ELEMANOLIDES FROM *CENTAUREA MELITENSIS**

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Key Word Index—*Centaurea melitensis*; Compositae; sesquiterpene lactones; elemanolides; melitensin; melitensin β -hydroxyisobutyrate; 11(13)-dehydromelitensin β -hydroxyisobutyrate.

Abstract—Two new elemanolides isolated from *Centaurea melitensis* L. have been shown to correspond to the β -hydroxyisobutyrate of melitensin (1c) and its 11(13)-dehydro derivative (1a).

INTRODUCTION

Centaurea melitensis L. (Compositae, tribe Cynar-
eae) is found widely distributed in Mediterranean
countries [1] and the Canary Isles [2] where its
leaves are used for treating hypoglycemia. In a
previous paper [3] we reported the isolation of
the dihydroxyelemanolide melitensin (1e), whose
structure and stereochemistry were determined by
NMR and synthesis from cnicin. The present
work gives the structure of two new elemanolides
obtained from the same plant, collected in the
same place but at another time, which are related
to melitensin.

RESULTS AND DISCUSSION

Melitensin β -hydroxyisobutyrate (1c),
 $C_{19}H_{28}O_6$, mp 107–108°, $[\alpha]_D +50^\circ$, exhibits the
typical IR bands of hydroxyl, conjugated lactone
and double bonds (3560, 1770, 1635 cm^{-1}). Its
molecular formula together with the fact that it
is readily hydrolyzed to melitensin (1e;
 $C_{15}H_{22}O_4$) suggest the presence of a hydroxy-
lated acyl moiety with four carbon atoms. This
was identified as β -hydroxyisobutyric acid since
in the MS of (1c) the ions $[M^+-C_4H_8O_3]$,
 $[M^+-C_4H_6O_2]$ and $[C_3H_7O]^+$ are observed and
in the NMR spectrum (Table 1) the characteristic
signals of this acid, i.e. a doublet at τ 8.87 (3H,

J 7 Hz, Me-CH), a complex signal at 6.25 (2H,
-CH₂OH) and a multiplet at 7.55 (1H, -CH-) [4].
The relation between these signals was revealed
by double resonance: irradiation of the doublet
at τ 8.87 resulted in simplification of the multiplet
at 7.55, while irradiation of the latter causes the
former to collapse into a singlet, at the same
time considerably modifying the shape of the sig-
nal at τ 6.25. Compound (1c) forms a diacetate
(1d) which lacks free OH groups and in whose
NMR spectrum the signals at τ 5.50 (H_{15}) and
5.82 (CH_2OAc) appear paramagnetically dis-
placed by 0.5 ppm with respect to the correspond-
ing ones of (1c). This indicates that the two pri-
mary OH groups, one of which is located in the
acyl rest, are acylated.

- (1a) $R_1 = H$; $R_2 = OC-CH(Me)-CH_2OH$; $R_3 = CH_2$
 (1b) $R_1 = H$; $R_2 = H$; $R_3 = CH_2$
 (1c) $R_1 = H$; $R_2 = OC-CH(Me)-CH_2OH$; $R_3 = \text{---}Me$
 (1d) $R_1 = Ac$; $R_2 = OC-CH(Me)-CH_2OAc$; $R_3 = \text{---}Me$
 (1e) $R_1 = H$; $R_2 = H$; $R_3 = \text{---}Me$
 (1f) $R_1 = Ac$; $R_2 = Ac$; $R_3 = \text{---}Me$

- (2a) $R = OC-CH(Me)-CH_2OH$
 (2b) $R = H$

* Part 27 in the series "Constituents of the Compositae".
For Part 26 see González, A. G., Estévez Reyes, R. and Her-
rera Velázquez, J. (1974) *Anal. Quím.* (in press).

