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GUAIANOLIDES FROM *CENTAUREA CANARIENSIS**

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Key Word Index—*Centaurea canariensis*; Compositae; sesquiterpene lactones; guaianolides; subexpinnatin B, subexpinnatin C; 3-epi-11,13-dihydrodeacylcynaropicrin; cynaropicrin; deacylcynaropicrin; 11,13-dihydrodeacylcynaropicrin.

Abstract—The reinvestigation of *Centaurea canariensis* var. *subexpinnata* provided, along with three known compounds, three new sesquiterpene lactones of the guaiane series.

INTRODUCTION

In previous communications [1, 2] several sesquiterpene lactones were reported as the sesquiterpene constituents of *Centaurea canariensis* Brouss (var. *subexpinnata* Burch). A new study of the plant material, and careful chromatography of the more polar fractions, has now allowed the isolation of six other sesquiterpene lactones, three of which, subexpinnatins B (**1**), C (**2**) and 3-epi-11,13-dihydrodeacylcynaropicrin (**5**), have not been reported before. The known compounds are cynaropicrin (**7**), deacylcynaropicrin (**8**) and 11,13-dihydrodeacylcynaropicrin (**6**) [3].

RESULTS AND DISCUSSION

Subexpinnatin B (**1**) was obtained as a non-crystalline compound; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1770 (γ-lactone), 1717 (α,β-unsaturated ester), 1650 (double bonds); MS, *m/z*: 374.1708 $[M]^+$, 334.1450 $[M-40]^+$, 272.1467 $[M-102]^+$, 290 $[M-84]^+$, 85 $[C_2H_5O_2]^+$. Its ^{1}H NMR data (Table 1) confirmed the presence of an ester of α-hydroxymethylacrylic acid with two broad singlets at δ6.18, and 5.83, and two protons as a quartet centred at δ4.32. Two pairs of broad singlets (δ5.17, 5.02 and 4.95, 4.88) were attributed to the hydrogens of exocyclic methylene groups attached to C-4 and C-10, respectively. The lactonic proton (H-6) appeared as a triplet at δ4.16 and the proton at C-8 as a multiplet at 5.45.

The ^{1}H NMR data lies in close correspondence with those of subexpinnatin (**10**) [1, 2] except for the features associated with the positions C-11 and C-13. The presence of a methyloxetane moiety at these positions is inferred from the signals of the ABX system (δ1.76, 1.63 and 4.75) and the C-17 methyl (1.12). The α-orientation for the oxetane oxygen is deduced from the chemical shift of the lactonic proton [4]. Spin decoupling confirmed the presence of the methyloxetane moiety. Irradiation at δ1.12 (C-17 Me) converted the multiplet at δ4.75 in a double doublet, while irradiation at δ4.75 reduced the signals at 1.76 and 1.63 to doublets and the doublets and the doublet at δ1.12 to a singlet.

The oxetane ring is easily opened by nucleophiles under mild conditions. Treatment of **1** with acetic anhydride–pyridine yielded the triacetate **3** whose structure was confirmed by the ^{1}H NMR spectrum with singlets at δ2.12, 2.07 and 2.04. Subexpinnatin C (**2**) was separated from **1** after repeated preparative TLC (silica gel), as a crystalline compound, mp 186–188°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1770 (γ-lactone), 1630 (double bonds); MS *m/z*: 290.1591 $[M]^+$, 272.1337 $[M-18]^+$, 250.1257 $[M-40]^+$. Its ^{1}H NMR spectrum (Table 1), clearly showed that **2** is the deacyl derivative of **1**. Thus the characteristic signals of the hydroxymetacrylate moiety were not observed, and the absorption of H-8 was shifted to δ4.24.

Alkaline treatment of **1** yielded **2**, thus confirming that the latter compound is the deacyl derivative of **1**. Acetylation of **2** also resulted in the opening of the oxetane ring, yielding the triacetate **4**. Acid treatment of **2** yielded the triol **4a**, mp 141–143°. Its ^{1}H NMR spectrum showed that the oxetane ring has been opened since the signals for H-16 shifted from δ4.88 to 4.10, H-13 from δ2.32 to 2.11 and H-13′ from δ1.80 to 2.11.

