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ALKALOID DISTRIBUTION IN SOME NEW WORLD *LUPINUS* SPECIES

A. DOUGLAS KINGHORN, MOHAMED A. SELIM and STANISLAUS J. SMOLENSKI

Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612, U.S.A.

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Abstract—Alkaloidal profiles of 21 *Lupinus* species indigenous to North and South America have been determined. Nineteen quinolizidine alkaloids were identified, including aphyllidine and *N*-methylcytisine, which have not previously been found in the genus. Two dipiperidine alkaloids were also detected. The pattern of alkaloidal distribution is related to a taxonomic classification of the genus.

INTRODUCTION

The diverse genus *Lupinus* (Leguminosae) is represented by *ca* 200 species in the New World, and a smaller number in the Mediterranean region [1]. Certain members of the genus are sources of oilseeds, with a high protein content. 'Sweet' lupines, with a low alkaloid level, have been cultivated for centuries as crop plants [1, 2]. Since the fresh foliage of many of these species contains 0.5–1.0% nitrogen, they are a useful source of fertilizer [1]. *Lupinus termis* is used clinically in Africa for the treatment of chronic eczema [3].

The ingestion of *Lupinus* species as forage has resulted in the loss of grazing sheep in the Rocky Mountain states. Poisoning symptoms in these animals consist of respiratory failure, convulsions and coma, which lead to death. The constituents responsible are normally considered to be quinolizidine alkaloids [4]. It has been suggested that not all North American lupines are poisonous [5], and that most of them are acceptable as forage plants under usual range conditions [4]. Recently, the alkaloid anagyrine has been implicated as a teratogen in several *Lupinus* species that are known to cause crooked calf disease [6, 7].

Although the genus is taxonomically confused [4, 8], chemical studies to help confirm or refute proposed taxonomic divisions have not been numerous. Previous reports have appeared in the literature on the distribution in *Lupinus* species of flavones, flavonols and *C*-glycoflavones [9], 5,7,2′4′-tetrahydroxy-6-(3,3-dimethylallyl)isoflavone [10], amino acids [11] and alkaloids [12, 13].

In this communication we report on the occurrence of alkaloids in 21 New World lupines in order that speculation may be made on their potential toxicity, and also to determine if the chemical relationships of these taxa can be related to existing taxonomic groupings. About 40 quinolizidine alkaloids, eight piperidine alkaloids, and the indole alkylamine, gramine, have been previously reported to occur in the genus [14–17].

RESULTS AND DISCUSSION

Table 1 shows the distribution of alkaloids, as determined in several plant parts of New World *Lupinus* species, collected at various times and locations. Two species collected in Europe, *L. hartwegii* and *L. polyphyllus*, are also indigenous to North America [18]. Several previous studies on *Lupinus* alkaloids have employed GC–MS [7, 19, 20]. Our data have been derived in a similar manner, leading to an extension of knowledge of the alkaloids in the species examined. A total of 67 alkaloids that have not been found before in the lupines represented are listed in Table 1. With certain exceptions to be discussed, this work confirms previous reports of alkaloids occurring in *L. arboreus* [12, 14–16], *L. chamissonis* [12, 16]. *L. hartwegii* [14–17, 19, 21], *L. hilarianus* [16], *L. latifolius* [13], *L. longifolius* [12, 16], *L. multiflorus* [15, 16], *L. nanus* [15–17, 21], *L. polyphyllus* [14–16, 21, 22] and *L. rivularis* [15]. There have been no reports of alkaloids in any of the other species listed in Table 1.

The presence of sparteine in *L. chamissonis* [12], and 13-hydroxylupanine in *L. arboreus* [12], *L. longifolius* [12] and *L. nanus* [21] were not confirmed in this study. However, since these compounds were identified on the basis of R_f data alone, their detection in these lupines must be considered questionable. The hydroxylated compounds virgiline and 13-hydroxylupanine, and the indole alkylamine gramine, which were previously identified in the seedlings of *L. hartwegii* using GC–MS [19], were absent from the seed sample of this plant investigated here. However, 17-oxolupanine and Δ^5-dehydrolupanine were found. A number of esterified alkaloids found previously in *L. polyphyllus* [16] were not detected in this study, and may not have been eluted from the GLC column, due to the long retention times of this class of quinolizidine alkaloid [19].

