Quinolizidine Alkaloids in Seeds of *Lupinus mutabilis*

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The quinolizidine alkaloid composition of *Lupinus mutabilis* seeds was studied by high-resolution capillary gas–liquid chromatography (GLC) and capillary GLC–mass spectrometry. The occurrence of the known alkaloids sparteine, lupanine, α-isolupanine, 4-hydroxylupanine, and 13-hydroxylupanine was confirmed. In addition, more than 20 other alkaloids were present, including tetrahydrorhombifoline (**6**), angustifoline (**7**), multiflorine (**12**), 13-(angeloyloxy)lupanine (**20**), 13-(tigloyloxy)lupanine (**21**), 13-(benzoyloxy)lupanine (**25**), *cis*-13-(cinnamoyloxy)lupanine (**26**), *trans*-13-(cinnamoyloxy)lupanine (**27**), and ammodendrine (**3**). Other alkaloids were tentatively identified as 4,13-dihydroxylupanine (**16**), 4-(angeloyloxy)lupanine (**23**), and 13-(angeloyloxy)-4-hydroxylupanine (**22**). The quantitative composition of the alkaloid fraction is discussed with respect to the use of debittered seeds for human nutrition.

In the course of the intensified utilization of rarely used plant foods, the lupine species should be employed on a greater scale for animal and human nutrition. The South American species *Lupinus mutabilis* is of special interest due to its high fat content of up to 25% in seeds (Torres, 1976). This species has been employed for the production of edible oil (Bocanegra et al., 1982; Hatzold et al., 1982a) in recent years. Moreover, the seeds contain 41% protein on average (Gross and Von Baer, 1975) and are similar to soybean seeds in their content of nutritive substances.

L. mutabilis has been used as a food crop in the Andean Highland for ages. The seeds, however, accumulate a high level (3%) of quinolizidine alkaloids. Therefore, a debittering process (removal of alkaloids) is necessary prior to consumption. For this purpose, the inhabitants of the highlands soak the seeds in running water for a few days after they have been cooked. During this process most of the bitter and toxic alkaloids are removed from the seeds (Gross and von Baer, 1975). For modern use of *L. mutabilis* seeds other debittering processes have been studied on an industrial scale (Hatzold et al., 1982a,b).

The main quinolizidine alkaloids of *L. mutabilis* seeds are lupanine, 13-hydroxylupanine, 4-hydroxylupanine, and sparteine. Additionally, α-isolupanine and some other alkaloids not yet identified are reported (Hudson et al., 1976; von Baer et al., 1979; von Baer, 1980). As there are great differences in toxicity and bitterness between the individual alkaloids, a more detailed investigation of the alkaloid fraction of *L. mutabilis* seeds is presented in this paper.

EXPERIMENTAL PROCEDURES

Materials. For identification of alkaloids by capillary gas–liquid chromatography, seeds of a mixed *L. mutabilis* population cultured in Peru in 1979–1980 were employed. For determination of variations in the alkaloid pattern, eight samples of each of two breeding lines (SCG 8; SCG 22) from the University Cuzco (Peru) were analyzed by conventional GLC with packed columns. The sites of cultivation were in the "Departamento Cuzco" in Peru (Urcos, 3125 m; Andenes, 3400 m; Ocongate, 3600 m; Paucartambo, 2910 m). The years of cultivation were 1978–1979 and 1979–1980. In 1979–1980 no cultivation was carried out in Ocongate. The original seed samples of the two breeding lines were additionally analyzed.

Methods. *Purification.* The extraction and purification of alkaloids were carried out by von Baer's method (von Baer, 1980): Seeds were ground at a 0.5-mm sieve opening. One gram meal was alkalinized with 1 mL of aqueous KOH (15%) and dried with 3 g of basic aluminum oxide (activity I). Then extraction was carried out with 50 mL of chloroform. The extract was evaporated under nitrogen and purified on a column filled with 1.5 g of silica gel 60 (Merck, 0.063–0.200 mesh). The lipid fraction was eluted with 25 mL of chloroform, and then the alkaloid fraction was eluted with 50 mL of methanol–diethylamine (49:1).

