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6-Methylcryptoacetalide, 6-methyl-epicryptoacetalide and 6-methylcryptotanshinone from *Salvia aegyptiaca*

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Abstract

From the whole plant of *Salvia aegyptiaca*, 6-methylcryptoacetalide, 6-methyl-epicryptoacetalide and 6-methylcryptotanshinone have been isolated and characterized, mainly by spectroscopic means. In addition to these novel diterpenoids, the known compounds 3β-hydroxy-olean-12-en-28-oic acid, 3β-hydroxy-oleana-11,13(18)-dien-28-oic acid, sitosterol-3β-glucoside, sitosterol, stigmasterol, 5-hydroxy-7,3′,4′-trimethoxyflavone and 5, 6-dihydroxy-7,3′,4′-trimethoxyflavone were isolated.

Keywords: *Salvia aegyptiaca*; Labiatae; Phytochemistry; Diterpenoids; 6-Methylcryptoacetalide; 6-Methyl-epicryptoacetalide; 6-Methylcryptotanshinone

1. Introduction

Salvia aegyptiaca (Labiatae/Lamiaceae) has been examined chemically because of its uses in folk medicine. The seeds of the plant are used as a demulcent and for the treatment of diarrhoea and haemorrhoids (Ghazanfar, 1994). *S. aegyptiaca* is also used against gonorrhoea and eye diseases, and as an antiseptic, cicatrizant, antispasmodic and stomachic (Rizk and El-Ghazaly, 1995). The plant has also been reported to be beneficial in cases of nervous disorders, dizziness, trembling and for stopping perspiration (Hussain, 1985).

Salvia species have yielded numerous diterpenoids, based mainly on abietane and clerodane skeletons (Rodríguez-Hahn et al., 1992). In this communication we report on the isolation and characterization of three novel diterpenoids from *S. aegyptiaca*.

2. Results and discussion

The acetone extract of the powdered whole plant of *Salvia aegyptiaca* was partitioned between acetonitrile and *n*-hexane to yield acetonitrile, *n*-hexane and insoluble fractions. The insoluble material, when fractionated on a column of silica gel, yielded two components which, from IR and NMR spectroscopic and mass spectrometric data, were proved to be 3β-hydroxy-olean-12-en-28-oic acid (Mahato and Kundo, 1994) and the 3β-glucoside of sitosterol (Agrawal et al., 1995).

Fractionation by silica gel column chromatography of the *n*-hexane extractive yielded a mixture of compounds that, from spectroscopic (^{1}H and ^{13}C NMR, IR) and mass spectrometric data, were proved to be sitosterol and stigmasterol, with the former predominating (Ahmed et al., 1992). Sitosterol has been reported for many *Salvia* species (e.g. Hussain et al., 1997; Maldonado and Ortega, 1997a).

The acetonitrile fraction was chromatographed on a silica gel column. Elution with ethyl acetate-*n*-hexane (15:85) yielded a fraction that, when subjected to preparative TLC and examined under UV light, revealed

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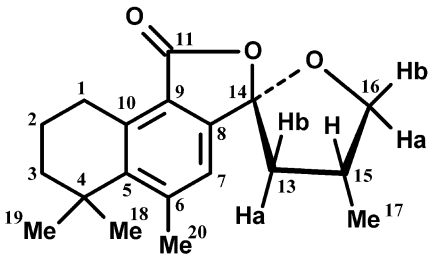

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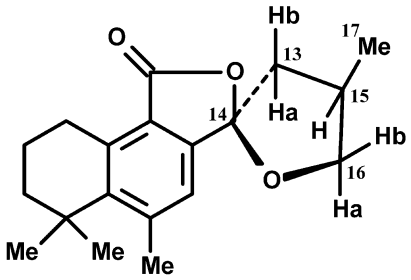

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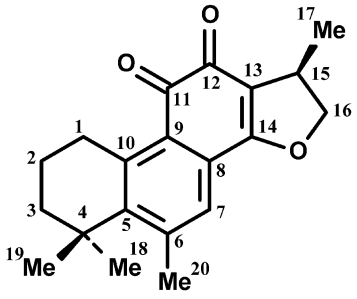

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two major bands, the R_f values of which were very close. The two compounds (**1** and **2**) were eluted from the silica, but it was not possible to separate one from the other. The IR spectrum of the mixture showed the presence of a γ-lactone (1760 cm^{-1}) and an aromatic moiety (1620 cm^{-1}).

