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GERMACRANOLIDES FROM *ALLAGOPAPPUS VISCOSISSIMUS*

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Key Word Index— *Allagopappus viscosissimus*; Inulinae; germacranolides.

Abstract—Five germacranolides related to the ineupatorolides have been obtained from the aerial part of *Allagopappus viscosissimus* as well as known flavonoids and other compounds. A close relationship between this genus and other members of the same subtribe is indicated.

INTRODUCTION

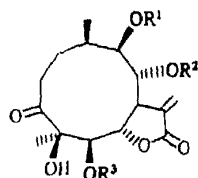
The small genus *Allagopappus*, of the sub-tribe Inulinae [1], is endemic to the Canary Islands. In the course of a study of sesquiterpene lactones from the Compositae, the chemical composition of *A. viscosissimus* Bolle was examined.

RESULTS AND DISCUSSION

The aerial part of *A. viscosissimus* yielded β -amyrin acetate, sitosterol- β -D-glucoside, the flavonoids quercetin 3-methyl ether, eriodictyol, kaempferol 3-methyl ether and naringenin, the sesquiterpene lactones ineupatorolide A [2], ineupatorolide C [2], incaspitolide D (1) [3] and analogues of 1, the lactones 2 (previously obtained from *Inula cappa* [4]) and 3 (new in the literature). The known compounds were identified by comparison of their spectral data with those of authentic samples.

Compound 3, empirical molecular formula $C_{24}H_{34}O_8$, greatly resembles 1 as can be seen from the 1H NMR spectral data (Table 1) and extensive spin decoupling experiments, only the ester groups are different. Both 1H NMR and mass spectra revealed isobutyryl and angeloyl ester side chains. The angelate moiety was sited at C-5 in view of the 0.11 ppm downfield shift of the H-5 signal in 3 as compared with 1.

Mono-acetate 3a was obtained from compound 3 as an



	R ¹	R ²	R ³
1	<i>i</i> Bu	H	<i>i</i> Bu
2	2-MeBu	H	Ang
3	<i>i</i> Bu	H	Ang
3a	<i>i</i> Bu	Ac	Ang

oil, empirical formula $C_{26}H_{36}O_{10}$. The formation of acetate 3a indicates that 3 has hydroxy groups at C-8 and C-4 and a tertiary methyl at C-4 (Table 1).

Table 1. 1H NMR spectral data of compounds 1, 3 and 3a (200 MHz, $CDCl_3$, TMS as int. standard)

H	1	3	3a
2	2.25 m 3.74 m	2.25 m 3.74 m	2.28 m 3.80 m
5	5.37 m	5.48 m	5.38 d (10.0)
6	4.70 m	4.74 m	4.71 m
7	3.00 m	3.03 m	3.09 m
8	4.28 m	4.20 m	5.71 m
9	5.03 d (10.5)	5.03 d (10.5)	5.23 dd (10.5, 1.5)
10	2.25 m	2.25 m	2.28 m
13	6.45 d (3.0)	6.45 d (3.0)	6.44 d (3.0)
13'	5.65 d (2.5)	5.66 d (2.5)	5.71 d (2.5)
14	0.99 d (7.0)	0.99 d (7.0)	0.98 d (7.0)
15	1.30 s	1.31 s	1.32 s
OCOR	2.66 qq (7.0) 1.26 d (7.0) 1.23 d (7.0) 1.21 d (<i>i</i> -Bu) (7.0)	2.66 sept (7.0) 1.22 d (7.0) 1.20 d (<i>i</i> -Bu) (7.0)	2.58 sept (7.0) 1.16 d (7.0) 1.13 d (<i>i</i> -Bu) (7.0)
	—	6.17 q (7.0)	6.15 q (7.0)
	—	2.01 dd (7.0, 1.5)	2.00 dd (7.0, 1.5)
	—	1.94 d (Ang) (1.5)	1.93 d (Ang) (1.5)
	—	—	1.92 (OAc)

Values in parentheses are coupling constants in Hz.

The presence of sesquiterpene lactones with a complex germacranolide skeleton in *Allagopappus viscosissimus* is of great interest, particularly as no such compounds were discovered in an earlier study of another endemic Canary species of *Allagopappus*, *A. dichotoma* [5]. These substances are similar to others obtained from *Inula* and *Dittrichia*, two genera which belong to the same group of the subtribe Inulinae [1].

EXPERIMENTAL

Mps: uncorr. ¹H NMR: CDCl₃, TMS as int. standard. MS: direct inlet. IR: CHCl₃. Plant material was collected in June 1986 at Mogán, Gran Canaria and a voucher specimen was filed with the Herbarium of the Viera y Clavijo Botanical Garden, Gran Canaria.