Capillary Gas–Liquid Chromatography. The purified extract was dissolved in 2 mL of chloroform, and 1 μL was injected in a Perkin-Elmer gas chromatograph (Sigma 1b) equipped with a FID (flame ionization detector) and PND (phosphorus–nitrogen detector). Alkaloid extracts were separated on a fused silica ("quartz") wall-coated (SE-30) capillary column (J & W Scientific) (Wink et al., 1981b, 1982).

Capillary Gas–Liquid Chromatography/Mass Spectrometry. A Perkin-Elmer gas chromatograph (F 22) was coupled with a AEI MS 30 mass spectrometer that was combined with the DS 50 data system. For capillary GLC–MS the same capillary column as above was used (Wink et al., 1980b, 1981b, 1982).

Conventional GLC with Packed Columns. For GLC on packed columns a Perkin-Elmer gas chromatograph (3920 B) was used equipped with a PND (nitrogen-specific detector). Separation was performed on a 1.8 m × 3 mm glass column packed with 3% OV-17 on Chromosorb Q, 100–120 mesh (Serva). The carrier gas was helium (35 mL/min). The temperature program was 4 min at 190 °C, then 4 °C/min to 300 °C, and 2 min at 300 °C. The injector temperature was 270 °C; the detector temperature was 280 °C (von Baer, 1980). Caffeine was used as the internal standard.

RESULTS AND DISCUSSION

Identification of the Quinolizidine Alkaloids. The combination of capillary gas–liquid chromatography and mass spectrometry is an effective method to study complex mixtures of quinolizidine alkaloids (Wink et al., 1980b,

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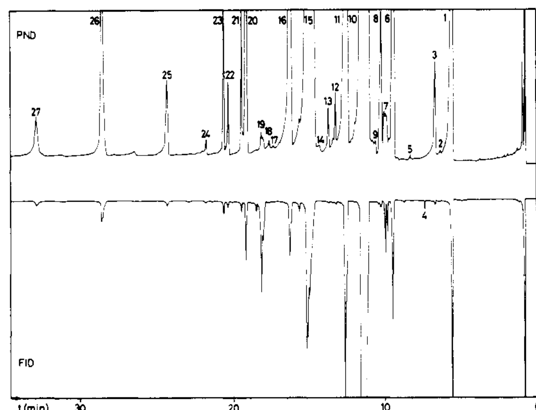


Figure 1. Separation of an alkaloid extract from *L. mutabilis* seeds by capillary gas-liquid chromatography. Injector, 250 °C; detector, 280 °C; oven, 150-270 °C, 6 °C/min; split injection, 1:60; carrier gas, helium, 1.2 bar; detection of alkaloids by nitrogen-specific detector (PND) and flame ionization detector (FID); numbers of the GLC peaks correspond to those in Table II and Scheme I.

1981b, 1982). A typical chromatogram of a purified alkaloid extract from *L. mutabilis* seeds separated on a capillary column shows about 26 signals when a nitrogen specific detector was used that are presumably alkaloids (Figure 1). Most of the GLC peaks were identified by comparing their retention times with those of known alkaloids (Wink et al., 1980b, 1981b, 1982) in combination with their mass spectral data (Cho and Martin, 1971, 1972a,b; Wink et al., 1980b, 1981b, 1982; von Baer, 1980).

The identification of the minor alkaloids in the alkaloid extracts was more complicated since their mass spectra often contained ions of alkaloids that were eluted from the column a short time before. The known retention indices of the relevant alkaloids (Wink et al., 1980b, 1981b, 1982), however, allowed a tentative identification of the respective compounds. Performing mass chromatograms of significant ions of the respective alkaloids in the mass spectra recorded usually permitted an unequivocal identification of a GLC peak.

