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ALKALOIDS FROM *SARCOCAPNOS SAETABENSIS*

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Key Word Index—*Sarcocapnos saetabensis*; Fumariaceae; alkaloid content; isoquinoline alkaloids; (+)-14-epichelidonine; isonoyaine; (−)-*N*-methylviguine.

Abstract—Twenty-one isoquinoline alkaloids were isolated from *Sarcocapnos saetabensis*. Eighteen of them were identified as the known alkaloids (+)-celtine, (+)-chelamine, (+)-chelidonine, (+)-crassifoline, (+)-cularine, dehydroglaucine, (+)-glaucine, (+)-4-hydroxysarcocapnidine, (+)-isocorydine, *O*-methylatheroline, (−)-*O*-methylpallidine, oxocularine, oxosarcocapnidine, pontevedrine, protopine, (+)-salutaridine, (+)-sarcocapnidine and (−)-scoulerine. The remaining three were the new alkaloids (+)-14-epichelidonine, isonoyaine and (−)-*N*-methylviguine, whose structures were established by spectroscopic and chemical methods.

INTRODUCTION

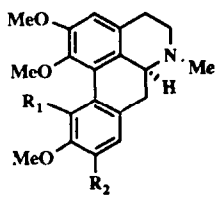
The genus *Sarcocapnos*, which has been extensively studied in our laboratory, has proved to be a rich source of isoquinoline alkaloids, most of them with a cularine skeleton [1–3]. As a continuation of our study on the alkaloids of Spanish Fumariaceae we have now investigated the alkaloid content of *Sarcocapnos saetabensis* Mateo and Figuerola, a species of Sarcocapnos endemic in southeastern Spain [4]. Like other species of this genus [5], *Sarcocapnos saetabensis* is a perennial herb growing mainly in rock crevices or on rock faces.

RESULTS AND DISCUSSION

Aerial parts of *S. saetabensis* collected in the Sierra de Játiva, Spain, were subjected to the usual procedures for the extraction and separation of the alkaloids (see Experimental). Eighteen known benzylisoquinoline alkaloids were isolated and identified as the aporphinoids (+)-glaucine (**1**), (+) isocorydine (**2**), *O*-methylatheroline (**3**), dehydroglaucine (**4**) and pontevedrine (**5**); the benzophenanthridines (+)-chelamine (**6**) and (+)-chelidonine (**7**); the 1-benzylisoquinoline (+)-crassifoline (**8**); the cularines (+)-celtine (**9**), (+)-cularine (**10**), (+)-sarcocapnidine (**11**), (+)-4-hydroxysarcocapnidine (**12**), oxocularine (**13**) and oxosarcocapnidine (**14**); the morphinandienones (−)-*O*-methylpallidine (**15**) and (+)-salutaridine (**16**); the protoberberine (−)-scoulerine (**17**), and protopine (**18**). The structures of these alkaloids were confirmed by comparison of their spectroscopic data and TLC R_f values with published data and those of authentic samples. Apart from these known alkaloids, three new alkaloids were isolated: (+)-14-epichelidonine (**19**), isonoyaine (**20**) and (−)-*N*-methylviguine (**21**). Their structures were established on the basis of their spectroscopic data and, in the case of isonoyaine and (−)-*N*-methylviguine, confirmed by syntheses.

The alkaloid (+)-14-epichelidonine (**19**) was isolated as prisms (mp 196°, EtOH). Its ^{1}H NMR spectrum is very similar to that of chelidonine (**7**), the main differences being in the chemical shifts of H-6 and H-14 (Table 1). Similar differences are exhibited by the ^{13}C NMR spectra (Table 2), with important changes in the chemical shifts of C-6, C-11 and C-14. These data suggested the structure of 14-epichelidonine (**19**) for the compound isolated, as the observed differences between the ^{1}H and ^{13}C NMR spectra and those of chelidonine must be due to the geometry of the new molecule preventing formation of the hydrogen bond that exists between the hydroxyl group and the nitrogen atom in chelidonine [6]. An X-ray diffraction study to confirm unequivocally the structure of 14-epichelidonine was unfortunately impossible because the small amount of compound isolated did not yield a proper crystal. 14-epichelidonine has not been found before in nature; 14-epicorynoline which has the same skeleton, has been isolated from *Corydalis incisa*, another member of the Fumariaceae [7].

