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ALKALOIDS OF SOME EUROPEAN AND MACARONESIAN SEDOIDEAE AND SEMPERVIVOIDEAE (CRASSULACEAE)

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Key Word Index—*Sedum*; *Aeonium*; *Greenovia*; *Jovibarba*; *Sempervivum*; Crassulaceae; pyrrolidine and piperidine alkaloids; chemotaxonomy; evolution.

Abstract—Some 22 pyrrolidine and piperdine alkaloids were detected in the leafy parts of *Sedum acre*, *S. aetnense*, *S. anglicum*, *S. brissemoreti*, *S. farinosum*, *S. fusiforme*, *S. lancerottense*, *S. melanantherum*, and *S. nudum*. In addition to the alkaloids known from *S. acre*, 1-(2-pyrrolidyl)-propan-2-one and 2-monosubstituted piperidine alkaloids bearing butan-2-one, butan-2-ol, pentan-2-one and pentan-2-ol sidechains were identified. Phenylethylamine was isolated from the vegetative parts of *S. album*. In *S. lydium*, *S. meyeri-johannis*, and 16 species of *S.* series *Rupestria*, *Aeonium*, *Greenovia*, *Jovibarba* and *Sempervivum* no alkaloids could be detected. The results indicate a correlation between the presence of alkaloids and the major evolutionary trends in the European and Macaronesian Crassulaceae.

INTRODUCTION

Of all Crassulaceae investigated for the presence of alkaloids, *Sedum acre* L. has received most attention. Some 20 piperidine alkaloids have been reported for this species alone [1, 2]. The major alkaloids of *S. acre* are the two 2-monosubstituted piperidine alkaloids sedridine and sedamine, and the three 2,6-disubstituted *N*-methylpiperidines sedacrine, sedinine and sedinone. In addition a number of minor alkaloids, 2-monosubstituted as well as 2,6-disubstituted, have been reported.

Of the Crassulaceae (*ca* 1500 species) which have been investigated for alkaloids some 25 species (about half the number studied) were found to be positive, though for most taxa contradictory results have also been reported [1, 3–10]. In most cases, however, the alkaloids have not been identified. The compounds which have been identified proved to be similar to the alkaloids found in *S. acre*. In general the alkaloid content of these species is *ca* 1–10% of the amount found in *S. acre* [3]. Occasionally nicotine has also been reported as a constituent of a number of *Sedum* species, and has once been found in *Sempervivum arachnoideum* L. [1, 9], but apparently occurs only in trace amounts.

Most positive reports of alkaloids in Crassulaceae relate to species of *Sedum* L. In *S. purpurem* L. (*S.* sect. *Telephium* S. F. Gray), and in *S. aizoon* L., and *S. hybridum* L. (*S.* sect. *Aizoon* Koch) *N*-methylpelletierine, sedamine and sedinine were found [8], and for *S. sarmentosum* Bunge *N*-methylpelletierine and its dihydro derivative have been reported [11]. In addition to *S. acre*, alkaloids have been reported for 11 European Crassulaceae, i.e. seven species of *S.* sect. *Sedum* (the Eurasiatic species of *S.* subg. *Sedum*), *Rhodiola rosea* L., and three species of Sempervivoideae [1, 3, 6, 9, 10]. However, except for *S. sexangulare* L. and *S. lydium* Boiss. the presence of alkaloids in these species has been doubted [4–6, 10]. From *S. lydium* sedamine, sedacrine and sedinone have been isolated [10], though the report of sedacrine most probably related to sedinine [12]. In the Sempervivoideae small amounts of unidentified alkaloids have been reported for *Aeonium arboreum* (L.) Webb & Berth. (= *Sempervivum arboreum* L.), *Sempervivum arachnoideum* and *S. tectorum* L. [1].

Because *S. acre* contains by far the greatest variety of piperidine alkaloids, we have primarily concentrated on related species in a search for alkaloids in European Sedoideae and Sempervivoideae. *Sedum acre* still retains several morphological characters which are considered to be primitive within the Crassulaceae [13, 14]. It is completely glabrous, and has free sepals (spurred) and a reticulate testa. A similar combination of primitive character states occurs in the European and Macronesian *S.* series *Anglica* 't Hart, *S.* series *Macronesia* Fröd., *S.* series *Macrosepala* (Regel & Schmalh.) Boriss., and *S.* series *Melananthera* 't Hart. The other European Sedoideae are more advanced, they all share the same combination of advanced characters. They are glandular pubescent (rarely glabrous) and have basally fused sepals and a costate testa. The Sempervivoideae also share this synapomorphy, and most probably evolved from the advanced European Sedoideae [15, 16]. In this study we have compared the alkaloid composition of 10 primitive *Sedum* species with 18 advanced species of *Sedum*, *Aeonium* Webb & Berth., *Greenovia* Webb & Berth., *Jovibarba* Opiz and *Sempervivum* L.

