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DITERPENOIDS FROM *HALIMIUM VISCOSUM*

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Key Word Index—*Halimium viscosum*; Cistaceae; rearranged *ent*-labdanes; diterpenoid acids; nor-diterpenoid acids; *ent*-halimane.

Abstract—In addition to three known acids, five new diterpenoid acids with a rearranged *ent*-labdane skeleton (*ent*-halimane) have been isolated from the acid fraction of *Halimium viscosum* as their methyl ester derivatives.

INTRODUCTION

Halimium viscosum is found in the Iberian peninsula where so far we have found three population types, including the one described in this work, which have different chemical compositions, probably because they are 'chemical families' or subspecies. A herbarium sample of the three plants is available from the Department of Botany, Faculty of Biology, University of Salamanca, Spain.

We have previously described the composition of two of these populations. The first [1] has rearranged *ent*-labdanes with a saturated side chain and the second [2] labdanes containing a C-17 carboxyl group. For this rearranged *ent*-labdane skeleton, which was described for the first time in compounds isolated from *Hymeneae courbaryl* [3], we propose the name of *ent*-halimane, in order to simplify its nomenclature.

RESULTS AND DISCUSSION

Specimens of *H. viscosum* were collected at Villarino de los Aires (Salamanca, Spain). The acid fraction from the methanol-soluble part of the hexane extract of the aerial parts of the plant was separated into two fractions from which, after methylation, eight methyl esters (**1**–**8**) were obtained by column chromatography.

Compounds **3** and **8** are the methyl esters of acetoxy *ent*-halimic and *ent*-halimic acids, respectively. These are *H. umbellatum* compounds whose structures were established some years ago [4–6].

The dimethyl esters **1** and **2** show in their ^{1}H NMR spectra signals corresponding to the same bicyclic system as **3** (CH=C, Me–C–COOMe, Me–C, Me–CH) and a Me–C=CH–COOMe group in the side chain at C-9. In **1** the double bond configuration is *Z* [Me-16: δ1.91 (^{1}H NMR) and 25.31 (^{13}C NMR)] while in **2** the group

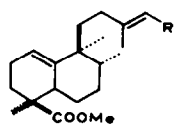
Table 1. ^{1}H NMR data of compounds **1**–**8** (200 MHz, $CDCl_3$, TMS as internal standard)

H	1	2	3	4	5	6	7	8
1	5.39 *br, t* (3.91)	5.25 *br, t* (3.91)	5.21 *br, s*	5.35 *ddd* (3.91; 3.91; 1.95)	5.39 *ddd* (3.91; 3.91; 1.46)	5.34 *br, t* (3.91)	5.23 *ddd* (3.90; 3.90; 1.60)	5.35 *br, t* (3.91)
				A 4.04 *ddd*				5.44 *br, t*
12				(10.86; 9.77; 6.1)				(7.32)
				B 3.90 *ddd*				
				(10.86; 9.77; 5.67)				
14	5.62 *br, s*	5.63 *s*	5.24 *br, t*		5.84 *dq* (8.30; 1.46)	5.93 *dq* (8.30; 1.46)		
15			4.46 *d* (7.32)		8.60 *d* (8.30)	8.61 *d* (8.61; 8.30)		4.15 *d* (7.32)
16	1.91 *br, s*	2.08 *s*	1.60 *s*		2.00 *d* (1.46)	2.18 *d* (1.46)	2.06 *s*	1.70 *s*
17	0.82 *d* (6.67)	0.72 *d* (7.70)	0.70 *d* (7.58)	0.79 *d* (6.93)	0.81 *d* (7.02)	0.81 *d* (6.97)	0.73 *d* (7.91)	0.82 *d* (6.72)
19	1.12 *s*	1.02 *s*	1.00 *s*	1.10 *s*	1.13 *s*	1.11 *s*	1.02 *s*	1.12 *s*
20	1.00 *s*	0.82 *s*	0.80 *s*	0.95 *s*	0.97 *s*	0.91 *s*	0.78 *s*	0.92 *s*
$COOCH_3$	3.66 *s*	3.56 *s*	3.53 *s*		3.66 *s*	3.63 *s*	3.55 *s*	3.66 *s*
$COOCH_3$	3.64 *s*	3.54 *s*		3.63 *s*				
OAc			1.93 *s*	2.01 *s*				

