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EUDESMANOLIDES FROM *ARTEMISIA PONTICA*

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Key Word Index—*Artemisia pontica*; Asteraceae; sesquiterpene lactones; eudesmanolides.

Abstract—The aerial parts of *Artemisia pontica* afforded seven new 5-hydroxyeudesmanolides in addition to the known sesquiterpene lactones artemin, 5-epi-artemin and 8α-hydroxytaurin. The structures of the new compounds were elucidated on the basis of the spectral findings.

INTRODUCTION

Recently, we reported the isolation of six new sesquiterpene lactones with the very rare tricyclic rotundane skeleton from *Artemisia pontica* L. [1]. Following our studies in search of sesquiterpene lactones, we have analysed another collection of the same plant species, which afforded eudesmanolides only, most of them bearing a hydroxyl group at C-5. Seven of the 10 isolated lactones, **2–6**, **8** and **9**, have not been described previously.

RESULTS AND DISCUSSION

The aerial parts of *A. pontica*, worked-up as described in Experimental, yielded 10 compounds, all of them γ-lactones (1770–1760 cm^{-1}) with a 6,12-*trans*-fused lactone ring (H-6, δ 4.25–4.56, *d*, $J = 10.5$–11.5 Hz) bearing an α-oriented methyl group at C-11 (H-11, δ 2.32–2.70, *dq*, $J = 6.5$ and 12 Hz). Artemin (**1**) [2], 5-epi-artemin (**7**) [3, 4] and 8α-hydroxytaurin (**10**) [5] are known, whereas compounds **2–6**, **8** and **9** are new natural products.

The lactone **2** furnished a molecular ion at *m/z* 282 in its mass spectrum, assignable to a molecular formula $C_{15}H_{22}O_5$. In addition, the peaks at *m/z* 264 and 246 suggested the presence of two hydroxyl groups. The ^1H NMR spectral data (Table 1) for **2** were very similar to those for **1**, but an additional low-field three-fold doublet appeared at δ 4.01. The latter collapsed to a doublet of doublets after irradiation of the H-7 signal (frequency at δ 2.44), thus indicating the location of the secondary hydroxyl group at C-8. The all-*trans*-disposition of H-6, H-7 and H-8 followed from the observed large vicinal couplings ($J_{6,7} = J_{7,8} = 10.5$ Hz). The location of the second hydroxyl group at C-5 followed from the lack of a coupling between H-5 and H-6. All these data led to the structure of 8α-hydroxyartemin for lactone **2**.

The IR spectra of compounds **3–6** showed, in addition to γ-lactone and hydroxyl groups, the presence of ester moieties (1730–1720 cm^{-1}). The ^1H NMR spectra (Table 1) of **3–6** were almost identical to those of **2**, the only difference being the replacement of the carbinolic signal by signals due to protons geminal to an ester group (δ 5.17–5.27). Accordingly, the lactones **3–6** were suggested to be C-8 acyl derivatives of **2**. The natures of the ester groups were deduced to be isovalerate, isobutyrate, senecionate and (1-hydroxyethyl)-acrylate, respectively, from typical ^1H NMR signals, as well as from the mass fragmentation (see Experimental). The chemical shifts and the coupling patterns of all the proton signals in **3–6** coincided well with those of the parent compound (**2**), thus showing that they shared a common stereochemistry.

The EI mass spectrum of lactone **8** was identical to that of **2**. The ^1H NMR spectra of **8** and **2** were again very similar, but differed in the chemical shifts and coupling constants of some signals, particularly of H-1, H-3 and H-14 (Table 1). In the case of **8** the signals of H-1 and H-3 were shifted upfield, the former appearing as a broad singlet, while those of H-14 and H-3′ were shifted downfield. An inspection of the Dreiding model showed that the observed differences only could be explained by different ring annelation of the eudesmane skeleton, i.e. a 5β-oriented hydroxyl group was present. Hence, the lactones **8** and **2** were epimeric at C-5.

The ^1H NMR spectrum of lactone **9** (Table 1), molecular formula $C_{20}H_{30}O_6$, again showed that a 5-hydroxyeudesmanolide with an isovaleryloxy and 8α-hydroxyl group was present. The signal at δ 5.05, therefore, was due to H-1 and the observed couplings of H-1 and H-2 required a 1α-isovaleryloxy group. Inspection of a model indicated that most likely a 5β-hydroxyl group was present. This was further supported

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Table 1. ^{1}H NMR spectral data for lactones **1–9** (250 MHz, TMS, $CDCl_3$)