RESULTS

The taxa examined by means of TLC and the results of GC-MS (operating in the EI and PICI mode) analysis of the basic fraction of the plant extracts which produced Dragendorff-positive spots on the TLC plate are shown in the Tables 1 and 2. The identities of the plant constituents were inferred from the GC-MS data, and

Table 1. Classification and origin of the species examined

Genera, sections, series and species	Origin and accession no.
A. Plants glabrous; sepals free (spurred); testa reticulate	
Sedum	
S. sect. *Sedum*	
S. series *Acria* Berger	
S. acre L.	Turkey (30869)
S. acre L.	Germany (31846)
S. series *Macaronesia* Fröd.	
S. brissemoreti Hamet	Madeira (29000)
S. fusiforme Lowe	Madeira (29011)
S. lancerottense Murray	Canary Islands (29060)
S. nudum Aiton	Madeira (28995)
S. farinosum Lowe	Madeira (29008)
S. series *Macrosepala* (Reg. & Schm.) Boriss.	
S. aetnense Tin.	Turkey (31712)
S. series *Anglica* 't Hart	
S. anglicum Huds.	France (21826)
S. series *Melananthera* 't Hart	
S. melanantherum DC.	Spain (29502)
S. sect. *Africana* Fröd.	
S. meyeri-johannis Engler	Kenya (15515)
B. Plants glandular pubescent; sepals basally fused; testa costate	
Sedum L.	
S. sect. *Sedum*	
S. series *Alba* Berger	
S. album L.	Spain (29329)
S. series *Lydia* 't Hart	
S. *lydium* Boiss.	Turkey (30939)
S. series *Rupestria* Berger	
S. forsterianum Sm.	Spain (29368)
S. montanum Song & Perr. ssp. *montanum*	France (5345)
S. montanum Song & Perr. ssp. *montanum*	France (5467)
S. montanum Song & Perr. ssp. *orientale* 't Hart	Jugoslavia (16729)
S. ochroleucum Chaix	France (8702)
S. rupestre L. ssp. *erectum* 't Hart	Italy (16705)
S. sediforme (Jacq.) Pau	Portugal (15429)
Aeonium Webb & Berth.	
A. decorum Webb	Canary Islands (30478)
A. glutinosum Webb & Berth.	Madeira (30452)
A. haworthii Salm-Dyck	Canary Islands (31487)
A. leucoblepharum Webb	Yemen (30669)
A. sedifolium (Webb) Pit. & Proust.	Canary Islands (31479)
A. simsii (Sweet) Stearn	Canary Islands (30438)
A. viscatum Bolle	Canary Islands (30481)
Greenovia Webb & Berth.	
G. aurea (Chr. Smith) Webb & Berth.	Canary Islands (30443)
Jovibarba Opiz	
J. heuffelii (Schott) A. & D. Löve	Greece (31467)
Sempervivum L.	
S. ciliosum Craib	Greece (31466)
S. tectorum L.	France (30603)
S. tectorum L.	Spain (29599)

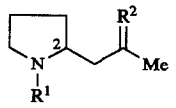
were confirmed by comparing the chromatographic behaviour of the natural alkaloids with reference compounds if possible. The major alkaloids of *S. acre* (sedridine, **3**; sedamine, **16**; sedacrine, **20** and sedinone, **22**) were isolated and sufficiently characterized to establish the identities. In addition, a number of 2-monosubstituted piperidines (compounds **2**, **6**, **10** and **13**) and 1-(2-pyrrolidyl)-propan-2-one (**1**) were prepared from piperidine or pyrrolidine and suitable β-keto acids via condensation, using the general procedure described in ref. [17]. *N*-Methylation of pelletierine (**2**) and norsedaminone (**13**) was conducted according to the reductive alkylation method of Eschweiler-Clarke [18], thus yielding *N*-methylpelletierine (**4**) and sedaminone (**15**).

Table 2. Alkaloids of some European and Macaronesian *Sedum* species

	Alkaloid category*																					
	A	B															C			D		
		8-Methyl				8-Ethyl				8-Propyl			8-Phenyl									
Species	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
S. acre (Germany)		+	+											+		+	+	+	+	+	+	+
S. acre (Turkey)		+	+		+											+	+	+	+	+	+	+
S. brissemoreti		+	+			+	+	+	+	+			+		+	+						
S. fusiforme		+	+	+		+	+	+	+		+		+	+	+	+						
S. lancerottense		+		+	+	+		+	+	+	+	+		+	+	+						
S. nudum		+	+	+		+		+	+		+		+		+	+						
S. farinosum	+	+	+		+																	
S. aetnense	+	+	+	+	+																	
S. anglicum			+	+	+																	
S. melanantherum	+	+	+	+	+																	

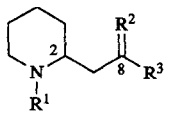
*A: Pyrrolidine alkaloids, B: 2-monosubstituted piperidines, C: hydroxysedamines, D: 2,6-disubstituted piperidine alkaloids.
Numbers correspond to the structures given below.
Major alkaloids: +, minor alkaloids: +.

