Phytochemistry, Vol. 28, No. 1, pp. 251 257, 1989.
Printed in Great Britain.

0031-9422/89 $3.00+0.00

ALKALOIDS OF *SARCOCAPNOS CRASSIFOLIA* SUBSP. *SPECIOSA*

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(*Received* 22 *March* 1988)

Key Word Index—*Sarcocapnos crassifolia* subsp.*speciosa*; Fumariaceae; alkaloid content of aerial parts; 1-benzylisoquinoline alkaloids; novel cularines.

Abstract—Thirty-four benzylisoquinoline alkaloids were isolated from the aerial parts of *Sarcocapnos crassifolia* subsp. *speciosa*. Twenty-seven of them were identified as the following known alkaloids. Benzophenanthridines: 8-hydroxymethyl dihydrosanguinarine, (+)-chelidonine and oxysanguinarine. Ribasines: (+)-ribasine. Aporphinoids: (+)-glaucine, (+)-*N*-methyl laurotetanine, (+)-isoboldine, *O*-methyl atheroline and corunnine. Morphinandienones: (−)-pallidine and (+)-salutaridine. 1-Benzylisoquinolines: (+)-crassifoline. Protopines: protopine. Protoberberines: (−)-scoulerine. Cularines and related compounds: (+)-cularine, (+)-cularidine, (+)-celtisine, (+)-breoganine, (+)-sarcocapnidine, (+)-claviculine, oxocularine, oxocompostelline, oxosarcocapnidine, oxosarcophylline, secocularine and secocularidine. Dibenzopyranazepines: (−) clavizepine. The remainder were seven new cularine-type alkaloids which we named (+)-enneaphylline, (+)-sarcophylline, (+)-norsarcocapnidine, oxocularidine, secosarcocapnidine, norsecocularidine and norsecosarcocapnidine. Their structures have been elucidated by spectroscopic and chemical methods.

INTRODUCTION

The Fumariaceae have been extensively studied due to their varied alkaloid content. The genus Sarcocapnos, which belongs to this family, has recently been shown to be a rich source of isoquinoline alkaloids, most of them with a cularine skeleton [1–3]. In continuance of our chemical research on the alkaloids of Spanish Fumariaceae, an intensive study of aerial parts of *Sarcocapnos crassifolia* subsp. *speciosa* was carried out in our laboratory. The plant is a caespitose perennial herb growing in shady crevices in the calcareous mountains of Southern Spain [4]. In a preliminary study we have isolated the new alkaloids (+)-ribasine **(4)** [5], (+)-crassifoline **(12)** [6], (+)-breoganine **(19)** [7], (+)-sarcocapnidine **(20)** [6], (+)-claviculine **(22)** [6], oxosarcocapniidine **(27)** [6] and secocularine **(29)** [8].

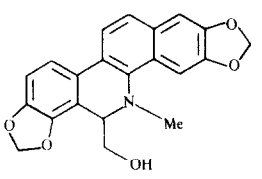
RESULTS AND DISCUSSION

After extraction by usual methods (see Experimental), the alkaloids of *Sarcocapnos crassifolia* subsp. *speciosa* were separated by CC and prep. TLC. Thirty-four different benzylisoquinoline alkaloids were isolated, 27 of them have been identified as the known alkaloids 8-hydroxymethyl dihydrosanguinarine **(1)**, (+)-chelidonine **(2)**, oxysanguinarine **(3)**, (+)-ribasine **(4)**, (+)-glaucine **(5)**, (+)-*N*-methyl laurotetanine **(6)**, (+)-isoboldine **(7)**, *O*-methyl atheroline **(8)**, corunnine **(9)**, (−)-pallidine **(10)**, (+)-salutaridine **(11)**, (+)-crassifoline **(12)**, protopine **(13)**, (−)-scoulerine **(14)**, (+)-cularine **(15)**, (+)-cularidine **(16)**, (+)-celtisine **(18)**, (+)-breoganine **(19)**, (+)-sarcocapnidine **(20)**, (+)-claviculine **(22)**, oxocularine **(24)**, oxocompostelline **(25)**, oxosarcocapnidine **(27)**, oxosarcophylline **(28)**, secocularine **(29)**, secocularidine **(30)** and (−)-clavizepine **(34)**. The structures of these alkaloids were confirmed by comparing their ^{1}H NMR and mass spectra, and TLC R_f values with published values and those of authentic samples.

The remaining seven compounds were new cularine-type alkaloids which we named (+)-enneaphylline **(17)**, (+)-sarcophylline **(21)**, (+)-norsarcocapnidine **(23)**, oxocularidine **(26)**, secosarcocapnidine **(31)**, norsecocularidine **(32)** and norsecosarcocapnidine **(33)**. Their structures were elucidated by spectroscopic analysis and further confirmed by chemical transformations and partial or total synthesis [9, 10].

(+)-Enneaphylline **(17)** was isolated as colourless prisms, mp 205–207°(EtOH), $[\alpha]_D$ + 256° (EtOH) and analysed as $C_{19}H_{21}NO_4$([M]$^+$, base peak, c:327.1470, HR f: 327.1464). The bathochromic shift of its UV spectrum in basic media together with the broad IR signal at 3440 cm^{-1} revealed its phenolic nature. The ^{1}H NMR spectrum showed one *N*-methyl group, two methoxyl groups, a methine group centred at δ 4.44 as a doublet of doublets (*dd*, $J_{1\text{-}\alpha\alpha}$: 3.7 Hz, $J_{1\text{-}\alpha\beta}$: 12.0 Hz) characteristic of the cularine skeleton, and four aromatic protons, two as singlets and two as an AB system. The mass spectrum, with its base peak at *m/z* 327 ([M]$^+$), showed the hydroxyl group to be located at C-3′[3]. Structure **17** for enneaphylline was finally confirmed by comparison with the synthetic product obtained from crassifoline **(12)** by phenolic coupling, which gave a mixture of sarcocapnidine **(20)** (6% yield) and enneaphylline **(17)** (3% yield) [11]. The co-occurrence of alkaloids **12, 17** and **20** in the same natural source and the above biogenetically patterned synthesis of **17** and **20** from **12** points to the direct oxidative coupling of a 7,8,3′,4′-tetraoxygenated tetrahydrobenzyl isoquinoline as being the most probable of the routes proposed for the biogenesis of cularines [12, 13].