Table 1. NMR spectra of *Centaurea melitensis* constituents and derivatives*

Compound	H ₁ †	H ₂	H ₃ ‡	H ₅ §	H ₆ §	H ₈	H ₁₁	H ₁₃	H ₁₄	H ₁₅	Miscellaneous
(1a)	4.22 <i>q</i>	5.00	4.59 <i>t</i> 5.04 <i>s</i>	7.45 <i>d</i>	5.77 <i>t</i>	5.00		3.85 <i>d</i> (3) 4.26 <i>d</i> (3)	8.88 <i>s</i>	6.04¶	6.25 [CH ₂ OH], 7.55 [CH], 8.87 <i>d</i> (7) [Me]
(1c)	4.22 <i>q</i>	5.00	4.61 <i>t</i> 5.10 <i>s</i>		5.76 <i>t</i>	5.00	7.33 <i>dq</i>	8.79 <i>d</i> (7)	8.89 <i>s</i>	6.04¶	as for 1a
(1d)	4.22 <i>q</i>	5.00	4.59 <i>t</i> 4.98 <i>s</i>		5.76 <i>t</i>	5.00	7.33 <i>dq</i>	8.75 <i>d</i> (7)	8.86 <i>s</i>	5.50¶	5.82 [CH ₂ OAc], 7.55 [CH], 8.87 <i>d</i> (7) 7.94 <i>s</i> and 7.99 <i>s</i> [OAc]
(1e)	4.20 <i>q</i>	5.00	4.58 <i>t</i> 5.00 <i>s</i>	7.66 <i>d</i>	5.80 <i>t</i>	6.00 <i>td</i>	7.40 <i>dq</i>	8.62 <i>d</i> (7)	8.90 <i>s</i>	5.97¶	
(1f)	4.20 <i>q</i>	5.00	4.58 <i>t</i> 5.00 <i>s</i>	7.66 <i>d</i>	5.77 <i>t</i>	4.90 <i>td</i>	7.40 <i>dq</i>	8.72 <i>d</i> (7)	8.82 <i>s</i>	5.48¶	7.95a [2OAc]
(2a)		9.15	8.98 <i>d</i> , or 9.03 <i>d</i>		5.94 <i>t</i>	4.95 <i>td</i>		8.78 <i>d</i> (7)	9.10 <i>s</i>	9.03 <i>d</i> , or 8.98 <i>d</i>	as for 1a
(2b)		9.15	8.98 <i>d</i> , or 9.03 <i>d</i>		6.02 <i>t</i>	6.18 <i>td</i>		8.68 <i>d</i> (7)	9.10 <i>s</i>	9.03 <i>d</i> , or 8.98 <i>d</i>	

* In CDCl₃ at 60 MHz (τ -scale) with TMS as internal reference; *d*—doublet, *t*—triplet, *q*—quartet, *td*—triplet of doublet, *dq*—doublet of quartet. Figures in parentheses are coupling constants (in Hz).

† *J* = 17 and 11 Hz.

‡ Triplet: *J* = 1 Hz, doublet, *J* = 7 Hz.

§ *J* = 11.5 Hz.

¶ *J* = 13.5 Hz; deformed AB system.

|| *J* = 11, 11 and 4.5 Hz.

Strong hydrogenation of (1c) produced hydrogenolysis of the OH group at C₁₅, yielding the two hexahydro derivatives (2a) and (2b), which show a one-proton signal at τ 4.95 and 6.18, respectively, with the same multiplicity as that observed for the CHOH in melitensin (1e). Hence, we deduce that this secondary OH function bears the acyl group in (1c).

The spectral data and MS fragments of the second lactone, 11(13)-dehydromelitensin β -hydroxyisobutyrate (1a), C₁₉H₂₆O₆, mp 115–117°, [α]_D + 87°, are very similar to those of (1c), except for the presence of two doublets at τ 3.85 and 4.26 in the NMR spectrum, characteristic of an α -methylene- γ -lactone. The corresponding alcohol (1b) has been isolated in our laboratory from *Centaurea pullata* L. [5]. Reduction of (1a) with NaBH₄ gave melitensin β -hydroxyisobutyrate (1c).

Although the lactones (1a) and (1c) might be artefacts formed *via* a Cope rearrangement of the corresponding germacranolides, the extraction procedure used by us does not seem likely to cause such a transformation.

The presence of elemanolides in composites is rather rare [6]. This is the first time that they

have been found in *Centaurea*. The fact that guaianolides, germacranolides [7] and eudesmanolides [8] have also been isolated from this genus shows that it can produce a variety of lactone types.

EXPERIMENTAL

Mps, determined on a Kofler block, are uncorrected. Unless otherwise stated, optical activities and IR spectra were measured in CHCl₃. Column and dry column chromatography were performed on Si gel 0.2–0.5 and 0.063–0.2 mm respectively.

