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REVISION OF THE STRUCTURE OF TORRENTIN

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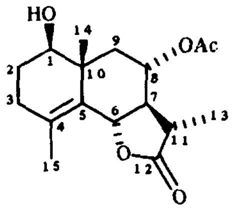
Key Word Index—*Artemisia herba-alba* subsp. *valentina*; Compositae; Anthemideae; sesquiterpene lactones; eudesmanolides; structure revision; torrentin.

Abstract—The structure of the eudesmanolide torrentin from *Artemisia herba-alba* subsp. *valentina* has been revised on the basis of high-field ^1H NMR spectroscopy and chemical correlations.

Eleven years ago, we reported the isolation of three sesquiterpene lactones from *Artemisia herba-alba* Asso subsp. *valentina* (= *A. valentina* Lam.) [1], one of the two Spanish subspecies of *A. herba-alba* Asso. One of these lactones, called torrentin, was assigned the new structure **1** with an eudesmane framework. The structural assignment was based solely on the interpretation of a 90 MHz ^1H NMR spectrum and comparison with literature spectra [2].

We have recently measured a certain number of NMR spectra of sesquiterpene lactones from natural and synthetic origin, most of which had a 8α-OR group (R = H, $SiMe_2Bu^t$, Ac). The signal from H-8 in the ^1H NMR spectra of these compounds always appeared as a double doublet of doublets, with coupling constants of *ca* 11, 11 and 4 Hz [3, 4]. In contrast with this, the corresponding signal in the 90 MHz ^1H NMR spectrum of torrentin was a broadened triplet at δ5.35. The broadening of the signal was attributed to the presence of long-range couplings, the origin of which, however, could not be ascertained at this frequency. Insight into the true structure of torrentin was gained by recording the ^1H NMR spectrum at 400 MHz. The higher resolution revealed in the broadened triplet at δ5.35 a marked fine structure, which was studied with the aid of decoupling experiments. Starting from this signal and from the other signals of the hydrogens on oxygenated carbon atoms at δ3.57 and 4.63 (see Table 1), these experiments allowed the establishment of the hydrogen connectivity and the allocation of the oxygen functions at C-1 (β-OH), C-6 (*trans*-lactone) and C-3 (β-OAc), as shown in structure **2**. For instance, irradiation of the signal at δ4.63 (H-6) caused the suppression of part of the small coupling constants in the signal at δ5.35. As a result, the broad triplet became a double doublet with $J = 9$ and 6.5 Hz. In agreement with the proposed structure, NOE effects were detected between the signals at δ3.57 (H-1) and δ5.35 (H-3), as well as between the signals from H-6, H-11 and H-14.

Further confirmation was sought by an independent chemical route. Structure **2** corresponds to an 11,13-dihydroderivative of montathanolide **3**, an eudesmanolide isolated 10 years ago (as the acetate **3a**) by Bohlmann and coworkers from *Athanasia montana* [5]. By reduction of **3a** with sodium borohydride, a product **2a** was obtained which proved identical (NMR and TLC) with the acetylated derivative of torrentin, thus definitively establishing the structure of the latter as **2**. Compound **2a** also showed the expected NOE effects between spatially neighbour protons.



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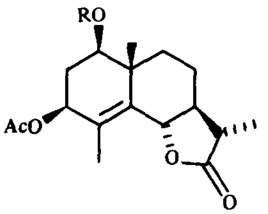
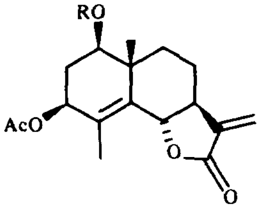


2 R = H
2a R = Ac



3 R = H
3a R = Ac

The ^{13}C NMR spectrum of torrentin [3] has been reassigned according to the new structure **2** (see Table 2). As the change from **1** to **2** implies the translation of the acetate group from C-8 to C-3, the signals from these atoms have to be interchanged. The shifts observed in the ^{13}C NMR spectrum of the acetate **2a** further help in the assignment of these and other signals.

Table 1. ^{1}H NMR data of compounds **2** and **2a***

H	**2**	**2a**
1	3.57 *ddd*	4.82 *dd*
2α	2.19 *ddd*	2.23 *ddd*
2β	1.75 *m*	1.80 *m*
3	5.35 *dddq*	5.40 *dddq*
6	4.63 *ddq*	4.60 *ddq*
7	1.75 *m*	1.80 *m*
8α	1.98 *dddd*	1.93 *dddd*
8β	1.52 *dddd*	1.51 *dddd*
9α	1.30 *ddd*	1.32 *ddd*
9β	2.07 *ddd*	1.80 *m*
11	2.29 *dq*	2.27 *dq*
13	1.24 *d*	1.24 *d*
14	1.19 *s*	1.25 *s*
15	1.81 *br s*	1.82 *br s*
OAc	2.10 *s*	2.08 *s*
		2.06 *s*
OH	1.65 *s*	—

*At 400 MHz in $CDCl_3$ (27°).

