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CLERODANE DITERPENOIDS OF *SALVIA LINEATA**

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Key Word Index—*Salvia lineata*; Labiatae; neo-clerodane derivatives; diterpenoids; 1,10-dehydrosalviarin; 1α,10α-epoxysalviarin; linearifoline.

Abstract—The aerial parts of *Salvia lineata* afforded, in addition to sitosterol, oleanolic acid and flavonoids of known structures, three clerodane derivatives related to salviarin and gensnerofolin B. The structures were elucidated by spectroscopic and chemical means.

INTRODUCTION

Salvia L. constitutes the largest genus in the Labiatae family with about 900 species in the world [1]. This genus is well represented in Mexico with *ca* 275 species [2] and a number have found local use as medicinal [3], hallucinogenic [4] and culinary herbs. In continuing our studies in Mexican Salvias [5–8], we wish to describe the isolation and characterization of the chemical constituents of *Salvia lineata* Benth, a shrub endemic to Mexico. Two populations of this plant were analysed. In addition to sitosterol, oleanolic acid and flavones of known structures, three diterpenoids were isolated. The major diterpenoid is identical to the anhydro derivative of the 'bitter principle' isolated from *S. rubescens* [9], to which structure **1** was previously assigned without stereochemistry. The two remaining compounds **4** and **5** are novel neo-clerodane diterpenoids, related to salviarin [10] and gensnerofolin B.

RESULTS AND DISCUSSION

Extraction of the aerial parts of a population of *Salvia lineata* Benth. collected near Tehuacan (Puebla, Mexico) afforded after extensive chromatography: sitosterol, oleanolic acid, the flavones 6-methoxygenkwanin (5,4'-dihydroxy-6,7-dimethoxyflavone) [11], cirsiliol (6,7-dimethoxy-5,3',4'-trihydroxyflavone) [12] and two diterpenoids to which we assigned structures **1** and **4** on the following considerations.

Compound **1** was isolated as a crystalline solid, mp 198–199°, and showed molecular formula $C_{20}H_{20}O_5$ (MS

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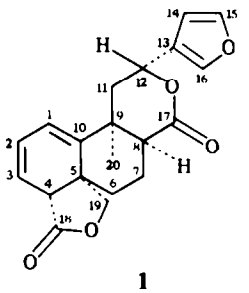

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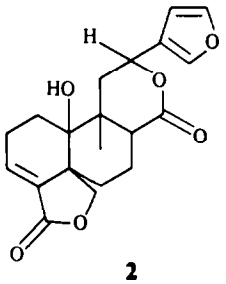

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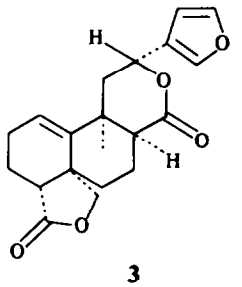

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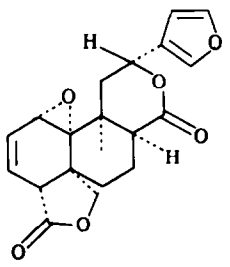

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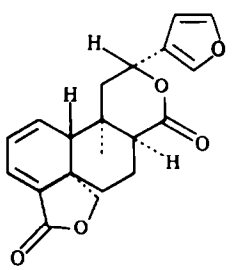