A Pyrrolidine alkaloids



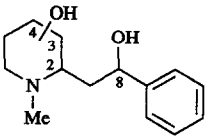
1 norhygrine: $R^1 = H$, $R^2 = O$
1a norhygroline: $R^1 = H$, $R^2 = H,OH$
1b hygrine: $R^1 = Me$, $R^2 = O$
1c hygroline: $R^1 = Me$, $R^2 = H,OH$

B 2-Monosubstituted piperidine alkaloids



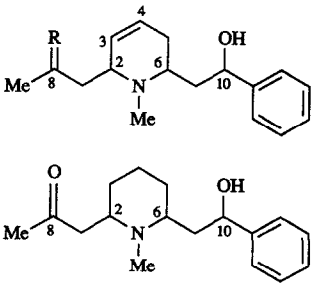
R^1	R^2	R^3 = Me	C_2H_5	C_3H_7	Ph
H	O	2	6	10	13
H	H,OH	3	7	-	14
Me	O	4	8	11	15
Me	H,OH	5	9	12	16

C 2-Monosubstituted hydroxypiperidine alkaloids (hydroxysedamines)



17 3-OH allosedamine
18 4-OH sedamine
19 a hydroxysedamine (isomer)

D 2,6-Disubstituted piperidine alkaloids



20 sedacrine: R = O
21 sedinine: R = H,OH

22 sedinone

Reduction of the ketones with sodium borohydride gave sedridine/allosedridine (**3**), norsedamine/norallosedamine (**14**) and their *N*-methylderivatives, **5** and 1-phenyl-2-(2-*N*-methylpiperidyl)-ethanol. The latter compound was separated into its diastereoisomers sedamine (**16**) and allosedamine. With the exception of 1-(2-piperidyl)-propan-2-ol (**3**), the reduction products showed two peaks in their gas chromatograms, which demonstrates the separation of the diastereoisomers. In most cases, however, only one of the two diastereoisomers was found in the basic fraction of the plant extracts.

The substitution patterns of the piperidines were inferred from the EI mass spectra. The 2-monosubstituted piperidines show base peaks at *m/z* 84 and the 2-monosubstituted-*N*-methyl derivatives at *m/z* 98 [19]. The 2,6-disubstituted alkaloids, sedacrine (**20**), sedinine (**21**) and sedinone (**22**), exhibit base peaks at *m/z* 94, 94 and 96 respectively [12], while base peaks at *m/z* 114 represent the hydroxysedamines [20]. The molecular ion peaks in the EI mass spectra possessed rather low relative intensities, and therefore the M_r was inferred from the PICI mass spectra, in which the base peaks represent the $[M+H]^+$ ion. The pyrrolidine compound **1** showed a base peak at *m/z* 70 (EIMS) representing the pyrrolidine ring.

The primitive species of *Sedum* were Dragendorff-positive, with the exception of *S. meyeri-johannis* Engler. GC-MS revealed the occurrence of 1-(2-pyrrolidyl)-propan-2-one (**1**) (trivial name: norhygrine), a number of 2-monosubstituted piperidines (**2–16**), hydroxysedamines (**17–19**) and 2,6-disubstituted piperidines (**20–22**) (Table 2). Furthermore, the GC-MS data indicated that **1** was accompanied by its related bases (norhygroline, **1a**; hygrine, **1b** and hygroline **1c**). Compounds **1b** and **2** had virtually the same EI and PICI mass spectra, which is also the case with **1c** and **3**: a distinction between the isomers was made by virtue of their retention times.

The advanced Crassulaceae were Dragendorff-negative, with the exception of *S. album* L. The alkaloidal compound of *S. album* was isolated by preparative TLC: GC-MS identified the substance as phenyl ethylamine, which was identical with synthetic phenyl ethylamine (TLC, GC). Despite the negative reaction towards Dragendorff, *S. lydium* and the species of *S.* ser. *Rupestria* Berger were analysed with GC-MS. Traces of nicotine were found in *S. forsterianum* Sm., *S. montanum* Song. & Perr. ssp. *montanum* (5467), and *S. rupestre* L. ssp. *erectum* 't Hart. In addition, *S. forsterianum*, *S. montanum* ssp. *montanum* (5467), *S. rupestre* ssp. *erectum*, *S. sediforme* (Jacq.) Pau, and *S. ochroleucum* Chaix contained a compound in trace amounts, of which the identity could not be established (EIMS: peaks at *m/z* 84, *m/z* 128 (100%), and *m/z* 157). *Sedum lydium* did not contain piperidine alkaloids.

DISCUSSION

The 2-monosubstituted piperidines bearing ethyl groups on the C-8 atom have not been reported before as constituents of *Sedum*, but these compounds are known as minor alkaloids from *Lobelia inflata* L. [1]: the 8-ethyl (nor) lobelone and 8-ethyl (nor) lobelol bases are stereoisomers of compounds **6–9**. The 2-monosubstituted piperidine alkaloids (**10–12**), which have a propyl group in common, are not yet known as natural alkaloids, though the propyl homologue of sedinone, 8-propyl-10-phenyllobeliolone (a 2,6-disubstituted piperidine), has been identified in *Sedum acre* [21]. Furthermore, neither **1** nor its related bases have been found in *Sedum* previously.

The number of alkaloids we detected in *S. acre* amounts to 11, which is smaller than the number of alkaloids reported for this species. The major alkaloids as well as the majority of the less prominent constituents, varying from the simple 2-monosubstituted piperidines to the larger 2,6-disubstituted piperidine alkaloids could be detected in a single GC-MS run. However, the 2,6-disubstituted *Lobelia* alkaloids lelobanidine and lobelanidine decomposed under the GC conditions, especially at higher injection temperatures, indicating that small amounts of similar compounds which have been reported for *S. acre* [21] most probably fell below our detection limit. Decomposition of sedacryptine, a minor base from *S. acre* [22], was also observed (a sample was kindly supplied by Dr C. Hootelé), and was not detected in our extracts with the GC-MS method. In addition the reports of nicotine [23], *N*-methylanabasine [24], sederine [25], sediene and sediendione [26] could not be confirmed.

