Callosine, a 3-Alkyl-Substituted Pyrrolizidine Alkaloid from *Senecio callosus*

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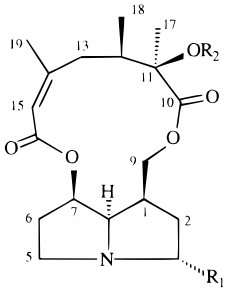
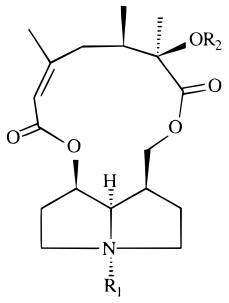
Two collections of *Senecio callosus* from different regions of Mexico contained a structural diversity of pyrrolizidine alkaloids (PAs), which may contribute to the easy adaptation of this species. In addition to some known compounds, two new PAs (**1** and **2**) were isolated, and their structures were established by chemical transformations and spectroscopic studies.

Most *Senecio* species contain pyrrolizidine alkaloids (PAs),[1,2] which frequently have toxic, carcinogenic, and mutagenic effects.[3,5] The interest in biosynthesis, transport, storage, metabolism, and pharmacology of PAs[4,5] is increasing with the results of new phytochemical investigations. Because the section *Mulgediifolii* of the genus *Senecio*[6] contains 15 species, most of which are indigenous to Mexico, we became interested in carrying out a systematic search for PAs in this section.[7,9] Now, in continuation of our early studies, we wish to report the alkaloidal composition of *Senecio callosus* Sch.-Bip. (Asteraceae), which tolerates disturbed habitats and is the most widespread member of the section.[6] The plants, collected in two different places, afforded two new PAs in addition to some known alkaloids. Their structures were determined by spectroscopic methods and chemical transformations.

S. callosus collected in Michoacán State, afforded the new compounds **1** and **2**, the latter was isolated as its hydrochloride. Compound **3**, the *N*-oxide of **2**, and two artifacts, bulgarsenine **4** (as the hydrochloride) and **5**, were also isolated.





1 R_1=$CH_2CO_2CH_3$ R_2=H
2 R_1=H R_2=$COCH_3$
4 R_1=H R_2=H

3 R_1=O R_2=$COCH_3$
5 R_1=CH_2Cl R_2=H

Compound **1** had a molecular formula $C_{21}H_{31}O_7N$, which was established by HRFABMS. Although **1** contained three C-atoms more than **4**, its ^{1}H NMR spectrum (Table 1) resembled that of **4**[7] in many respects, except for the signals arising from a methylene carbomethoxy group (δ 2.56, dd, J = 6, 15 Hz, H-1a′; δ 2.36, dd, J = 7, 15 Hz, H-1b′ and δ 3.69, s, OCH_3). This group was bonded to C-3 as inferred from the ^{13}C NMR spectrum (Table 2), which showed the C-3 signal as a doublet at δ 62.8 in addition to signals of the side chain (δ 41.4 t, C-1′; 172.3 s, C-2′, and 51.5 q, OCH_3). The above assumption was corroborated by 2D-NMR experiments. The COSY spectrum showed that H-3 was coupled to H-2b (δ 1.99) and to the methylene hydrogens of the side chain (H-1a′ and H-1b′). The HMBC spectrum showed that both methylene hydrogens of the side chain were coupled to C-2, C-3, and C-2′ (δ 38.4, 62.8, and 172.3 respectively), and that the hydrogens of the methoxy group (δ 3.69) were coupled to the carbonyl of the carbomethoxy group (C-2′).

Compound **1** was saponified, in an attempt to establish its stereochemistry, but unfortunately only a complex mixture was obtained. A NOESY experiment (Figure 1) showed a correlation between H-15 and H-19, which indicated a *Z* configuration of the double bond. Because H-8 correlated with H-7 and H-1, and H-2b correlated with H-1 and H-1b′, it was inferred that H-7, H-8, H-1, H-2b, and H-1b′ were on the same side of the molecule. The absolute stereochemistry of **1** was not determined, but is assumed to be the same as bulgarsenine (**4**), and the C-3 side chain should have an α-orientation. Thus, the new alkaloid callosine **(1)** is the first macrocyclic PA containing an alkyl side chain at C-3.