5

and elemental analysis). Its IR spectrum exhibited the characteristic absorption for a furan ring (3141, 1502, 874 cm^{-1}), γ and δ lactones (1773 and 1703 cm^{-1}), double bonds (1662, 1655, 1647, 1594 cm^{-1}) and the absence of hydroxyl groups. The UV spectrum showed absorptions at 263 nm ($\log \varepsilon = 4$), 272 ($\log \varepsilon = 4.1$) and 281 (shoulder), indicating the presence of a homoannular conjugated diene system [9, 13] in **1**. These data, in addition to the ^{1}H NMR spectrum (Table 1), are in agreement with those described for the 1(10),2-dienic derivative of product **2** isolated from *S. rubescens* [9]. Spectral data (IR, ^{1}H NMR, MS) of **1** are identical to those obtained from an authentic sample of a 1(10),2-dienic derivative of **2**, now isolated as a natural product. Nevertheless, the stereochemistry was not assigned to **1** in the work on *S. rubescens*. The relative stereochemistry proposed for **1** in this paper, is supported by the following data. The ^{1}H NMR spectrum of **1** (Table 1) showed, in addition to the characteristic signals for a β-substituted furan ring and the protons of a dienic moiety (H-1, H-2 and H-3), an AB system at δ3.19 and 4.45 ($J = 8$ Hz) which was assigned to the C-19 methylene group. The *pro-S* diasterotopic proton of this group is also W-coupled with the C-6 β-proton ($^4J = 2$ Hz). This behaviour has been described in several clerodan-18,19-olides, with C-19 axially oriented and lacking a C-6 β substituent [14]. The ^{1}H NMR spectrum of **1** also exhibited an ABX system. The X part, ascribed to H-12, was located at δ5.45. The J values (12 and 4 Hz) of this signal suggested an axial orientation for H-12 [13]. The AB part (C-11 methylene protons) was localized at δ2.66 and 1.92 (Table 1). A triplet at δ2.55 ($J = 2.4$ Hz) was assigned to H-8. The coupling constant indicated an equatorial orientation for this proton, and therefore the C-8 substituent (C-17) must be β-axially oriented. A three proton signal at δ1.25 was assigned to the α-axial methyl group attached to C-9. The orientation proposed for this group was supported by NOE difference spectroscopy. Irradiation at δ1.25 produced clear NOEs with the C-19 protons, H-8 and the axial C-11 proton. Inspection of molecular models showed that this could be expected for the relative stereochemistry proposed for the B ring of **1**. The ^{13}C NMR spectrum of **1** not previously described, is included in Table 2 and agrees with the proposed stereochemistry. Comparison of ^{13}C NMR data of **1** with those described for salviarin [10], the configuration of which was supported by X-ray work, suggested a half-chair conformation of the δ-lactone ring in **1** and therefore a 12*R*-configuration, as well as a *cis* fusion of the γ-lactone ring as depicted in **1**. Based on the previous discussion, compound **1** must be named 1(10)-dehydrosalviarin.

Catalytic hydrogenation of **1** in mild conditions gave the dihydro derivative **3**. The presence of a doublet at δ123.8 and a singlet at 137.5 in the ^{13}C NMR spectrum of **3** (Table 2) indicated that the hydrogenation had occurred in the 2,3-double bond of **1**. The ^{1}H NMR spectrum of **3** (Table 1) showed a triplet at δ5.8 ($J = 4$ Hz) ascribed to H-1.

The second diterpenoid isolated from this population of *S. lineata* was a novel compound, with a molecular formula $C_{20}H_{20}O_6$ (MS). Its IR spectrum showed absorptions very similar to those present in the IR spectrum of **1** (see Experimental). The ^{1}H NMR and ^{13}C NMR spectra, as well as a series of spin decoupling experiments, led us to assign structure **4** to this novel diterpenoid. The