Our study of the distribution of alkaloids in European Sedoideae and Sempervivoideae show a clear difference between *Sedum* species which have retained primitive characters and the advanced Crassulaceae with regard to

the occurrence of pyrrolidine and piperidine alkaloids. In the primitive species a total of 22 alkaloids were found, whereas these compounds were all completely absent in advanced Crassulaceae, though traces of nicotine and an unidentified piperidine alkaloid were found in a few advanced taxa. These results agree with earlier reports, except for *S. lydium* in which the occurrence of alkaloids was not confirmed. Whether the occurrence of alkaloids may be considered a primitive character in other groups of Sedoideae as well is not yet quite clear. The presence of alkaloids in the American *S. potosinum* which has also retained some primitive morphological characters supports our results. However, the absence of alkaloids in the primitive *S. meyeri-johannis* from Africa, and the reports of the presence of alkaloids in the Asiatic Sedoideae with flat leaves (in species of *Rhodiola* L., *S.* sect. *Telephium*, *S.* sect. *Aizoon*, and in *S. sarmentosum*), which all belong to the more advanced Sedoideae, indicate that the evolution of alkaloids in the Crassulaceae may be more complicated.

The European and Macaronesian primitive species of *S.* sect. *Sedum* contain complex patterns of relatively simple piperidine alkaloids, and the species can be divided into three distinct groups each characterized by a unique combination of compounds, i.e. (1) *S.* series *Acria* (*S. acre*) with the hydroxysedamines **17–19** and the 2,6-disubstituted piperidines **20–22**; (2) *S.* series *Macaronesia*, except for *S. farinosum*, with the piperidines **6–16**, which bear 8-ethyl, 8-propyl and 8-phenyl groups; (3) *S. anglicum*, *S. aetnense*, *S. farinosum*, and *S. melanantherum* with the 8-methyl alkaloids **2–5**, and in the latter three species **1** (in combination with related pyrrolidine compounds). When quantitative aspects are also taken into account (Table 2) the distribution of alkaloids agrees perfectly well with the infrageneric classification of the species [14], except for the position of *S. farinosum*. The latter, however, only agrees with the other species of *S.* series *Macaronesia* in its distribution (endemic to Madeira). *Sedum farinosum* differs significantly from the other four species of *S.* series *Macaronesia* in oecological preference, polyploidy level, colour of the flowers and hybridization pattern, and should be classified in another series.

In general the Crassulaceae are poor in alkaloids, and moreover, their pyrrolidine and piperidine alkaloids are biogenetically simple compounds derived from ornithine and lysine. These observations both agree with the moderately advanced position of the Crassulaceae within the system of the angiosperms [27, 28]. The occurrence of alkaloids within the Crassulaceae appears to be correlated with the major evolutionary trends within the family. A variety of alkaloids is present in species of *Sedum* which have retained primitive morphological characters, whereas in general the phylogenetically more advanced Crassulaceae do not contain alkaloids. Within a given biogenetic group of alkaloids, the complexity of the substitution patterns increases during evolution [28]. The presence of the more complex alkaloids in *S. acre* indicate that this species is the most advanced (Fig. 1) and specialized within the group of European and Macaronesian alkaloid containing, primitive Sedoideae.

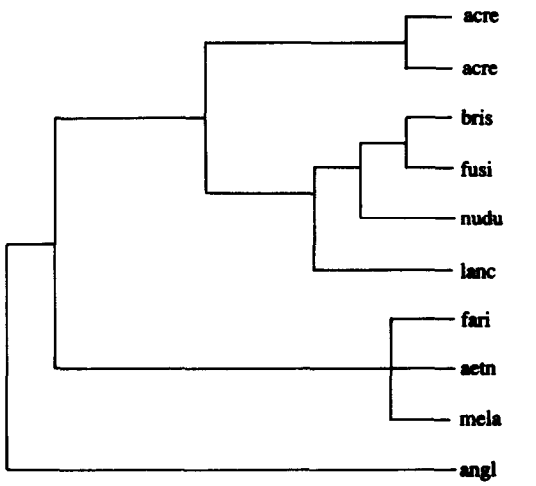


Fig. 1. Most parsimonious phylogenetic tree based on pyrrolidine and piperidine alkaloid variation for European species of *Sedum*. Data were analysed using the CAFCA program (version 1.9.8., M. Zandee, Dept. Inst. Theor. Biol., Univ. Leiden, The Netherlands). For abbreviations compare Table 2.

EXPERIMENTAL

Plant material. Living plants were collected in the wild, and for further study cultivated under uniform conditions in the experimental garden at Utrecht. The origins of the cultivated plants are given in Table 1. Voucher specimens, preserved in 70% alcohol, are deposited in the Botanical Institute at Utrecht. The vegetative (leafy) parts of the cultivated plants were either used fresh or kept at −18° prior to phytochemical analysis. The moisture content of the plant material was determined by lyophylization after grinding under liquid N_2. It amounted to 80–85% in species of *Sedum*, and over 90% in species of *Sempervivum* and *Aeonium*.