The ^{13}C NMR spectrum (Table 1) showed the presence of 19 carbon atoms in both **1** and **2** (eight quaternary, two methine, five methylene and four methyl), which were present in a ratio of approximately 52:48, respectively. The spectrum of **1** indicated the presence of a lactone carbonyl (δ 168.7), a substituted benzene ring (δ 153.1, 144.7, 143.9, 138.0, 121.6 and 117.6) and a quaternary acetalic carbon (δ 112.9). The degree of unsaturation suggested that there must be two more rings other than the benzene and lactone rings. ^1H–^1H COSY results suggested the partial structures –CH_2–CH_2–CH_2–$C(CH_3)_2$,–O–CH_2–$C(CH_3)$–CH_2, and –CH = C–CH_3 (of the benzene ring). 2D-NMR (HMQC and HMBC) spectra of **1** showed correlation between the *gem*-dimethyl protons (δ 1.32 and 1.33) and an aromatic proton (δ 7.32, H-7). The Me-20 protons, as well as the methylene protons of C-1 (δ 2.69) were also coupled to C-5 (δ 138.0). From these signals, as well as from the correlations between Me-20 protons and C-8, H-7 and C-9, and CH_2-1 and C-9, it was deduced that a tetrahydronaphthalene ring system was present. Correlation was also shown between proton Ha-13 and both an aromatic carbon (C-8, δ 144.7) and a quaternary carbon (C-14, δ 112.9). The coupling of this latter quaternary carbon with H-7 and its chemical shift suggested that this was an acetal carbon (Asari et al., 1990). Thus a spiroacetal-lactone moiety was deduced for **1**. This was confirmed by the sharp singlet signal of the lactone carbon (δ 168.7, C-11) in the proton coupled ^{13}C NMR spectrum.

A NOE difference spectroscopic experiment showed the close proximity of H-7 and Ha-13. The latter also displayed a NOE with Me-17, which established the *syn* relationship of the methyl and benzene rings with respect to the tetrahydrofuran ring. NOE correlations were also observed in the 2D-spectrum between Me-17 and Ha-16, Hb-16 and H-15, and between H-15 and Hb-13.

The HR EI mass spectrum of **1** showed a M^+ ion at *m/z* 300.1707 (calculated for $C_{19}H_{24}O_3$, 300.1722), whereas the CI mass spectrum displayed a $(M+1)^+$ ion at *m/z* 301. On the basis of the above data, to this compound was assigned structure **1** and it was named 6-methylcryptoacetalide.

The ^1H (Table 2) and ^{13}C NMR (Table 1) spectroscopic data for **2** were very similar to that of **1.** However,

Table 1
^{13}C NMR chemical shifts (δ) of 6-methylcryptoacetalide (**1**), 6-methylepicryptoacetalide (**2**) and 6-methylcryptotanshinone (**3**)

Compound	Chemical shifts (δ)									
	1	2	3	4	5	6	7	8	9	10
1	27.4	19.0	38.2	35.1	138.0	143.9	117.6	144.7	121.6	153.1
2	27.4	19.0	38.2	35.1	138.1	143.9	117.6	144.7	122.0	153.2
3	28.6	19.1	37.8	34.9	144.0	141.2	121.7	126.2	125.6	152.5
	11	12	13	14	15	16	17	18	19	20
1	168.7		44.9	112.9	33.3	77.0	18.2	32.0	31.8	13.3
2	168.7		45.9	112.88	32.4	77.0	17.4	32.0	31.8	13.3
3	184.5	176.3	118.2	171.1	34.6	81.4	18.8	31.3	31.3	16.6

Table 2
^{1}H NMR spectral details (in $CDCl_3$) of 6-methylcryptoacetalide (**1**), 6-methylepicryptoacetalide (**2**) and 6-methylcryptotanshinone (**3**)

