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EUDESMANOLIDES OF *ARTEMISIA BARRELIERI*

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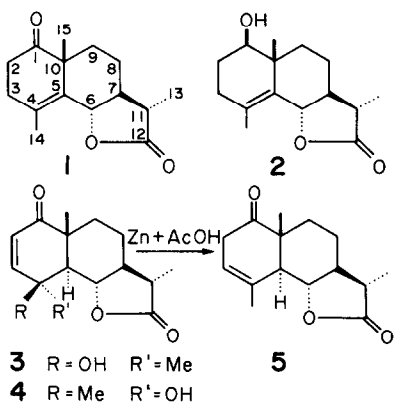
Key Word Index—*Artemisia barrelieri*; Asteraceae; eudesmanolides; barrelin; ^{13}C NMR.

Abstract—A new eudesmanolide, barrelin, was identified from the herbal part of *Artemisia barrelieri*. 1-Oxo-6β,7α,11β-*H*-eudesm-4-en-6,12-olide and 1β-hydroxy-6β,7α,11β-*H*-eudesm-4-en-6,12-olide were also isolated from the same source.

INTRODUCTION

Artemisia barrelieri Besser is endemic to south-eastern Spain. It is utilized in native medicine as a relief of intestinal spasms, and this property has been confirmed through determination of muscle relaxing activity [1]. From the flowering herb three eudesmanolides were isolated, two of which were already known, 1-oxo-6β,7α,11β-*H*-eudesm-4-en-6,12-olide (**1**) and 1β-hydroxy-6β,7α,11β-*H*-eudesm-4-en-6,12-olide (**2**), whereas the third named barrelin was a new one to which a structure (**3**) epimeric with vulgarin (**4**) was assigned.



RESULTS AND DISCUSSION

By CC on Si gel and subsequent purification through counter-current distribution (H_2O–EtOH–*n*-hexane–Me_2CO, 10:1:18:10) the sesquiterpene lactones **1** (K_r 0.54), **2** (K_r 0.29) and **3** (K_r 0.11) were separated. Compounds **1** and **2**, by comparison of physico-chemical data (mp, optical rotation and ^1H NMR), were identified, respectively, as 1-oxo-6β,7α,11β-*H*-eudesm-4-en-6,12-olide and 1β-hydroxy-6β,7α,11β-*H*-eudesm-4-en-6,12-olide, isolated previously from *A. granatensis* Boiss. [2].

Lactone **3**, named barrelin, $C_{15}H_{20}O_4$, mp 178–178.5°, M^+ *m/z* 264 (base peak), $[\alpha]_D^{20} = +148°$ ($CHCl_3$; *c* 2), showed IR bands ($\nu_{max}^{CCl_4}$) at 3560 (OH), 1770 (γ-lactone) and 1680 (α,β-unsaturated ketone) cm^{-1} and a UV maximum at 214 nm (log ε 2.63). In the ^1H NMR spectrum of barrelin the following groups are evident: two tertiary methyl groups (δ 1.21 and 1.57), a secondary methyl group (δ 1.23), a hydroxyl group (δ 3.07), the sequence CH_a–CH_b (H_a δ 2.43, *d*, *J* = 12 Hz; H_b 4.20, *dd*, *J* = 10 and 12 Hz) and the vinylidene group (δ 5.87 and 6.63, *J* = 10 Hz). These data supported a similar eudesmanolide structure for barrelin as for **1** and **2**. The coupling constants of H-6 (δ 4.20) indicated a *trans*-relationship with H-5 and H-7 and, therefore, a *trans*-junction for the lactone ring. Furthermore, the shape of H-5, a perfect doublet at δ 2.43, required complete substitution of the adjacent C-4. Therefore, the hydroxy group was located in the γ-position to the α,β-unsaturated ketone, as in vulgarin (**4**), in agreement with the abnormally low wavelength of the UV spectrum of **3** [3]. Moreover, barrelin and vulgarin showed a remarkable similarity of ^1H NMR spectra, however, the two substances had different rotatory powers ($[\alpha]_D = +40.3°$, $CHCl_3$ for vulgarin [4]), and different mp's and chromatographic mobilities (direct comparison). The ^{13}C NMR spectral data of **3** (see Table 1) and **4** [5] were practically identical except for C-14 (δ 19.7 in **3** and δ 22.7 in **4**). In barrelin the upfield shift of C-14 pointed out a steric interaction with the oxygen of the lactone ring which could be related to the different configuration of C-4.