Coupling constants in Hz: **2** $J_{1,2\beta} = 12.5$; $J_{1,2\alpha} = 3.5$; $J_{1,OH} = 5.5$; $J_{2\alpha,2\beta} = 12$; $J_{2\alpha,3} = 6.5$; $J_{2\beta,3} = 9$; $J_{3,6} = J_{3,15} = J_{6,15} = 1$; $J_{6,7} = 11$; $J_{7,11} = 12$; $J_{7,8\alpha} = 4$; $J_{7,8\beta} = 12$; $J_{8\alpha,8\beta} = 13$; $J_{8\alpha,9\alpha} = 4.5$; $J_{8\alpha,9\beta} = 3$; $J_{8\beta,9\alpha} = 13$; $J_{8\beta,9\beta} = 3.5$; $J_{9\alpha,9\beta} = 13$; $J_{11,13} = 7$. **2a** $J_{1,2\beta} = 13$; $J_{1,2\alpha} = 3.5$; $J_{2\alpha,2\beta} = 12$; $J_{2\alpha,3} = 7$; $J_{2\beta,3} = 9$; $J_{3,6} = J_{3,15} = J_{6,15} = 1.5$; $J_{6,7} = 11.5$; $J_{7,11} = 12$; $J_{7,8\alpha} = 3$; $J_{7,8\beta} = 13$; $J_{8\alpha,8\beta} = 13.5$; $J_{8\alpha,9\alpha} = 4.5$; $J_{8\alpha,9\beta} = 3$; $J_{8\beta,9\alpha} = 13$; $J_{8\beta,9\beta} = 4$; $J_{9\alpha,9\beta} = 13.5$; $J_{11,13} = 7$.

Table 2. ^{13}C NMR data of compounds **2** and **2a**

C	**2***	**2a**†
1	74.19	75.12
2	33.01	29.90
3	72.77	72.23
4	133.90^a	133.21^a
5	125.10^a	125.66^a
6	82.51	82.18
7	52.59	52.28
8	24.51	24.28
9	38.15	37.76
10	42.66	41.43
11	41.18	41.09
12	178.30	178.22
13	12.41	12.36
14	18.45	19.48
15	14.50	14.48
OAc	170.79	170.55
		170.15
	21.15	21.09
		21.07

*At 50.32 MHz in $CDCl_3$ (27°).
†At 67.89 MHz in $CDCl_3$ (27°).
^{a}May be interchanged.

EXPERIMENTAL

The ^{1}H NMR spectra were measured at 400 MHz. The ^{13}C NMR spectra were measured at the frequencies indicated in Table 2.

Torrentin (**2**). White needles, mp 157–159° (hexane–EtOAc). For IR and MS data, see ref. [1]. For NMR data, see Tables 1 and 2.

11β,13-Dihydromontathanolide acetate (*torrentin acetate*) (**2a**). Montathanolide acetate **3a** [5] (10 mg) was dissolved in MeOH (1 ml) and allowed to react with $NaBH_4$ (10 mg) at 0° for 6 hr (until consumption of the starting product). The reaction was quenched with aq. NH_4Cl and extracted with Et_2O. The extract was then submitted to prep. TLC on silica gel (hexane–Et_2O 1 : 1). This gave **2a** (6 mg), which crystallized from hexane–Et_2O as colourless needles, mp 125–126°, $[\alpha]^{23}_D - 7°$ ($CHCl_3$; *c* 0.6). IR ν_{max}^{KBr} cm^{-1}: 1740 (acetate C=O). EIMS (probe) *m/z* (rel. int.): 350 $[M]^+$ (0.5), 290 $[M - HOAc]^+$ (2.5), 248 $[M - HOAc\text{-}C_2H_2O]^+$ (100), 233 (15), 215 (6). High resolution MS: found, M = 290.1537; calc. for $C_{17}H_{22}O_4$, M = 290.1520. For NMR data, see Tables 1 and 2. The product had identical NMR spectra and R_f values on several chromatographic systems as torrentin acetate, prepared from torrentin in the usual way (Ac_2O–pyridine).

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