Phytochemistry, 1975, Vol. 14, pp. 2039–2041. Pergamon Press. Printed in England.

ELEMANOLIDES FROM *CENTAUREA MELITENSIS**

ANTONIO G. GONZÁLEZ, JOSÉ M. ARTEAGA and JOSÉ L. BRETÓN

Department of Organic and Biochemistry, University of La Laguna, Instituto de Investigaciones Quimicas, C.S.I.C., Tenerife, Spain

(*Received* 7 *October* 1974)

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

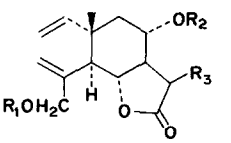
Abstract—Two new elemanolides isolated from *Centaurea melitensis* L. have been shown to correspond to the β-hydroxyisobutyrates of melitensin (**1c**) and its 11(13)-dehydro derivative (**1a**).

INTRODUCTION

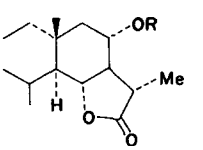
Centaurea melitensis L. (Compositae, tribe Cynareae) is found widely distributed in Mediterranean countries [1] and the Canary Isles [2] where its leaves are used for treating hypoglycemia. In a previous paper [3] we reported the isolation of the dihydroxyelemanolide melitensin (**1e**), whose structure 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°, 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 hydroxylated 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, $-CH_2OH$) 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 signal 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 displaced by 0·5 ppm with respect to the corresponding ones of (**1c**). This indicates that the two primary 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= ---Me
(**1d**) R_1=Ac; R_2=OC–CH(Me)–CH_2OAc; R_3= ---Me
(**1e**) R_1=H; R_2=H; R_3= ---Me
(**1f**) R_1=Ac; R_2=Ac; R_3= ---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 Herrera 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	5·00	4·59*t*	7·45	5·77	5·00		3·85*d* (3)	8·88	6·04¶	6·25 [CH$_2$OH], 7·55 [CH],
	q		5·04*s*	*d*	*t*			4·26*d* (3)	*s*		8·87*d* (7) [Me]
(1c)	4·22	5·00	4·61*t*		5·76	5·00	7·33	8·79*d* (7)	8·89	6·04¶	as for 1a
	q		5·10*s*		*t*		*dq*		*s*		
(1d)	4·22	5·00	4·59*t*		5·76	5·00	7·33	8·75*d* (7)	8·86	5·50¶	5·82 [CH$_2$OAc], 7·55 [CH],
	q		4·98*s*		*t*		*dq*		*s*		8·87*d* (7)
											7·94*s* and 7·99*s* [OAc]
(1e)	4·20	5·00	4·58*t*	7·66	5·80	6·00	7·40	8·62*d* (7)	8·90	5·97¶	
	q		5·00*s*	*d*	*t*	*td*‖	*dq*		*s*		
(1f)	4·20	5·00	4·58*t*	7·66	5·77	4·90	7·40	8·72*d* (7)	8·82	5·48¶	7·95*a* [2OAc]
	q		5·00*s*	*d*	*t*	*td*‖	*dq*		*s*		
(2a)		9·15	8·98*d*,		5·94	4·95		8·78*d* (7)	9·10	9·03*d*,	as for 1a
			or							or	
		t	9·03*d*		*t*	*td*‖			*s*	8·98*d*	
(2b)		9·15	8·98*d*,		6·02	6·18		8·68*d* (7)	9·10	9·03*d*,	
			or							or	
		t	9·03*d*		*t*	*td*‖			*s*	8·98*d*	

* In $CDCl_3$ 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 C_{15}, 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**), $C_{19}H_{26}O_6$, mp 115–117°, $[\alpha]_D$ + 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 $NaBH_4$ 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 $CHCl_3$. 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 H_2O (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. C_6H_6 eluted a mixture of compounds (50 g) which was separated by rechromatography on Si gel (1 kg)/20% $AgNO_3$, elution with C_6H_6–Me_2CO (7:3) yielding (**1c**) (4·1 g) and (**1a**) (6·3 g) impurified by oils; C_6H_6–Me_2CO (6:4) yields melitensin, mp 167–168° (AcOEt–light petrol), $[\alpha]_D$ + 81° [3]. Purification was achieved by dry column chromatography of the individual fractions with C_6H_6–EtOAc (4:1 and 7:3, respectively). 11(13)-*Dehydromelitensin β-hydroxyisobutyrate* (**1a**; 800 mg), mp 115–117° (C_6H_6–*n*-C_6H_{14}), $[\alpha]_D$ + 87° (*ca* 0·5). (Found: C, 65·16; H, 7·50. $C_{19}H_{26}O_6$ 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° (*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° (*ca* 0·5); IR 1770, 1720 (OAc, ester), 1635 (double bonds), 1220 cm^{-1}. NMR: Table 1.

$NaBH_4$ reduction of **1a**. To a soln of (**1a**) (200 mg) in EtOH (10 ml) $NaBH_4$ (200 mg) in EtOH (10 ml) was added. After 1 hr the mixture was poured into H_2O 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 PtO_2 (200 mg) at room temp. and atm. pres. for 78 hr. Dry column chromatography (C_6H_6–EtOAc 9:1) of the residue yielded hexahydromelitensin (**2b**) and its β-hydroxyisobutyrate (**2a**), besides other not identified products. (**2b**), mp 220–221° (C_6H_6-light petrol.), $[\alpha]_D$ + 45° (*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° had been given; NMR: Table 1. (**2a**), liquid, $[\alpha]_D$ + 39° (*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].

Acknowledgement—We thank Prof. J. Seibl, ETH Zürich, for the mass spectra.

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