The alkaloids sparteine (GLC peak 1), ammodendrine (peak 3), tetrahydrorhombifoline (peak 6), angustifoline (peak 7), α-isolupanine (peak 8), lupanine (peak 10), 4-hydroxylupanine (peak 11), multiflorine (peak 12), and 13-hydroxylupanine (peak 15) were identified unequivocally on the basis of their retention time values and their mass spectral data (Table I). Tetrahydrorhombifoline (peak 6) had been taken for *N*-methylangustifoline in earlier publications, but its structure was confirmed by Wink et al. (1983). Tetrahydrorhombifoline, ammodendrine, and multiflorine have not been previously reported in *L. mutabilis* but were found in *Lupinus polyphyllus* and other legumes (Kinghorn et al., 1980; Wink et al., 1981b, 1982). The mass spectrum of GLC peak 16 is identical with that of an alkaloid found in *Sarothamnus scoparius*, which is probably 4,13-dihydroxylupanine (Table I) (Wink et al., 1981b).

The substances with a retention time of GLC peak 20 and higher belong to the fraction of hydroxylupanine esters, which can be easily identified on the basis of their significant retention indices and significant peaks at *m/e* 246 and 134 in the respective mass spectra [details in Wink et al. (1982)]. GLC peak 20 has been identified as 13-angeloyloxylupanine (Wink et al., 1980b, 1982), peak 21 as 13-(tigloyloxy)lupanine (Wink et al., 1980b, 1982) (see Table I and Figure 2), peak 25 as 13-(benzoyloxy)lupanine, peak 26 as *cis*-13-(cinnamoyloxy)lupanine, and peak 27 as *trans*-13-(cinnamoyloxy)lupanine. These ester alkaloids

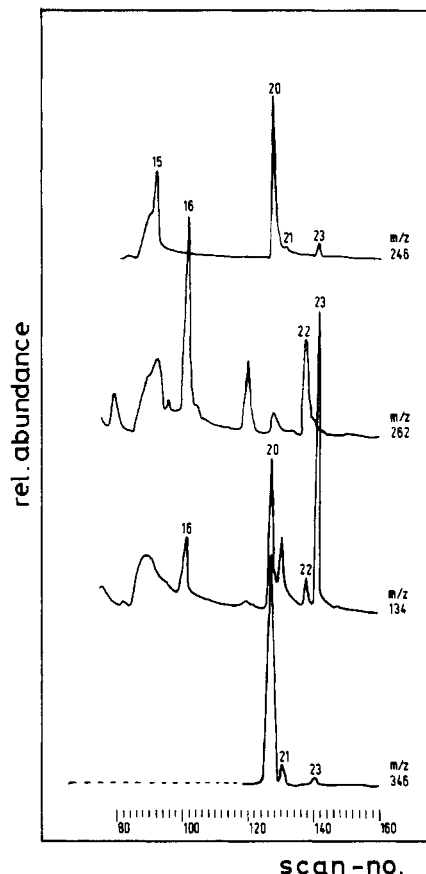


Figure 2. Mass chromatogram of significant ions of hydroxylupanine esters.

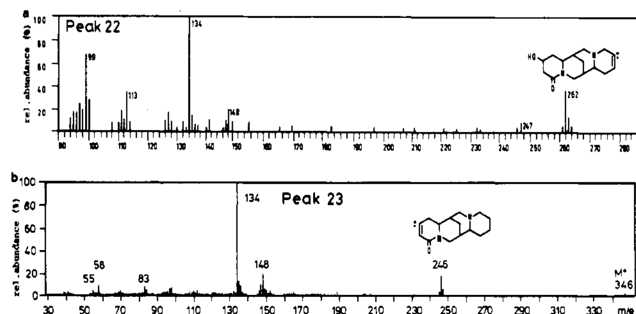


Figure 3. Mass spectrum of GLC peak 22 (a) and 23 (b). Compound **22** was tentatively identified as 13-angeloyl-4-hydroxylupanine, compound **23** as 4-(angeloyloxy)lupanine.

are common for *Lupinus polyphyllus* and other lupines (Wink et al., 1980, 1982) but hitherto have not been identified in *L. mutabilis*. For GLC peak 23 (Figures 2 and 3), a mass spectrum with fragment ions similar to those of 13-(tigloyloxy)lupanine was recorded. Characteristic ions appear at *m/e* 346 and 246, indicating that the carbonic acid component is tiglic or angelic acid (Wink et al., 1982). Contrary to 13-(tigloyloxy)lupanine, which shows a base peak at *m/e* 246, this compound has a base peak at *m/e* 134. Therefore, 13-hydroxylupanine cannot be the corresponding alkaloid component. In the alkaloid mixture studied 4-hydroxylupanine is present in reasonable amounts. This alkaloid shows *m/e* 134 as a significant ion in its mass spectrum. Therefore, 4-hydroxylupanine may be the respective alkaloid component and—since esters with angelic acid are predominant in lupine seeds (Wink et al., 1980b, 1982)—we tentatively identify GLC peak 23 as 4-(angeloyloxy)lupanine.