General. TLC: chromatograms were run on silica gel plates (Merck art. 5715) with $CHCl_3$–MeOH–NH_4OH (85:14:1) as the eluent. After drying in air, the plates were sprayed with Dragendorff's reagent (undiluted).

GC: R_t values were determined under the following conditions; capillary column, fused silica CP Sil 5 CB, 25 m × 0.32 mm i.d., film thickness of the stationary phase: 0.12 μm (Chrompack, Middelburg, The Netherlands); temp. program: 70–295° at 6° min^{-1}; temp. of the injector: 175°; temp. of the FID: 250°. Carrier gas and flow: N_2 at 2 ml min^{-1}. Inj. vol. 1.0 μl; split ratio was 1:70.

MS: low resolution mass spectra were obtained by sample introduction via the GC. Ionization took place by 70 eV electron impact or by positive ion chemical ionization with NH_3 as the reagent gas; ion source temp.: 250°. Capillary column: fused silica CP Sil 5 CB, 25 m × 0.32 mm i.d., film thickness of the stationary phase: 0.4 μm (Chrompack, Middelburg, The Netherlands); temp. program: 70–295° at 6° min^{-1}; the inj. temp. was 250° or 175°. Carrier gas and flow: He at 1 ml min^{-1}. Inj. vol.: 1.0 or 2.0 μl; the split ratio was 1:12. HRMS were obtained in the 70 eV EI mode with sample introduction via the solid probe at 100–120°.

^1H NMR analysis of the reference compounds (free bases) was performed on a 300 MHz instrument in $CDCl_3$ with TMS as the int. standard.

Extraction and analysis of the alkaloids. Frozen vegetative parts (*Sedum*: 40–50 g, *Aeonium* and *Greenovia*: 100 g, *Sempervivum* and *Jovibarba*: 40–70 g) were ground under liquid N_2. MeOH (100 ml) was added, and the mixture was homogenized with an Ultra Turrax for 2 min. After addition of conc HCl

(6 ml), the mixt. was left standing overnight and then filtered. The filtrate was concd to *ca* 50 ml *in vacuo* at 40°; the aq. soln was extracted with $CHCl_3$ (1 × 100 ml, 2 × 50 ml; the combined organic layers were discarded), and, after basification with 10 M NaOH to pH 11, extracted with $CHCl_3$ (1 × 100 ml, 2 × 50 ml) again. Since the extraction produced persistent emulsions, sepn of the layers was achieved by centrifugation. The combined organic layers were dried with Na_2SO_4 and evapd *in vacuo* at 40°. The residue was taken up in 0.5 ml $CHCl_3$ and stored for TLC. For GC analysis, the extracts were diluted with $CHCl_3$ if necessary.

Isolation of alkaloids from Sedum acre. *Sedum acre* plants (37 kg) were collected near Lathen (Germany) in July 1990, and soaked in 2% aq. HCl (160 l). The mixt. was left standing for 4 days, during which period the mixture was stirred from time to time, and then filtered. After basification with 10 M NaOH to pH 11, the aq. soln was extracted with $CHCl_3$. Evapn of the combined organic layers yielded the crude mixture of alkaloids (27 g), which was distributed between $CHCl_3$ (250 ml) and McIlvaine buffer pH 5.2 (250 ml). The $CHCl_3$ layer gave fraction A (7.9 g) after evapn. The aq. layer was basified and extracted with $CHCl_3$ (1 × 250 ml, 2 × 150 ml); evapn of the combined organic layers yielded fr. B (18.8 g) [12]. Fr. B was sepd on silica gel columns with mixtures of $CHCl_3$–MeOH–1% NH_4OH as eluents; frs mainly containing sedacrine (**20**), sedinone (**22**), sedamine (**16**) and 'hydroxy' sedamine were thus obtained.

Sedridine (**3**). This polar alkaloid was removed from the column by elution with MeOH. After evapn, the crude substance was extracted × 3 with hot petrol; the extracts were combined and evapd. The residue was taken up in a min. vol. of hot petrol, and a white ppt. formed after standing overnight at −18°. Two successive crystallizations from petrol yielded 332 mg sedridine with mp 72–73° (lit. [29]: 75°). R_f 0.10. R_t: 7.83 min. IR ν_{max}^{KBr} cm^{-1}: 3290, 2940, 2830, 1460, 1375, 1340, 1160, 1130, 1110, 1090, 1060, 955, and 890. EIMS, *m/z* (rel. int.): 143.130 $[M]^+$ (calc. for $C_8H_{17}NO$: 143.131) (3), 98 (4), 84 (100). CIMS, *m/z* (rel. int.): 144 $[M+H]^+$ (100), 84 (2).