The more polar fractions also contained a mixture of small amounts of the sesquiterpene lactones **5**–**8**, which were separated with difficulty by preparative TLC on silica gel. 3-epi-11,13-Dihydrodeacylcynaropicrin (**5**) is a non-crystalline compound; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1740 (γ-lactone), 1640 (double bond); MS *m/z*: 264 $[M]^+$, 246 $[M-18]^+$, 228 $[M-36]^+$. The ^{1}H NMR data (Table 1) show that the compound was an isomer of **6** with the 3α-configuration of the hydroxyl group. Therefore H-6β is less deshielded than in **6** and H-1 and H-5 are clearly deshielded.

With the aim of confirming the above suggestions cynaropicrin (**7**) was reduced with sodium borohydride, then mesylated to yield **9** and finally treated with aqueous 5% sodium hydroxide. From the reaction mixture was isolated a noncrystalline compound identical to the natural product **5**. The structures of the known compounds were assigned by spectral methods, as well as by comparison with authentic samples.

*Part 4 in the series "Structure and Chemistry of Secondary Metabolites from Compositae". For Part 3 see González Collado, I., Macías, F. A., Massanet, G. M., Oliva, J. M., Rodríguez Luis, F. and Vergara, C. (1984) *An. Quim.* **80**, 100.

Table 1. ^{1}H NMR spectral data of compounds 1–5 (360 MHz, $CDCl_3$, TMS as internal standard)

	1	2	3	4	4a	5
H-1	2.87 *ddd* (*br*)	2.88 *ddd* (*br*)	2.95 *ddd* (*br*)	2.95 *ddd* (*br*)	2.89 *ddd*	3.12 *ddd*
H-2						2.25 m
H-2′	1.78 *m*	1.87 *m*	1.82 *m*	1.82 *m*	1.86 *m*	1.85 *m*
H-3	2.39 *ddddd*	2.51 *m*	2.49 *m*	2.49 *m*	2.50 *m*	—
H-3′	2.46 *m*					4.62 *t* (*br*)
H-5	2.67 *dd* (*br*)	2.67 *dd* (*br*)	2.70 *dd* (*br*)	2.73 *dd* (*br*)	2.71 *dd* (*br*)	3.04 *dd*
H-6	4.16 *dd*	4.13 *dd*	4.32 *dd*	4.29 *dd*	4.17 *dd*	3.82 *dd*
H-7	1.96 *dd*	2.17 *dd*	1.96–2.15*	2.00–2.15*	2.32 *dd*	2.02 *ddd*
H-8	5.45 *ddd*	4.24 *ddd*	5.26 *m*	5.26 *m*	4.20 *ddd*	3.71 *m*
H-9	2.56 *dd*	2.64 *dd*	2.63 *dd*	2.63 *dd*	2.65 *dd*	2.68 *dd*
H-9′	2.27 *dd*	2.27 *dd*	2.39 *dd*	2.39 *dd*	2.21 *dd*	2.15 *dd*
H-11	—	—	—	—	—	2.50 *dq*
H-13	1.76 *dd*	2.30 *dd*	1.94 *dd*	1.94 *dd*	2.20 *dd*	1.40 *dd*
H-13′	1.63 *dd*	1.80 *dd*	1.96–2.15*	2.00–2.15*	2.05 *dd*	—
H-14	4.95 *s* (*br*)	4.96 *s* (*br*)	5.06 *s* (*br*)	5.06 *s* (*br*)	4.94 *s* (*br*)	4.97 *s* (*br*)
H-14′	4.88 *s* (*br*)	4.93 *s* (*br*)	4.93 *s* (*br*)	4.93 *s* (*br*)	4.93 *s* (*br*)	4.88 *s* (*br*)
H-15	5.17 *s* (*br*)	5.20 *d* (*br*)	5.20 *s* (*br*)	5.20 *s* (*br*)	5.19 *s* (*br*)	5.45 *t* (*br*)
H-15′	5.02 *s* (*br*)	5.05 *d* (*br*)	5.06 *s* (*br*)	5.06 *s* (*br*)	5.05 *s* (*br*)	5.32 *t* (*br*)
H-16	4.75 *ddq*	4.82 *ddq*	4.95 *m*	4.95 *m*	4.10 *m*	—
H-17	1.12 *d*	1.23 *d*	1.28 *d*	1.31 *d*	1.26 *d*	—
H-3′$_1$	6.18 *d* (*br*)	—	6.35 *s* (*br*)	—	—	—
H-3′$_2$	5.83 *d* (*br*)	—	5.94 *s* (*br*)	—	—	—
H-4′$_1$	4.36 *d* (*br*)	—	4.83 *d* (*br*)	—	—	—
H-4′$_2$	4.27 *d* (*br*)	—	4.77 *d* (*br*)	—	—	
			2.12 *s*	2.09 *s*		
AcO			2.07 *s*	2.06 *s*		
			2.04 *s*	2.05 *s*		