Extraction and isolation. The aerial part of *A. viscosissimus* (2 kg) was extracted with hot EtOH. The solvent was removed at red. pres. giving a gummy residue (246 g) which was chromatographed on silica gel with hexane and then with mixts of hexane–Me₂CO. The frs eluted with hexane–Me₂CO (4:1) were re-chromatographed in silica gel and prep. TLC (silica gel) with hexane–EtOAc (2:1) of the least polar fractions yielded ineupatorolide A (65 mg) and ineupatorolide C (25 mg). The more polar frs afforded a crystalline residue and prep. TLC (silica gel) in hexane–EtOAc (1:1) gave 1 (35 mg); 2 (100 mg) and 3 (80 mg). The fractions eluted with hexane–Me₂CO (2:1) were rechromatographed on silica gel to give naringenin (50 mg) and kaempferol 3-methyl ether (120 mg). Rechromatography (silica gel) of the 1:2 hexane–Me₂CO frs gave eriodictyol (100 mg) and quercetin 3-methyl ether (150 mg) as well as sitosterol-β-D-glucoside (28 mg).

Compound 3. C₂₄H₃₄O₉, needles, mp 231–233° (EtOAc–hexane); IR ν_{max}, cm⁻¹: 3440, 1740, 1710, 1700, 1609,

1205, 1010, 945, 915, 860; MS *m/z* (rel. int.): 466 [M]⁺ (1), 448 (1), 366 (1), 340 (2), 295 (2), 279 (4), 267 (6), 250 (5), 207 (7), 194 (13), 165 (9), 85 (23), 83 (100), 71 (44); ¹H NMR (see Table 1).

Acetylation of compound 3. Compound 3 was acetylated with Ac₂O (1 ml) and pyridine (1 ml) at room temp. overnight. After the reagents were evapd under vacuum, monoacetate 3a was obtained as a gum: C₂₆H₃₆O₁₀; IR ν_{max}, cm⁻¹: 3420, 1752, 1730, 1700, 1630, 1230, 1125, 1010, 970, 870; MS *m/z* (rel. int.): 508 [M]⁺ (3), 466 (1), 448 (1), 420 (2), 393 (3), 349 (3), 321 (3), 279 (6), 257 (6), 250 (8), 233 (9), 147 (7), 83 (100), 71 (34); ¹H NMR (see Table 1).

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THYMOL DERIVATIVES FROM *VIERAEA LAEVIGATA*

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Key Word Index—*Vieraea laevigata*; Compositae; Inuleae; thymol derivatives.

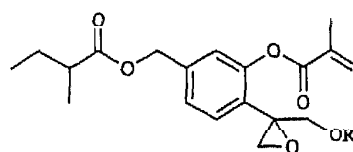
Abstract—The aerial parts of *Vieraea laevigata* afforded, in addition to the known compounds stigmasterol and 9-acetoxy-7-isobutyryloxy-8,10-dihydro-8,10-epoxythymol-angelate, six new thymol derivatives, 7,9-di-(2-methylbutyryloxy)-8,10-epoxythymol-angelate, 9-isobutyryloxy-7-(2-methylbutyryloxy)-8,10-epoxythymol-angelate, 9-angeloyloxy-7,10-di-(2-methylbutyryloxy)-8-hydroxy-thymol, 10-acetoxy-9-angeloyloxy-7-(2-methylbutyryloxy)-8-hydroxy-thymol, 9-angeloyloxy-7-(2-methylbutyryloxy)-8,10-dihydroxy-thymol and 9-acetoxy-7-(2-methylbutyryloxy)-8,10-dihydroxy-thymol.

INTRODUCTION

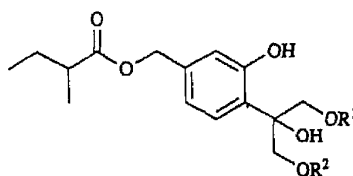
The genus *Vieraea* (tribe Inuleae) [1] is endemic to the Canary Islands and comprises a single species, *V. laevigata* (Brouss. ex Willd) Webb which upon investigation has been shown to produce thymol derivatives. We describe, in addition to the known compound 9-acetoxy-7-isobutyryloxy-8,10-dihydro-8,10-epoxythymol-angelate (1), six new thymol derivatives 7,9-di-(2-methylbutyryloxy)-8,10-epoxythymol-angelate (2), 9-isobutyryloxy-7-(2-methylbutyryloxy)-8,10-epoxythymol-angelate (3), 9-angeloyloxy-7,10-di-(2-methylbutyryloxy)-8-hydroxy-thymol (4), 10-acetoxy-9-angeloyloxy-7-(2-methylbutyryloxy)-8-hydroxy-thymol (5), 9-angeloyloxy-7-(2-methylbutyryloxy)-8,10-dihydroxy-thymol (6) and 9-acetoxy-7-(2-methylbutyryloxy)-8,10-dihydroxy-thymol (7).