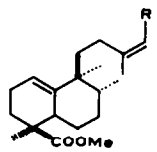
Table 2. ^{13}C NMR data of compounds 1–7 (50.3 MHz, $CDCl_3$, TMS as internal standard)

C	1	2	3	4	5	6	7
1	119.88	120.15	119.71	120.24	120.58	120.44	120.19
2	22.75	22.96	22.83	22.89	23.03	23.08	23.12
3	29.72	30.05	30.50	30.44	30.45	30.12	29.83
4	45.07	44.82	44.86	45.00	45.04	45.01	44.95
5	37.91	38.28	38.37	38.42	38.57	38.42	38.26
6	22.80	23.16	22.99	23.04	23.18	23.25	23.34
7	28.33	28.52	28.41	28.52	28.56	28.61	28.62
8	38.57	38.79	38.47	38.75	38.75	38.90	39.02
9	43.07	42.95	42.81	42.06	43.46	43.13	42.73
10	141.28	141.04	141.31	140.78	140.92	141.08	141.31
11	37.67	37.39	37.55	37.39	38.90	37.15	38.95
12	31.24	35.56	33.94	62.08	27.78	35.42	32.63
13	161.96	161.74	143.20	—	166.03	165.66	209.65
14	115.37	114.74	117.90	—	128.09	127.13	—
15	166.73	167.13	61.30	—	191.23	191.19	—
16	25.31	19.00	16.51	—	25.19	17.81	29.87
17	15.69	15.51	15.47	15.22	15.61	15.57	15.60
18	178.65	178.02	178.06	178.32	178.31	178.24	178.18
19	19.31	20.71	20.06	20.18	20.46	20.80	21.00
20	22.54	22.19	22.24	22.70	22.28	22.22	22.10
$COO\underline{CH_3}$	51.69	51.54	51.40	51.70	51.77	51.65	51.54
$COO\underline{CH_3}$	50.70	50.46					
$OCO\text{-}\underline{CH_3}$			20.76	21.03			
$O\underline{CO}\text{-}CH_3$			170.59	171.04			

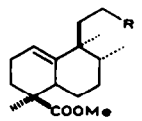
Assignment based on DEPT experiments and particularly in the case of 3 on C/H (HCCORR) two-dimensional correlations.



R
2 COOMe
3 CH_2OAc
6 CHO
8 CH_2OH



R
1 COOMe
5 CHO



R
4 OAc
7 COMe

has an *E* configuration [Me-16: δ2.08 (^{1}H NMR) and 19.0 (^{13}C NMR)] [7, 8]. All the data of the ^{1}H NMR and ^{13}C NMR spectra are shown in Tables 1 and 2, respectively.

Compound **4** is an acetoxy ester (1750 and 1240 cm^{-1}) with the same bicyclic system as compounds **1**, **2**, **3** and **8** (Table 1) and a CH_2–CH_2OAc group (^{1}H NMR: H_a-12, δ4.04 *ddd*; H_b-12, δ3.90 *ddd*, Table 1). Its ^{13}C NMR spectrum, however, shows signals for only 19 carbons: five Me, six CH_2, three CH (1 sp^2) and five completely substituted carbons (three sp^2 and two sp^3). It is therefore a tetranor-derived product: methyl 12-acetoxy-13,14,15,16-tetranor-1(10)-*ent*-halimen-18-oate.

Besides a bicyclic system, compounds **5** and **6** have a $(CH_3)C{=}CH{-}CHO$ group (2880, 1680 and 1630 cm^{-1}) and the only difference between them is in the configuration of the 13-14 double bond. The less polar **5** is the *Z* isomer [Me-16: δ2.0 (^{1}H NMR) and 25.15 (^{13}C NMR)] while **6** is the *E*-isomer [δ2.18 (^{1}H NMR) and 15.81 (^{13}C NMR)] [7, 8]. **5** and **6** are obtained by oxidation of **8** [9].

Compound **7** is a methyl ketone (Table 1) with the same bicyclic system as the previous compounds. Its ^{13}C NMR spectrum shows signals for 19 carbons, in agreement with the structure proposed which has been described as a component of *H. umbellatum* [5].