Sedamine (**16**). Crude **16** was dissolved in dry Et_2O and treated with an ethereal soln of HCl, after which a ppt. was formed. Successive crystallizations of the ppt. from MeCOEt gave **16**·HCl (209 mg), mp 203–205° (lit. [3]: 207°). R_f 0.36. R_t: 20.85 min. IR ν_{max}^{KBr} cm^{-1}: 2960, 1460, 1380, 1210, 1130, 1110, 1085, 1060, 755 and 710. ^{1}H NMR: δ 7.4–7.2 (5H, phenyl), 4.9 (1H, *dd*, H-8), 3.1 (1H, *m*, H-6?), 2.85 (1H, *m*, H-2), 2.55 (1H, *m*, H-6'?), 2.50 (3H, *s*, N-Me), 2.10 (1H, *m*, H-7?), 1.8–1.2 (8H). EIMS, *m/z* (rel. int.): 219.162 $[M]^+$ (calc. for $C_{14}H_{21}NO$: 219.162) (5), 98 (100). CIMS, *m/z* (rel. int.): 220 $[M+H]^+$ (100), 98 (6).

Sedacrine (**20**). Fraction A (7.9 g) mainly contained sedacrine, and was dissolved in MeCOEt (50 ml). $HClO_4$ (70%) was added until the soln was slightly acidic. The soln was left standing overnight, and then the crystalline ppt. collected. Successive crystallizations from MeCOEt yielded **20**·$HClO_4$ (1.05 g), mp 166–167° (lit. [12]: mp 168–169°). R_f: 0.68. R_t: 27.33 min. IR ν_{max}^{KBr} cm^{-1}: 3450, 3100, 2930, 1715 (>C=O), 1495, 1370, 1315, 1110, 770, and 710. A portion of the perchlorate was converted to the free base (oil). ^{1}H NMR: δ 7.4–7.2 (5H, *m*, phenyl), 5.8 (1H, *m*, H-4), 5.65 (1H, *m*, H-3), 4.9 (1H, *dd*, H-10), 3.6 (1H, *m*, H-2), 3.35 (1H, *m*, H-6), 2.9 (1H, *dd*, H-7), 2.65 (1H, *dd*, H-7'), 2.4 (3H, *s*, N-Me), 2.2 (3H, *s*, −CO-Me), 2.1–1.4 (5H). EIMS, *m/z* (rel. int.): 273.172 $[M]^+$ (calc. for $C_{17}H_{23}NO_2$: 273.173) (24), 216 (67), 152 (74), 96 (41), 94 (100). CIMS, *m/z* (rel. int.): 274 $[M+H]^+$ (100), 216 (36), 154 (12). CC of fr. B yielded an additional amount of **20**, which was converted to the perchlorate (98 mg, mp 166–167°).

Sedinone (**22**). Crude **22** was purified on a silica gel column with $CHCl_3$–MeOH–NH_4OH (190:10:1) as the eluent. The fractions containing **22** were combined and evapd. The residue was dissolved in dry Et_2O; treatment of the soln with ethereal HCl yielded a ppt., which was recrystallized twice from MeCOEt–EtOH to give **22**·HCl (122 mg), mp 177–178° (lit. [12]: mp 176–178°). A portion of the hydrochloride was converted to the free base, mp 93° (lit. [3] mp 93°). R_f: 0.54. R_t: 28.11 min. IR ν_{max}^{KBr} cm^{-1}: 2940, 1720 (>C=O), 1375, 1365, 1180, 1065, 775, and 710. ^{1}H NMR: δ 7.4–7.2 (5H, *m*, phenyl), 4.95 (1H, *dd*, H-10), 3.4 (1H, *m*, H-2 or H-6), 3.2 (1H, *m*, H-6 or H-2), 2.65 (1H, *dd*, H-7?), 2.5 (1H, *dd*, H-7'?), 2.3 (3H, *s*, N-Me), 2.2 (3H, *s*, CO-Me), 2.0–1.1 (9H). EIMS, *m/z* (rel. int.): 275.189 $[M]^+$ (calc. for $C_{17}H_{25}NO_2$: 275.189) (8), 218 (19), 154 (81), 96 (100). CIMS, *m/z* (rel. int.): 276 $[M+H]^+$ (100), 218 (50), 154 (16).

Hydroxysedamines **17** and **18** were generous gifts from Dr C. Hootelé. 3-Hydroxy allosedamine (**17**), R_t: 24.15 min. 4-Hydroxy sedamine (**18**), R_t: 24.73 min. Compound **19** was not available as a reference substance and proved to be another hydroxysedamine, R_t: 24.53 min. The mass spectra of the hydroxysedamines were virtually identical. EIMS, *m/z* (rel. int.): 235 $[M]^+$ (3), 114 (100). CIMS, *m/z* (rel. int.): 236 $[M+H]^+$ (100), 114 (12).

Sedinine (**21**) was kindly supplied by Dr C. Hootelé. R_t: 27.29 min. EIMS, *m/z* (rel. int.) 275 $[M]^+$ (4), 216 (68), 154 (62), 94 (100). CIMS, *m/z* (rel. int.): 276 $[M+H]^+$ (100), 216 (6), 154 (16).

Synthesis of 1-(2-*pyrrolidyl*)-*propan*-2-*one and the* 2-*monosubstituted piperidines*. Reference compounds **1**, **2**, **6**, **10** and **13** were prepared from pyrrolidine or piperidine and β-keto acids using the general procedure of ref. [17]. In addition compounds **3–5**, **14–16** were prepared from the above ketones via reduction and/or *N*-methylation. Authentic samples of **7–9**, **11** and **12** were not available, and the identities of these compounds were tentatively inferred from the GC-MS data.