The range of compounds identified in the lupines investigated is shown in Table 1. Although lupanine was the compound most often detected, ammodendrine, Δ^5-

Table 1. Alkaloids of New World *Lupinus* species*

Section/plant/origin collection date	Plant part(s)	Ammodendrine	*N*'-Methylammodendrine	Epilupinine	α-Isolupanine	Thermopsine	Epiaphylline	Sparteine	17-Oxosparteine	Multiflorine	Lupanine	Δ^5-Dehydrolupanine	Anagyrine	Aphylline	Aphyllidine	13-Hydroxylupanine	Angustifoline	Nuttalline	17-Oxolupanine	10,17-Dioxosparteine	β-Isosparteine	*N*-Methylcytisine	Unknown
		I		II	III			IV													V	VI	
A. *Microcarpi*																							
L. densiflorus Benth. California, 04/65	Rt, St, Lf, Fl										+	+	+									+	0
C. *Concinni*																							
L. agardhianus Heller (syn. *L. concinnus* var. *agardhianus* (Heller) C. P. Smith) California, 03/65	Rt, St, Lf, Fl				+						+	+							+				0
L. concinnus J. G. Agardh California, 04/62	St, Lf, Fl, Fr										+							+					0
F. *Sparsiflori*																							
L. hirsutissimus Benth. California, 05/62	St, Fr minus Sd	+	+																				2
L. hirsutissimus Benth. California, 03/65	Rt, St, Lf, Fl	+									+												1
L. truncatus Nutt. ex Hook & Arn. California, 03/65	Rt, St, Lf, Fl	+						+	+		+							+					2
L. sparsiflorus Benth. Arizona, 04/63	St, Lf, Fl	+						+			+	+	+										1
L. arizonicus (Wats.) Wats. (syn. *L. sparsiflorus* var. *arizonicus* (S. Wats.) C. P. Smith Baja California, 04/66	St, Lf, Fr	+			+			+			+								+				0
G. *Micranthi*																							
L. nanus Dougl. ex Benth. California, 03/65	St, Lf, Fl				+	+					+		+					+					2
L. polycarpus Greene (syn. *L. micranthus* Dougl. ex Lindl.) California, 07/57	Px										+		+									+	0
L. *Sericei*																							
L. chamissonis Eschsch. California, 04/65	St, Lf	+		+							+												1
M. *Arborei*																							
L. longifolius (Wats.) Abrams. California, 03/65	St, Lf, Fl				+	+		+			+		+								+		4
L. arboreus Sims California, 03/65	St, Lf, Fl							+	+		+	+							+				1
L. rivularis Dougl. ex Lindl. California, 06/62	Rt				+			+			+							+					1
O. *Latifolii*																							
L. latifolius J. G. Agardh. California, 04/65	Rt, St, Lf, Fl, Fr										+		+									+	0
L. latifolius J. G. Agardh. Washington, 09/65	St, Lf, Fr							+	+		+												0
L latifolius J. G. Agardh. Washington, 09/65	Rt																						0