(+)-Sarcophylline **(21)** was isolated as an amorphous powder, $[\alpha]_D$ + 200° ($CHCl_3$) and analysed as $C_{19}H_{21}NO_4$. Its phenolic nature was deduced from its



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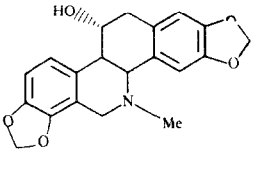

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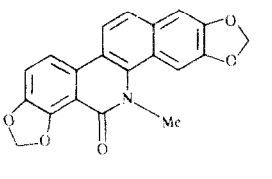

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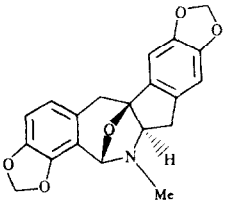

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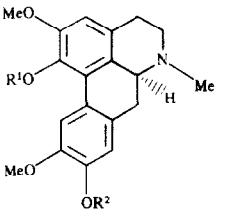

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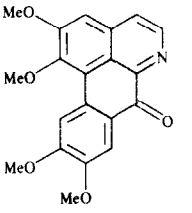
7 $R^1 = R^2 = H$



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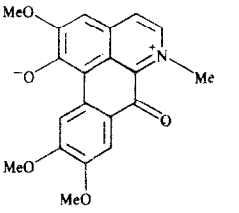

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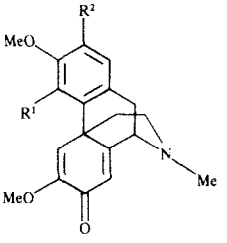

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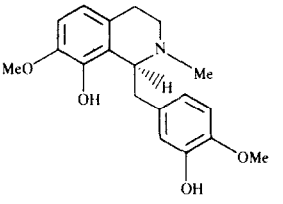

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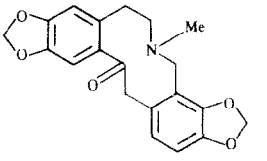

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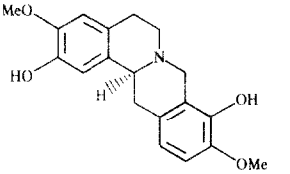

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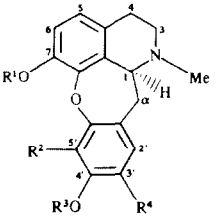

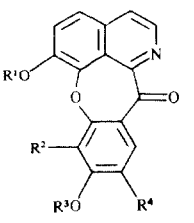

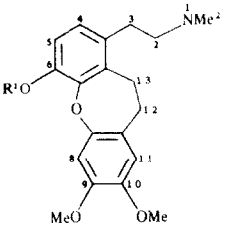

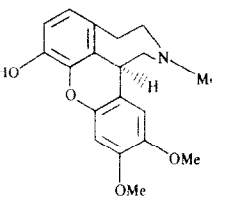

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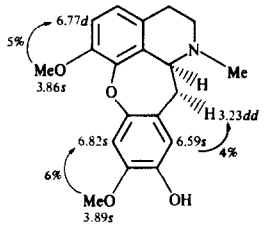
15 $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = OMe$
16 $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = OMe$
18 $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
19 $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = OH$
20 $R^1 = R^3 = Me$, $R^2 = OH$, $R^4 = H$
22 $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = Me$
24 $R^1 = R^3 = Me$, $R^2 = H$, $R^4 = OMe$
25 $R^1 = Me$, $R^2 = H$, $R^3 + R^4 = CH_2O$
27 $R^1 = R^3 = Me$, $R^2 = OH$, $R^4 = H$
28 $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = Me$
29 $R^1 = Me$
30 $R^1 = H$

UV (bathochromic shift in basic media) and IR (3400 cm^{-1}) spectra. The ^1H NMR spectrum showed one *N*-methyl group, two methoxyl groups, one culanine-like C_1 methine proton centred at δ 4.46 (*dd*, $J_{1-\alpha\alpha}$: 4.3 Hz, $J_{1-\alpha\beta}$: 12.0 Hz), and two AB systems in the aromatic region, which suggested a phenolic isocularine structure. The mass spectrum presented a significant peak at *m/z* 162 which showed the phenolic group to be located at C-7 [3]. Subsequent confirmation of structure **21** for sarcophylline was obtained by its conversion into sarcocapnine [14] after methylation with diazomethane.

The molecular formula of (+)-norsarcocapnidine **(23)** $C_{18}H_{19}NO_4$, was established by high resolution mass spectrometry [c: 313.1318, HR f: 313.1314 (100)]. Its phenolic nature was deduced from its UV (bathochromic shift in basic media) and IR (3450 cm^{-1}) spectra. Its ^1H NMR spectrum, with no *N*-methyl absorption, suggested a norisocularine skeleton. The absence of the characteristic downfield methoxyl group at C-5′ allowed this position to be attributed to a hydroxyl group. The assignments of the chemical shifts for the methoxyl groups and aromatic protons were established by NOE and COSY experiments. The substitution pattern was confirmed by partial synthesis (Scheme 1) from the parent sarcocapnidine **(20)** by means of Fremy's salt oxidation [14, 15] of its *O*-methoxymethyl protected derivative **35**



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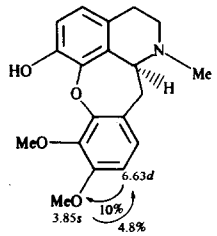

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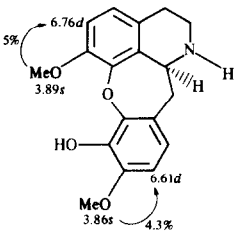

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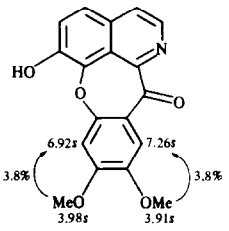

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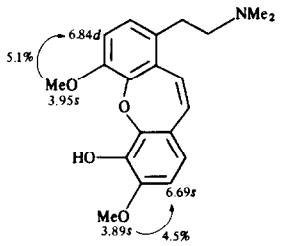

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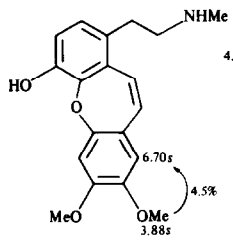

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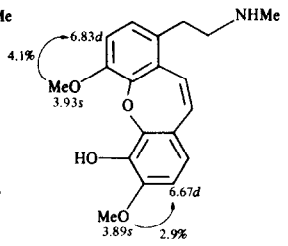