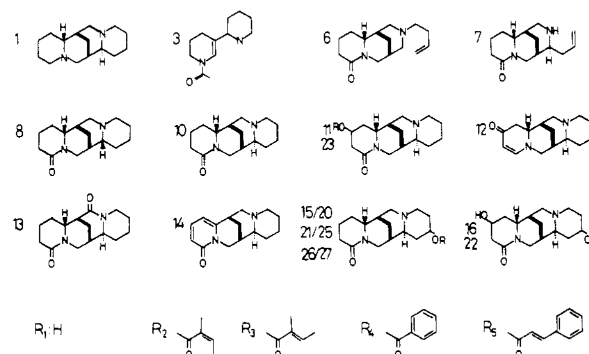
In the mass spectrum of GLC peak 22 (Figure 3) a significant fragment ion is present at *m/e* 262 and 134, but

Table I. Mass Spectral Data of Some *L. mutabilis* Alkaloids Obtained in GLC Runs of Crude Alkaloid Extracts on Capillary Columns

peak no.	alkaloid	M^+	characteristic ions (rel abundance)	reference
1	sparteine	234	137 (100), 98 (40), 234 (30), 191 (25), 150 (10)	Cho and Martin (1971); Wink et al. (1980b); von Baer (1980)
3	ammodendrine	208	208 (100), 165 (90), 179 (40), 123 (70), 136 (50)	Wink et al. (1981b)
6	tetrahydrorhombifoline	248	207 (100), 58 (90), 112 (30), 248 (2)	Wink et al. (1983)
8	α-isolupanine	248	136 (100), 149 (50), 248 (40)	Cho and Martin (1972b, 1971); von Baer (1980)
10	lupanine	248	136 (100), 149 (60), 150 (40), 248 (45)	Cho and Martin (1971); Wink et al. (1980b); von Baer (1980)
11	4-hydroxylupanine	264	264 (100), 136 (100), 134 (40), 150 (40), 247 (15)	Cho and Martin (1971, 1972a)
12	multiflorine	246	134 (100), 246 (40), 110 (20), 98 (25)	Wink et al. (1981b)
15	13-hydroxylupanine	264	152 (100), 246 (50), 165 (40), 264 (40), 134 (30)	Cho and Martin (1971, 1972b); Wink et al. (1981b); von Baer (1980)
16	4,13-dihydroxylupanine	280	152 (100), 280 (60), 134 (50), 165 (40), 262 (20), 246 (15)	Wink et al. (1981b)
20	13-(angeloyloxy)lupanine	346	246 (100), 134 (30), 148 (15), 112 (10), 346 (2)	Wink et al. (1980b, 1982)
22	4-hydroxy-13-(angeloyloxy)lupanine[b]	362[a]	134 (100), 262 (40), 148 (20), 247 (10)	
23	4-(angeloyloxy)lupanine[b]	346	134 (100), 246 (15), 148 (15), 346 (1)	

[a] Value is taken from the literature (von Baer, 1980). [b] Tentative identification.