RESULTS AND DISCUSSION

The aerial parts of *Vieraea laevigata* [2] afforded a complex mixture of seven thymol derivatives which were separated by repeated TLC. Their structures were deduced by spectroscopic methods. 9-Acetoxy-7-isobutyryloxy-8,10-dihydro-8,10-epoxythymol-angelate (1) was previously isolated from *Doronicum hungaricum* [3]. The structures of 2–7 clearly follow the mass spectra and especially the $^1\text{H NMR}$ data (see Table 1). The relative positions of the different ester groups can only be assigned by comparison of the observed chemical shifts with those of corresponding esters [4, 5]. The presence of the phenolic group in 4–7 was confirmed upon obtaining their respective acetylated derivatives. (δ 2.37, s, 3H). Acetylation of 5 yielded the diacetate of compound 6.



R
1 Ac
2 Mebu
3 iBu



R ¹	R ²
4 Ang	Mebu
5 Ang	Ac
6 Ang	H
7 Ac	H

EXPERIMENTAL

$^1\text{H NMR}$ spectra were recorded at 200 MHz; MS: 70 eV. Analytical TLC was performed on silica gel and CC was on silica gel. The plant material was extracted with EtOH. *Vieraea laevigata*, collected in Teno (Tenerife) in July 1990, was identified by Prof. Dr Pérez de Paz from the Department of Botany, University of La Laguna, where a specimen is deposited (Herbarium TFC).

Table 1. ¹H NMR data of compounds 1-7 (200 MHz CDCl₃, TMS as int. standard)

	1	2	3	4	5	6	7
H-2	7.08 <i>d</i> (1, 5)	7.12 <i>d</i> (1, 5)	7.13 <i>d</i> (1, 5)	6.85 <i>s</i> (<i>br</i>)	6.89 <i>d</i> (1, 5)	6.87 <i>d</i> (1, 5)	6.88 <i>d</i> (1, 5)
H-5	7.44 <i>d</i> (8)	7.49 <i>d</i> (8)	7.49 <i>d</i> (8)	7.03 <i>d</i> (8)	7.03 <i>d</i> (8)	7.06 <i>d</i> (8)	7.03 <i>d</i> (8)
H-6	7.19 <i>dd</i> (8; 1, 5)	7.22 <i>dd</i> (8; 1, 5)	7.22 <i>dd</i> (8; 1, 5)	6.80 <i>dd</i> (8; 1, 5)	6.81 <i>dd</i> (8; 1, 5)	6.81 <i>dd</i> (8; 1, 5)	6.83 <i>dd</i> (8; 1, 5)
H-7	5.07 <i>s</i>	5.11 <i>s</i>	5.11 <i>s</i>	5.04 <i>s</i>	5.04 <i>s</i>	5.04 <i>s</i>	5.05 <i>s</i>
H-9	4.49 <i>d</i> (12)	4.64 <i>d</i> (12)	4.60 <i>d</i> (12)	4.53 <i>s</i>	4.54 <i>s</i>	4.63 <i>d</i> (12)	4.48 <i>d</i> (12)
H-9'	4.13 <i>d</i> (12)	4.13 <i>d</i> (12)	4.14 <i>d</i> (12)	4.53 <i>s</i>	4.54 <i>s</i>	4.53 <i>d</i> (12)	4.57 <i>d</i> (12)
H-10	2.99 <i>d</i> (5)	3.03 <i>d</i> (5)	3.04 <i>d</i> (5)	4.53 <i>d</i> (12)	4.47 <i>s</i>	3.80 <i>d</i> (12)	3.82 <i>d</i> (12)
H-10'	2.77 <i>d</i> (5)	2.81 <i>d</i> (5)	2.82 <i>d</i> (5)	4.42 <i>d</i> (12)	4.47 <i>s</i>	3.95 <i>d</i> (12)	3.92 <i>d</i> (12)
OR-3	6.26 <i>m</i>	6.31 <i>m</i>	6.32 <i>m</i>	9.1 (<i>br</i>)	8.95 (<i>br</i>)	9.10 (<i>br</i>)	9.0 (<i>br</i>)
	2.02 <i>s</i>	2.06 <i>s</i>	2.07 <i>s</i>				
OR-7	2.37 <i>m</i>	2.40 <i>m</i>	2.40 <i>m</i>	2.38 <i>m</i>	2.38 <i>m</i>	2.43 <i>m</i>	2.45 <i>m</i>
	1.11 <i>d</i> (7)	1.16 <i>d</i> (7)	1.16 <i>d</i> (7)	1.16 <i>d</i> (7)	1.17 <i>d</i> (7)	1.13 <i>d</i> (7)	1.18 <i>d</i> (7)
	0.84 <i>t</i> (7, 5)	0.89 <i>t</i> (7, 5)	0.89 <i>t</i> (7, 5)	0.90 <i>t</i> (7, 5)	0.90 <i>t</i> (7, 5)	0.90 <i>t</i> (7, 5)	0.91 <i>t</i> (7, 5)
OR-9	1.94 <i>s</i>	2.40 <i>m</i>	2.40 <i>m</i>	6.13 <i>qq</i> (7; 1, 5)	6.14 <i>qq</i> (7; 1, 5)	6.16 <i>qq</i> (7; 1, 5)	2.10 <i>s</i>
		1.06 <i>d</i> (7)	1.09 <i>d</i> (7)	1.93 <i>dd</i> (7; 1, 5)	1.93 <i>dd</i> (7; 1, 5)	1.94 <i>dd</i> (7; 1, 5)	
		0.77 <i>t</i> (7, 5)	1.07 <i>d</i> (7)	1.85 <i>d</i> (1, 5)	1.84 <i>s</i> (<i>br</i>)	1.85 <i>d</i> (1, 5)	
OR-10				2.38 <i>m</i>	2.07 <i>s</i>		
				1.09 <i>d</i> (7)			
				0.82 <i>t</i> (7, 5)			