The slower chromatographic mobility of barrelin in comparison with vulgarin was in agreement with the β-configuration of the hydroxy group in **3** which does not allow the formation of a hydrogen bond with the oxygen of the lactonic ring as occurs in **4**.

In confirmation of the structure of **3**, barrelin, as in the case of vulgarin [3], gave desoxyvulgarin (**5**) on reduction with zinc and acetic acid.

Previously the isolation of an oily isomer of vulgarin with a similar ^1H NMR spectrum had been reported from

Table 1. ^{13}C NMR chemical shifts for **1–3** (TMS as int. standard)

Carbon No.	**1** ($CDCl_3$)	**2** (DMSO-d_6)	**3** ($CDCl_3$)
1	212.2	84.7	201.6
2	32.8	40.9	125.1
3	34.9*	29.5	152.0
4	129.9	132.7	69.8
5	126.2	126.3	54.4
6	81.3	78.2	79.3
7	52.9	55.1	52.2
8	23.7	26.2	22.6
9	35.8*	35.7	34.1
10	48.7	44.3	46.3
11	40.6	42.6	40.4
12	177.6	180.7	178.2
13	12.3	14.7	12.4
14	19.7	21.0	19.7
15	23.2	22.0	23.6

*These values may be reversed.

A. ludoviciana [5] but its stereochemistry was not elucidated.

In Table 1 ^{13}C NMR data of **1** and **2** (besides those of **3**) were reported. By comparison with the data of other eudesmanolides [6] they were in agreement with the *trans*-junction of the lactonic ring and with the α-configuration of Me-13. On the basis of the octant rule, the negative Cotton effect of **1** (ORD: $\phi + 4600$ at 273 nm and -3700 at 312 nm) was in agreement with the β-configuration of Me-15 and with the resulting atom predominance in negative octants. Like other α,β-unsaturated ketones, barrelin showed a Cotton effect at 330 nm (ORD: $\phi + 1900$ at 295 nm and -1000 at 353 nm), but it was impossible to relate the sign to the structure.

The occurrence of **1–3** in *A. barrelieri* and of **1, 2** and **4** in *A. granatensis* suggests an identical biogenetic pathway wherein the formation of a C-4 cation may be involved.

EXPERIMENTAL

Extraction and separation. The flowering herb *Artemisia barrelieri* Besser was collected in the region of Granada (Spain). The dried powdered material (6 kg) was extracted with EtOH × 3 and the residue was submitted to CC on Si gel ($CHCl_3$). Through subsequent purification by counter-current distribution (H_2O–EtOH–*n*-hexane–Me_2CO, 10:1:18:10), monitored by TLC (Si gel F_{254}, $CHCl_3$–EtOAc, 1:1), three substances, **1–3**, were obtained. Compounds **1** (K_r 0.54, 520 mg) and **2** (K_r 0.29, 350 mg), by comparison of physico-chemical data, were identified as 1-oxo-6β,7α,11β-*H*-eudesm-4-en-6,12-olide and 1β-hydroxy-6β,7α,11β-*H*-eudesm-4-en-6,12-olide, respectively [2].

Barrelin (**3**). K_r 0.11, 285 mg. Crystals from EtOAc and *n*-hexane, mp 178–178.5°, $[\alpha]_D^{20}$ +148° ($CHCl_3$; *c* 2). (Found: C, 67.89; H, 7.37. $C_{15}H_{20}O_4$ requires: C, 68.16; H, 7.63%.) UV λ_{max}^{EtOH} nm: 214 (log ε 2.63); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3560, 1770 and 1680; ^1H NMR ($CDCl_3$, TMS as int. standard): δ 6.63 (1H, *d*, *J* = 10 Hz), 5.87 (1H, *d*, *J* = 10 Hz), 4.20 (1H, *dd*, *J* = 10 and 12 Hz), 3.07 (1H, *s*, OH exchangeable with D_2O), 2.43 (1H, *d*, *J* = 12 Hz), 1.57 (3H, *s*, Me), 1.23 (3H, *d*, *J* = 7 Hz, Me), 1.21 (3H, *s*, Me); MS *m/z* (rel. int.): 264 $[M]^+$ (100), 249 (95), 246 (3), 231 (22), 204 (5). 203 (45), 191 (9), 185 (22); R_f 0.55; R_f vulgarin 0.70.

Reduction of barrelin (**3**). The reduction was carried out with Zn in boiling HOAc soln as reported for vulgarin [3] and the compound obtained was identical with desoxyvulgarin (**5**) obtained by reduction of a sample of vulgarin. Crystals from EtOAc and *n*-hexane, mp 135–138°, MS *m/z*: 248 (base peak, M^+).

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