Scheme I. Structures of Quinolizidine Alkaloids Present in *L. mutabilis*[a]



[a] 1, sparteine; 3, ammodendrine; 6, tetrahydrorhombifoline; 7, angustifoline; 8, α-isolupanine; 10, lupanine; 11, 4-hydroxylupanine (R_1); 12, multiflorine; 13, 17-oxolupanine; 14, anagyrine; 15, 13-hydroxylupanine (R_1); 16, 4,13-dihydroxylupanine (R_1); 20, 13-(angeloyloxy)lupanine (R_2); 21, 13-(tigloyloxy)lupanine (R_3); 22, 4-hydroxy-13-(angeloyloxy)lupanine (R_2); 23, 4-(angeloyloxy)-lupanine (R_2); 25, 13-(benzoyloxy)lupanine (R_4); 26, *cis*-13-cinnamoyloxy)lupanine (R_5); 27, *trans*-13-(cinnamoyloxy)lupanine (R_5, but trans).

we could not record a molecular ion due to its low abundance. von Baer, who studied the alkaloids in *L. mutabilis* seeds recently (von Baer, 1980), described an alkaloid with similar fragmentation as compound **22**. He recorded m/e 362 as the corresponding molecular ion. The difference between m/e 362 and 262 can be explained by postulation of angelic or tiglic acids as acid components in analogy to 13-(angeloyloxy)lupanine and 13-(tigloyloxy)lupanine (Wink et al., 1980b, 1982). The difference of 16 mass units between m/e 262 of compound **22** and m/e 246 of 13-(tigloyloxy)lupanine may be explained as the presence of a second hydroxyl group. The respective nonesterified alkaloid was found to be present in the alkaloid mixture studied and identified as 4,13-dihydroxylupanine (GLC peak 16). Therefore, GLC peak 22 probably is an ester of 4,13-dihydroxylupanine with angelic acid. This ester has not been previously reported and needs further investigation.

Other minor alkaloids were present but could not be identified unequivocally. GLC peak 7 was not fully resolved and the mass spectra revealed beside angustifoline characteristic ions at m/e 248 and 220, which are significant for 17-oxosparteine or 10-oxosparteine. Both compounds display retention time values correspondent to GLC peak 7. According to a molecular ion at m/e 246, GLC peak 9 belongs to a dehydrolupanine that has also been recorded from *L. polyphyllus* (Wink et al., 1980b, 1982). But this needs further investigation.

For GLC peak 13, a molecular ion was found at m/e 262. Since m/e 234 (M^+ − CO) was also recorded, we assume that this compound is 17-oxolupanine, which shows these characteristic ions in its mass spectrum (Wink et al., 1981b). Keeler and Gross (1980) describe a compound from *L. mutabilis* they could not identify. It was 17-oxolupanine according to the mass spectrum reported.

Peak 14 might be anagyrine on account of the retention time found for this compound (Wink et al., 1981a) and the corresponding molecular ion at m/e 244.

For GLC peak 2 the retention time indicated the presence of 11,12-dehydrosparteine (Wink et al., 1981b). This seems plausible, since m/e 232, the corresponding molecular ion, was found. GLC peaks 17–19 and 24 could not

Table II. Alkaloid Composition of a Mixed *L. mutabilis* Seed Sample As Determined by Capillary GLC

peak no.	compound	rel abundance, g/100 g of alkaloids	concn, % dry
1	sparteine	7.4	0.23
2	11,12-dehydrosparteine[a]	0.07	0.002
3	ammodendrine	0.2	0.007
4	no alkaloid		
5	not identified	0.2	0.005
6	tetrahydrorhombifoline	3.5	0.11
7	angustifoline/oxosparteine[a]	0.6	0.02
8	α-isolupanine	0.3	0.009
9	dehydrolupanine[a]	0.1	0.003
10	lupanine	57.5	1.78
11	4-hydroxylupanine	8.7	0.27
12	multiflorine	0.14	0.004
13	17-oxolupanine[a]	0.1	0.003
14	anagyrine[a]	0.03	0.001
15	13-hydroxylupanine	14.9	0.46
16	4,13-dihydroxylupanine	2.12	0.066
17-19	not identified	0.09	0.003
20	13-(angeloyloxy)lupanine	1.57	0.05
21	13-(tigloyloxy)lupanine	0.3	0.01
22	13-(angeloyloxy)-4-hydroxylupanine[a]	0.2	0.007
23	4-(angeloyloxy)lupanine[a]	0.25	0.007
24	not identified		
25	13-(benzoyloxy)lupanine	0.21	0.007
26	*cis*-13-(cinnamoyloxy)lupanine	1.15	0.036
27	*trans*-13-(cinnamoyloxy)lupanine	0.39	0.012
	total alkaloid content		3.1

[a] Tentative identification.

be identified due to their low intensity and interference of N-free compounds. GLC peak 4 was not considered further since it did not constitute an alkaloid (see Scheme I).