Table 1.— *Continued*

Section/plant/origin collection date	Plant part(s)	Ammodendrine	*N*-Methylammodendrine	Eplupinine	α-Isolupanine	Thermopsine	Epiaphylline	Sparteine	17-Oxosparteine	Multiflorine	Lupanine	Δ^5-Dehydrolupanine	Anagyrine	Aphylline	Aphyllidine	13-Hydroxylupanine	Angustifoline	Nuttalline	17-Oxolupanine	10,17-Dioxosparteine	β-Isosparteine	*N*-Methylcytisine	Unknown
		I		II	III			IV													V	VI	
P. *Polyphylli*																							
L. polyphyllus Lindl. France, 11/66, unclassified by Smith	Rt										+	−				+	+	+					1
L. aduncus Greene Colorado, 07/64	Rt, St, Lf, Fl										+							+					0
L. aduncus Greene New Mexico, 06/64	St, Lf, Fl, Fr				+	+								+									3
L. greenei A. Nels. Colorado, 08/64	Rt, St, Lf, Fl, Fr	+													+			+					3
L. hartwegii Lindl. Germany, 11/66	Sd				+		+				+	+		+				+	+	+			0
L. hilarianus Benth. Uruguay, 10/65	St, Lf, Fr										+	+				+							0
L. multiflorus Desr. Uruguay, 12/64	St, Lf										+												0
L. oscar-haughtii C. P. Smith Colombia, 03/72	St							+	+		+										+		1
L. oscar-haughtii C. P. Smith Colombia, 03/72	If(Fr)							+	+		+										+		1

*Classified according to Smith (in Abrams) [29].

Key: Fl, flower, Fr, fruit; If, inflorescence; Lf, leaf; Px, aerial parts; Rt, root; Sd, seed; St, stem.

dehydrolupanine and nuttalline were shown to have a wider distribution in the genus than previously suspected [16, 17, 20, 23]. The observation of *N*-methylcytisine in *L. densiflorus*, *L. latifolius* (collected in California) and *L. polycarpus*, in each case without its postulated precursor, cytisine [24, 25], is interesting, since cytisine has never been found in the genus, and thus apparently does not accumulate in *Lupinus*. *N*-Methylcylcytisine, which has not previously been reported to occur in the lupines, was found to co-exist with anagyrine in these three species. Thermopsine was absent in every case. These results suggest a possible biosynthetic link of *N*-methylcytisine with anagyrine, rather than with thermopsine. This is in contrast to a biogenetic proposal [25] in which *N*-methylcytisine is elaborated, through various intermediates, from either anagyrine or thermopsine. However, the detection of thermopsine with α-isolupanine, and anagyrine with lupanine, in several species in both instances (Table 1), lends support to the independent parallel biogenetic pathways for the generation of these pyridone bases put forward by Nowacki and Waller [25]. Aphyllidine, a second alkaloid reported here for the first time in the lupines, was identified in *L. greenei* as well as in *L. aduncus*, obtained from New Mexico.

Considerable variations in the alkaloidal profiles of *Lupinus* species were exhibited by samples of the same species collected at different times of the year and in different locations. All three such species that were studied, namely *L. aduncus*, *L. hirsutissimus* and *L. latifolius* exhibited differences in alkaloidal composition (Table 1). At least one common plant part was present within the samples investigated. Alkaloidal variations were not so marked when different parts of the same plants, collected simultaneously, were examined. While the composition of alkaloids in a mixture of the stems, leaves and fruits of *L. latifolius* (collected in Washington) differed from those in the roots, the stems and fruiting inflorescences of *L. oscar-haughti* contained the same alkaloids (Table 1). The variations of quinolizidine alkaloids of species of the legume genus *Baptisia* with respect to plant age, collection location, hybridization and introgression, and the plant part collected have been discussed [16]. More recently, the fluctuations of nine unidentified alkaloids in populations of four subspecies of *L. nanus* were studied [26].

Since the samples available to us were in the form of ethanolic extracts rather than the original plant material, and because of the lack of baseline separation in the GLC detector response of the components of many species, no

attempt was made to quantitate the alkaloids identified. However, lupanine was the major alkaloid present in most of the lupines examined. As (+)-lupanine exhibited the most potent toxic effect on guinea pigs, among several quinolizidine alkaloids tested [27], all species in Table 1 which contain lupanine must be considered potentially toxic, and unsuitable for forage. Interestingly, among the few species examined where lupanine was absent, *L. greenei* is the only lupine in this study to be cited by Kingsbury [4] as being toxic to livestock. The occurrence of anagyrine in *L. densiflorus*, *L. latifolius* (collected in California), *L. longifolius*, *L. nanus*, *L. polycarpus* and *L. sparsiflorus*, seems to prohibit the use of these species as grazing plants, because of the danger of livestock fetal deformities [6, 7].