The new compound **2**, isolated as the hydrochloride (**2**·HCl) is the acetyl derivative of **4**.[10] Its MS spectrum showed a $[M]^+$ at *m/z* 379, 42 mu higher than **4**·HCl. The ^{1}H and ^{13}C NMR spectra of **2**·HCl (Tables 1 and 2) were almost superimposable with those of bulgarsenine hydrochloride (**4**·HCl) except for the signals of the acetyl group (δ 2.07 s on ^{1}H NMR, 21.5 q and 169.5 s on ^{13}C NMR). The saponification products of **2** are the same as those of **4** (platynecine and nemorensic acid).[10] Acetylation of bulgarsenine gave **2**, which was the same compound obtained by washing **2**·HCl with a NaOH solution.

Another compound isolated from this plant collection was 11-*O*-acetyl bulgarsenine *N*-oxide (**3**), whose spectral data (Tables 1 and 2) were very similar to those of **2**·HCl. The identity of the *N*-oxide derivative was established when **2**·HCl was converted into **3** after treatment with *m*-chloroperbenzoic acid. The existence of an *N*-oxide indicated either that the reduction process was insufficient or that this compound was very stable.

Bulgarsenine was isolated as the hydrochloride (**4**·HCl), as was shown by the IR bands at 2311 and 830 cm^{-1}, and the downfield shift of H-3, H-5, and H-8 signals in its ^{1}H

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Table 1. ^{1}H NMR Spectral Data of Compounds **1**, **2**·HCl, **3**, **4**·HCl, and **5**·Cl (300 Hz, $CDCl_3$)[a]

proton(s)	**1**[b,c]	**2**·HCl[d]	**3**[d]	**4**·HCl[b,e]	**5**·Cl[f]
1	2.65 m	2.94 dtd (like) (3.3, 9.0, 16.8)	3.37 m	2.94 dtd (like) (3.0, 9.0, 17.5)	3.13 m
2a	2.06 ddd (5.5, 6.5, 12.5)	2.37 m	2.74 m	2.49 m	2.33 m
2b	1.99 dt (8.5, 12.5)	2.11 m	2.10 m	2.13 ddd (like) (7.0, 13.5, 14.0)	2.33 m
3a	3.21 br dd (7.0, 8.5)	3.78 dt (7.3, 11.4)	4.51 dt (6.0, 12.0)	3.88 dt (6.5, 11.5)	3.9−4.1 m
3b		3.10 m	3.83 m	3.08 dt (7.5, 11.5)	3.9−4.1 m
5a	3.15 ddd (2.0, 7.5, 9.5)	3.98 ddd (1.7, 7.7, 11.3)	4.64 br dd (7.5, 12.3)	3.94 ddd (2.5, 8.0, 11.0)	3.9−4.1 m
5b	2.72 ddd (6.5, 9.5, 11.0)	3.07 m	3.86 m	3.12 td (6.0, 11.5)	3.9−4.1 m
6a	2.17 m	2.50 m	3.04 dddd (4.5, 7.5, 12.3, 14.4)	2.51 m	2.4−2.6 m
6b	2.12 ddt (2.0, 7.0, 13.5)	2.30 m	2.34 m	2.37 m	2.4−2.6 m
7	5.38 td (2.0, 3.5)	5.70 td (1.8, 4.2)	5.86 br t (4.2)	5.69 td (2.5, 4.5)	5.84 dt (6.0, 7.2)
8	3.76 dd (4.0, 7.5)	4.43 t (4.2)	4.96 dd (5.4, 9.3)	4.47 dd (4.5, 8.5)	4.65 dd (7.2, 8.4)
9a	4.51 dd (11.0, 11.5)	4.46 dd (9.3, 12.2)	4.38 dd (10.0, 12.0)	4.57 dd (9.0, 12.0)	4.44 dd (9.9, 11.4)
9b	4.05 dd (3.0, 11.5)	4.19 dd (3.3, 12.2)	4.16 dd (3.9, 12.0)	4.18 dd (3.5, 12.0)	4.23 dd (4.2, 11.4)
12	2.44 dt (6.5, 9.5)	2.34 m	2.34 m	2.35 m	2.61 m
13a	2.65 br dd (5.0, 13.5)	2.80 br dd (3.9, 13.8)	2.75 m	2.57 br dd (4.5, 12.0)	2.74 ddd (1.5, 5.4, 13.2)
13b	2.22 dd (9.5, 13.5)	2.41 m	2.38 m	2.32 dd (9.0, 12.0)	2.27 dd (9.6, 13.2)
15	5.66 t (1.5)	5.66 t (1.2)	5.66 t (1.2)	5.67 br s	5.73 br s
17	1.29 s	1.66 s	1.65 s	1.33 s	1.31 s
18	0.99 d (6.8)	1.15 d (6.6)	1.14 d (6.7)	1.03 d (6.5)	1.0 d (6.9)
19	1.88 d (1.5)	1.95 d (1.2)	1.93 d (0.9)	1.93 d (1.0)	1.96 d (1.2)
1′	2.56 dd (6.0, 15.0)				5.44 s
1b′	2.36 dd (7.0, 15.0)				