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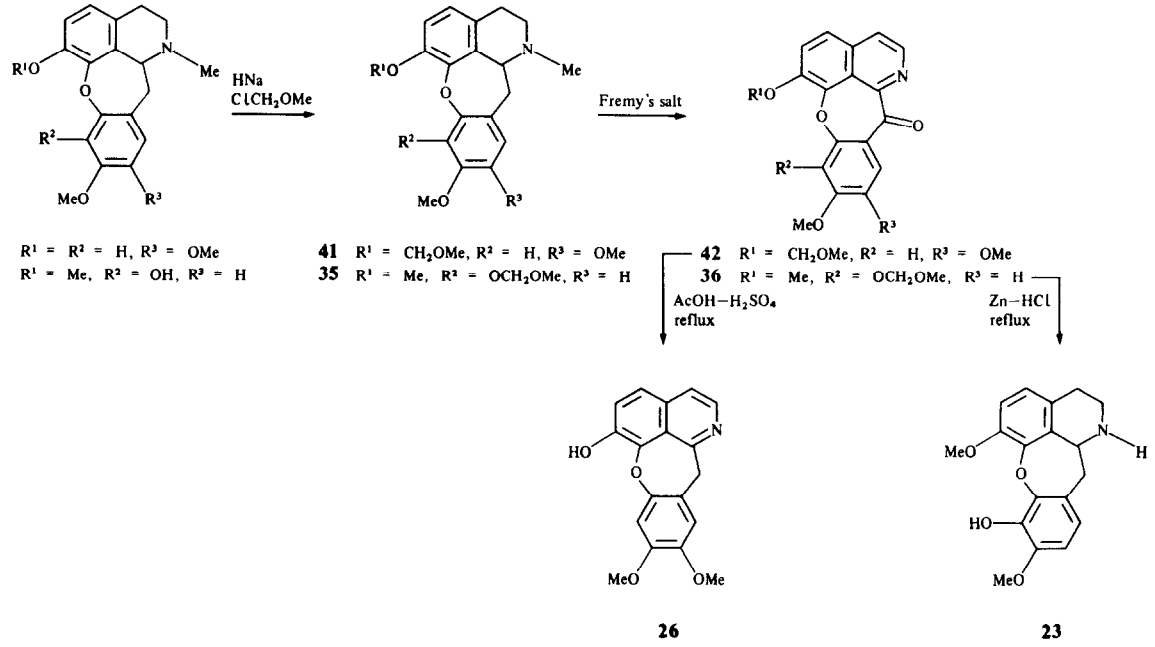
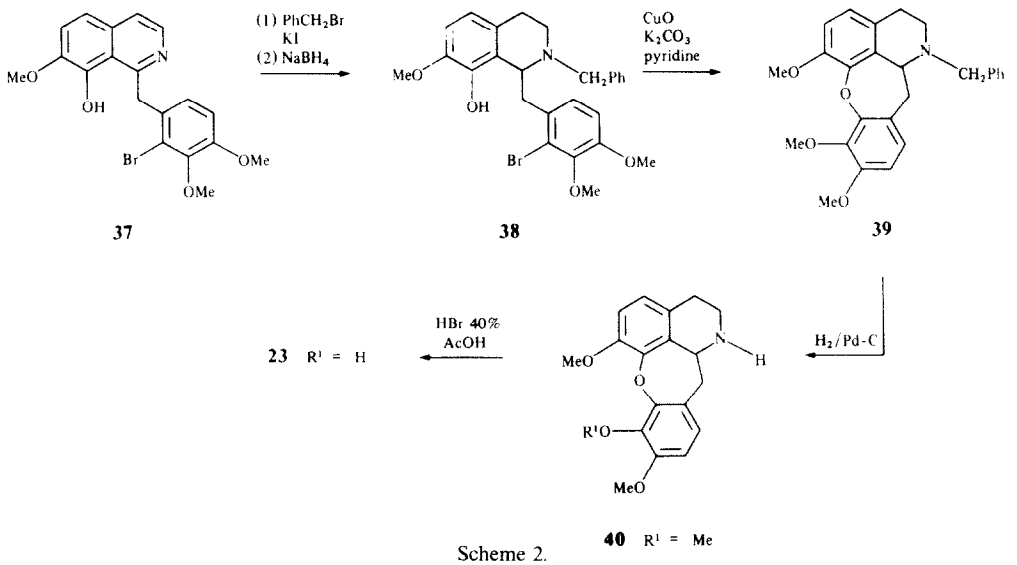


26 23

Scheme 1.

[6] to give *O*-methoxymethyl oxosarcocapnidine **(36)**, which was then subjected to Zn–HCl reduction to norsarcocapnidine **(23)**.

Total synthesis of norsarcocapnidine (Scheme 2) was based on our synthetic approach to cularines [16] which uses an Ullmann condensation for the formation of the diaryl ether linkage. As Ullmann condensation gives a very low yield with 1-benzyl-1,2,3,4-nortetrahydro iso-



Scheme 2.

quinolines, we decided to protect the nitrogen with the easily removable benzyl group. Accordingly the 2-benzyl-1-(2′-bromo-3′,4′-dimethoxybenzyl)-8-hydroxy-7-methoxy-tetrahydroisoquinoline **(38)**, obtained by *N*-benzylation ($PhCH_2Br$, KI, acetone) of **37** [16] and subsequent sodium borohydride reduction of the crude product, was reacted with cupric oxide and potassium carbonate in dry pyridine to give the *N*-benzyl norisocularine **39** in 94% yield. *N*-debenzylation (H_2,Pd/C) of **39** afforded the known norsarcocapnine **(40)**[14]. Selective demethylation of **40** (48% HBr–AcOH, 1:2) at its C-5′ position [17], afforded norsarcocapnidine **(23)** in 70% yield. The synthetic product proved identical (TLC, mass spectrum, ^{1}H NMR) to the natural product.

Oxocularidine **(26)** was isolated as an amorphous orange powder. Its UV spectrum showed absorptions bands at 254 (3.86), 266 (3.67), 304 sh (3.28), 350 (3.18) and 410 (3.20) nm, on addition of acid these bands underwent a bathochromic shift to 254 (3.7), 278 (3.7), 335 (3.28) and 490 (3.16) nm. Its phenolic nature was dedeuced from a strong bathochromic shift observed on addition of base. The IR spectrum displayed absorption bands at 3400 (OH) and 1670 (conjugated carbonyl) cm^{-1}. The molecular formula $C_{18}H_{13}NO_5$ was established from the high resolution mass spectrum, which showed the $[M]^+$ at *m/z* (rel.int.) 323.0797 (100) (c: 323.0791). the cularine skeleton was deduced from its ^{1}H NMR spectrum, which exhibited two methoxyl singlets and six aromatic protons, four as two AB systems and two as singlets. the phenolic group was located at the C-7 position by comparison of the mass spectrum (which exhibits a low peak at $[M-43]^+$) with those of the oxocularines which have a methoxyl group at C-7 [18] and exhibit significant peaks at *m/z* $[M-43]^+$. This assignment was supported by NOE experiments. Structure **26** for oxocularidine was finally confirmed by comparison with synthetic material obtained by partial synthesis from cularidine **(16)** (Scheme 1): Fremy's salt oxidation of *O*-methoxymethyl cularidine **(41)** led to *O*-methoxymethyl oxocularidine **(42)**, acid deprotection of which gave oxocularidine **(26)** in 40% yield.

The secocularine nature of the new alkaloids secosarcocapnidine **(31)**, norsecocularidine **(32)** and norsecosarcocapnidine **(33)** was deduced on the basis of their ^{1}H NMR spectra, which showed signals in the aliphatic region suggesting the presence of a $-CH_2CH_2NMe_2$ side chain in **31** and a $-CH_2CH_2NHMe$ side chain in compounds **32** and **33**. The spectra also exhibited a characteristic AB system in the aromatic region, with a very large coupling constant ($J = 11.6$ Hz), corresponding to H-12 and H-13 of the secocularine structure. Their secocularine nature was also supported by the presence of a base peak in the mass spectrum at *m/z* 58 $[CH_2{=}NMe_2]^+$ for **31** and at *m/z* 44 $[CH_2{=}NHMe]^+$ for **32** and **33**. Further proof of structure **31** came from direct comparison with synthetic material that was easily obtained by Hoffman degradation of sarcocapnidine methiodide [8]. Structures **32** and **33** were confirmed by transformation into secocularidine and secosarcocapnidine, respectively, by *N*-methylation with $HCHO/NaBH_4$.