Table 1. ^{1}H NMR spectral data of compounds **1**, **3**, **4** and **5***

H	1†	3‡	4‡	5‡
1	6.0 *d* (7)	5.8 *t* (4)	3.5 *dd* (4, 2)	6.25 *m*
2	6.1 *ddd* (10, 7, 3)		6.25 *ddd* (9, 4, 2)	6.25 *m*
3	5.5 *dd* (10, 3)		5.65 *dt* (9, 2)	6.9 *br d* (4)
4	3.05 *t* (3)		2.85 *t* (2)	
8	2.55 *t* (2.5)		2.5 *m*	2.35 *m*
11_{ax}	1.92 *dd* (16, 12)		1.65 *dd* (16, 12)	2.75 *dd* (16, 8)
11_{eq}	2.6 *dd* (16, 4)		2.15 *dd* (4, 16)	2.15 *dd* (16, 1)
12	5.45 *dd* (12, 4)	5.5 *dd* (12, 4)	5.75 *dd* (12, 4)	5.75 *dt* (8, 1)
14	6.4 *br s*	6.4 *br s*	6.35 *t* (2)	6.4 *br s*
15,16	7.42 *m*	7.42 *m*	7.35 *d* (2)	7.4 *m*
19 *pro S*	3.95 *dd* (8, 2)	4.05 *dd* (9, 1)	4.1 *d* (8)	4.0 *dd* (9, 1)
19 *pro R*	4.45 *d* (8)	4.5 *d* (9)	4.4 *d* (8)	4.5 *d* (9)
3H-20	1.25 *s*	1.2 *s*	1.2 *s*	1.3 *s*

*Run using $CDCl_3$ as solvent and TMS as internal standard. Coupling constants in Hz are in parentheses. Chemical shifts are in δ values.

†Run at 300 MHz.

‡Run at 80 MHz.

Table 2. ^{13}C NMR data for compounds **1**, **3**, **4** and **5***

C	1	3	4	5
1	119.7 (*d*)†	123.9 (*d*)	51.5 (*d*)	126.0 (*d*)†
2	119.1 (*d*)†	24.1 (*t*)	126.2 (*d*)†	128.5 (*d*)†
3	125.0 (*d*)	21.3 (*t*)	126.7 (*d*)†	133.4 (*d*)
4	51.7 (*d*)	47.9 (*d*)	49.7 (*d*)	133.0 (*s*)
5	42.5 (*s*)	42.2 (*s*)	44.1 (*s*)	40.0 (*s*)
6	32.1 (*t*)	32.2 (*t*)	30.0 (*t*)	22.0 (*t*)
7	19.2 (*t*)	19.2 (*t*)	18.8 (*t*)	16.8 (*t*)
8	48.5 (*d*)	48.8 (*d*)	46.3 (*d*)	50.2 (*d*)
9	37.7 (*s*)	38.4 (*s*)	37.7 (*s*)	35.3 (*s*)
10	139.8 (*s*)	137.8 (*s*)	67.3 (*s*)	41.4 (*d*)
11	40.7 (*t*)	41.2 (*t*)	39.0 (*t*)	36.7 (*t*)
12	70.8 (*d*)	70.7 (*d*)	72.0 (*d*)	71.0 (*d*)
13	124.8 (*s*)	125.3 (*s*)	125.9 (*s*)	127.3 (*s*)
14	108.5 (*d*)	108.4 (*d*)	108.3 (*d*)	108.7 (*d*)
15	143.8 (*d*)	143.8 (*d*)	143.8 (*d*)	144.5 (*d*)
16	139.6 (*d*)	139.6 (*d*)	139.4 (*d*)	138.8 (*d*)
17	171.3 (*s*)	171.5 (*s*)	171.2 (*s*)	172.6 (*s*)
18	177.1 (*s*)	178.2 (*s*)	174.8 (*s*)	168.6 (*s*)
19	75.8 (*t*)	75.6 (*t*)	70.9 (*t*)	77.0 (*t*)
20	32.1 (*q*)	30.8 (*q*)	26.1 (*q*)	31.4 (*q*)

*Recorded at 20 MHz, as $CDCl_3$ solutions. Chemical shifts in δ values from TMS.

†Values in any vertical column may be interchanged.