H	1	2	3	4	5	6*	7	8	9
1	4.15 *dd*	4.18 *dd*	4.17 *dd*	4.18 *dd*		4.11 *dd*	3.45 *br s*	3.46 *br s*	5.05 *dd*
2	1.75 *m*†	1.78 *m*	1.80 *m*	1.80 *m*		1.70 *m*	1.90 *m*†	1.90 *m*	1.60 *m*
2′	1.60 *m*†	1.55 *m*	1.60 *m*	1.65 *m*		1.55 *m*	1.80 *m*†	1.80 *m*	2.05 *m*
3	2.65 *m*	2.68 *m*	2.68 *m*	2.68 *m*		2.70 *m*	2.07 *ddd*	2.10 *ddd*	2.18 *m*
3′	2.17 *ddd*	2.12 *ddd*	2.16 *ddd*	2.18 *ddd*		2.10 *ddd*	2.90 *m*	2.89 *m*	2.70 *m*
6	4.25 *d*	4.25 *d*	4.33 *d*	4.34 *d*	4.36 *d*	4.56 *d*	4.35 *d*	4.37 *d*	4.39 *d*
7	2.35 *m*	2.44 *dt*	2.60 *dt*	2.60 *dt*		2.70 *m*	2.32 *dt*	2.41 *dt*	2.60 *dt*
8	1.85 *m*†	4.01 *ddd*	5.17 *ddd*	5.16 *ddd*	5.19 *ddd*	5.29 *ddd*	1.85 *m*†	4.11 *ddd*	4.05 *m*
8′	1.55 *m*†	—	—	—		—	1.60 *m*†	—	—
9	1.85 *m*†	2.05 *dd*	2.10 *dd*	2.10 *dd*		2.10 *dd*	1.60 *m*†	1.60 *dd*	1.89 *dd*
9′	1.60 *m*†	1.95 *dd*	1.76 *dd*	1.78 *dd*		1.75 *dd*	1.30 *m*†	1.58 *dd*	1.65 *dd*
11	2.40 *dq*	2.60 *dq*	2.60 *dq*	2.60 *dq*		2.70 *m*	2.32 *dq*	2.58 *dq*	2.60 *dq*
13	1.24 *d*	1.41 *d*	1.25 *d*	1.25 *d*		1.32 *d*	1.23 *d*	1.38 *d*	1.39 *d*
14	0.90 *s*	0.90 *s*	0.95 *s*	0.95 *s*	0.96 *s*	0.95 *s*	1.34 *s*	1.35 *s*	1.19 *s*
15	5.03 *d*	5.05 *d*	5.07 *d*	5.07 *d*		5.03 *d*	5.14 *d*	5.19 *d*	5.15 *d*
15′	4.98 *br s*	5.00 *br s*	5.02 *br s*	5.02 *br s*		4.99 *s*	5.08 *br s*	5.12 *br s*	5.11 *br s*
R			2.20 *m*	2.45 *m*	5.66 *br s*	6.22 *br s*			2.20 *m*
			2.05 *m*	1.18 *d*	1.92 *s*	5.95 *br s*			2.00 *m*
			0.97 *d*		2.19 *s*	4.63 *q*			0.97 *d*
						1.20 *d*			

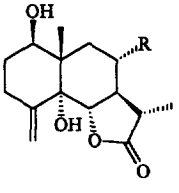
*Recorded in CD_3OD.

†Overlapped signals.

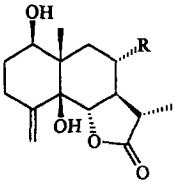
J[Hz]: **1–6**: 1,2 = 11.5; 1,2′ = 2,3′ = 5; 3,3′ = 14; 3,15 = 3′,2′ = 2; 6,7 = 10.5; 7,11 = 12; 11,13 = 6.5; **2–6**: 7,8 = 8,9 = 10.5; 8,9′ = 4.7; 9,9′ = 12; **7–8**: 3,3′ = 14; 2,3′ = 3,15 = 2; 2′,3′ = 4.5; 6,7 = 11.5; 7,11 = 12; 11,13 = 6.4; **8**: 7,8 = 8,9 = 11; 8,9′ = 5.4; 9,9′ = 11.9; **9**: 1,2 = 5, 1,2′ = 11.5; 6,7 = 7,8 = 8,9 = 11; 8,9′ = 5; 9,9′ = 7,11 = 12; 3,15 = 2; 11,13 = 6.5; OiVal: 3″,4″ = 3″,5″ = 6.5; OiBu: 2″,3″ = 2″,4″ = 6.5; OA: 4″,5″ = 6.5.

by the chemical shift of the angular methyl group (δ 1.19). All the above data agreed well with the structure of 1α-isovaleryloxy-8α-hydroxy-5-epi-artemin for lactone **9**. Recently, the corresponding 1α-acetoxy analogue (**11**) was isolated from *A. hugueti* [4] and its ^{1}H NMR data coincided very well with those presented in Table 1 for **9**.

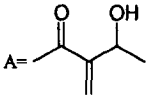
It is worth noting that we isolated from this location of *A. pontica* only closely related eudesmanolides and failed to detect, even in traces, any rotundopontilides reported previously for another *A. pontica* location [1]. The fact that the two Bulgarian locations of *A. pontica* are producing sesquiterpene lactones of different skeletal type allowed the suggestion that we were dealing with two different chemotypes.