Isonoyaine (**20**) was isolated as an amorphous optically inactive substance. Its molecular formula was established as $C_{21}H_{23}NO_7$ by high resolution mass spectrometry [calculated: 401.14736, found: 401.14744]. Its IR spectrum had peaks at 1720 and 1650 cm^{-1}, revealing the presence of an ester and an amide group in the molecule. The ^{1}H NMR spectrum exhibited two multiplets centred at δ2.87 (2H) and 3.45 (2H), a singlet at δ3.08 (3H, NMe), four singlets at δ3.49, 3.56, 3.75 and 3.85 (3H each) corresponding to four methoxyl groups, and two AB systems in the aromatic region, one of them centred at δ6.58 and 7.58 with a coupling constant of 8.8 Hz and the other at δ6.80 and 6.87 (J=8.2 Hz). The ^{13}C NMR spectrum confirmed the presence of two carbonyl groups in the molecule; a methoxyl group at unusually high field and the presence of the second carbonyl group established a carboxymethyl group as a benzene ring substituent. All these data are in keeping with the new alkaloid,



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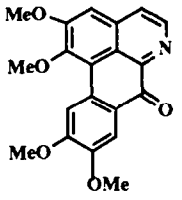

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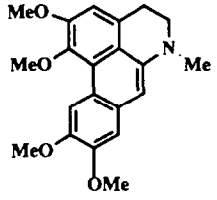

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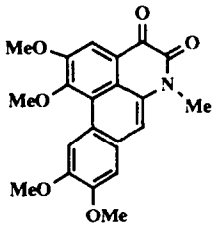

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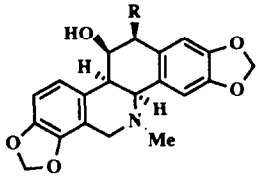

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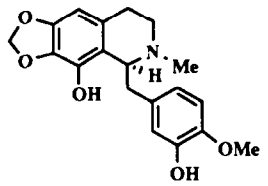

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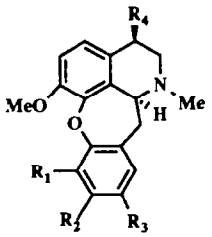

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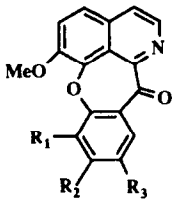
10 R_1=H, R_2=OMe, R_3=OMe, R_4=H
11 R_1=OH, R_2=OMe, R_3=H, R_4=H
12 R_1=OH, R_2=OMe, R_3=H, R_4=OH



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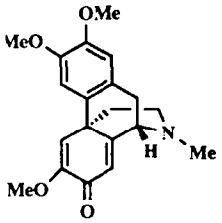

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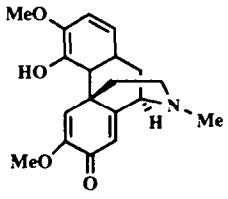

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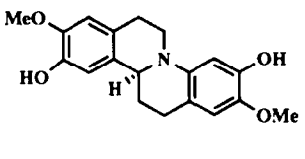

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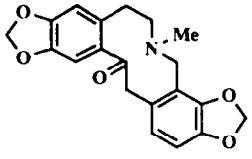

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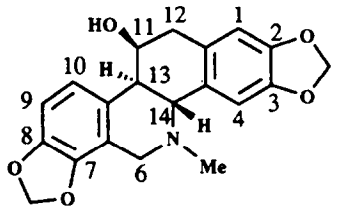
which we named isonoyaine, having structure **20**. This was confirmed by comparison with synthetic material obtained by Ullmann condensation of 1,2,3,4-tetrahydro-8-hydroxy-7-methoxy-2-methylisoquinoline and methyl 2-bromo-3,4-dimethoxybenzoate followed by oxidation of the 1,2,3,4-tetrahydroisoquinoline obtained with tetrabutylammonium permanganate [8]. Isonoyaine is the second *C*-secocularine alkaloid; the first member of this group, noyaine, was isolated from *Corydalis claviculata*, another member of the Fumariaceae [9].