*Obscured by other signals.

J (Hz): compound **1**: 1, 2 = 1, 2′ = 1, 5 = 8; 2, 3 = 2, 3′ = 8.5; 3, 3′ = 17; 5, 6 = 6, 7 = 7, 8 = 10; 8, 9 = 4; 8, 9′ = 5; 9, 9′ = 13; 13, 13′ = 14.5; 13, 16 = 7.5; 13′, 16 = 2.5; 16, 17 = 6; 4′$_1$, 4′$_2$ = 13.5; 3′$_1$, 3′$_2$ = 1. Compound **2**: 1, 2 = 1, 2′ = 1, 5 = 7.5; 2, 3′ = 2′, 3 = 8; 3, 3′ = 16.5; 5, 6 = 6, 7 = 7, 8 = 9.5; 8, 9 = 4; 8, 9′ = 5; 9, 9′ = 12.5; 13, 13′ = 15; 13, 16 = 7; 13′, 16 = 2.5; 16, 17 = 6; 15, 15′ = 2; Compound **5**: 1, 2 = 1, 2′ = 1, 5 = 7.5; 3, 2 = 3, 2′ = 7; 5, 6 = 6, 7 = 7, 8 = 9.5; 8, 9 = 4.5; 8, 9′ = 5; 9, 9′ = 12.5; 7, 11 = 10; 3, 15 = 3, 15′ = 1.5; 11, 13 = 7.

EXPERIMENTAL

For general experimental details see ref. [1]. The more polar fractions were chromatographed on a column of silica gel, and after repeated preparative TLC (silica gel) afforded: **1** (6 mg), **2** (3, 5 mg) (CH_2Cl_2–*t*-BuOH, 9.5:0.5), **5** (2 mg), **6** (2 mg), **7** (4 mg), **8** (3 mg) ($CHCl_3$–*t*-BuOH, 9:1).

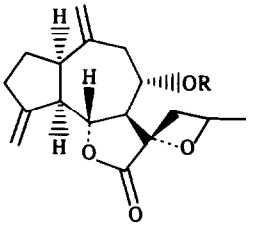
Subexpinnatin B (**1**). A non-crystalline compound. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1770, 1717, 1650. MS *m/z* (rel. int.): 374.1708 $[M]^+$ (0.65), ($C_{21}H_{26}O_6$, requires 374.1994), 346.1752 $[M-CO]^+$ (0.84), 334.1450 $[M-C_3H_4]^+$ (9.96), 290 $[M-84]^+$ (0.75), 272.1467 $[M-102]^+$ (7.62), 85 $[C_4H_5O_2]^+$ (100). The triacetate (**3**) was prepared by acetylation of **1** with 1 ml Ac_2O–pyridine (3:1) for 24 hr, room temp. to afford **3** as a colourless gum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1730, 1720, 1635.

Subexpinnatin C (**2**). Mp 186–188°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1770, 1630 MS *m/z* (rel. int.): 290.1591 $[M]^+$ (3.38) ($C_{17}H_{22}O_4$, requires 290.1698), 272.1337 $[M-18]^+$ (5.35), 250.1257 $[M-40]^+$ (17.7). The triacetate (**4**) was obtained by acetylation of **2** with 1 ml Ac_2O–pyridine (3:1) for 24 hr, room temp to afford **4** as a colourless gum. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1730, 1720, 1635. The 1,3-diol (**4a**) was prepared by mixing 2 mg **2** with aq. 5% H_2SO_4 (3 ml) and stirring for 5 hr. After neutralization with aq. 5% K_2CO_3 the mixture was extracted with $CHCl_3$ to yield 1.5 mg **4a**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1770, 1715, 1630. MS *m/z* (rel. int.): 308 $[M]^+$ (0.26), 290 $[M-18]^+$ (3.38), 272 $[M-2\times18]^+$ (5.90).