According to Turner [28], the capricious nature of alkaloids in the legume subfamily Papilionoideae makes them less useful at the specific level in systematic studies than amino acids and flavonoids. However, this opinion was made without the benefit of alkaloidal studies using GC–MS. This technique allows much more precise alkaloidal identifications to be made than by comparative TLC and GLC methods, and enables even trace constituents to be analysed. While the variations in legume quinolizidine alkaloids are undisputed, it is apparent from Table 1 that the differences in alkaloidal profile in different populations of the same species are less marked than the variation of any one particular alkaloid. There are six subdivisions that may be made on the lysine-derivable alkaloids listed in Table 1, based on different ring systems and the stereochemistry of the ring-junction protons [16, 17, 25]. In the following discussion we will attempt to relate the occurrence of alkaloids within these groupings with the taxonomy of the North American lupines here studied. The compounds in Table 1 are grouped into: (I) dipiperidine alkaloids, (II) the bicyclic quinolizidine alkaloid, epilupinine, (III) tetracyclic quinolizidine alkaloids where the C-11 proton is *cis* to the methylene bridge, (IV) the tricyclic quinolizidine alkaloid angustifoline, and tetracyclic quinolizidine alkaloids where the C-11 proton is *trans* to the methylene bridge, (V) the tetracyclic quinolizidine alkaloid *β*-isosparteine, where both the C-6 and C-11 protons are *trans* to the methylene bridge, and (VI) the tricyclic pyridone base, *N*-methylcytisine, in which no ring junction proton occurs at C-6, and two methylene protons occur at C-11. The compounds in groups III and IV are arranged, as far as possible, according to published biogenetic sidepaths [25] (Table 1).

The classification by Smith (in Abrams) [29] is a modern treatment of North American lupines, and 84 species and varieties, indigenous to the Pacific States are subdivided into 18 sections. Over two-thirds of the species in this study are included, and there are four sections in which more than one species in Table 1 is dealt with, and these will be considered in turn. In section *Concinni*, *L. agardhianus*, which is classified as a variety of *L. concinnus* by Smith [29], and *L. concinnus* were studied. Although these annual/biannual species differ only in flower pigmentation, leaflet shape and their degree of pubescence [29, 30], lupanine was their only common alkaloid, and the results in Table 1 offer further evidence for the distinct specific nature of these lupines.

L. hirsutissimus, *L. truncatus*, *L. sparsiflorus* and *L. arizonicus* are classified in the section *Sparsiflori* [29], and all were shown to contain lupanine and the dipiperidine alkaloid, ammodendrine. The latter compound appears to be a characteristic of this section, being the major alkaloid of *L. hirsutissimus*, and it occurred in minor amounts in *L. sparsiflorus* and *L. arizonicus*, and was a trace constituent of *L. truncatus*. *L. arizonicus* is accorded varietal status of *L. sparsiflorus* by Smith [29], but full specific status by Dunn and associates [30]. The results in Table 1 seem to vindicate the opinion of the latter group, since, even though lupanine, ammodendrine and sparteine were in common, Δ^5-dehydrolupanine and anagyrine were also found in *L. sparsiflorus*, while *α*-isolupanine occurred in *L arizonicus*. Studies on the profiles of other phytoconstituents would help to resolve this conflict.

In section *Micranthi* [29] two species, *L. nanus* and *L. polycarpus*, are classified. Both contain lupanine and various pyridone bases, but *L. nanus* also accumulates *α*-isolupanine. Since there is an absence of dipiperidine and bicyclic quinolizidine alkaloids, as well as *β*-isosparteine in the two species, these chemical results support their placement together in the same section of the genus.

