and therefore unsymmetrical. Exogenous cadaverine enters the pathway at this point by absorption on to the enzyme to give (IV). In order to explain the incorporation of lysine into some alkaloids by way of a symmetrisation step it is necessary only to postulate equilibration of bound with unbound cadaverine. The proposal that pyridoxal phosphate is involved in this pathway is more than mechanistically attractive, for L-lysinedecarboxylase and diamine oxidase, the two enzymes whose participation in the conversion of lysine into Δ^1 -piperideine (V) is likely, both require pyridoxal phosphate as a co-factor⁽¹⁸³⁾. From Δ^1 -piperideine (V), piperidine alkaloids are synthesised.

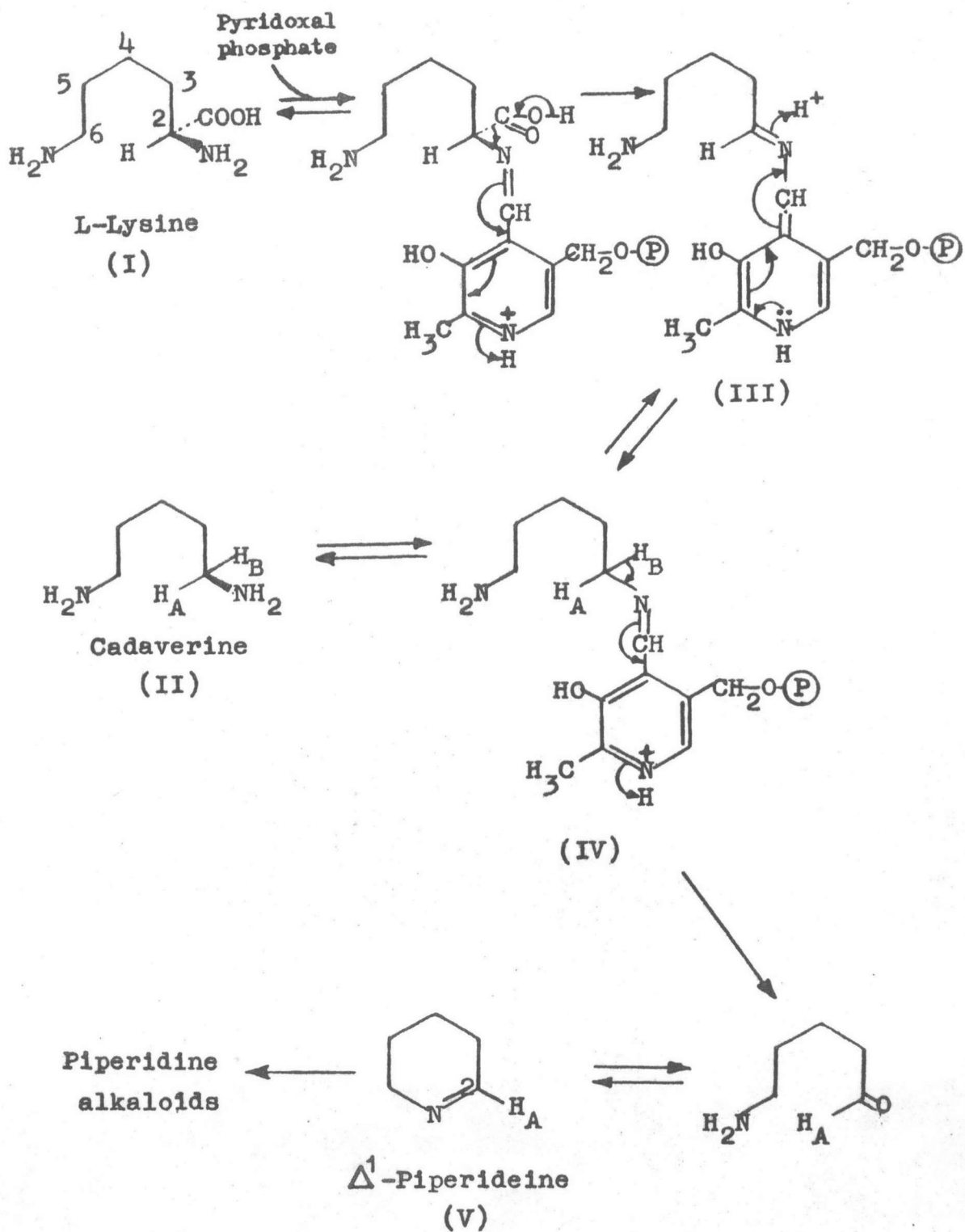


Figure X. General biosynthesis of piperidine alkaloids derived from lysine.