	^{1}H NMR chemical shifts (δ)						
	1	**2**	**3**		**1**	**2**	**3**
H-1	2.69 (2H, *m*)	2.69 (2H, *m*)	2.72 (2H, *t*, *J* = 6.6, 6.6 Hz)	H-16a	3.75 (1H, *t*, *J* = 8.1, 8.1 Hz)	4.38 (1H, *t*, *J* = 8.1, 8.1 Hz)	4.37 (1H, *dd*. *J* = 5.9, 9.2 Hz)
H-2	1.85 (2H, *m*)	1.85 (2H, *m*)	1.86 (2H, *m*)	H-16b	4.40 (1H, *t*, *J* = 8.1, 8.1 Hz)	3.85 (1H, *t*, *J* = 8.1, 8.1 Hz)	4.90 (1H, *dd*, *J* = 9.2, 9.5 Hz)
H-3	1.67 (2H, *m*)	1.67, 2H, *m*)	1.65, (2H, *m*)	Me-17	1.27 (3H, *d*, *J* = 7.0 Hz)	1.22 (3H, *d*, *J* = 7.0 Hz)	1.36 (3H, *d*, *J* = 6.6 Hz)
H-7	7.32 (1H, *s*)	7.26 (1H, *s*)	7.54 (1H, *s*)	Me-18	1.33 (3H, *s*)	1.33 (3H, *s*)	1.32 (3H, *s*)
H-13a	1.97 (1H, *dd*, *J* = 10.6, 12.8 Hz)	2.29 (1H, *dd*, *J* = 7.0, 13.7 Hz)		Me-19	1.32 (3H, *s*)	1.32 (3H, *s*)	1.32 (3H, *s*)
H-13b	2.44 (1H, *dd*, *J* = 7.1, 12.8 Hz)	2.13 (1H, *dd*, *J* = 5.2, 13.5 Hz)		Me-20	2.57 (3H, *s*)	2.57 (3H, *s*)	2.59 (3H, *s*)
H-15	2.90 (1H, *m*)	2.88 (1H, *m*)	3.60 (1H, *m*)				

2 showed NOE correlation between Ha-13 and H-7, as well as between Ha-13 and H-15. Therefore, the methyl group and benzene ring are located in an *anti*-relationship. Other NOE correlations were observed between H-15 and Ha- 16, Hb-16 and Me-17, and Me-17 and Hb-13. On the basis of this information, to this compound was assigned structure **2** and it was named 6-methyl-epicryptoacetalide.

From the roots of *S. miltiorrhiza*, Asari et al. (1990) isolated an inseparable mixture of spirolactone diterpenes named cryptoacetalide and epicryptoacetalide. The NMR spectra of **1** and **2** very closely matched those of cryptoacetalide and epicryptoacetalide, but differed as a result of the additional methyl group at C-6 in **1** and **2**. The ^{1}H NMR spectroscopic shift values for H-1 for **1** and **2** were also different from those for cryptoacetalide and epicryptoacetalide, but this difference can probably be explained by the change in conformation of ring A caused by the introduction of the methyl group at C-6. All these data confirm the identity of **1** and **2** as 6- methylcryptoacetalide and 6-methyl-epicryptoacetalide, which, to our knowledge, are novel compounds. Calculation of ^{13}C chemical shift effects also confirmed the placement of the methyl substituent at C-6. The reported ^{13}C chemical shifts of tanshinone 11-type diterpenoids (Nagy et al., 1999) and calculation of chemical shifts for methyl substitution at C-6 on ring B, led to the assignments for C-5 and C-10 to be reversed in comparison to the values given by Asari et al. (1990).

Further elution of the silica gel column containing the acetonitrile fraction with chloroform-*n*-hexane (5:95) afforded a mixture of compounds. The major component was isolated from this by centrifugal and preparative TLC. The isolated compound (**3**), was crystallized from methanol to give orange, needle-shaped crystals. The IR spectrum of **3** exhibited carbonyl stretching vibrations at 1650 and 1625 cm^{-1}, reminiscent of an *ortho*-quinone moiety. The ^{1}H NMR (Table 2) spectrum of the compound suggested a dihydro furan ring. The signals for Me-17 and H-15 exhibited as a doublet at δ 1.36 (3H, *J* = 6.6 Hz) and a multiplet at δ 3.60 (1 H), respectively. The presence of a dihydro furan ring was also supported by the appearance of signals for CH_2-16 (1H, δ 4.37, *dd*, *J* = 5.9, 9.2 Hz and 1H, δ 4.90, *dd*, *J* = 9.5, 9.2 Hz). The spectrum also showed a singlet for an aromatic proton (H-7) at δ 7.54 and an aromatic methyl singlet at δ 2.59. The Me-18 and-19 singlets were observed at δ 1.32 (6H). Three CH_2 signals were apparent at δ 1.65 (*m*, H-3), 1.86 (*m*, H-2) and 2.72 (*t*, *J* = 6.6 Hz; H-1).

The ^{13}C NMR spectrum of **3** (Table 1) showed the presence of 20 carbon atoms (10 quaternary, 4 methyl, 4 methylene and 2 methine). The spectroscopic data were similar to those of tanshinone-type compounds, such as 20-nor-5(10),6,8,13-abietatetraene-11,12-dione, with a furan attachment at C-13 and -14. The results were in good agreement with the tanshinone II-type diterpenoids reported by Nagy et al. (1999). The HR mass spectrum of **3** showed a M^+ ion at *m*/*z* 310.1549 calculated for $C_{20}H_{22}O_3$, 310.1566). Other significant ions were observed at *m*/*z* 282 (71%; M^+–CO) and *m*/*z* 267 (100%; M^+–CO–CH_3). Based on the spectroscopic and spectrometric data, to this compound was assigned structure **3** and it was named 6-methylcryptotanshinone (14,16-epoxy-6-methyl-5(10),6,8,13-abietatetraene-11,12-dione), which appears to be a new compound.