EXPERIMENTAL

General. Mps: uncorr. MS were recorded at 70 eV. HR-MS at the Midwest Center for Mass Spectrometry (University of Nebraska, USA). ^{1}H NMR were measured at 250 MHz in $CDCl_3$ solns (chemical shifts reported are relative to TMS). CC was carried out on Merck silica gel and Woelm N (grade IV) neutral alumina. TLC was performed on Merck GF-254 type 60 silica gel and neutral alumina plates with the following solvent systems: C_6H_6–Et_2O (1:3), Et_2NH–EtOAc–C_6H_6(1:2:7), CH_2Cl_2, CH_2Cl_2–MeOH (19:1), (9:1) and (17:3). Alkaloids were detected by UV and after spraying with Dragendorff's reagent or I_2 vapour. Reactions sensitive to air or moisture were conducted in oven-dried glass-ware under an atmosphere of dry N_2 or Ar using dry freshly dist. solvents. Pyridine was dried by refluxing with KOH for 8 hr followed by dist. Me_2CO was dried and dist. from Na_2CO_3. HBr was distilled under vacuum over a trace (1%) of hypobromous acid prior to use. KI and K_2CO_3 were previously dried at 300° for 12 hr. DMF was dried over CaH_2, dist under red. pres. and stored over 4 Å molecular sieves.

Plant material. Aerial parts of *S. crassifolia* (Desf.) DC subsp. *speciosa* (Boiss.) Rouy were collected in Granada (Spain) during the flowering season and identified by Dr J.M. Losa *et al.*, University of Granada. A voucher specimen is kept in the herbarium of the Department of Botany University of Granada.

Extraction of alkaloids. Dried, powdered aerial parts (6.7 kg) were extracted with MeOH (15 l) in a Soxhlet until a Mayer's test was negative. After removal of solvent under red. pres., the dark

green residue remaining was taken up in 10% HCl (8 l) and filtered. The acidic aq. extracts was washed with petrol (3 × 2 l) to remove neutral components. The aq. soln was extracted with CH_2Cl_2 at pH 6,8 and 14, after successive additions of NH_4OH and NaOH. The extracts were washed with H_2O, dried and evaporated *in vacuo*. The extracts taken at pH 8 and 14 showed a similar TLC composition and were combined. Thus, two different crude alkaloid mixts were obtained: Extract A (pH 6, 37.11 g, 5.54 g/kg dry plant), and Extract B (Ph 8 and 14, 27.75 g, 4.14 g/kg). TLC showed both crudes extracts to be very complex mixtures. They were purified on silica gel columns eluted with CH_2Cl_2 containing increasing preparations of MeOH and finally with H_2O and MeOH–HOAc (1–5%).

The 33 fractions, collected from Extract A were purified by prep. TLC and fractionally crystallized to afford 24 alkaloids, which were by order of increasing polarity on TLC: 8-hydroxymethyl dihydrosanguinarine **(1)** (0.07 g), (+)-chelidonine **(2)** (2 g), (+)-*ribasine* **(4)** (0.80 g), *oxysanguinarine* **(3)** (0.09 g), *oxocompostelline* **(25)** (0.09 g), oxosarcocapnidine **(27)** (1.70 g), oxosarcophylline **(28)** (0.4 g), oxocularine **(24)** (0.03 g), *O*-methyl atheroline **(8)** (0.03 g), (+)-sarcocapnidine **(20)** (8 g), (+)-cularine **(15)** (0.03 g), (+)-glaucine **(5)** (0.4 g), (+)-enneaphylline **(17)** (0.06 g), (+)-cularidine **(16)** (4.50 g), (+)-norsarcocapnidine **(23)** (0.03 g), (+)-crassifoline **(12)** (0.35 g), (+)-claviculine **(22)** (1 g), (+)-*N*-methyl laurotetanine **(16)** (0.04 g), (+)-celtisine **(18)** (1.90 g), protopine **(13)** (4.70 g), secocularine **(29)** (0.015 g), (+)-breoganine **(19)** (1.30 g), norsecosarcocapnidine **(33)** (0.03 g) and norsecocularidine **(32)** (0.01 g). The 20 fractions collected from Extract B were subjected to the same process to afford 25 alkaloids: (+)-chelidonine **(2)** (1.50 g), (+)-ribasine **(4)** (0.40 g), oxosarcocapnidine **(27)** (1 g), oxosarcophylline **(28)** (0.20 g), *O*-methyl atheroline **(8)** (0.01 g), (+)-sarcocapnidine **(20)** (4 g), (+)-glaucine **(5)** (0.50 g), (+)-sarcophylline **(21)** (0.03 g), (+)-cularidine **(16)** (3 g), (+)-crassifoline **(12)** (0.15 g), (+)-claviculine **(22)** (1.30 g), (+)-celtisine **(18)** (2 g), protopine **(13)** (4 g), oxocularidine **(26)** (0.01 g), (−)-clavizepine **(34)** (0.01 g), (+)isoboldine **(7)** (0.045 g), (−)-scoulerine **(14)** (0.04 g), corunnine**(9)** (0.02 g), secosarcocapnidine **(31)** (0.03 g), (+)-salutaridine **(11)** (0.04 g), (−)-pallidine**(10)** (0.03 g), (+)-breoganine **(19)** (1 g), secocularidine **(30)** (0.05 g), norsecosarcocapnidine **(33)** (0.01 g) and norsecocularidine **(32)** (0.02 g).

8-Hydroxymethyl dihydrosanguinarine **(1).** All physical and spectroscopic data were identical with those reported in the lit. [19]. This alkaloid is known to be an artefact formed during extraction with MeOH [20].

(+)-Chelidonine **(2),** *oxysanguinarine* **(3),** *(−)-pallidine* **(10),** *(+)-salutaridine* **(11),** *protopine* **(13)** and *(−)-scoulerine* **(14)** were identified by comparison of their TLC R_f values and MS and ^{1}H NMR with those of authentic samples.

(+)-Ribasine **(4),** *(+)-crassifoline* **(12),** *(+)-breoganine* **(19),** *(+)-sarcocapnidine* **(20),** *(+)-claviculine* **(22),** *oxosarococapnidine* **(27)** and *secocularine* **(29)** were identified by comparison of their chromatographic, physical and spectroscopic data with those of authentic products isolated in the preliminary study of this plant. [5–8].

(+)-Glaucine **(5),** (+)-N-*methyl laurotetanine* **(6),** (+)-isoboldine **(7),** *O-methyl atheroline* **(8)** and *corunnine* **(9)** were identified by comparison of their physical constants and spectroscopic data with those reported in the lit. [21].

(+)-Cularine **(15),** *(+)-cularidine* **(16),** *(+)-celtisine* **(18),** *oxocularine* **(24),** *oxocompostelline* **(25),** *oxosarcophylline* **(28),** and *secocularidine* **(30)** were identified by comparison of their physical constants and spectroscopic data with those reported in the lit. [1].