Quantitative Aspects and Nutritional Significance. A quantitative evaluation of the alkaloid composition of *L. mutabilis* seeds is given in Table II. The main alkaloids are lupanine, sparteine, 13-hydroxylupanine, and 4-hydroxylupanine. This is in agreement with the literature on the composition of *L. mutabilis* seed alkaloids (Hudson et al., 1976; von Baer, 1980).

In addition to the major alkaloids, a number of minor constitutents of the alkaloid fraction are present. They have not been described in *L. mutabilis* before [except α-isolupanine (von Baer et al., 1979; von Baer, 1980)].

More than seven hydroxylupanine esters were recorded in *L. mutabilis* for the first time. The toxicity of these substances is not known and might be different from that of the other alkaloids because of their increased hydrophobic properties. Engelmann et al. (1974), who studied the pharmacology of 17-alkylsparteines, observed that the increased lipophilic properties of these compounds enhanced the heart activity and significantly inhibited the acetylcholinesterase activity. The case may be similar for the ester alkaloids. Due to the low concentration of the ester alkaloids in the seed (3.6% of total alkaloids), this fraction seems to be of limited toxicological importance. In crude and semirefined seed oil samples, however, the relative percentage of the ester alkaloids can rise up to 54% of total alkaloids (Hatzold et al., 1982a).

From the nutritional point of view the low content or even the absence of quinolizidine alkaloids of the α-pyridone type such as cytisine is remarkable, since these alkaloids are supposed to be especially toxic. Thus, the lethal dose of cytisine for cats is 3 mg/kg of body weight when applied subcutanously (Gessner, 1953). In comparison, the respective lethal dose of lupanine is reported to range from 75 to 110 mg/kg of body weight in different animal species (Gray and Plentl, 1958). For sparteine similar values have been found (51-100 mg/kg of body weight), and 13-hydroxylupanine is even less toxic: A lethal dose of 456 mg/kg of body weight was reported for the guinea pig (Couch, 1926; Zipf and Triller, 1943; Poe and Johnson, 1954). These data refer to subcutanous application. For further toxicological data, see Gordon and Henderson (1951), Novacki and Wezik (1960), Lu (1964), Schmidlin-Meszaros (1973), and Zetler and Strubelt (1980). Of the α-pyridone alkaloids only anagyrine may be present in *L. mutabilis* seeds. This compound has a teratogenic effect on cattle, causing the "crooked calf disease" (Keeler, 1973, 1976). The content of this alkaloid, which was not identified with certainty, is very low (0.03% of total alkaloids) and is therefore of little toxicological importance.

Variation in Alkaloid Content. Breeding lines of *L. mutabilis* show a certain variation in alkaloid content and pattern when cultured in different years or locations. As

Table III. Alkaloid Composition of the Seeds of Two *L. mutabilis* Breeding Lines Cultured under Different Environmental Conditions[a]

peak no.	alkaloid	breeding line	$\bar{x} \pm s$[b]	$100s/\bar{x}$	x_{min}	x_{max}
		Total Alkaloids, g/100 g				
		271	3.03 ± 0.34	11	2.41	3.45
		272	3.44 ± 0.36	10	2.84	3.87
		Alkaloid Composition, g/100 g of Alkaloids				
1	sparteine	271	7.3 ± 1.4	19	5.9	9.1
		272	11 ± 3.0	27	5.9	14
6	tetrahydrorhombifoline	271	3.1 ± 1.8	58	1.2	4.5
		272	2.5 ± 1.8	72	1.2	5.4
8 7	α-isolupanine angustifoline oxosparteine	271 272	0.33 ± 0.23 0.49 ± 0.34	69 69	0.0 0.0	0.69 1.2
10	lupanine	271	65.8 ± 5.9	9.0	57.2	70.9
		272	65.9 ± 2.4	3.6	62.4	69.6
11	4-hydroxylupanine	271	9.5 ± 3.7	39	2.8	14.1
		272	8.6 ± 3.0	35	2.7	12.3
15	13-hydroxylupanine	271	11.7 ± 3.3	28	8.4	18.4
		272	10.0 ± 2.5	25	7.1	14.4
20	13-(angeloyloxy)lupanine	271	1.7 ± 0.4	24	1.1	2.4
21	13-(tigloyloxy)lupanine	272	1.2 ± 0.5	41	0.6	2.1