[a] Assignments are based on COSY, LR-HETCOR, COLOC, HMQC, and HMBC experiments. [b] **1** and **2**·HCl were run at 500 MHz. [c] OCH_3: δ 3.69 s. [d] OAc: δ 2.07 s for **2**·HCl and 2.08 s for **3**. [e] OH: δ 3.01 br s. [f] **5**·Cl in CH_3OH-d_4.

Table 2. ^{13}C NMR Spectral Data of Compounds **1**, **2**·HCl, **3**, **4**·HCl and **5**·Cl (75 MHz, $CDCl_3$)[a]

carbon	**1**[b]	**2**·HCl[c,d]	**3**[c]	**4**·HCl[e]	**5**·Cl[f]
1	37.9 d	37.9 d	36.4 d	38.5 d	42.1 d
2	38.4 t	29.6 t	29.6 t	30.5 t	30.1 t
3	62.8 d	53.6 t	67.5 t	53.9 t	66.6 t
5	50.9 t	52.3 t	66.2 t	51.8 t	63.2 t
6	36.3 t	354.1 t	33.9 t	35.3 t	32.6 t
7	74.3 d	72.3 d	72.2 d	72.5 d	73.1 d
8	69.7 d	70.3 d	86.5 d	69.8 d	78.1 d
9	67.2 t	63.2 t	63.4 t	64.0 t	64.0 t
10	178.7 s	171.2 s	170.9 s	178.2 s	178.2 s
11	75.6 s	82.7 s	82.3 s	75.8 s	76.8 s
12	36.8 d	39.6 d	39.2 d	37.3 d	37.2 d
13	37.0 t	36.2 t	36.4 t	36.9 t	38.7 t
14	153.6 s	156.3 s	156.8 s	156.3 s	160.3 s
15	118.2 d	116.6 d	116.2 d	116.3 d	117.5 d
16	166.9 s	165.7 s	165.6 s	165.8 s	166.9 s
17	26.5 q	22.9 q	22.9 q	26.3 q	26.9 q
18	14.9 q	15.9 q	16.2 q	14.5 q	15.6 q
19	28.0 q	27.5 q	27.5 q	28.1 q	28.4 q
1′	41.4 t				70.6 s
2′	172.3 s				

[a] Assignments are based on DEPT, LR-HETCOR, COLOC, HMQC, and HMBC experiments. [b] OCH_3: δ 51.5 q. [c] OAc: δ 169.5 s, 21.5 q. [d] Run at 50 MHz. [e] Run at 125 MHz. [f] In CH_3OH-d_4.