(+)-Enneaphylline **(17).** Colourless prisms, mp 205–207° (EtOH), $[\alpha]_D$ +256° (EtOH). UV λ_{max}^{EtOH} (log ε) nm: 226 (4.04), 284 (3.85), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 223 (4.33), 303 (3.71). IR ν^{KBr} cm^{-1}: 3440. ^{1}H NMR ($CDCl_3$): δ 6.88 (*d*, *J* = 8.4 Hz, 1H, H-5), 6.82 (*s*, 1H, H-5'), 6.77 (*d*, *J* = 8.4 Hz, 1H, H-6), 6.59 (*s* 1H, H-2'), 4.44 (*dd*, $J_{1-\alpha\alpha}$ = 3.7 and $J_{1-\alpha\beta}$ = 12.0 Hz, 1H, H-1), 3.89 (*s*, 3H, OMeC-4'), 3.86 (*s*, 3H, OMeC-7), 3.23 (*dd*, $J_{\alpha\alpha-\alpha\beta}$ = 16.0 Hz, 1H, $H_{\alpha\alpha}$), 2.95 (*dd*, 1H, $H_{\alpha\beta}$), 3.20–2.70 (*m*, 4H, H-3 and H-4), 2.59 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel.int.): 327[M]$^+$ (100), 312 [M − Me]$^+$ (64), 174 (39). Molecular formula $C_{19}H_{21}NO_4$ [M]$^+$ (c: 327.1470; HRMS f: 327.1465). The structure was further confirmed by comparison of the spectroscopic and chromatographic data with those of the synthetic compound [11] which were identical.

(+)-Sarcophylline **(21).** Amorphous powder, $[\alpha]_D$ +200° ($CHCl_3$). UV λ_{max}^{EtOH} (log ε) nm: 219 (4.01), 282 (3.36), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 222 (4.10), 293 (3.40). IR ν^{KBr} cm^{-1}: 3400. ^{1}H NMR ($CDCl_3$): δ 6.83 (*d*, *J* = 8.3 Hz, 1H, H-5), 6.80 (*d*, *J* = 8.7 Hz, 1H, H-2'), 6.77 (*d*, *J* = 8.3 Hz, 1H, H-6), 6.63 (*d*, *J* = 8.7 Hz, 1H, H-3'), 4.46 (*dd*, $J_{1-\alpha\alpha}$ = 4.3 and $J_{1-\alpha\beta}$ = 12.0 Hz, 1H, H-1), 4.03 (*s*, 3H, OMeC-5'), 3.85 (*s*, 3H, OMeC-4'), 3.37 (*dd*, $J_{\alpha\alpha-\alpha\beta}$ = 16.2 Hz, 1H, $H_{\alpha\alpha}$), 2.97 (*dd*, 1H, $H_{\alpha\beta}$), 3.15–2.70 (*m*, 4H, H-3 and H-4), 2.60 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel.int.): 327 [M]$^+$ (100), 312[M − Me]$^+$ (56), 294 (53), 162 (66). Molecular formula $C_{19}H_{21}NO_4$ [M]$^+$ (c: 327.1470; HRMS f: 327.1470).

O-Methylation of **21.** A MeOH soln of sarcophylline **(21)** was left overnight with excess CH_2N_2 in dry Et_2O. Air was then bubbled to eliminate excess reagent and the solvent removed under red pres. R_f values, ^{1}H NMR and MS of the resulting product were identical with those of natural sarcocapnine [14].

Norsarcocapnidine **(23).** Amorphous powder, $[\alpha]_D$ +347.5° (EtOH). UV λ_{max}^{EtOH} (log ε) nm: 225 (4.16), 278 (3.52), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 227 (4.30), 284 (3.73), 293 sh (3.69). IR ν^{KBr} cm^{-1}: 3450. ^{1}H NMR ($CDCl_3$): δ 6.90 (*d*, *J* = 8.4 Hz, 1H, H-5), 6.76 (*d*, *J* = 8.4 Hz, 1H, H-6), 6.61 (*d*, *J* = 8.6 Hz, 1H, H-3'), 6.56 (*d*, *J* = 8.6 Hz, 1H, H-2'), 4.75 (*dd*, $J_{1-\alpha\alpha}$ = 5.3 and $J_{1-\alpha\beta}$ = 11.1Hz, 1H, H-1), 3.89 (*s*, 3H, OMeC-7), 3.86 (*s*, 3H, OMeC-4'), 3.28 (*dd*, $J_{\alpha\alpha-\alpha\beta}$ = 16.5 Hz, 1H, $H_{\alpha\alpha}$), 3.15 (*dd*, 1H, $H_{\alpha\beta}$), 3.20–2.70 (*m*, 4H, H-3 and H-4). EIMS 70 eV *m/z* (rel. int.): 313 [M]$^+$ (100), 312 [M − 1]$^+$ (35.5), 298 [M − Me]$^+$ (21), 160 (16). Molecular formula $C_{18}H_{19}NO_4$ [M]$^+$ (c: 313.1318; HRMS f: 313.1314).

Partial synthesis of norsarcocapnidine **(23).** *O-Methoxymethyl sarcocapnidine* **(35).** NaH (80% in oil dispersion, 0.05 g, 1.68 mmol) was washed free of oil with dry THF (2 × 5 ml) and DMF (5 ml) was added under inert atm. The suspension was stirred at room temp and a soln of sarcocapnidine **(20)** (0.5 g, 1.5 mmol) in dry DMF (50 ml) was added to the resulting mixt.; a soln of $ClCH_2OMe$ (0.174 g, 2.16 mmol) in THF (5 ml) was added dropwise. The mixt. was stirred for a further 3 hr, dil with H_2O (25 ml) and extracted with CH_2Cl_2 (3 × 15 ml). The exts were dried (Na_2SO_4) and evapd to dryness to give **35** as a white amorphous solid, in quantitative yield. ^{1}H NMR ($CDCl_3$): δ 6.91 (*d*, *J* = 8.4 Hz, 1H, H-5), 6.82 (*d*, *J* = 8.6 Hz, 1H, H-2'), 6.81 (*d*, *J* = 8.4 Hz, 1H, H-6), 6.61 (*d*, *J* = 8.6 Hz, 1H, H-3'), 5.31 (*d*, *J* = 5.7 Hz, 1H, $-OCH_2O-$), 5.27 (*d*, *J* = 5.7 Hz, 1H, $-OCH_2O-$), 4.46 (*dd*, $J_{1-\alpha\alpha}$ = 3.2 and $J_{1-\alpha\beta}$ = 11.7 Hz, 1H, H-1), 3.84 (*s*, 3H, OMe), 3.83 (*s*, 3H, OMe), 3.67 (*s*, 3H, aliphatic OMe), 3.40 (*dd*, $J_{\alpha\alpha-\alpha\beta}$ = 16.3 Hz, 1H, $H_{\alpha\alpha}$), 3.17 (*dd*, 1H, $H_{\alpha\beta}$), 3.20–2.80 (*m*, 4H, H-3 and H-4), 2.65 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel. int.): 371 [M]$^+$ (10), 356 [M − Me]$^+$ (20), 326 [M − CH_2OMe]$^+$ (40), 298 (12), 174 (10), 45 [CH_2OMe]$^+$ (100). Molecular formula $C_{21}H_{25}NO_5$ [M]$^+$ (c: 371.1725, HRMS f: 371.1713).