^{1}H NMR spectrum of **4** (Table 1) showed a double doublet at δ3.5 (J = 4, 2 Hz) which was ascribed to the oxirane proton (H-1). It also exhibited the signals for two olefinic protons at δ5.65 (*ddd*, J = 10, 3 and 2 Hz) and 6.25 (*ddd*, J = 10, 4, 2 Hz) assigned to H-3 and H-2, respectively. The 4β-proton is responsible for a double doublet (J = 2, 3 Hz) at δ2.85. These assignments were confirmed by double resonance experiments. Irradiation at δ3.5 (H-1) removed a 2 Hz coupling in the signal ascribed to H-3 (now as *dd*, J = 10, 3 Hz), at the same time the signal due to H-2 changed to a double doublet (J = 10, 2 Hz). Irradiation at δ2.85 (H-4) removed a 3 Hz coupling in the signal at δ5.65 (H-3) (now as a *dd*, J = 10, 2 Hz) and a 2 Hz coupling to H-2 (now as a *dd*, J = 10, 4 Hz). The presence of signals at δ51.47 (*d*, C-1), 67.4 (*s*, C-10), 126.21 (*d*, C-2), 126.74 (*d*, C-3) and 49.71 (*d*, C-4) in the ^{13}C NMR spectrum of **4** are in agreement with the previous discussion.

Other relevant signals in the ^{1}H NMR spectrum of **4**, are those due to an ABX system at δ5.75 (X part J_{AX} = 12, J_{AX} = 4 Hz), 2.15 (J_{BX} = 4, J_{AB} = 16 Hz) and 1.65 (J_{AX} = 12 Hz) ascribed to the axial H-12 and to the C-11 methylene moiety. A three proton signal at δ1.2 was assigned to the methyl group bound to C-9. An AB system at δ4.1 and 4.4 (J = 8 Hz) was attributed to the C-19 methylene protons. Although there is no C-6 β-substituent, neither of the two protons showed a long-range coupling. Inspection of molecular models of **4** indicated that this fact is due to the presence of the oxirane ring, which avoids the W arrangement of the *pro-S* C-19 proton with the C-6 β-proton.

Comparison of the ^{13}C NMR spectrum of **4** with that of salviarin and of 1(10)-dehydrosalviarin (**1**), suggested a 12*R*-configuration, as well as a *cis* β-fusion of the δ-lactone ring. The orientation for the oxirane ring rests in the upfield shift observed for C-19 ($\Delta\delta$ = 4.85) and C-20 ($\Delta\delta$ = 6.1) in the ^{13}C NMR spectrum of **4** with respect to **1**. This upfield shift could be expected only if the oxirane ring is 1α,10α-oriented (see molecular models). Based on these data compound **4** is also related to salviarin and must be named 1α,10α-epoxysalviarin.

A second population of *S. lineata*, collected in Oaxaca (Mexico) was analysed. Chromatographic separation of the acetonic extract yielded again sitosterol and oleanolic acid. Compound **1** was also isolated as the major diterpenoid constituent. Product **4** was not isolated in this case. Instead a novel neo-clerodane type diterpenoid, named linearifoline (**5**), was isolated. Linearifoline (**5**) was isolated as a crystalline product, mp 229–230° and showed a $C_{20}H_{20}O_5$ molecular formula (by MS). The structure and relative stereochemistry proposed for linearifoline as depicted in **5**, were established from the ^{1}H NMR and ^{13}C NMR data. In agreement with the existence of an α,β-γ,δ-diunsaturated γ-lactone ring (IR 1750 cm^{-1}), the UV spectrum of **5** showed typical absorption for this chromophore at 300 nm (ε = 9842), and the ^{1}H NMR spectrum (Table 1) similar resonances for H-1, H-2 and H-3 to those described for gensnerofolin B from *S. gensneraefolia* [15] and salvifaricin from *S. farinacea* [16]. Comparison of the ^{13}C NMR spectrum (Table 2) of **5** with those of **1**, **3**, **4**, salviarin and salvifaricin supports the relative stereochemistry proposed for **5**, except for the C-10 configuration. The presence of a long-range coupling in the ^{1}H NMR signal of the *pro-S* H-19 proton present in **5**, suggested an A/B *trans* ring fusion [13] for linearifoline, and therefore a β-orientation for the C-10 proton.