In section *Arborei*, *L. arboreus*, *L. longifolius* and *L. rivularis* [29] were shown to biosynthesize lupanine and sparteine, and have no dipiperidine alkaloids present. While *L. longifolius* contains pyridone bases, and *L. arboreus* a trace amount of aphylline, there is some support for their inclusion in one section. It must be pointed out that the results in Table 1 do not bear out the assertion of Nowacki and Dunn [12] that the sympatric Californian species *L. arboreus* and *L. chamissonis* contain the same alkaloids. In this study their only common alkaloid was found to be lupanine. *L. chamissonis*, which is in Smith's section *Sericei* [29], also contains epilupinine and ammodendrine.

In conclusion, it is to be noted that these results are preliminary, and are based on arbitrary divisions of alkaloidal types, and the restricted nature of the samples available to us do not allow adequate conclusions to be made about alkaloidal tissue variability. However, an expansion of this approach on more species will help establish if alkaloidal distribution profiles will aid systematic studies at the specific level in *Lupinus* and other Papilionoideae genera.

EXPERIMENTAL

UV: MeOH, ^{1}H NMR: 60 MHz, $CDCl_3$; MS: 70 eV, GC–MS: Varian-MAT 112S, with Varian 166 data system, 70 eV, Varian 1400 gas chromatograph. Mps are uncorr. TLC and PLC carried out on Si gel, GF_{254} (Merck), with Dragendorff's and PDAB visualizing reagents.

Plant material. Lyophilized 80% ethanolic extracts of *Lupinus* species were supplied through the Developmental Therapeutics Program (Natural Products Branch) of the National Cancer Institute, formerly the Cancer Chemotherapy National Service Center, Bethesda, MD. Specimens representing the collection of plant material are deposited at the Herbarium of the National Arboretum, Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C.

Chromatographic methods. GC MS was performed on a 2 m × 3 mm glass column, packed with 3% OV-210 on Chromosorb W(HP), 80–100 mesh, temp. programmed 150 to 250° at 4°/min. He flow rate 18 ml/min. Injector temp. 260°, interface separator temp. 236°, spectra recorded with 6 sec between scans. TLC: S_1, MeOH–28% NH_4OH (131.2); S_2, $CHCl_3$–MeOH–28% NH_4OH (85:15:1); S_3, C_6H_{12}–diethylamine (7:3).

Reference alkaloids. Ammodendrine HI, anagyrine $HClO_4$, epilupinine, 13-hydroxylupanine, (+)-α-isolupanine, β-isosparteine $HClO_4$, (±)-lupanine, lupinine *N*-methylcytisine, multiflorine, 17-oxolupanine, 17-oxosparteine, (−)-sparteine, (−)-thermopsine and virgiline were generously supplied by other workers in this area. *N'*-Methylammodendrine was synthesized from ammodendrine using formaldehyde and $NaBH_4$ [31], and (−)-α-isosparteine and gramine were purchased commercially. All reference alkaloids were checked for purity by TLC and MS (probe). Aphylline, 10,17-dioxosparteine, epiaphylline and nuttalline, from *L. hartwegii* [19], and angustifoline, from *L. polyphyllus* [22] were isolated and characterized as previously described [19, 22, 32, 33, 35, 39]. Aphyllidine, obtained from *L. greenei* PLC in S_1 and S_2 was similar in UV and MS to previous data [34, 35]. The identity of this compound was confirmed by hydrogenation over Adam's catalyst, and the product shown to be identical to aphylline by GC–MS. Δ^5-Dehydrolupanine was isolated from *L. densiflorus* and characterized (UV, MS ^{1}H NMR, TLC, visualization with PDAB reagent, hydrogation to lupanine) by a known method [36].

Extraction of plant material and identification of alkaloids. Crude alkaloidal extracts were obtained by the method of ref. [37], and subjected to TLC in S_1–S_3 and GC–MS. PLC in S_1 was carried out on complex alkaloidal mixtures, and up to 5 zones, eluted from Si gel by MeOH, were individually examined by GC–MS. The following compounds were identified by the combination of RR_t (to lupanine), MS and R_f data: Dipiperidine alkaloids—Ammodendrine, RR_t: 0.56; MS *m/e* 208 (M^+) [40]; R_f: S_1 0.17, S_2 0.23, S_3 0.37. *N'*-Methylammodendrine, RR_t: 0.49; MS *m/e* 222 (M^+) [40]; R_f: S_1 0.48, S_2 0.55, S_3 0.48.