O-Methoxymethyl oxosarcocapnidine **(36).** To a soln of **35** (0.47 g, 1.26 mmol) in 20 ml of pyridine–H_2O (1:1) was added a soln of excess Fremy's salt in 20 ml of pyridine–2% Na_2CO_3 (1:1) and the mixt stirred at room temp for 72 hr. Solvent was removed under vacuum, the residue washed with H_2O (20 ml) and extd with $CHCl_3$ (3 × 15ml). Removal of solvent gave the

oxoisocularine **36** as a yellow amorphous solid in 15% yield. ^{1}H NMR ($CDCl_3$): δ8.62 (*d*, J = 5.4 Hz, 1H, H-3), 7.73 (*d*, J = 5.4 Hz, 1H, H-4), 7.73 (*d*, J = 9.1 Hz, 1H, H-6), 7.60 (*d*, J = 9.1 Hz, 1H, H-5), 7.51 (*d*, J = 8.7 Hz, 1H, H-3'), 6.84 (*d*, J = 8.7 Hz, 1H, H-2'), 5.43 (*s*, 2H, $-OCH_2O-$), 4.09 (*s*, 3H, OMe), 3.91 (*s*, 3H, OMe), 3.69 (*s*, 3H, aliphatic OMe). EIMS 70 eV *m/z* (rel.int.): 367 $[M]^+$ (15), 322 $[M-CH_2OCH_3]^+$ (10), 294 (11), 45 $[CH_2OMe]^+$ (100). Molecular formula $C_{20}H_{17}NO_6[M]^+$ (c: 367.1050, HRMS f: 367.1054)

Norsarcocapnidine **(23).** To a red soln of **36** (0.05 g, 0.13 mmol) in 18 ml of HOAc–H_2O (1 : 1) were added 64 ml of concd HCl. Zn was added in small portions during a reflux time of 24 hr until there was total decoloration of the soln. The mixt. was then dil with H_2O (10 ml), neutralized with aq. NH_3 and extracted with CH_2Cl_2 (3 × 20 ml) to afford **23** in 80% yield.

Total synthesis of norsarcocapnidine **(23).** *2-Benzyl-1-(2'-bromo-3',4'-dimethoxybenzyl)-8-hydroxy-7-methoxy-1,2,3,4-tetra hydroisoquinoline* **(38).** A mixt. of **37** [17] (0.67 g, 1.65 mmol), KI (1.2 g, 7.24 mmol), $PhCH_2Br$ (0.39 g, 2.28 mmol) and dry Me_2CO (50 ml) was heated at 60–80° under an inert atm. for 6 days. Solvent was removed under vacuum, the unstable product suspended in MeOH (30ml) containing a trace of H_2O (0.5ml), $NaBH_4$ added in small portions over 60 min at room temp. and stirring maintained for an additional 2 hr. Solvent was removed, the residue dil with H_2O (50 ml) and extracted with CH_2Cl_2 to afford **38** as a white amorphous solid in 72% yield. UV λ_{max}^{EtOH} nm: 235, 285; $\lambda_{max}^{EtOH/NaOH}$ nm: 240, 300. ^{1}H NMR ($CDCl_3$): δ7.17–7.14 (*m*, 5H, ArH), 7.05 (*d*, J = 8.5 Hz, 1H, ArH), 6.80 (*d*, J = 8.3 Hz, 1H, ArH), 6.79 (*d*, J = 8.5 Hz, 1H, ArH), 6.71 (*d*, J = 8.3 Hz, 1H, ArH), 4.22 (*dd*, J = 4.7 and J = 9.4 Hz, 1H, H-1), 3.93 (*s*, 3H, OMe), 3.92 (*s*, 3H, OMe), 3.90 (*s*, 3H, OMe), 3.73 (*d*, J = 13.6 Hz, 1H, $-NC\underline{H}_2Ph$), 3.58 (*d*, J = 13.6 Hz, 1H, $-NC\underline{H}_2Ph$). EIMS *m/z* (rel.int.): 498 $[M]^+$ (< 1), 268 (100) $[C_{17}H_{18}NO_2]^+$ (c: 268.1332; HR-MS f: 268.1340)*, 91(74).

N-*Benzyl norsarcocapnine* **(39).** A mixt. of **38** (0.377 g, 0.757 mmol), dry pyridine (10 ml) and dry K_2CO_3 (0.368 g, 2.66 mmol) was heated to 135° under an inert atmosphere and purified CuO (0.54 g, 6.8 mmol) added. The temp. was then raised to 160° with efficient stirring over 3 hr. After cooling, the soln was filtered through Celite, which was washed thoroughly with CH_2Cl_2 (100 ml). Solvent was removed under vacuum and the residue dissolved in CH_2Cl_2 (3 × 40 ml) and washed with H_2O (2 × 25 ml), 10% $CuSO_4$ (2 × 30 ml) and H_2O (2 × 25 ml). The dried (Na_2SO_4) exts were purified by silica gel CC, affording **39** as a white solid in 94% yield. Mp 98° (EtOH). ^{1}H NMR ($CDCl_3$): δ 7.41–7.23 (*m*, 5H, ArH), 6.89 (*d*, J = 8.4 Hz, 1H, ArH), 6.77 (*d*, J = 8.4 Hz, 1H, ArH), 6.73 (*d*, J = 8.6 Hz, 1H, ArH), 6.57 (*d*, J = 8.6 Hz, 1H, ArH), 4.55 (*dd*, $J_{1-\alpha\alpha}$ = 4.7 and $J_{1-\alpha\beta}$ = 10.7 Hz, 1H, H-1), 4.04 (*s*, 3H, OMe), 3.84 (*s*, 3H, OMe), 3.82 (*s*, 3H, OMe), 3.22–2.55 (*m*, 6H, H_α, H-3 and H-4). EIMS 70 eV *m/z* (rel.int.): 417 $[M]^+$ (50), 402 $[M-Me]^+$ (25), 384 (12), 252 (50), 91 (100). Anal.: calcd. for $C_{26}H_{27}NO_4$: C, 74.78; H, 6.52; N, 3.35. Found: C, 74.65; H, 6.84; N, 3.34.

Norsarcocapnine **(40).** *N*-Benzyl norsarcocapnine **(39)** (0.025 g, 0.060 mmol) in HOAc (0.25 ml) was stirred with 10% Pd-C (25 mg) under H_2 for 3 hr. After filtration through Celite and removal of solvent, the residue was dissolved in H_2O (10 ml), basified with aq. NH_3 to pH9 and extracted with $CHCl_3$ (3 × 10 ml). The dried extracts (Na_2SO_4) were concd to give **40** in 80% yield. Crystallized as its HBr from MeOH as a white solid. Mp 250° (MeOH). ^{1}H NMR($CDCl_3$): δ 6.86 (*d*, J = 8.4 Hz, 1H, H-5), 6.79 (*d*, J = 8.4 Hz, 1H, H-6), 6.79 (*d*, J = 8.3 Hz, 1H, H-2'), 6.61 (*d*, J = 8.3 Hz, 1H, H-3'), 4.50 (*dd*, $J_{1-\alpha\alpha}$ = 3.6 and $J_{1-\alpha\beta}$ = 11.3 Hz, 1H, H-1), 4.01 (*s*, 3H, OMe), 3.88 (*s*, 3H, OMe), 3.84 (*s* 3H, OMe), 3.40–2.70 (*m*, 6H, H_α, H-3 and H-4). EIMS 70 eV *m/z* (rel.int.): 327 $[M]^+$ (100), 312 $[M-Me]^+$ (32), 294 (20), 162 (47). Anal. calcd for the hydrobromide $C_{19}H_{21}NO_4$·HBr: C, 55.87; H, 5.43; N, 3.43; Br, 19.58. Found: C, 55.57; H, 5.51; N, 3.33; Br, 19.84.