(−)-*N*-Methylviguine (**21**) was isolated as an amorphous powder. The UV spectrum showed absorption peaks at λ208, 232, 287. The most significant signals in its ^{1}H NMR spectrum were a pair of doublets at δ6.95 and 7.48 (2H each, J = 8.7 Hz) due to a *para*-substituted benzene ring, a singlet attributable to a deshielded N-Me group (3.18), and two AB systems centred at 4.30 and 4.52 (J = 14.9 Hz) and 4.78 and 4.88 (J = 12.8 Hz) corresponding to two CH_2 groups with non-equivalent hydrogens due to the presence of one stereocentre. The remaining signals were two aromatic singlets (1H each) at δ6.53 and 6.65, an OCH_2O group at 5.97, a methoxyl group at 3.83 and two multiplets (2H each) at 3.14 and 3.88. These data suggested that the isolated alkaloid is *N*-methyl-*N*-



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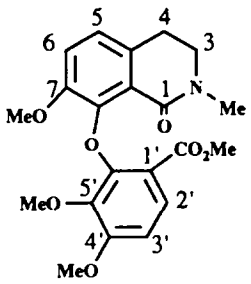

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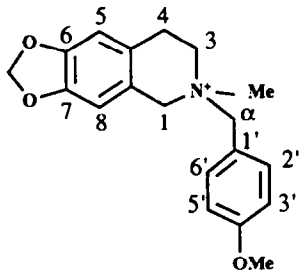

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Table 1. ^{1}H NMR data of compounds 7 and 19

H	Chelidonine	14-Epichelidonine
1	6.65 *s*	6.65 *s*
4	6.67 *s*	6.78 *s*
6	3.43 *d*, J = 15.6 Hz	4.20 *m*
	4.09 *d*, J = 15.6 Hz	4.20 *m*
9	6.76 *s*	6.80 *s*
10	6.76 *s*	6.80 *s*
11	4.23 *br s*	4.58 *br s*
12	3.08 *dd*, J = 17.5, 4.5 Hz	3.04 *dd*, J = 17.4, 4.1 Hz
	3.21 *d*, J = 17.5 Hz	3.18 *d*, J = 17.4 Hz
13	2.99 *t*, J = 2.6 Hz	2.90 *t*, J = 2.8 Hz
14	3.58 *br s*	4.20 *br s*
NMe	2.28 *s*	2.38 *s*
OCH_2O	5.97 *m*	5.97 *m*
OCH_2O	5.97 *m*	5.97 *m*

Table 2. ^{13}C NMR data of compounds 7 and 19

C	Chelidonine	14-Epichelidonine
1	107.4	108.1
2	145.3	145.5
3	145.6	145.7
4	111.9	109.3
4a	128.9	128.5
6	53.9	61.1
6a	117.1	118.5
7	143.1	143.3
8	148.2	147.9
9	109.2	111.6
10	120.4	121.0
10a	131.4	132.2
11	72.4	55.7
12	39.7	39.2
12a	125.8	126.0
13	42.1	41.1
14	62.9	72.3
NMe	42.4	38.8
OCH_2O	101.1	101.2
OCH_2O	101.4	100.9

benzyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**21**), the N-Me derivative of the alkaloid viguine. This was corroborated by ^{13}C NMR and mass spectra and confirmed by comparison (^{1}H and ^{13}C NMR) with synthetic *N*-methylviguine obtained by methylation (MeI) of viguine, a benzylisoquinoline alkaloid found in *Corydalis claviculata* [10]. The fact that all the new alkaloids isolated from *Sarcocapnos saetabensis* possess skeletons similar to those of *Corydalis* alkaloids underlines the close relationship between the genera *Sarcocapnos* and *Corydalis* [11].