EXPERIMENTAL

Mps (Kofler hot stage apparatus): uncorr; ^{1}H NMR: 200 MHz, $CDCl_3$ TMS as int. standard; ^{13}C NMR: 50.3 MHz.

Extraction and isolation. The aerial parts of *H. viscosum* (3.1 kg) collected in Villarino de los Aires (Salamanca, Spain) were dried and extracted with *n*-hexane in a Soxhlet apparatus for 24 hr. The extract (371 g) was dewaxed with MeOH (18.3 g) and then extracted with 10% Na_2CO_3 (47.1 g) and 4% NaOH (27.9 g). The neutral fraction weighed 23.8 g.

A portion of the Na_2CO_3-soluble acid fraction (33 g) was separated by CC into two major fractions, I (37.8%) and II

(35.1%), which were then methylated with CH_2N_2. CC of the methyl esters from fraction I gave **3** (3.8 g), **4** (187 mg), **5** (71 mg), **6** (35 mg), **7** (620 mg) and **8** (320 mg), while those from fraction II gave **1** (217 mg), **2** (45 mg), **3** (260 mg), **7** (1.1 g) and **8** (586 mg).

Dimethyl 1(10),13Z-ent-*halimadien*-15,18-*dioate* (**1**). Colourless oil. $[\alpha]_D^{22} = +68.43°$ (*c*, 0.8, $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 1730, 1650, 1380, 920. *Dimethyl* 1(10),13E-ent-*halimadien*-15,18-*dioate* (**2**). Colourless oil; $[\alpha]_D^{22} = +73.35°$ (*c*, 1.2, $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 1730, 1650, 1380. *Methyl* 15-*acetoxyl*(10),13E-ent-*halimadien*-18-*oate* (**3**). Colourless oil; $[\alpha]_D^{22} = +51.1$ (*c*, 1.2, $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 3040, 1740, 1730, 1660, 1240, 830. *Methyl* 12-*acetoxy*-13,14,15,16-*tetranor*-1(10)-ent-*halimen*-18-*oate* (**4**). Colourless oil; $[\alpha]_D^{22} = +34.5°$ (*c*, 1.2; $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 1750, 1380, 1370, 1240. *Methyl* 15-*al*-1(10),13Z-ent-*halimadien*-18-*oate* (**5**). Colourless oil; $[\alpha]_D^{22} = +61.54°$ (*c*, 1.31, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε): 238 (3.2); IR ν_{max}^{film} cm^{-1}: 3060, 2880, 1735, 1680, 1630, 1380, 750. *Methyl* 15-*al*-1(10),13E-ent-*halimadien*-18-*oate* (**6**). Colourless oil; $[\alpha]_D^{22} = +64.12°$ (*c*, 1.05, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 240 (3.5); IR ν_{max}^{film} cm^{-1}: 3060, 2880, 1735, 1680, 1630, 1380, 980. *Methyl* 13-*oxo*-14,15-*dinor*-1(10)-ent-*halimen*-18-*oate* (**7**). Colourless oil; $[\alpha]_D^{22} = +72.51°$ (*c*, 2.1; $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 3050, 1740, 1730, 1175, 1190. *Methyl* 15-*hydroxy*-1(10),13E-ent-*halimadien*-18-*oate* (**8**). Colourless oil; $[\alpha]_D^{22} = +57.8°$ (*c*, 1.25, $CHCl_3$); IR ν_{max}^{film} cm^{-1}: 3200, 1730, 1380, 1000, 760. *Oxidation of* **8** *with Sarret Collins reagent*. To a soln of 3 ml C_5H_5N and 4 ml CH_2Cl_2 was added 45 mg CrO_3. After shaking for 0.5 hr, 280 mg of **8** dissolved in 2 ml CH_2Cl_2 were added. The reaction mixture was kept at room temp. for 2 hr. It was then filtered and evaporated. The residue was extracted with Et_2O which was then washed with NaOH, HCl and H_2O. Evaporation of the solvent gave 220 mg reaction product which on silica gel CC (*n*-hexane–Et_2O, 9:1) gave **5** and **6**.

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