Selective demethylation of **40.** A stirred mix. of **40** (0.1 g, 0.3 mmol), HOAc (1 ml) and 48% HBr (0.5 ml) was heated to 60° under an inert atmosphere for 36 hr. After dil with H_2O (20 ml), the soln was basified with NH_3 and extracted with CH_2Cl_2 (5 × 20 ml). The dried (Na_2SO_4) exts were concd *in vacuo* to afford **23** in 60% yield.

Oxocularidine **(26).** Amorphous yellow powder. UV λ_{max}^{EtOH} (logε) nm: 254 (3.86), 266 (3.67), 304sh (3.28), 350 (3.18), 410 (3.20); $\lambda_{max}^{EtOH/HCl}$ (log ε) nm: 254 (3.7), 278 (3.7), 335 (3.28), 490 (3.16); $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 256 (3.70), 286 (3.76), 365 (3.25), 510 (3.25). ^{1}H NMR ($CDCl_3$): δ 8.66 (*d*, J = 5.4 Hz, 1H, H-3), 7.78 (*d*, J = 5.4 Hz, 1H, H-4), 7.68 (*d*, J = 8.9 Hz, 1H, H-5), 7.55 (*d*, J = 8.9 Hz, 1H, H-6), 7.26 (*s*, 1H, H-2'), 6.92 (*s*, 1H, H-5'), 3.98 (*s*, 3H, OMeC-4'), 3.91 (*s*, 3H, OMeC-3'), EIMS 70 eV *m/z* (rel. int.): 323$[M]^+$ (100), 308 $[M-Me]^+$ (10), 296 (27), 280 (10), 237 (8), 209 (14). Molecular formula $C_{18}H_{13}NO_5$ $[M]^+$ (c: 323.0791; HRMS f: 323. 0797).

Partial synthesis of oxocularidine **(26).** *Preparation of O-methoxymethyl cularidine* **(41).** A soln of cularidine **(16)** (0.5 g, 1.5 mmol) in dry DMF (50 ml) was reacted with NaH (80% in oil dispersion, 0.05 g, 1.68 mmol) and $ClCH_2OMe$ (0.174 g, 2.16 mmol) using the same conditions as in the prepn of **35**. *O*-Methoxymethyl cularidine **(41)** was obtained in quantitative yield as a white amorphous solid. ^{1}H NMR($CDCl_3$): δ6.98 (*d*, J = 8.4 Hz, 1H, ArH), 6.86 (*d*, J = 8.4 Hz, 1H, ArH), 6.82 (*s*, 1H, ArH), 6.51 (*s*, 1H, ArH), 5.26 (*d*, J = 6.6 Hz, 1H, $-OC\underline{H}_2O-$), 5.18(*d*,J = 6.6 Hz, 1H, $-OC\underline{H}_2O-$), 4.49 (*dd*, $J_{1-\alpha\alpha}$ = 3.9 and $J_{1-\alpha\beta}$ = 12.0 Hz, 1H, H-1), 3.87 (*s*, 3H, OMe), 3.81 (*s*, 3H, OMe), 3.49 (*s*, 3H, aliphatic –OMe), 3.29 (*dd*, $J_{\alpha\alpha-\alpha\beta}$ = 16.2 Hz, 1H, $H_{\alpha\alpha}$), 3.20–2.70 (*m*, 5H, $H_{\alpha\beta}$, H-3 and H-4), 2.62 (*s*, 3H, NMe). Molecular formula $C_{21}H_{25}NO_5$ $[M]^+$ (c: 371.1725, HRMS f: 371.1718).

Oxidation of O-methoxymethyl cularidine **(41).** A soln of **41** (0.47 g, 1.26 mmol) in 20 ml pyridine–H_2O (1 : 1) was treated with a soln of excess Fremy's salt in 20 ml pyridine–2% Na_2CO_3 (1 : 1) and the mixt stirred for 72 hr at room temp. Work-up as in the prepn of **36**, afforded **42**, as a yellow amorphous solid in 13% yield. ^{1}H NMR ($CDCl_3$): δ 8.69 (*d*, J = 5.3 Hz, 1H, H-3), 7.78 (*d*, J = 5.3 Hz, 1H, H-4), 7.76 (*d*, J = 9.1 Hz, 1H, H-5), 7.71 (*d*, J = 9.1 Hz, 1H, H-6), 7.27 (*s*, 1H, H-2'), 6.95 (*s*, 1H, H-5'), 5.47 (*s*, 2H, $-OCH_2O-$), 3.98 (*s*, 3H, OMe), 3.91 (*s*, 3H, OMe), 3.63 (*s*, 3H, aliphatic OMe). EIMS 70 eV *m/z* (rel.int.): 367 $[M]^+$ (< 2), 322 $[M-CH_2OMe]^+$ (5), 294 (4), 45$[CH_2OMe]^+$ (100). Molecular formula $C_{18}H_{12}NO_5$ $[M-CH_2OMe]^+$ (c: 322.0711, HRMS f: 322.0703).

Deprotection of O-methoxymethyl oxocularidine **(42).** **42** 0.035 g (0.095 mmol) was dissolved in a mixt of HOAc–H_2O (12 ml, 1 : 1) and a drop of concd H_2SO_4 added. The reaction mixt was refluxed for 15 min. After basification (NaOH, 10%) and extraction with $CHCl_3$ (3 × 5 ml), the dried extracts were cond to afford oxocularidine **(26)** in 80% yield.

Secosarcocapnidine **(31).** White crystals, mp 240–241° (HCl). UV λ_{max}^{EtOH} (logε) nm: 214 (3.9), 314 (3.6), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 226 (4.1), 280 (3.6), 310 (3.6), 350 (3.5). ^{1}H NMR ($CDCl_3$): δ6.94 (*d*, J = 8.4 Hz, 1H, H-4), 6.85 (*d*, J = 11.6 Hz, 1H, H-13), 6.84 (*d*, J = 8.4 Hz, 1H, H-5), 6.79 (*d*, J = 11.6 Hz, 1H, H-12), 6.69 (*s*, 2H, H-11 and H-10), 3.95 (*s*, 3H, OMeC-6), 3.89 (*s*, 3H, OMeC-9), 2.80 (*m*, 2H, H-3), 2.40 (*m*, 2H, H-2), 2.30 (*s*, 6H, NMe_2). EIMS 70 eV

*The 1-benzyl-1,2,3,4-tetrahydroisoquinolines show in their mass spectrum a molecular ion with a very low intensity so we refer the molecular formula of **38**, deduced from its HRMS, to the base peak.

m/z (rel.int.): 341 $[M]^+$ (5), 58 $[CH_2{=}NMe_2]^+$ (100). Molecular formula $C_{20}H_{23}NO_4[M]^+$ (c:341.1620; HRMS f:341.1662).