EXPERIMENTAL

General. Mps: uncorr. IR: film. UV: EtOH. MS: at 70 eV ^{1}H and ^{13}C NMR spectra: 250 MHz for ^{1}H and 62.83 MHz for ^{13}C in $CDCl_3$ solns with TMS as int. standard; all signals are expressed as δ values ppm downfield from TMS. The assignment of the signals was based on NOE and XH CORR experiments. CC was carried out on Merck type 60 silica gel and Woelm N (grade IV) neutral alumina. TLC was performed on Merck GF-254 type 60 silica gel and 60 GF-254 type E neutral alumina plates with the solvent systems CH_2Cl_2 and CH_2Cl_2–MeOH (19:1, 9:1 and 17:3); alkaloids were detected by UV and spraying with Dragendorff's reagent or I_2 vapour.

Plant material. Aerial parts of *Sarcocapnos saetabensis* were collected in the Sierra de Játiva, Valencia, Spain. A voucher specimen (vs 16001) is kept in the Herbarium of the Departamento de Botánica, Universidad de Valencia.

Extraction of alkaloids. Dried powdered aerial parts of *Sarcocapnos saetabensis* (400 g) were extracted in a Soxhlet with MeOH (2 l) until a negative Dragendorff test was achieved. The solvent was evapd and the residue (103 g) taken up in 5% HCl and filtered. This soln was washed with Et_2O to remove neutral components and then extracted with CH_2Cl_2 at pH 6, 8 and 12, (achieved by successive addition of aq. NH_3 and NaOH). The extracts were dried and the solvent evapd *in vacuo* to afford extract A (pH 6, 3.397 g, 8.492 g kg^{-1} dry plant), extract B (pH 8, 0.342 g, 0.855 g kg^{-1} dry plant) and extract C (pH 12, 0.175 g, 0.437 g kg^{-1} dry plant). All three extracts were purified on silica gel columns eluted first with CH_2Cl_2 containing increasing percentages of MeOH and finally with MeOH–HOAc (1–5%). The frs collected were purified by fractional crystallization and prep. TLC to afford 21 alkaloids, listed here in order of increasing polarity on TLC: dehydroglaucine (**4**) (8 mg), (+)-chelidonine (**7**) (328 mg), oxosarcocapnidine (**14**) (5 mg), oxocularine (**13**) (70 mg), (+)-sarcocapnidine (**11**) (792 mg), (+)-chelamine (**6**) (18 mg), (+)-14-epichelidonine (**19**) (9 mg), (−)-scoulerine (**17**) (9 mg), isonoyaine (**20**) (11 mg), (+)-cularine (**10**) (6 mg), (+)-4-hydroxysarcocapnidine (**12**) (16 mg), (+)-celtine (**9**) (30 mg), (+)-glaucine (**1**) (53 mg), pontevedrine (**5**) (3 mg), (+)-isocorydine (**2**) (8 mg), *O*-methylatheroline (**3**) (9 mg),

(−)-*O*-methylpallidine (**15**) (27 mg), (+)-crassifoline (**8**) (80 mg), protopine (**18**) (185 mg), (+)-salutaridine (**16**) (3 mg), (−)-*N*-methylviguine (**21**) (7 mg). All the know alkaloids were identified by comparison of their chromatographic, physical and spectroscopic data with those of authentic samples.

(+)-14-*Epichelidonine* (**19**). Prisms, mp 196° (EtOH). UV λ_{max} nm: 209, 240, 292. ^{1}H NMR: δ2.38 (3H, *s*, NMe), 2.90 (*t*, J = 2.8 Hz, 1H, H-13), 3.04 (*dd*, J = 17.4 and 4.1 Hz, 1H, H-12), 3.18 (*d*, J = 17.4 Hz, 1H, H-12), 4.20 (*m*, 3H, H-6 and H-14), 4.58 (*br s*, 1H, H-11), 5.97 (*m*, 4H, 2 × OCH_2O), 6.65 (1H, *s*, H-1), 6.78 (1H, *s*, H-4), 6.80 (2H, *s*, H-9 and H-10). ^{13}C NMR: 38.8 (*q*, NMe), 39.2 (*t*, C-12), 41.1 (*d*, C-13), 55.7 (*d*, C-11), 61.1 (*t*, C-6), 72.3 (*d*, C-14), 100.9 (*t*, OCH_2O), 101.2 (*t*, OCH_2O), 108.1 (*d*, C-1), 109.3 (*d*, C-4), 111.6 (*d*, C-9), 118.5 (*s*, C-6a), 121.0 (*d*, C-10), 126.0 (*s*, C-12a), 128.5 (*s*, C-4a), 132.2 (*s*, C-10a), 143.3 (*s*, C-7), 145.5 (*s*, C-2), 145.7 (*s*, C-3), 147.9 (*s*, C-8). MS *m/z* (rel. int.): 353 $[M]^+$ (17), 352 (85), 332 (10), 303 (28), 149 (60), 69 (100).