[a] Number of samples: $n = 8$ for each breeding line. [b] $\bar{x}$ = promedium; s = standard deviation.

shown in Table III, the alkaloid content of one breeding line can differ in a range of 1% from that of the same breeding line cultured under different environmental conditions.

The relative standard deviation, however, is only about 10%. Supposing that low-alkaloid varieties show the same relative standard deviation as the bitter ones studied here, a sweet breeding line with 0.01% alkaloid content would vary from 0.009 to 0.011%. This is acceptable from the toxicological point of view.

In the alkaloid composition, too, a certain variation can be observed. But in all samples lupanine was the main alkaloid. Sparteine, 4-hydroxylupanine, and 13-hydroxylupanine were other major components. Each of the other alkaloids only occur in amounts lower than 6% of total alkaloids.

Among the major alkaloids the contents of 4-hydroxylupanine showed the highest and that of lupanine the lowest relative standard deviation. 4-Hydroxylupanine is more difficult to extract from the oil cake by washing with ethanol–water than the other major alkaloids (Hatzold et al., 1982a). Because its toxicity is not known, it may be important to reduce its content in the seed.

The alkaloid content of lupine products derived from the seeds must be reduced from 3.1 to about 0.02% in order to obtain edible and nontoxic food. This has been tried by means of plant breeding (von Baer and Gross, 1977) or by technological processes (Bocanegra et al., 1982; Hatzold et al., 1982a,b). Breeding measures demand knowledge of the biochemistry of quinolizidine alkaloid formation (Wink and Hartmann, 1980; Wink et al., 1980a) and of the genetics of inheritance of the pathways leading to the individual alkaloids. For the debittering technology, the precise alkaloid composition of the seeds is important, since different physicochemical properties must be considered for the individual alkaloids. The hydroxylupanine esters, for example, are more soluble in hydrophobic solvents than the nonesterified alkaloids.

In addition to their undesirable properties, some lupine alkoloids are known for their pharmacological effects. Sparteine is used in cardiac medicine due to its antiarrhythmic capacities (McCawley, 1955) and is frequently used in obstetrics. It induces the contraction of the uterus and hastens parturition by supporting the synthesis of prostaglandin F (Gray and Plentl, 1958; Abathi et al., 1978). The other lupine alkaloids present in *L. mutabilis* have not been employed medically. But recent studies show the increasing interest in quinolizidine alkaloids for pharmacological research (Engelmann et al., 1974; Raschack, 1974; Zetler and Strubelt, 1980).

In this respect it should be considered that the evaporated extract produced by the large-scale debittering process contains large amounts of alkaloids. These may be exploited to obtain individual quinolizidine alkaloids in amounts sufficient for pharmacological and other biomedical purposes.

Registry No. 1, 90-39-1; **3**, 494-15-5; **6**, 3382-84-1; **7**, 550-43-6; **8**, 486-87-3; **10**, 550-90-3; **11**, 81149-32-8; **12**, 529-80-6; **13**, 4697-83-0; **15**, 15358-48-2; **16**, 81149-31-7; **20**, 57943-35-8; **21**, 57943-34-7; **22**, 86632-27-1; **23**, 86632-28-2; **25**, 34226-97-6; **26**, 6068-29-7; **27**, 5835-04-1; 11,12-dehydrosparteine, 65876-94-0; oxosparteine, 489-72-5; dehydrolupanine, 69010-08-8; anagyrine, 486-89-5.

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Received for review September 28, 1982. Revised manuscript received May 19, 1983. Accepted June 22, 1983. The study was supported by the Deutsche Gesellschaft für Technische Zusammenarbeit (to I.E.) and research grants from the Deutsche Forschungsgemeinschaft and the Land Niedersachsen (to T. Hartmann).