1-(*pyrrolidyl*)-*Propan*-2-*one* (*norhygrine*) (**1**). Prepared from pyrrolidine (7.1 g) and ethyl acetoacetate (39.0 g). Treatment of the crude product with ethereal HCl yielded 4.2 g **1**·HCl (26%) after recrystallization from MeCOEt, mp 117–118°. R_f: 0.16. R_t: 5.27 min. IR ν_{max}^{KBr} cm^{-1}: 1715 (>C=O). EIMS, *m/z* (rel. int.): 127.100 $[M]^+$ (calc. for $C_7H_{13}NO$: 127.100) (8), 84 (12), 70 (100). CIMS, *m/z* (rel. int.): 128 $[M+H]^+$ (100), 70 (20).

Pelletierine (**2**) Prepared from piperidine (8.5 g) and ethyl acetoacetate (39.9 g). Treatment of the crude product with ethereal HCl gave **2**·HCl after recrystallization from MeCOEt. The yield of **2**·HCl was 7.4 g (42%), mp 145–146° (lit. [30]: mp 144–145°). R_f. 0.33. R_t: 6.72 min. IR ν_{max} film of the free base cm^{-1}: 1715 (>C=O). ^{1}H NMR: δ 2.90 (2H, *m*, H-6), 2.60 (1H, *m*, H-2), 2.45 (2H, *d*, H-7), 2.15 (1H, *s*, N-H), 2.10 (3H, *s*, Me), 1.8–1.0 (6H). EIMS, *m/z* (rel. int.): 141.115 $[M]^+$ (calc. for $C_8H_{15}NO$: 141.115) (11), 98 (11), 84 (100). CIMS, *m/z* (rel. int.): 142 $[M+H]^+$ (100), 84 (22).

1-(2-*piperidyl*)-*Propan*-2-ol (**3**). Prepared by reduction of **2**: pelletierine (**2**) (282 mg) and $NaBH_4$ (100 mg) were dissolved in MeOH (50 ml). The soln was stirred for 2 hr and then evapd. The residue was dissolved in 1 M NaOH and extracted with $CHCl_3$; evapn of the organic phase gave a mixture of sedridine and allosedrine. The substance was identical with the natural base, isolated from *Sedum acre* (TLC, GC, MS: no distinction was made between the diastereoisomers).

N-Methylpelletierine (**4**). Prepared by *N*-methylation of **2**. A mixture of **2** (1.41 g), 90% HCO_2H (2.55 g), and HCOH 35% (0.94 g) was kept at 100° for 6 hr, and then diluted with H_2O. The soln was basified and extracted with $CHCl_3$. Evapn of the combined $CHCl_3$ layers, treatment of the residue with ethereal

HCl, and recrystallization of the ppt. from MeCOEt yielded **4**·HCl, mp 155–156° (lit. [31]: 156°). R_f: 0.47. R_t: 8.06 min. IR ν_{max}^{KBr} cm^{-1}: 1720 (>C=O). ^{1}H NMR: δ2.7 (2H, *m*, H-6), 2.5 (1H, *m*, H-2), 2.3 (1H, *dd*, H-7?), 2.15 (3H, *s*, N-Me), 2.10 (3H, *s* CO-Me), 2.10 (1H, H-7'?), 1.7–1.1 (6H). EIMS, *m/z* (rel. int.): 155.131 $[M]^+$ (calc. for $C_9H_{17}NO$: 155.131) (5), 98 (100), 96 (30), 84 (9). CIMS, *m/z* (rel. int.): 156 $[M+H]^+$ (100), 98 (16).

1-(2-*N-methylpiperidyl*)-*Propan-2-ol* (**5**). Prepared by reduction of **4** (155 mg) with $NaBH_4$ (46 mg) in MeOH (20 ml). Work-up of the reaction mixture in the usual manner yielded **5**. R_f 0.15 and 0.24. R_t: 8.02 and 8.54 min (separation of the diastereoisomers). EIMS, *m/z* (rel. int.): 157 $[M]^+$ (1), 98 (100). CIMS, *m/z* (rel. int.): 158 $[M+H]^+$ (100), 98 (6).

1-(2-*piperidyl*)-*Butan-2-one* (**6**). The above procedure was employed to synthesize **6** from piperidine (4.25 g) and ethyl propionylacetate, which was prepared from diethyl malonate and propionyl chloride [32]. The yield of **6**·HCl was 2.6 g (27%), mp 151–153° (lit. [30]: mp 147–148°). R_f 0.39. R_t: 8.92 min. IR ν_{max}^{KBr} cm^{-1}: 1720 (>C=O). ^{1}H NMR: δ2.90 (2H, *m*, H-6), 2.60 (1H, *m*, H-2), 2.42 (2H, *d*, H-7), 2.38 (2H, *q*, H-9), 2.10 (1H, *s*, N-H), 1.75–1.05 (6H), 1.00 (3H, *t*, Me). EIMS, *m/z* (rel. int.): 155.131 $[M]^+$ (calc. for $C_9H_{17}NO$: 155.131) (8), 98 (13), 84 (100). CIMS, *m/z* (rel. int.): 156 $[M+H]^+$ (100), 84 (28).

1-(2-*piperidyl*)-*Butan-2-ol* (**7**). R_t: 10.0 min. CIMS, *m/z* (rel. int.): 158 $[M+H]^+$ (100), 84 (6).