Quinolizidine alkaloids—Angustifoline, RR_t: 0.99; MS: *m/e* 234 (M^+ missing), 193 [33]; R_f: S_1 0.41, S_2 0.63. Anagyrine, RR_t: 1.49; MS *m/e* 244 (M^+) [33]; R_f: S_1 0.49, S_2 0.66, S_3 0.28. Aphyllidine, RR_t: 0.78; MS *m/e* 246 (M^+) [35]; R_f: S_1 0.61, S_2 0.81, S_3 0.61. Aphylline, RR_t: 1.03; MS *m/e* 248 (M^+) [35]; R_f: S_1 0.60, S_2 0.80, S_3 0.52. Δ^5-Dehydrolupanine, RR_t: 0.85, MS *m/e* 246 (M^+) [33]; R_f: S_1 0.48, S_2 0.71; S_3 0.51. 10,17-Dioxosparteine, RR_t: 1.50; MS *m/e* 262 (M^+) [35]; R_f: S_1 0.59, S_2 0.78. Epiaphylline, RR_t: 0.81; MS *m/e* 248 (M^+) [35]; R_f: S_1 0.65; S_2 0.85; S_3 0.57. Epilupinine, RR_t: 0.10. Epilupinine and lupinine were differentiated by temp. programming 100–150° at 2°/min, RR_t (to sparteine): epilupinine 0.61, lupinine 0.74; MS *m/e* 169 (M^+) [38]; R_f: S_1 0.24, S_2 0.10, S_3 0.49. 13-Hydroxylupanine, RR_t: 1.57; MS *m/e* 264 (M^+) [33]; R_f: S_1 0.28, S_2 0.24, S_3 0.16. α-Isolupanine, RR_t: 0.95; MS *m/e* 248 (M^+) [33]; R_f: S_1 0.51, S_2 0.69, S_3 0.50. β-Isosparteine, RR_t: 0.23; MS *m/e* 234 (M^+) [20]; R_f: S_1 0.11, S_2 0.15, S_3 0.79. Lupanine, RR_t: 1.00; MS *m/e* 248 (M^+) [35]; R_f: S_1 0.30, S_2 0.65, S_3 0.51. *N*-Methylcytisine, RR_t: 0.95; MS *m/e* 204 (M^+) [38]; R_f: S_1 0.53, S_2 0.61, S_3 0.23. Multiflorine, RR_t: 1.45; MS *m/e* 246 (M^+, 64%), 149 (21), 148 (23), 134 (100), 126 (22), 110 (21), 98 (29), 97 (20), 67 (21) and 41 (27); R_f: S_1 0.27, S_2 0.35, S_3 0.26. Nuttalline, RR_t: 1.07; MS *m/e* 264 (M^+) [39]; R_f: S_1 0.26, S_2 0.56, S_3 0.44. 17-Oxolupanine, RR_t: 1.60; MS *m/e* 262 (M^+) [35]; R_f: S_1 0.60, S_2 0.80, S_3 0.54. 17-Oxosparteine, RR_t: 0.83; MS *m/e* 248 (M^+) [35]; R_f: S_1 0.61, S_2 0.80, S_3 0.55. Sparteine, RR_t: 0.19; MS *m/e* 234 (M^+) [33]; R_f: S_1 0.08, S_2 0.07, S_3 0.80. Since GC–MS and TLC did not differentiate between sparteine and α-isosparteine, sparteine was confirmed by PLC of extracts in S_1, elution of the zone R_f 0–0.20 with MeOH, and the formation of sparteine methiodide, mp 235–237° [20]. Thermopsine RR_t: 1.40; MS *m/e* 244 (M^+) [33]; R_f: S_1 0.63, S_2 0.77, S_3 0.35.

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