Biogenetically, the 6-methyl groups of **1**, **2** and **3** might arise by a series of methyl group shifts from C-10 to C-5 and then C-6.

Three further compounds were also isolated from the acetonitrile fraction. One was identified as 3β-hydroxy-oleana-11,13(18)-dien-28-oic acid, as its spectroscopic and spectrometric data closely matched those published

(Ikuta et al., 1995). By comparison with published data, the second compound was shown to be 5-hydroxy-7,3′,4′-trimethoxyflavone (Herrera et al., 1996) and the third, 5,6- dihydroxy-7,3′,4′-trimethoxyflavone (Miski et al., 1983; Maldonado and Ortega, 1997b). This last compound has been isolated previously also from *S. thymoides* (Maldonado and Ortega, 1997b).

3. Experimental

3.1. General experimental procedures

Mps: uncorrected. UV and IR spectra were obtained using Perkin-Elmer Lambda 3 UV–vis and Perkin-Elmer 521 spectrophotometers, respectively. ^{1}H (270 MHz) and ^{13}C NMR (67.8 MHz) spectra, in $CDCl_3$, were recorded using a Jeol GSX 270 FT–NMR spectrometer, with TMS as internal standard. Assignments were based on ^{1}H–^{1}H COSY, HMQC and HMBC techniques. Mass spectra were obtained using a Jeol DX 303 spectrometer coupled to a DA 5000 data system. Prep. TLC was conducted on 500 μm layers of silica gel 60 F (Merck 5729 and 5715), activated at 110 °C for 60 min.

3.2. Plant material

Salvia aegyptiaca L. was collected from Al Maleha, United Arab Emirates (UAE) from March to May, 1997. The plant material was authenticated by the National Herbarium, UAE University, where a voucher specimen (1662) is deposited. A further sample is lodged with the Hampshire County Council Museums Service, Winchester, Hampshire, UK (accession number Bi 2000. 16. 130). The whole plant was air-dried in the shade and coarsely powdered.

3.3. Extraction and fractionation of extract

Powdered *S. aegyptiaca* (whole plant; 4.6 kg) was extracted in a Soxhlet apparatus for 18 h with Me_2CO to yield, after conc. to dryness, 189.6 g dry extract. This was partitioned between CH_3CN and *n*-hexane (4:1) to afford 41 g CH_3CN dry extract, 43 g *n*-hexane dry extract and 105 g insoluble material.

3.4. Isolation of compounds from the acetonitrile and n-hexane insoluble fractions

The insoluble fr was mixed with 100 g silica gel (28–200 mesh; Sigma) and subjected to CC by placing the mixture on a column (125×5 cm) filled with silica gel (28–200 mesh, 850 g). Elution was first with *n*-hexane (frs 1–4) and subsequently with mixtures of *n*-hexane and EtOAc (95:5, fr 5–9; 90:10, fr 10–19; 85:15, fr 20–485; 80:20); 200 ml frs were collected. The frs, after conc, were examined by TLC using MeOH–$CHCl_3$ (0.25:9.75, fr 1–38; 0.5:9.5, fr 39–431; 1:9, frs 432–485). The TLC plates were examined first under UV light (λ 254 nm) and then after spraying with *ρ*-anisaldehyde-H_2SO_4 and heating. Similar frs were combined.

The combined frs 152–231 were conc to dryness and the powder washed with MeOH to afford 3β-hydroxy-olean-12-en-28-oic acid (125.2 mg). Combined frs 432–485 were divided into two batches of 400 and 500 mg and each was subjected to centrifugal TLC using silica gel layers (4 mm) and MeOH–$CHCl_3$ as the mobile phase. Both batches afforded sitosterol-3β-glucoside.

3.5. Isolation of compounds from the n-hexane fraction

The *n*-hexane fr (27.6 g) was coated onto silica gel (70–230 mesh; 34 g; Aldrich Chemical Co.) and placed on the top of a column (125×5 cm) filled with silica gel (70–230 mesh: 500 g). Elution was first with *n*-hexane (frs 1–15) and subsequently with mixtures of *n*-hexane and $CHCl_3$ (97.5:2.5, frs 16–39; 96:4, frs 40–242; 95:5, frs 243–272; 93–7, frs 273–494); 200 ml fractions were collected.