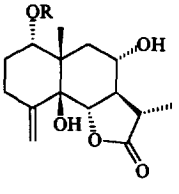


1 R=H
2 R=OH
3 R=OiVal
4 R=OiBu
5 R=OSen
6 R=OA

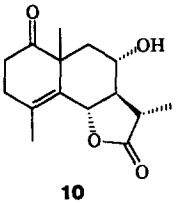


7 R=H
8 R=OH





9 R=iVal
11 R=Ac



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EXPERIMENTAL

The plant material was collected in July 1994 in the vicinity of Yablanitza (Bulgaria). Voucher specimen SOM-Co-299 is deposited in the Herbarium of the Institute of Botany, Bulgarian Academy of Sciences.

The air-dried and ground aerial parts (400 g) of *A. pontica* were extracted with $CHCl_3$ at room temp. and the total extract (47 g) was worked-up as described in ref. [1] to give the crude lactone fr. (6.6 g). The latter was subjected to CC on silica gel using $CHCl_3$–Me_2CO with increasing polarity and 6 frs were collected. Fr. 1 (3 g) was further sepd by CC on silica gel ($CHCl_3$–Et_2O, 1:1) and prep. TLC (hexane–Et_2O, 1:1 and 1:2) to give lactones **3** (50 mg), a mixt. of **4** and **5** (50 mg), **9** (25 mg), **1** (80 mg), **7** (45 mg) and **10** (60 mg). Fr. 2 (1.8 g) yielded **6** (40 mg) after purification by CC on silica gel ($CHCl_3$–Me_2CO, 2:1) and prep. TLC ($CHCl_3$–Et_2O, 1:2). Prep. TLC ($CHCl_3$–Me_2CO, 2:1) of frs. 3 (350 mg) and 4 (450 mg)

afforded **8** (80 mg) and **2** (180 mg), respectively. Frs 5 and 6 did not contain sesquiterpene lactones (deduced from IR and ^{1}H NMR). The known lactones were identified by comparison of their spectral data with those reported in the literature.

1β,5α,8α - *Trihydroxyeudesm* - 4(15) - *en* - 6β,11βH-12,6-*olide* (8α-*hydroxyartemin*) (**2**). Crystals, mp 220–222° ($CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3400, 1770, 1650. EIMS (probe) *m/z* (rel. int.): 282 $[M]^+$ (25), 264 $[M - H_2O]^+$ (8), 246 $[M - 2H_2O]^+$ (25), 218 (13), 83 (100).

1β,5α - *Dihydroxy* - 8α - *isovaleryloxyeudesm* - 4(15)-*en*-6-β,11βH-12,6-*olide* (8α-*isovaleryloxyartem*) (**3**). Crystals, mp 229–231° (hexane–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3450, 1760, 1730, 1650. EIMS (probe) *m/z* (rel. int.): 366 $[M]^+$ (33), 264 $[M - C_5H_{10}O_2]^+$ (13), 246 $[264 - H_2O]^+$ (25), 57 (100).

Mixture of 1β,5α-*dihydroxy*-8α-*isobutyryloxyeudesm*-4(15)-*en*-6β,11βH-12,6-*olide* (8α-*isobutyryloxyartemin*) (**4**) *and* 1β,5α-*dihydroxy*-8α-*senecionyloxyeudesm*-4(15)-*en*-6β,11βH-12,6-*olide* (8α-*senecionyloxyartemin*) (**5**). Oil, IR ν_{max}^{film} cm^{-1}: 3450, 1770, 1730, 1700, 1640, 1450. EIMS (probe) *m/z* (rel. int.): 364 $[M']^+$ (4), 352 $[M'']^+$ (13), 264 $[C_{15}H_{20}O_4]^+$ (8), 246 $[M - H_2O]^+$ (25), 83 (100), 43 (80).

1β,5α - *Dihydroxy* - 8α - (1 - *hydroxyethyl*)*acryloyl* - *oxyeudesm*-4(15)-*en*-6β,11βH-12,6-*olide* (8α-(1-*hydroxyethyl*)*acryloyloxyartemin*) (**6**). Crystals, mp 205–206° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400, 1770, 1720, 1630, 1250, 1170, 1140. EIMS (probe) *m/z* (rel. int.): 380 $[M]^+$ (85), 264 $[M - C_5H_8O_3]^+$ (46), 246 $[264 - H_2O]^+$ (58), 99 (100), 81 (95), 55 (85), 43 (90).

1β,5β,8α - *Trihydroxyeudesm* - 4(15) - *en* - 6β, 11βH-12,6-*olide* (8α - *hydroxy* - 5 - *epi-artemin*) (**8**). Oil, IR ν_{max}^{film} cm^{-1}: 3450, 1760, 1640. EIMS (probe) *m/z* (rel. int.): 282 $[M]^+$ (4), 264 $[M - H_2O]^+$ (25), 246 $[M - 2H_2O]^+$ (13), 122 (100), 55 (80), 43 (80).

5β,8α - *Dihydroxy* - 1α - *isovaleryloxyeudesm* - 4(15) - *en*-6β,11βH-12,6-*olide* (**9**). Oil, IR ν_{max}^{film} cm^{-1}: 3450, 1760, 1720, 1630, 1460, 1375. EIMS (probe) *m/z* (rel. int.): 366 $[M]^+$ (25), 264 $[M - C_5H_{10}O_2]^+$ (25), 246 $[264 - H_2O]^+$ (13), 57 (100).

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