1-(2-N-*methylpiperidyl*)-*Butan-2-one* (**8**). R_t: 10.2 min. EIMS, *m/z* (rel. int.): 169 $[M]^+$ (2), 98 (100). CIMS, *m/z* (rel. int.): 170 $[M+H]^+$ (100), 98 (24).

1-(2-N-*methylpiperidyl*)-*Butan-2-ol* (**9**). R_t: 10.8 min. EIMS, *m/z* (rel. int.): 171 $[M]^+$ (1), 98 (100). CIMS, *m/z* (rel. int.): 172 $[M+H]^+$ (100), 98 (7).

1-(2-*piperidyl*)-*Pentan-2-one* (**10**) Prepared from piperidine (8.5 g) and ethyl butyrylacetate (47.5 g). The yield **10**·HCl amounted to 7.9 g (39%), mp 128° (lit. [30]: mp 127.5–129°). R_f 0.44. R_t: 10.93 min. IR ν_{max}^{KBr} cm^{-1}: 1720 (>C=O). ^{1}H NMR: δ2.90 (2H, *m*, H-6), 2.58 (1H, *m*, H-2), 2.38 (2H, *d*, H-7), 2.33 (1H, *s*, N-H), 2.30 (2H, *t*, H-9), 1.75–1.00 (8H), 0.82 (3H, *t*, Me). EIMS, *m/z* (rel. int.): 169.147 $[M]^+$ (calc. for $C_{10}H_{19}NO$: 169.147 (9), 98 (13), 84 (100). CIMS, *m/z* (rel. int.): 170 $[M+H]^+$ (100), 84 (32).

1-(2-N-*methylpiperidyl*)-*Pentan-2-one* (**11**). R_t: 12.2 min. EIMS, *m/z* (rel. int.): 183 $[M]^+$ (1), 98 (100). CIMS, *m/z* (rel. int.): 184 $[M+H]^+$ (100), 98 (90).

1-(2-N-*methylpiperidyl*)-*Pentan-2-ol* (**12**). R_t: 12.9 min. EIMS, *m/z* (rel. int.): 185 $[M]^+$ (1), 98 (100). CIMS, *m/z* (rel. int.): 186 $[M+H]^+$ (100), 98 (18).

Norsedaminone (**13**). Prepared from piperidine (8.5 g) and ethyl benzoylacetate. 10.1 g **13**·HCl was obtained (yield 42%), mp 168–169° (lit. [30]: mp 170–172°). R_f: 0.48, R_t: 19.61 min. IR ν_{max}^{KBr} cm^{-1}: 1690 (Ph-CO-). ^{1}H NMR: δ8.0–7.2 (5H, phenyl), 3.13–3.04 (2H, *m*, H-6), 2.99 (2H, *d*, H-7), 2.68 (1H, *m*), 2.35 (1H, *s*, N-H), 1.8–1.1 (6H). EIMS, *m/z* (rel. int.): 203.131 $[M]^+$ (calc. for $C_{13}H_{17}NO$: 203.131) (2), 120 (43), 105 (100), 83 (38). CIMS, *m/z* (rel. int.): 204 $[M+H]^+$ (100), 84.

1-*Phenyl*-2-(2-*piperidyl*)-*ethanol* (**14**). Prepared by reduction of **13** (203 mg) with $NaBH_4$ (46 mg) in MeOH (20 ml). Work-up of the reaction mixture in the usual manner yielded **14** (mp 80–82°), which consisted of norsedamine and norallosedamine. R_f: 0.16. R_t: 20.10 and 20.48 min. EIMS, *m/z* (rel. int.): 205 $[M]^+$ (4), 84 (100). CIMS, *m/z* (rel. int.): 206 $[M+H]^+$ (100), 84 (14).

Sedaminone **15**. *N*-Methylation of **13** (2.03 g) gave crude **15**, which was purified by CC. The free base was converted to its hydrochloride, mp 162–163°. R_f: 0.62. R_t: 20.41 min. IR ν_{max}^{KBr} cm^{-1}: 1695 (Ph-CO-). ^{1}H NMR: δ8.0–7.2 (5H, phenyl), 3.35 (1H, *dd*, H-7?), 3.9–3.7 (3H), 2.15 (3H, *s*, N-Me), 2.10 (1H, *m*), 1.8–1.2 (6H). EIMS, *m/z* (rel. int.): 217.147 $[M]^+$, (calc. for $C_{14}H_{19}NO$: 217.147) (2), 120 (44), 105 (100), 96 (68). CIMS, *m/z* (rel. int.): 218 $[M+H]^+$ (82), 98 (100).

Sedamine **16**. Reduction of **15** (169 mg) with $NaBH_4$ (36 mg) in MeOH (20 ml) yielded a mixture of sedamine (**16**) and allosedamine. The two diastereoisomers were separated on a silica gel column, employing mixtures of $CHCl_3$ – MeOH – 1% NH_4OH (the % MeOH was stepwise increased from 0 to 10%) as eluents. Sedamine (48 mg, mp 89°; lit. [29]: mp 89–90°) was thus obtained and proved to be identical with the natural base, isolated from *Sedum acre* (TLC, GC, IR, ^{1}H NMR, MS).

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