On the addition of MeOH to combined frs 419–427, dissolved in $CHCl_3$, a mixture of sitosterol and stigmasterol were pptd.

3.6. Isolation of compounds from the acetonitrile fraction

The CH_3CN fr (41 g) was coated onto an equal weight of silica gel (70–230 mesh) and chromatographed on a column (125×5 cm) filled with 480 g silica gel (70–230 mesh) and eluted first with *n*-hexane (frs 1–33) and subsequently with mixtures of *n*-hexane and EtOAc (95:5, frs 34–98; 90:10, frs 99–123; 85:15, frs 124–207; 80:10, frs 208–271; 75:25, frs 272–317; 70:30, frs 318–374; 60:40, frs 375:451; 50:50, frs 452–526); fractions of 200 ml were collected.

Combined frs 53–69 were subjected to prep. TLC using *n*-hexane-EtOAc (8.5:1.5) as the development solvent. Examination under UV light (λ 254 nm) revealed a major band, which was scraped from the plates and the compounds eluted with $CHCl_3$–MeOH (99:1) to yield a mixture of **1** and **2** (9.6 mg; ratio approximately 52:48).

Combined frs 136–141 (400 mg) were fractionated by centrifugal TLC using silica gel 60 F (4 mm) layers and *n*-hexane–EtOAc (9:1) as the mobile phase; 315 mg of a semi-pure product was obtained. This was treated by prep. TLC using $CHCl_3$–MeOH (9:1). A major band was observed when examined under UV light. This was scraped from the plates and the compound eluted with $CHCl_3$–MeOH (99:1) to afford **3** (79.6 mg).

Combined frs 153–216 (2.84 g) were coated onto 2.8 g silica gel (70–230 mesh) and added to the top of a column

(45×2.5 cm) filled with 76 g silica gel (70–230 mesh) and eluted first with *n*-hexane (frs 1–17) and subsequently with mixtures of *n*-hexane–EtOAc (98:2, frs 18–26; 95:5, frs 27–44; 93:7, frs 45–151; 90:10, frs 152–273; 87.5:12.5, frs 274–301; 85:15, frs 302–307); frs of 80 ml each were collected. The frs, after conc, were analysed on silica gel F-254 TLC plates using a mixture of either *n*-hexane–EtOAc (8:2, frs 1–44) or $CHCl_3$–MeOH (8.2:0.8, frs 45–273). Frs were detected under UV light (λ 254 nm) and then sprayed with *ρ*-anisaldehyde-H_2SO_4 reagent and heated. Frs 153–181 were combined, conc to dryness and subjected to prep. TLC for further purification. Two major bands were observed when viewed under UV light. These were scraped separately from the plates and eluted with $CHCl_3$–MeOH (99:1) to afford 3β-hydroxy-oleana-11,13(18)-dien-28-oic acid (11.8 mg) and 5-hydroxy-7,3′,4′-trimethoxyflavone (23.0 mg)

Frs 390–417 were combined, conc to dryness, dissolved in CH_2Cl_2 and allowed to stand overnight. Yellow crystals of 5,6-dihydroxy-7,3′,4′-trimethoxyflavone (19.8 mg) were deposited.

*3.7. 6-Methylcryptoacetalide (**1**) and epi-6-methylcryptoacetalide (**2**)*

$C_{19}H_{24}O_3$. UV λ_{max}^{MeOH} nm: 212, 246. IR ν_{max}^{KBr} cm^{-1}: 1760, 1620, 1460, 1350. CIMS *m/z*: 301 $(M+H)^+$. EI MS (probe) 70 eV *m/z* (rel. int.): 300.1707 $[M^+]$ (38), 285 (5), 257 (12), 245 (100), 243 (26), 242 (20), 241 (92), 229 (36). ^1H NMR (Table 2); ^{13}C NMR: (Table 1).

*3.8. 6-Methylcryptotanshinone [14, 16-epoxy-6-methyl-5(10), 6, 8, 13-abietatetraene- 11, 12-dione] (**3**)*

$C_{20}H_{22}O_3$. Orange needles (MeOH) mp 115–117 °C (uncorrected). UV λ_{max}^{MeOH} nm (log ε): 273, 268, 222, 202. IR ν_{max}^{KBr} 1690, 1660, 1650, 1625, 1580. EI MS (probe) 70 eV *m/z* (rel. int.): 310.1549 $[M^+]$ (47), 308 (18), 298 (49), 282 (71), 267 (100). ^1H NMR (Table 2); ^{13}C NMR (Table 1).

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