Partial synthesis of secosarcocapnidine **(31)**. *Preparation of the sarcocapnidine methiodide.* **20** 0.2 g (0.6 mmol) was dissolved in MeOH (10 ml), and MeI (7 ml) added. The reaction mixt was stirred at room temp. for 36 hr. After removal of solvent, sarcocapnidine MeI was obtained in 93% yield. ^{1}H NMR ($CDCl_3$): δ 7.11 (*d*, $J = 8.6$ Hz, 1H, ArH), 6.98 (*d*, $J = 8.6$ Hz, 1H, ArH), 6.78 (*d*, $J = 8.7$ Hz, 1H, ArH), 6.66 (*d*, $J = 8.7$ Hz, 1H, ArH), 5.30 (*dd*, $J_{1-\alpha\alpha} = 4.0$ and $J_{1-\alpha\beta} = 11.8$ Hz 1H, H-1), 3.94 (*s*, 3H, OMe), 3.86 (*s*, 3H, OMe), 3.66 (*s*, 3H, NMe), 3.60 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel.int.): 342 $[M]^+$ (1), 341 $[M-1]^+$ (4), 327 $[M-Me]^+$ (44), 312 $[M-2Me]^+$ (20), 142 (100). Molecular formula $C_{20}H_{23}NO_4$ $[M-1]^+$ (c:341.1620, HRMS f:341.1617).

Hoffman degradation of sarcocapnidine methiodide. To 0.120 g (0.35 mmol) of the MeI dissolved in EtOH (10 ml) was added NaOEt (1g Na in 20 ml EtOH). The reaction mixt. was refluxed for 5 hr. After removal of solvent, the mixt. was neutralized (HCl 10%) and extracted with CH_2Cl_2 (3 × 15 ml). Prep. TLC purification gave **31** in 69% yield, which was identical (R_f, MS, ^{1}H NMR) to the natural product. A small amount of the corresponding styrene was also obtained as an amorphous solid in 5% yield. ^{1}H NMR ($CDCl_3$): δ 7.23 (*d*, $J = 8.7$ Hz, 1H, ArH), 7.07 (*dd*, $J = 17.3$ and $J = 11.0$ Hz, 1H, Ar-CH=C–), 6.82 (*d*, $J = 8.7$ Hz, 1H, ArH), 6.62 (*d*, $J = 8.4$ Hz, 1H, ArH), 6.57(*d*, $J = 8.4$ Hz, 1H, ArH), 5.43 (*dd*, $J = 17.3$ and $J = 1.5$ Hz, 1H, $=CH_2$), 5.17 (*dd*, $J = 11.0$ and $J = 1.5$ Hz, 1H, $=CH_2$), 4.01 (*dd*, $J = 8.3$ and $J = 5.3$ Hz, 1H, Ar–CH–N), 3.94 (*s*, 3H, OMe), 3.84 (*s*, 3H, OMe), 3.56 (*dd*, $J = 15.0$ and $J = 8.3$ Hz, 1H), 2.91 (*dd*, $J = 15.0$ and $J = 5.3$ Hz, 1H), 2.35 (*s*, 6H, NMe_2). EIMS 70 eV *m/z* (rel.int.): 341 $[M]^+$ (100), 326 $[M-Me]^+$ (80), 297 $[M-2Me]^+$ (86). Molecular formula $C_{20}H_{23}NO_4$ $[M]^+$ (c:341.1620, HRMS f:341.1584).

Norsecocularidine **(32)**. Amorphous white powder. UV λ_{max}^{EtOH} (log ε) nm: 219 (4.0), 234 (4.0), 296 (3.5), 318 (3.6), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 227 (4.2), 322 (3.7). ^{1}H NMR ($CDCl_3$): δ 6.89 (*d*, $J = 8.6$ Hz, 1H, H-4), 6.84 (*d*, $J = 11.3$ Hz, 1H, H-13), 6.71 (*d*, $J = 8.6$ Hz, 1H, H-5), 6.71 (*d*, $J = 11.3$ Hz, 1H, H-12), 6.70 (*s*, 1H, H-11), 6.65 (*s*, 1H, H-8), 3.88 (*s*, 3H, OMeC-10), 3.85 (*s*, 3H, OMeC-9), 2.84 (*m*, 2H, H-3), 2.80 (*m*, 2H, H-2), 2.47 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel. int.): 327 $[M]^+$ (5), 44 $[CH_2{=}NHMe]^+$ (100). Molecular formula $C_{19}H_{21}NO_4$ $[M]^+$ (c:327.1464; HRMS f:327.1464).

Norsecosarcocapnidine **(33)**. Amorphous white powder. UV λ_{max}^{EtOH} (log ε) nm: 222 (3.9), 264 (3.6), 284 (3.6), 314 (3.8), $\lambda_{max}^{EtOH/NaOH}$ (log ε) nm: 228 (4.1), 264 (3.7), 284 (3.6), 314 (3.6), 350 (3.5). ^{1}H NMR ($CDCl_3$): δ 6.96 (*d*, $J = 8.3$ Hz, 1H, H-4), 6.87 (*d*, $J = 11.6$ Hz, 1H, H-13), 6.84 (*d*, $J = 11.6$ Hz, 1H, H-12), 6.83 (*d*, $J = 8.3$ Hz, 1H, H-5), 6.67 (*d*, $J = 8.6$ Hz, 1H, H-10), 6.64 (*d*, $J = 8.6$ Hz, 1H, H-11), 3.93 (*s*, 3H, OMeC-6), 3.89 (*s*, 3H, OMeC-9), 3.09 (*m*, 2H, H-3), 2.93 (*m*, 2H, H-2), 2.58 (*s*, 3H, NMe). EIMS 70 eV *m/z* (rel. int.): 327 $[M]^+$ (5), 44 $[CH_2{=}NHMe]^+$ (100). Molecular formula $C_{19}H_{21}NO_4$ $[M]^+$ (c: 327.1464; HRMS f: 327.1473).

N-Methylation of **32** *and* **33**. To a soln of **32** or **33** (0.01 g, 0.03 mmol) in MeOH (2 ml) was added 1 ml HCHO (23%) and the mixt. heated to 45–50° for 30 min. After cooling, excess $NaBH_4$ was added and the reaction mixt. stirred at room temp. for 1.5 hr. After removal of solvent, the residue was washed with H_2O (3 × 5 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The dried exts (Na_2SO_4) were concd and purified by prep. TLC. Synthetic **30** and **31** were identical to the natural products.

(−)-*Clavizepine* **(34)** was identified by comparison of its spectroscopic and chromatographic data with those of the authentic product isolated from *Corydalis claviculata* [22].

Acknowledgements—We thank the CAICYT (Spain) for financial support, the Midwest Center for Mass Spectrometry (Department of Chemistry, University of Nebraska, U.S.A.) for performing high-resolution MS and Profs Cavé and Preininger for supplying reference (−)-pallidine and (+)-salutaridine, respectively. S.L. thanks the Ministerio de Educación y Ciencia (Spain) for an FPI grant.

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