The chemical constituents of *S. lineata*, a species endemic to Mexico, are closely related to salviarin obtained from *S. splendens*, a Brazilian species. In spite of the chemical relationship, these species are placed in unrelated sections: *S. lineata*, section Fulgentes and *S. splendens*, section Secundae, Epling [17]. On the other hand compounds **1**, **4** and **5** are related to the diterpenoid constituents of *Salvia gensneraefolia* (section Nobiles) an endemic shrub to Mexico from which gensnerofolins A and B were reported. Gensnerofolin A has been shown to be identical to salviarin [M. Jiménez, E. Diaz and M. Soriano-García, private communication]. These relationships could be of taxonomic importance since our ongoing studies on Mexican Salvias suggested that sections Fulgentes and Nobiles may not be distinct from one another and this group of species may be closely related to section Holwayii. Further studies on species belonging to the previously mentioned sections are in progress to support this taxonomic suggestion.

EXPERIMENTAL

Mps are uncorr. MS were obtained by direct inlet at 70 eV. ^{1}H NMR spectra were performed at 80 and 300 MHz, in $CDCl_3$ or C_6D_6 solns with TMS as internal standard. ^{13}C NMR spectra were performed at 20 MHz, in $CDCl_3$ solns with TMS as internal standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance, noise-decoupled, APT and gated-decoupling ^{13}C NMR spectra. Plant materials were collected in November 1984, in Tehuacan (Puebla, Mexico) and near Oaxaca (Oaxaca, Mexico) and the voucher specimens were deposited at the herbarium of the Instituto de Biología, UNAM.

Isolation of the constituents from Salvia lineata (*voucher MEXU* 404010). Dried aerial parts (3.1 kg) of *S. lineata* Benth, were extracted with Me_2CO (15 l.) at room temp. for 1 week. The solvent was removed under red. pres. and the gummy residue obtained (45 g) chromatographed over silica gel (1 kg deactivated with 5% H_2O). Elution with petrol–EtOAc (9:1) gave sitosterol (400 mg). Elution with petrol–EtOAc (6:4) gave **1** (5 g, 0.16% dry weight): mp 198–199° from MeOH; $[\alpha]_D^{20}$ = −199.5° ($CHCl_3$; c 0.22); UV λ_{max}^{MeOH} nm (ε): 208 (16 000), 263 (15 000), 272 (14 000), 281 (shoulder); IR ν_{max}^{nujol} cm^{-1}: 3129, 3066, 1773, 1703, 1662, 1647, 1594, 1502, 1460, 1446, 874; ^{1}H NMR: Table 1; ^{13}C NMR ($CDCl_3$, 20 MHz): Table 2; MS m/z (rel. int.): 340 (42), 253 (10), 230 (10), 202 (40), 143 (100), 128 (82), 95 (82), 91 (40), 81 (20), 77 (20). $C_{20}H_{20}O_5$ requires C 70.57, H 5.9, O 23.5%. Found: C 70.20, H 5.87, O 23.5%. Spectroscopic data for **1** are in agreement with those described by Brieskorn and Stehle for the anhydro derivative of the 'bitter principle' from *S. rubescens* [9].

Elution with petrol–EtOAc (4:1) afforded 2.8 g of oleanolic acid, identified by comparison of the methyl ester derivative with an authentic sample (mp, mmp, IR, ^{1}H NMR).