2.3 Piperidine Alkaloids Bearing Plants

Botanical origin	Piperidine alkaloid	Reference
<u>Acacia pentadenia</u> Lindl. (Mimosaceae) (fresh plant)	4-Hydroxypipericolic acid 5-Hydroxypipericolic acid	184
<u>A. retinodes</u> Schlecht. (<u>A. neriifolia</u> A. Cunn.)	4-Hydroxypipericolic acid 5-Hydroxypipericolic acid	184
<u>A. willardiana</u> Rose (seed)	4-Hydroxypipericolic acid	185
<u>Acalypha indica</u> Linn. (Euphorbiaceae)	Triacetoneamine	186
<u>Achillea atrata</u> Linn. (Compositae)	1-Homostachydrine	186
<u>A. millefolium</u> Linn.	N-Acylpiperidine	187
<u>A. moschata</u> Jacq.	1-Homostachydrine	186
<u>Adenocarpus foliosus</u> DC. (Papilionaceae) (leaf)	d-Adenocarpine d-Santiaguine	188
<u>A. grandiflorus</u> Boiss. (Papilionaceae) (leaf)	dl-Adenocarpine l-Adenocarpine Isoorensine Orensine d-Santiaguine l-Santiaguine	189

Botanical origin	Piperidine alkaloid	Reference
<u>Adenocarpus intermedius</u> DC. (<u>A. commutatus</u> Guss.; <u>A. complicatus</u> J. Gay; <u>A. parvifolius</u> DC.) (Papilionaceae) (leaf)	dl-Adenocarpine l-Adenocarpine Isoorensine d-Santiaguine	190 191 192,193 190,191
<u>A. mannii</u> Hook. (leaf, branch)	d-Adenocarpine α, β' -Dipiperidine Isoorensine Santiaguine	194
<u>A. viscosus</u> Webb et Berth. (<u>A. anagyris</u> Spreng.)	d-Adenocarpine	184
<u>Albizzia lophantha</u> Benth. (Mimosaceae) (fresh plant)	4-Hydroxypipelic acid	184
<u>Allium ursium</u> Linn. (Alliaceae)	Pipelic acid	195
<u>Ammodendron conollyi</u> Bunge (Papilionaceae) (leaf)	d-Ammodendrine dl-Ammodendrine	196 197,198
<u>Anabasis aphylla</u> Linn. (Chenopodiaceae)	Anabasamine Anabasine l-N-Methylanabasine	199 184 186

Botanical origin	Piperidine alkaloid	Reference
<u>Armerria maritima</u> Willd. (Plumbaginaceae) (leaf)	4-Hydroxypipericolic acid	200
<u>Astrocasia phyllanthoides</u> Robinson et Millsp. (Euphorbiaceae)	Astrocasine Astrophylline	201
<u>Azima tetracantha</u> Lamk. (Salvadoraceae)	Azacarpine Azimine	186
<u>Baikiaea plurijuga</u> Harms (Caesalpinaceae) (seed, wood)	5-Hydroxypipericolic acid Pipericolic acid	202
<u>Bathiorhamnus cryptophorus</u> R. Capuron (Rhamnaceae) (leaf)	Cryptophorine Cryptophorinine	203
<u>Boehmeria cylindrica</u> Sw. (Urticaceae) (whole fruiting plant)	3,4-Dimethoxy- ω -(2'-piperidyl)- acetophenone	204
<u>B. platyphylla</u> D. Don (whole plant)	3,4-Dimethoxy- ω -(2'-piperidyl)- acetophenone	205
<u>Calliandra haematocephala</u> Hassk. (Mimosaceae) (leaf)	1-4,5-Dihydroxypipericolic acid	206
<u>Campanula medium</u> Linn. (Campanulaceae) (seed)	Campidine 1-Lobeline	207

Botanical origin	Piperidine alkaloid	Reference
<u>Carica dodecaphylla</u> Vell. (Caricaceae)	Carpaine	186
<u>C. hastata</u> Brign.	Carpaine	186
<u>C. papaya</u> Linn. (leaf)	Carpaine Pseudocarpaine	208
<u>Cassia carnaval</u> Speg. (Caesalpiaceae) (leaf)	Carnavaline Cassine Prosopinone	50 49
<u>C. excelsa</u> Shrad. (leaf)	Casselsine Cassine	7
<u>C. jahnii</u> Britton et Rose (leaf)	Dihydrocassine Cassine	80
<u>C. spectabilis</u> DC. (leaf, seed)	Cassine Cassinicine Iso-6-carnavaline Iso-6-cassine Spectaline Spectalinine	16,137 16 137 15,137 137
<u>Ceratonia siliqua</u> Linn. (Caesalpiaceae)	5-Hydroxypipicollic acid	202