Isonoyaine (**20**). Amorphous powder. UV λ_{max} nm: 241, 292, 313. IR ν_{max} cm^{-1}: 1650, 1720. ^{1}H NMR: 2.87 (*m*, 2H, H-4), 3.08 (3H, *s*, NMe), 3.45 (2H, *m*, H-3), 3.49, 3.56, 3.75 and 3.85 (3H each, 4*s*, 4 × OMe), 6.58 and 7.58 (2H, AB, J = 8.8 Hz, H-2′ and H-3′), 6.80 and 6.87 (AB, J = 8.2 Hz, 2H, H-5 and H-6). ^{13}C NMR: 28.7 (*t*), 34.8 (*q*), 48.2 (*t*), 51.5 (*q*), 55.8 (*q*), 56.6 (*q*), 60.5 (*q*), 105.0 (*d*), 115.7 (*s*), 115.9 (*d*), 121.1 (*d*), 121.25 (*s*), 126.5 (*d*), 131.9 (*s*), 139.6 (*s*), 147.4 (*s*), 150.5 (*s*) 152.0 (*s*), 156.8 (*s*), 162.6 (*s*), 166.4 (*s*). MS *m/z* (rel. int.): 401 $[M]^+$ (26), 370 (12), 224 (11), 205 (16), 204 (100), 192 (16), 190 (12), 176 (8), 149 (11), 104 (10). HRMS *m/z* $[M]^+$ calculated for $C_{21}H_{23}NO_7$ 401.14736, found 401.14744.

(−)-N-*Methylviguine* (**21**). Amorphous powder. UV λ_{max} nm: 208, 232, 287. ^{1}H NMR: 3.18 (3H, *s*, NMe), 3.83 (3H, *s*, OMe), 3.88 (*m*, 2H, H-3), 3.14 (2H, *m*, H-4) 4.30 and 4.52 (2H, AB, J = 14.9 Hz, CH_2), 4.78 and 4.88 (2H, AB, J = 12.8 Hz, CH_2), 5.97 (2H, *s*, OCH_2O), 6.53 (1H, *s*, H-8), 6.65 (1H, *s*, H-5), 6.95 and 7.48 (4H, AB, J = 8.7 Hz, H-2′, H-3′ and H-5′, H-6′). ^{13}C NMR 23.8 (*t*), 46.0 (*q*), 55.2 (*q*), 56.7 (*t*), 60.3 (*t*), 66.0 (*t*), 101.5 (*t*), 106.9 (*d*), 108.4 (*d*) 114.6 (*d*), 118.4 (*s*), 118.7 (*s*), 122.3 (*s*), 134.8 (*d*), 147.4 (*s*), 148.7 (*s*), 161.4 (*s*). MS *m/z* (rel. int.): 313 ($[M]^+$, 2), 190 (95), 148 (100), 121 (60).

N-*Methylation of viguine*. Viguine (31 mg, 0.067 mmol) was dissolved in 4 ml dry Me_2CO and 0.67 mmol MeI were added. The mixt. was kept at room temp. for 1 hr before the solvent was evapd to afford (±)-*N*-methylviguine (**21**) in 91% yield (42 mg). The R_f and ^{1}H and ^{13}C NMR spectra of the compound obtained were identical with those of natural *N*-methylviguine.

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