From the fractions eluted with petrol–EtOAc (1:1) 97.9 mg of a solid were isolated. TLC in several solvent systems, revealed a two components mixture which was resolved by flash chromatography using MeOH–C_6H_6 (7:93) as eluent. Fractions 2–6 afforded **4** (38 mg, 0.0012% dry wt): mp 255–256° from MeOH–(*iso*-Pr)$_2$O; $[\alpha]_D^{20}$ = −90.32° (MeOH; c 0.155); UV λ_{max}^{MeOH} nm (ε): 210 (18 518): IR ν_{max}^{nujol} cm^{-1}: 3108, 3141, 1784, 1707, 1655, 1502, 1459, 1375, 1162, 1018, 912, 876, 842. ^{1}H NMR ($CDCl_3$, 80 MHz): Table 1; ^{13}C NMR ($CDCl_3$, 20 MHz): Table 2; MS m/z (rel. int.): 356 (4), 341 (0.7), 340 (0.7), 246 (5), 202 (5), 201 (5), 188 (15), 143 (48), 129 (20), 95 (100), 91 (30), 81 (20), 79 (20), 77 (30), 65 (20), 39 (37). $C_{20}H_{20}O_6$ requires $[M]^+$ at m/z 356.

Fractions 8–16 afforded 42 mg of a pale yellow crystalline product identified as 5,4'-dihydroxy-6,7-dimethoxy flavone by comparison with literature data [11].

Repeated chromatography of the fraction eluted with petrol–EtOAc (4:6) gave 70 mg of a crystalline product identified as 6,7-dimethoxy-5,3',4'-trihydroxyflavone by comparison with literature data [12].

Catalytic hydrogenation of **1**. Compound **1** (100 mg) in EtOAc (5 ml) was hydrogenated using Pd/C (10%, 25 mg) as catalyst, during 2 hr. After usual work up, product **3** (85 mg) was obtained. Mp 154–155° from MeOH; $[\alpha]_D^{20} = -42.9°$ ($CHCl_3$; *c* 0.17); UV λ_{max}^{MeOH} nm (ε): 204 (18000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1779, 1722, 1598, 1504, 1450, 1366, 1303, 1236, 1184, 1166, 1142, 1096, 1021, 991, 875; ^1H NMR ($CDCl_3$, 80 MHz) Table 1; ^{13}C NMR ($CDCl_3$, 20 MHz) Table 2; MS *m/z* (rel. int.): 342 (41), 324 (5), 314 (10), 298 (10), 232 (50), 206 (20), 205 (100), 204 (70), 176 (20), 161 (50), 159 (35), 147 (87), 105 (50), 95 (97.9), 91 (92.7), 81 (30), 79 (25), 77 (50), 41 (30), 39 (40). $C_{20}H_{22}O_5$ requires $[M]^+$ at *m/z* 342.

Isolation of constituents from S. lineata (*voucher MEXU* 402748). Dried aerial parts (3.1 kg) of a second pupulation of *S. lineata* was treated as above. The Me_2CO extract (70 g) was chromatographed over silica gel (1 kg, deactivated with 5% H_2O). In addition to sitosterol (200 mg) oleanolic acid (2 g) and **1** (2 g), 80 mg (0.024%) of **5** were isolated from the fractions eluted with petrol–EtOAc (6:4): mp 229–230° from MeOH. $[\alpha]_D^{20} = -68.7°$ (MeOH; *c* 0.19); UV λ_{max}^{MeOH} nm (ε): 208 (13000), 300 (9842). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1730, 1660, 1570, 1370, 1320, 1100, 1060, 1030, 970, 870. ^1H NMR ($CDCl_3$, 80 MHz): Table 1; ^{13}C NMR ($CDCl_3$, 20 MHz): Table 2. MS *m/z* (rel. int): 340 (20), 278 (3), 217 (2), 203 (10), 189 (15), 176 (5), 171 (10), 133 (20), 128 (20), 115 (30), 105 (50), 95 (100), 94 (60), 91 (50), 82 (55), 81 (35), 77 (50), 65 (40), 55 (30), 41 (40), 39 (70). $C_{20}H_{20}O_5$ requires $[M]^+$ at *m/z* 340.

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