Botanical origin	Piperidine alkaloid	Reference
<u>Cerbera ahouai</u> Linn. (<u>Thevetia ahouai</u> A. DC.) (Apocynaceae)	Carpaine	186
<u>Coelidium fourcadei</u> Compton (Papilionaceae) (branch, leaf)	dl-Ammodendrine	209
<u>Conium maculatum</u> Linn. (Umbelliferae)	Conhydrine dl-Conhydrine d- and l-Coniine d- and l-Methylconiine 2-Methylpiperidine Pseudoconhydrine	184 210 184 186 184
<u>Croton humilis</u> Linn. (Euphorbiaceae)	Glutarimide peptides	211
<u>Cryptocarya pleurosperma</u> C.T. White et Francis (Lauraceae) (leaf)	Pleurospermine	212
<u>Cytisus</u> sp. (Papilionaceae)	Isoorensine l-Santiaguine	186
<u>Dichroa febrifuga</u> Lour. (Saxifragaceae) (leaf, root)	Febrifugine	213

Botanical origin	Piperidine alkaloid	Reference
<u>Duboisia myoporoides</u> R. Br. (Solanaceae) (leaf)	Anabasine dl-Isopelletierine	214
<u>Gaillardia pulchella</u> Foug. (Compositae)	Neopulchellidine Pulchellidine	215 216
<u>Genista hystrix</u> Lange (<u>Retama hystrix</u> Lange) (Papilionaceae)	Sphaerocarpine	217
<u>G. monosperma</u> Boiss. (<u>Retama monosperma</u> Boiss.)	d-Ammodendrine	186
<u>G. sphaerocarpa</u> Lamk. (<u>Retama sphaerocarpa</u> Lamk.) (seed)	Sphaerocarpine	218
<u>Girgensohnia diptera</u> Bunge (Chenopodiaceae)	Girgensonine N-Methylpiperidine	186 184
<u>G. oppositiflora</u> Pall. (Chenopodiaceae) (the green plant)	Girgensonine N-Methylpiperidine	219
<u>Haloxylon salicornium</u> Bunge (Chenopodiaceae)	l-Halosaline Piperidine	220,221 220

Botanical origin	Piperidine alkaloid	Reference
<u>Himantandra baccata</u> Bail. (<u>Galbulimima baccata</u> Bail.) (Himantandraceae) (bark)	Himbacine Himgravine	222,223
<u>H. belgraveana</u> F. Muell (<u>G. belgraveana</u> Sprague) (Himantandraceae) (bark)	Himandravine Himbacine Himbeline	222,223
<u>Isotoma longiflora</u> Presl (Lobeliaceae) (fresh herb)	Lobelanidine 1-Lobeline	224
<u>Julocroton camporum</u> (Euphorbiaceae)	Julocrotine	225
<u>J. montevidensis</u> Klotzsch (root)	Julocrotine	225,226
<u>J. subpannosus</u> Muell.	Julocrotine	225
<u>Laburnum vulgare</u> J. Presl (<u>L. anagyroides</u> Medic.) (Papilionaceae)	Pipecolic acid	195
<u>Lathyrus</u> sp. (Papilionaceae)	Pipecolic acid	195
<u>Leucaena glauca</u> Benth. (Mimosaceae) (leaf)	5-Hydroxypipecolic acid	227

Botanical origin	Piperidine alkaloid	Reference
<u>Lobelia cardinalis</u> Linn. (Lobeliaceae)	Lobenaline Lobeline	228 229
<u>L. decurrens</u> Cav.	1-Lobeline	230
<u>L. elongata</u> Small	Lobenaline	186
<u>L. inflata</u> Linn.	8,10-Diethyl-lobelidiol dl-8-Ethyl-10-phenyl-norlobelidiol 8-Ethyl-10-phenyl-norlobelidione 1-8-Ethyl-10-phenyl-norlobelionol dl-Lelobanidine-I 1-Lelobanidine-I 1-Lelobanidine-II Lobelanidine Lobelanine dl-Lobeline 1-Lobeline dl-8-Methyl-10-ethyl-lobelidiol d-8-Methyl-10-phenyl-lobelidiol d-Norlelobanidine Norlobelanidine Norlobelanine 1-8-Phenyl-lobelol-I d-8-Phenyl-norlobelol-I	184
<u>L. nicotianaefolia</u> Heyne	1-Lelobanidine-II 1-Lelobanidine-III Lobelanidine 1-Lobeline Norlobelanidine	231 184