Extraction. The whole, air-dried plant (30 kg), collected in May, near Las Caletillas (Tenerife), was finely cut and extracted with EtOH in a Soxhlet. The conc. extract was dissolved in EtOH (1 litre) and treated with a soln of Pb(OAc)₂ (25 g) in H₂O (1 litre) at room temp. for 24 hr. After filtering and eliminating the EtOH the aqueous phase was extracted with EtOAc. Evaporation of the solvent yielded a residue (160 g) which was chromatographed. C₆H₆ eluted a mixture of compounds (50 g) which was separated by rechromatography on Si gel (1 kg)/20% AgNO₃, elution with C₆H₆–Me₂CO (7:3) yielding (1c) (4.1 g) and (1a) (6.3 g) impurified by oils; C₆H₆–Me₂CO (6:4) yields melitensin, mp 167–168° (AcOEt–light petrol), [α]_D + 81° [3]. Purification was achieved by dry column chromatography of the individual fractions with C₆H₆–EtOAc (4:1 and 7:3, respectively). 11(13)-Dehydromelitensin β -hydroxyisobutyrate (1a; 800 mg), mp 115–117° (C₆H₆–*n*-C₆H₁₄), [α]_D + 87° (ca 0.5). (Found: C, 65.16; H, 7.50. C₁₉H₂₆O₆ requires: C, 65.12; H, 7.48%). IR: 3560 (OH), 1770 (α,β -unsaturated γ -lactone), 1730 (ester), 1635 cm⁻¹

(double bonds). MS: m/e 350 (2%; M^+), 264 (1%; $M^+ - C_4H_6O_2$), 246 (9.5%; $M^+ - C_4H_8O_3$), 119 (89%), 59 (100%; $C_2H_7O^+$). NMR: Table 1. *Melitensin β -hydroxyisobutyrate* (1c; 1g), mp 107–108° (EtOAc-*n*- C_6H_{14}), $[\alpha]_D + 50^\circ$ (ca 0.05). (Found: C, 64.75; H, 8.01. $C_{19}H_{28}O_6$ requires: C, 64.75; H, 8.01%). IR: 3590 (OH), 1775 (γ -lactone), 1725 (ester), 1635 cm^{-1} (double bonds). MS: m/e 352 (5%; M^+), 266 [2%; $M^+ - C_4H_6O_2$, equal to the MW of melitensin (1e)], 248 (20%; $M^+ - C_4H_8O_3$), 121 (100%), 59 (63%; $C_3H_7O^+$). NMR: Table 1. Its *diacetate* (1d), prepared as usual, would not crystallize; $[\alpha]_D + 34^\circ$ (ca 0.5); IR 1770, 1720 (OAc, ester), 1635 (double bonds), 1220 cm^{-1} . NMR: Table 1.

NaBH₄ reduction of 1a. To a soln of (1a) (200 mg) in EtOH (10 ml) NaBH₄ (200 mg) in EtOH (10 ml) was added. After 1 hr the mixture was poured into H₂O and extracted with EtOAc. Dry column chromatography (C_6H_6 -EtOAc 4:1) gave (1c), identified with the natural product (mmp, TLC, IR, NMR).

Hydrogenation of (1c). A soln of (1c) (200 mg) in EtOH-EtOAc (1:1; 10 ml) was hydrogenated over PtO₂ (200 mg) at room temp. and atm. pres. for 78 hr. Dry column chromatography (C_6H_6 -EtOAc 9:1) of the residue yielded hexahydro-melitensin (2b) and its β -hydroxyisobutyrate (2a), besides other not identified products. (2b), mp 220–221° (C_6H_6 -light petrol.), $[\alpha]_D + 45^\circ$ (ca 0.6, EtOAc-light petrol), was identified by TLC and IR with the product obtained previously [3] for which mp 185–187° and $[\alpha]_D + 35.8^\circ$ had been given; NMR: Table 1. (2a), liquid, $[\alpha]_D + 39^\circ$ (ca 0.2); IR: 3595 (OH), 1765 (γ -lactone), 1720 cm^{-1} (ester); NMR: Table 1.

Melitensin diacetate (1f). A soln of (1c) (200 mg) in EtOH (1 ml) was refluxed with 0.1 N ethanolic NaOH (50 ml) for

1 hr. After evaporating the solvent *in vacuo* and adding dil HCl the soln was extracted with EtOAc, obtaining melitensin (1e) which was identified as its diacetate (1f) (IR, NMR spectra superimposable with those of an authentic sample) [3].

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