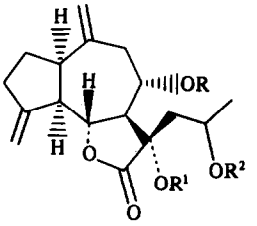
Saponification of **1**. Subexpinnatin B (4 mg) was mixed with aq. 5% K_2CO_3 (3 ml) and stirred for 24 hr. After acidification with dil. HCl the mixture was extracted with $CHCl_3$. The organic soln was washed with H_2O, dried and evaporated to dryness. Crystallization of the residue from EtOAc–petrol yielded **2** (2 mg).

3-*epi*-11,13-*Dihydrodeacylcynaropicrin* (**5**). The compounds **5** and **6** were separated with difficulty by preparative TLC (silica gel) ($CHCl_3$–*t*-BuOH, 9:1). Compound **5** (1 mg) was non-crystalline; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1750, 1640. MS *m/z*: 264 $[M]^+$, 246 $[M-18]^+$, 228 $[M-2\times18]^+$.

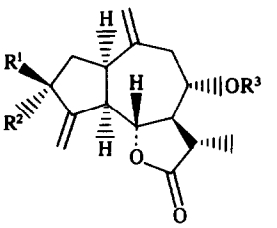
Conversion of **7** *to* **5**. A soln of 60 mg **7** in 10 ml MeOH was cooled to 0° and stirred with 60 mg $NaBH_4$ for 5 min, acidified with HCl 5% and extracted with $CHCl_3$ and EtOAc. The washed and dried extract was evaporated; purification of the residue by preparative TLC yielded 15 mg of a non-crystalline compound which was identical in all respects (IR, ^{1}H NMR, MS) with **6a**. Treatment of **6a** with methanesulphonyl chloride (15 mg) in pyridine (0.5 ml) for 12 hr at room temp. yielded **9**. This latter



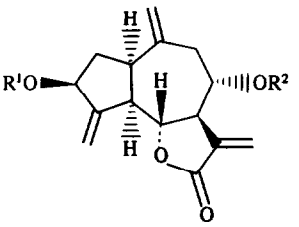
1 R = —C(=O)—C(=CH$_2$)—CH$_2$OH
2 R = H



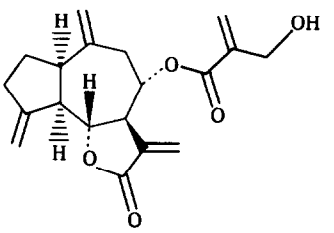
3 R = —C(=O)—C(=CH$_2$)—CH$_2$OAc, R^1 = R^2 = Ac
4 R = R^1 = R^2 = Ac
4a R = R^1 = R^2 = H



5 R^1 = R^3 = H, R^2 = OH
6 R^1 = OH, R^2 = R^3 = H
6a R^1 = OH, R^2 = H, R^3 = —C(=O)—C(=CH$_2$)—CH$_2$OH



7 R^1 = H, R^2 = —C(=O)—C(=CH$_2$)—CH$_2$OH
8 R^1 = R^2 = H
9 R^1 = Ms, R^2 = —C(=O)—C(=CH$_2$)—CH$_2$OMs



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compound could not be isolated (it may have suffered some polymerisation and degradation reactions), so aq. 5% NaOH was added to give a basic pH. The mixture was stirred for 24 hr at room temp., acidified with 5% HCl and extracted with EtOAc. Evaporation of the washed and dried extract followed by preparative TLC ($CHCl_3$–*t*-BuOH, 9:1) yielded 2 mg of a non-crystalline compound which was identical in all respects (IR, ^{1}H NMR, MS, TLC) with **5** from the plant material.

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