Botanical origin	Piperidine alkaloid	Reference
<u>Lobelia polyphylla</u> Hook. (Lobeliaceae) et Arn.	Norlobelanidine	232
<u>L. puberula</u> Michx.	Lobeline	229
<u>L. radicans</u> Thunb.	Lobelanine l-Lobeline	233
<u>L. salicifolia</u> Sweet (leaf, root, stem)	Lobelanidine d- and l-Lobelanine dl-Lobeline Norlobelanidine Norlobelanine	234
<u>L. sessilifolia</u> Lamb.	l-Lobeline Norlobelanine	235
<u>L. syphilitica</u> Linn.	l-cis-8,10-Diethyl-lobelionol 8,10-Diethyl-norlobelidione cis-8,10-Diethyl-norlobelionol Norlobelanine	221 186
<u>L. tupa</u> Linn. (leaf, root, stem)	Lobelanidine Lobelanine l-Lobeline Norlobelanine	236

Botanical origin	Piperidine alkaloid	Reference
<u>Lobelia urens</u> Linn. (Lobeliaceae)	Lobelanidine l-Lobeline	237
<u>Lupinus formosus</u> Greene (Papilionaceae) (whole plant)	d-Ammodendrine l-Anabasine d-N-Methylammodendrine l-N-Methylanabasine dl-N-Methylisopelletierine Smipine	238
<u>Lysiloma bahamensis</u> Benth. (<u>L. latisiliqua</u> Benth.) (Mimosaceae) (seed)	4-Hydroxypipelic acid	185
<u>Lythrum anceps</u> Makino (Lythraceae)	Lythranidine Lythranine	239
<u>Medicago sativa</u> L. Grimm (Papilionaceae) (seed)	l-Homostachydrine	240
<u>Morus alba</u> Linn. (Moraceae) (leaf)	5-Hydroxypipelic acid Pipelic acid	241
<u>Nanophyton erinaceum</u> Bunge (<u>N. caspicum</u> Less.) (Chenopodiaceae)	l-2,6-Dimethylpiperidine l-1,2,6-Trimethylpiperidine	184

Botanical origin	Piperidine alkaloid	Reference
<u>Nicotiana acuminata</u> Hook. (Solanaceae)	dl- and l-Anabasine	184
<u>N. alata</u> Link et Otto (<u>N. affinis</u> Hort.)	dl- and l-Anabasine	184
<u>N. debneyi</u> Domin	dl- and l-Anabasine	184
<u>N. glauca</u> R. Grah. (leaf, root)	dl- and l-Anabasine	242,243
<u>N. glutinosa</u> Linn.	l-Anabasine	184
<u>N. langsdorffii</u> Schrank	l-Anabasine	184
<u>N. longiflora</u> Cav.	l-Anabasine	184
<u>N. paniculata</u> Linn.	l-Anabasine	184
<u>N. rotundifolia</u> Lindl. (<u>N. suaveolens</u> Lehm.)	l-Anabasine	184
<u>N. rustica</u> Linn.	l-Anabasine	184
<u>N. silvestris</u> Speg. et Comes	l-Anabasine	184
<u>N. tabacum</u> Linn. (root)	Anabasine Anatalline l-N-Methylanabasine Piperidine	184 244 184

Botanical origin	Piperidine alkaloid	Reference
<u>Nicotiana texana</u> Hort. (Solanaceae)	Anabasine	184
<u>Nitraria schoberi</u> Linn. (Zygophyllaceae)	Nitramine	245
<u>Nuphar japonicum</u> DC. (Nymphaeaceae) (rhizome)	Anhydronupharamine Nuphamine Nupharamine	246 247
<u>N. luteum</u> Sibth. et Sm. ssp. <u>variegatum</u>	Epinuphamine	248
<u>N. variegatum</u> Engelm. (rhizome)	3-Epinupharamine Nuphenine	246 249
<u>Oncinotis nitida</u> Benth. (Apocynaceae)	Iso-oincinotine Neo-oincinotine Oncinotine	187
<u>Parietaria officinalis</u> (Urticaceae) Linn.	.d- and l-Coniine	186
<u>Peganum harmala</u> Linn. (Zygophyllaceae) (seed)	1-4-Hydroxypipericolic acid	250
<u>Petrosimonia monandra</u> (Chenopodiaceae) ^{Bunge}	Piperidine	184