NMR spectrum (Table 1), similar to those observed for retroisosenine hydrochloride.[7] Bulgarsenine hydrochloride (**4**·HCl) washed with a NaOH solution gave **4**, identified by comparison of its spectroscopic features with those of an authentic sample.[8] *N*-Chloromethyl bulgarsenine chloride (**5**·Cl) was also isolated. Its structure was determined by an analysis of the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2), including bidimensional techniques. The presence of Cl^- was supported by the *m*/*z* 35 and 37 fragments observed in negative ion FABMS of **5**·Cl. Both compounds, **4**·HCl and **5**·Cl, could be artifacts formed during the purification process with CH_2Cl_2.[11]

S. callosus collected in Oaxaca, afforded open-chain diesters 7β-angelyl-1-methylene-8α-pyrrolizidine,[12] sarracine,[13] and neosarracine,[13] as their hydrochlorides, which were converted to free alkaloids by treatment with a NaOH solution. The free PAs were identified by comparison of their spectroscopic data (NMR, IR, and MS) with those described in the literature.[12,13]

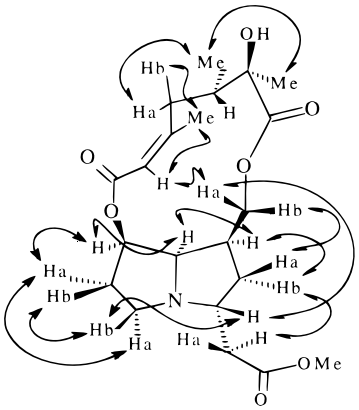

Figure 1. Results of NOESY experiment of **1**.

Thus, 13-membered macrocyclic PAs were isolated from *S. callosus* collected in the state of Michoacán, and open-chain diester PAs were isolated from the same species collected in the state of Oaxaca. The fact that these two collections produced PAs that are different from a 12-membered one in the collection reported previously,[9] may contribute to the characteristic easy adaptation of this plant.[6]

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher Jones melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-360 digital polarimeter. IR spectra were recorded on a Nicolet Magna-IR 750 spectrometer. EIMS data were determined on a JEOL JMS-AX505HA mass spectrometer at 70 eV. FABMS were obtained on a JEOL, JMS-SX102A mass spectrometer operated with an acceleration voltage of 10 kV, and samples were desorbed from a nitrobenzyl alcohol matrix using 6 keV Xenon atoms. HRFABMS performed at 10 000 resolution using electric field scans and poly(ethylene glycol) ions (Fluka 200 and 300), as the reference material. ^{1}H NMR and ^{13}C NMR data were obtained on Varian Unity Plus 500, Varian Unity 300, and/or Varian Gemini 200 instruments. Chemical shifts were referred to TMS (δ 0). Standard Varian programs were used for COSY and NOESY spectra at 300 or 500 MHz. HETCOR and HMQC experiments were obtained

for $^1J_{CH}$ = 140 Hz at 75 and 500 MHz, respectively. Long-range HETCOR and HMBC experiments were obtained for $^nJ_{CH}$ = 9 Hz at 75 and 500 MHz, respectively. Column chromatographies were carried out on Kieselgel G (Merck, Darmstadt, Germany). TLC was performed on Si gel 60 and preparative TLC on Si gel GF_{254} (Merck), layer thickness 2.0 mm.

Plant Material. *Senecio callosus* was collected in San José de la Cumbre, Michoacán, Mexico, in August 1996 (MEXU 663362), and in Juxtlahuaca, Oaxaca, Mexico, in December 1996 (MEXU 773353). Voucher specimens are deposited at the Herbario del Instituto de Biología, UNAM, Coyoacán, D. F., México.