Values in parentheses are coupling constants in Hz.

33.850). The aerial parts (1.4 kg) afforded 147 mg 1, 18 mg 2, 20 mg 3, 47 mg 4, 53 mg 5, 20 mg 6 and 10 mg 7.

7,9-Di-(2-methylbutyryloxy)-8,10-epoxythymol-angelate (2). Oil. IR ν_{film} cm^{-1} : 1734, 1644, 1622, 1459, 1142; MS m/z (rel. int.): [M]⁺ not present, 346 [M-C₄H₇CO₂H]⁺ (2), 262 (5), 245 (22), 85 (26), 83 (100), 57 (39); ¹H NMR: see Table 1.

9-Isobutyryloxy-7-(2-methylbutyryloxy)-8,10-epoxythymol-angelate (3). Oil. IR ν_{film} cm^{-1} : 1734, 1648, 1458, 1223, 1139; MS m/z (rel. int.): [M]⁺ not present, 332 [M-C₄H₇CO₂H]⁺ (2, 4), 319 (2, 2), 262 (7, 1), 245 (26, 2), 85 (15, 7), 83 (100), 71 (14, 0), 57 (23, 3); ¹H NMR: see Table 1.

9-Angeloyloxy-7,10-di-(2-methylbutyryloxy)-8-hydroxythymol (4). Oil. IR ν_{film} cm^{-1} : 3402, 1736, 1619, 1460, 1233; MS m/z (rel. int.): 464 [M]⁺ (0, 7), 446 [M-H₂O]⁺ (0, 6), 351 (12, 8), 262 (32, 8), 249 (58, 2), 178 (45, 1), 85 (47, 7), 83 (100), 57 (62); ¹H NMR: see Table 1.

10-Acetoxy-9-angeloyloxy-7-(2-methylbutyryloxy)-8-hydroxythymol (5). Oil. IR ν_{film} cm^{-1} : 3331, 1717, 1616, 1461, 1381, 1174; MS m/z (rel. int.): 422 [M]⁺ (5), 404 (2), 370 (2), 349 (9), 309 (20), 249 (22), 207 (47), 85 (18), 83 (100), 57 (42); ¹H NMR: see Table 1.

9-Angeloyloxy-7-(2-methylbutyryloxy)-8,10-dihydroxythymol (6). Oil. IR ν_{film} cm^{-1} : 3381, 1717, 1576, 1456, 1232, 1150; MS m/z (rel. int.): 380 [M]⁺ (3), 349 [M-CH₂OH]⁺ (13), 267 (18), 147 (20), 85 (10), 83 (100), 57 (42); ¹H NMR: see Table 1.

9-Acetoxy-7-(2-methylbutyryloxy)-8,10-dihydroxythymol (7). Oil. IR ν_{film} cm^{-1} : 3300, 1725, 1650, 1570, 1220; MS m/z (rel. int.): 340 [M]⁺ (2, 4), 309 [M-CH₂OH]⁺ (14, 1), 262 (39, 9), 249 (27, 6), 207 (53, 1), 178 (85, 8), 85 (47, 1), 57 (100); ¹H NMR: see Table 1.

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