Botanical origin	Piperidine alkaloid	Reference
<u>Phaseolus vulgaris</u> Linn. (Papilionaceae) (seed)	l-Pipecolic acid	251
<u>Phoenix dactylifera</u> Linn. (Palmae) (fruit)	5-Hydroxypipecolic acid Pipecolic acid	227 202
<u>Pinus jeffreyi</u> Balfour (Pinaceae) (needle)	Pinidine	252
<u>P. sabiniana</u> Dougl. (needle and twig)	Pinidine d- α -Pipecoline	252
<u>P. torreyana</u> Parry (needle)	Pinidine	252
<u>Piper aurantiacum</u> Wall (Piperaceae) (fruit)	Piperettine Piperine	253
<u>P. chaba</u> Blume	Piperine	184
<u>P. clusii</u> C. DC.	Piperine	184
<u>P. famechoni</u> Heckel	Piperine	184
<u>P. geniculatum</u> Sw.	Piperine	184

Botanical origin	Piperidine alkaloid	Reference
<u>Piper guineense</u> Schum. et (Piperaceae) Thom (fruit, root)	4,5-Dihydro-2-methoxy- piperine 4,5-Dihydropiperine Piperine Wisanine	254 242
<u>P. longum</u> Linn.	Chavicine Piperine	221 184
<u>P. lowong</u> Blume	Piperine	184
<u>P. nigrum</u> Linn. (fruit)	Chavicine Piperettine Piperidine Piperine Piperoleine-A Piperoleine-B	184 256 184 257
<u>P. novae-hollandiae</u> Miq.	4,5-Dihydropiperine	209
<u>P. officinarum</u> C. DC. (<u>P. chaba</u> Hunter)	Chavicine Piperine	221 184
<u>Pongamia glabra</u> Vent. (Papilionaceae)	4,5-Dihydroxy-1-methyl- pipecolic acid	258

Botanical origin	Piperidine alkaloid	Reference
<u>Prosopis africana</u> Taub. (Mimosaceae)	Isoprosopinine-A Isoprosopinine-B Prosopfrine Prosopfrinine Prosophylline Prosopine Prosopinine	259
<u>P. spicigera</u> Linn.	Spicigerine	260
<u>Psilocaulon absimile</u> N.E.Br. (Aizoaceae)	Piperidine Piperine	184 186
<u>Punica granatum</u> Linn. (Punicaceae) (bark)	dl-Isopelletierine l-Isopelletierine dl-Methylisopelletierine N-Methylpelletierine dl-Pelletierine l-Pelletierine ψ-Pelletierine Pseudopelletierine	184 186 261 184
<u>Rhapis flabelliformis</u> Ait. (Palmae)	5-Hydroxypipelic acid	262

Botanical origin	Piperidine alkaloid	Reference
<u>Rhododendron fauriae</u> Franch. (Ericaceae) var. <u>rufescens</u>	Piperine	186
<u>Salsola kali</u> Linn. (Chenopodiaceae)	Triacetoneamine	263
<u>S. longifolia</u> Forsk.	Triacetoneamine	263
<u>S. rigida</u> Pall.	Triacetoneamine	263
<u>S. tetrandra</u> Forsk. (<u>S. tetragona</u> Delile) (Chenopodiaceae)	Triacetoneamine	263
<u>Sedum acre</u> Linn. (Crassulaceae) (dry plant)	d-8-Methyl-10-phenyl- lobelidiol Pelletierine dl-Sedamine l-Sedamine Sedridine	186 264, 265 266, 267
<u>S. sarmentosum</u> Bunge (dry plant)	d-Methylallosedridine N-Methyl-2- β -hydroxy- -propyl]-piperidine dl-Methylisopelletierine l-Sedamine	261 268 186

Botanical origin	Piperidine alkaloid	Reference
<u>Strelitzia reginae</u> Ait. (Strelitziaceae)	4-Hydroxypipelic acid 5-Hydroxypipelic acid	184
<u>Trifolium pratense</u> Linn. (Papilionaceae)	Pipelic acid	195
<u>T. repens</u> Linn. (leaf)	1-Pipelic acid	195
<u>Vaccinium vitis-idaea</u> Linn. (Ericaceae) (berry)	5-Hydroxypipelic acid	184
<u>Viola odorata</u> Linn. (Violaceae)	Triacetoneamine	186
<u>Withania somnifera</u> Dun (Solanaceae)	Anaferine Anahygrine 1-Isopelletierine Pelletierine	228 186
<u>Xylopiya brasiliensis</u> Spreng. (Annonaceae)	Piperine	186
<u>Zinnia elegans</u> Jacq. (Compositae)	Anabasine	186