Extraction and Isolation. Dried and ground leaves (1.05 kg) of *S. callosus* from Michoacán were extracted with MeOH until the extract gave a negative test with Dragendorff reagent. The extract was concentrated to one-third of its original volume. The residue was treated with 2.5% aqueous H_2SO_4 to pH 1, and stirred overnight with Zn powder (5.3 g). The mixture was filtered, and the filtrate was washed twice with CH_2Cl_2, treated with aqueous NH_3 to pH 10, and extracted with CH_2Cl_2 until the extract gave a negative test with Dragendorff reagent. The CH_2Cl_2 extracts were combined and concentrated, giving 19.3 g. The same procedure was carried out with the roots (624.6 g) and the stems (215.0 g), which afforded 9.5 and 4.8 g of extract, respectively. The three extracts had similar alkaloidal compositions, as shown by a TLC. The combined total extract (33.6 g) gave 118 fractions by column chromatography, eluting with CH_2Cl_2−MeOH (95:5). Fractions 3−4 (630.0 mg) were treated by column chromatography eluting with Me_2CO and preparative TLC developing with CH_2Cl_2−MeOH, 95:5 (× 3), to give 106.0 mg of **1**. Fractions 5−26 (11.9 g) were fractionated by column chromatography using CH_2Cl_2−MeOH (95:5) as eluent. A total of 168 fractions were obtained and out of these, fractions 7−11 (2.31 g) afforded 666.0 mg of **2**·HCl after a column chromatography using Me_2CO−MeOH (95:5) as eluent. The compound **4**·HCl (818.0 mg) was obtained by crystallization from fractions 12−34, and compound **5**·Cl (63.5 mg) was obtained from fractions 35−96 (2.24 g) by column chromatography and elution with CH_2Cl_2−EtOAc−Et_3N−MeOH (7:1:0.5:0.2). Fractions 35−84 (11.5 g) of the first column chromatography gave 83.9 mg of **3** by consecutive column chromatographies using CH_2Cl_2−MeOH (95:5 and 98:2).

Dried and ground roots (90.0 g) of *S. callosus* from Oaxaca were worked up in a similar manner to give 2.0 g of alkaloidal extract. This was column chromatographed using EtOAc−MeOH (7:3) to obtain 213 fractions. Fractions 4−9 (500.0 mg) gave 176 fractions by column chromatography eluting with CH_2Cl_2−Me_2CO (95:5). Fractions 41−43 were suspended in 5% aqueous NaOH (5 mL) and extracted with $CHCl_3$ (3 × 5 mL) to afford 13.0 mg of 7β-angelyl-1-methylene-8α-pyrrolizidine.[12] Fractions 73−119 (300.0 mg) were submitted to the same treatment, and the residue (82.0 mg) gave 32.0 mg of a mixture of sarracine and neosarracine (4:1)[13] by column chromatography, eluting with $CHCl_3$−MeOH (9:1) and preparative TLC developed with $CHCl_3$−MeOH (9:1). Fractions 10−37 of the first column chromatography afforded 740.0 mg of the same mixture. Compounds 7β-angelyl-1-methylene-8α-pyrrolizidine, sarracine, and neosarracine were identified by comparison of their spectral data with those described in the literature.

Callosine (1): colorless oil; $[\alpha]_D$ −14.7° (*c* 0.23, MeOH); UV (MeOH) λ_{max} (log ϵ) 206.8 (3.94) nm; IR ($CHCl_3$) ν_{max} 3528, 1725, 1649 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; HRFABMS *m*/*z* found $[M + 1]^+$ 410.2178 ($C_{21}H_{32}O_7N$ requires 410.2179).

11-*O*-Acetyl bulgarsenine hydrochloride (2·HCl): white crystals from EtOAc; mp 123−125 °C; $[\alpha]_D$ −46.9° (*c* 0.26, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 222.5 (3.90) nm; IR ($CHCl_3$) ν_{max} 2300, 1732, 1738, 1647, 835 cm^{-1};^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 379 $[C_{20}H_{29}O_6N]^+$ (19), 320 (8), 253 (39), 210 (100), 180 (18), 138 (60), 122 (55), 96 (16), 82 (40), 55 (16), 43 (16); HRFABMS *m*/*z* found 380.2079 ($C_{20}H_{30}O_6N$ requires 380.2073). A suspension of **2**·HCl (30.0 mg) in aqueous NH_3 (3 mL) was extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried with Na_2SO_4 and concentrated to afford 25 mg of **2** as colorless oil; $[\alpha]_D$ −54.35° (*c* 0.39, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1737, 1717, 1645 cm^{-1}; EIMS m/*z* 379 $[M + 1]^+$ (29), 320 (8), 253 (39), 210 (100), 180 (14), 138 (55), 122 (54), 96 (17), 82 (39), 55 (13), 43 (44).

11-*O*-Acetyl bulgarsenine *N*-oxide (3): white crystals from EtOAc; mp 142−144 °C; $[\alpha]_D$ −60.48° (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 224 (3.87) nm; IR ($CHCl_3$) ν_{max} 1739, 1647 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS m/*z* 396 $[M + 1]^+$ (13), 379 (17), 320 (9), 253 (34), 210 (86), 180 (28), 139 (100), 138 (63), 82 (69), 43 (94); HRFABMS *m*/*z* found 396.2031 ($C_{20}H_{30}O_7N$ requires 396.2022).

Bulgarsenine hydrochloride (4·HCl): white crystals from EtOAc; mp 118−120 °C; $[\alpha]_D$ −58.94° (*c* 0.207, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 223.5 (3.76) nm; IR ($CHCl_3$) ν_{max} 3505, 2312, 1732, 1644, 830 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; EIMS *m*/*z* 337 $[M]^+$ (20), 211 (50), 140 (100), 138 (52). A suspension of this compound (18.0 mg) in 5% aqueous NaOH (3 mL) was extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried with Na_2SO_4 and concentrated, and afforded a colorless oil (15.0 mg), which was identified as **4** by comparison with authentic spectral data.[8]

***N*-Chloromethyl bulgarsenine chloride (5·Cl):** white crystals from hexane−EtOAc; mp 173−175 °C; $[\alpha]_D$ −48.06° (*c* 0.31, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 227 (4.19) nm; IR ($CHCl_3$) ν_{max} 3546, 1733, 1642, 835 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR data, see Table 2; HRFABMS *m*/*z* found $[M]^+$ 386.1735 ($C_{19}H_{29}O_5NCl$ requires 386.1734).

Saponification of 11-*O*-Acetyl Bulgarsenine Hydrochloride (2·HCl). A mixture of **2**·HCl (100.0 mg) and KOH (103.0 mg) in MeOH (5 mL) was refluxed for 3 h. The solvent was evaporated under reduced pressure to dry and the residue was extracted with hot $CHCl_3$ (10 × 5 mL). By the evaporation of the solvent the extract gave 39.4 mg of platynecine[8,10] as a brown oil. The basic residue was dissolved in 2.5% aqueous H_2SO_4 (10 mL), extracted with ether (10 × 10 mL), and dried with Na_2SO_4. The elimination of the solvent afforded a residue that was purified by column chromatography using as eluent CH_2Cl_2−Me_2CO (95:5) to give nemorensic acid (5.0 mg).[10] Platynecine was identified by comparison with an authentic sample, and the nemorensic acid by comparison of its spectral data with those described in the literature.[10]

Acetylation of Bulgarsenine Hydrochloride (4·HCl). Compound **4**·HCl (18.5 mg) and DMAP (10.0 mg) in Ac_2O (0.25 mL) and Et_3N (0.25 mL) were stirred overnight at room temperature. The reaction mixture was dried under an air stream, and the residue afforded 12.5 mg of **2** by preparative TLC ($CHCl_3$−MeOH, 95:5).

Oxidation of 11-*O*-Acetyl Bulgarsenine Hydrochloride (2·HCl). Compound **2**·HCl (35.0 mg) and *m*-chloroperbenzoic acid (35.0 mg) in $CHCl_3$ (3 mL) were stirred at room temperature for 1 h. The reaction mixture was purified by column chromatography using as eluent CH_2Cl_2−Me_2CO (9:1) to yield 28.6 mg of **3**.

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