Phytochemistry, Vol. 28, No. 5, pp. 1535–1536, 1989.
Printed in Great Britain.

0031–9422/89 $3.00 + 0.00
Pergamon Press plc.

A MELAMPOLIDE AND TWO DIHYDRO ARTEMORIN DERIVATIVES FROM *ARTEMISIA GYPSACEA*

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(*Received* 20 *September* 1988)

Key Word Index—*Artemisia gypsacea*; Compositae; sesquiterpene lactones; melampolide; dihydro artemorin; dihydro anhydroverlotorin; β-pinene derivative.

Abstract—The aerial parts of *Artemisia gypsacea* afforded in addition to known compounds a dihydro eudesmanolide, three 11,13-dihydro germacranolides, one being a melampolide derivative and two derived from artemorin. Furthermore, a derivative of β-pinene was present. The structures were elucidated by high field ^{1}H NMR spectroscopy.

INTRODUCTION

The large genus *Artemisia* (Compositae, tribe Anthemideae) has a worldwide distribution, though the species are mainly concentrated in the Northern hemisphere. The genus is not very uniform and the chemistry is somewhat diverse. However, most species contain sesquiterpene lactones, especially 11,13-dihydro derivatives. We now have studied a further Iranian species, *A. gypsacea* Krasch. Popov Lin. ex P. Poljakov. The results are discussed in this paper.

RESULTS AND DISCUSSION

The extract of the aerial parts gave by column chromatography and HPLC the dihydro eudesmanolides **1** and **2** [1–3], the former only being prepared by reduction of the natural occurring methylene lactone [3], phloracetophenone 20,40-dimethyl ether (**7**), the β-pinene derivative **6** and three germacranolides, the melampolide **3** and the 11,13-dihydro derivatives **4** and **5**.

The structure of **6**, molecular formula $C_{10}H_{14}O_2$, followed from its ^{1}H NMR spectrum (Experimental). All signals could be assigned by spin decoupling clearly indicating the presence of a derivative of β-pinene with a keto and a hydroxy group. The relative position of these groups followed from the observed chemical shifts and coupling of H-4 and H-6 which required a keto group at C-5. As H-4 showed vicinal couplings with H-3 the hydroxy group was at C-2. Inspection of models further showed that the coupling of H-2 required a β-orientation of this group. The observed ^{13}C NMR data further supported the proposed structure (Experimental).

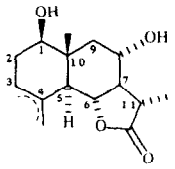
The ^{1}H NMR spectrum of **3** (Table 1) indicated that 11,13-dihydro germacronolide was present as followed from the signals and δ2.57 *dq* and 1.43 *d* (3H). Spin decoupling allowed the assignment of all signals. Starting with that of H-11, that of H-7 could be determined. As the latter was coupled with a triplet at δ4.52 (H-6) and a doublet of triplets at δ3.90 (H-8), subsequent decouplings led to the whole sequence, as allylic couplings were detected between H-1 and H-9 as well as between H-5 and H-3. The observed couplings of H-1 and H-5 required the proposed configuration of the double bonds, and also the configuration at C-6, C-8 and C-11 could be deduced from the observed couplings and from the observed NOE's. Saturation of H-1 (δ5.49 *dd*) gave clear effects with H-14 (5%) and H-14′ (5%). Further NOE's were observed between H-6, H-11 (4%), H-8 (4%) and H-15 (12%) as well as between H-8, H-6 (7%) and H-11 (8%).

The ^{1}H NMR spectrum of **4** (Table 1) was in part similar to that of artemorin [4]. Signals at δ2.54 *dq* and 1.45 *d* (3H) again showed that a dihydro derivative was present. The couplings of H-1 and H-8 were identical with

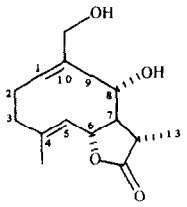
Table 1. ^{1}H NMR spectral data of **3–5** (400 MHz, $CDCl_3$, δ-values)

H	**3**	**4**(60°)	**5**(60°)
1	5.49 *br t*	3.91 *m*	—
2	1.86 *m*	1.96 *m*	2.89 *m*
2′	1.91 *m*		2.77 *m*
3	2.15 *m*	2.15 *m*	2.55 *ddd*
3′			2.35 *ddd*
5	5.01 *br d*	5.19 *br d*	4.97 *br d*
6	4.52 *t*	4.35 *t*	4.39 *t*
7	2.11 *ddd*	2.16 *ddd*	1.92 *ddd*
8	3.90 *ddd*	3.93 *m*	3.69 *ddd*
9	2.35 *br d*	2.54 *br d*	2.68 *br d*
9′	2.25 *dd*	2.34 *dd*	2.62 *dd*
11	2.57 *dq*	2.54 *dq*	2.70 *dq*
13	1.43 *d*	1.45 *d*	1.39 *d*
14	4.35 *br d*	5.22 *br s*	5.84 *br s*
14′	4.14 *br d*	5.11 *br s*	5.76 *br s*
15	1.81 *d*	1.68 *d*	1.71 *d*

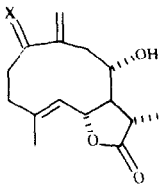
J[Hz]: compound **3**: 1,2 = 7.5; 5,6 = 6,7 = 7,8 = 10; 5,15 = 1; 7,11 = 11; 8,9 = 2; 8,9′ = 3.5; 9,9′ = 15; 14,14′ = 12; compound **4**: 5,6 = 6,7 = 7,8 = 10; 5,15 = 1; 7,11 = 11; 8,9′ = 7; 9,9′ = 16; compound **5**: 5,6 = 6,7 = 7,8 ~ 10; 5,15 = 1.5; 7,11 = 11; 8,9 = 3; 8,9′ = 7; 9,9′ = 14.



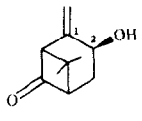
1 Δ^3
2 $\Delta^{4(15)}$



3



4 X = O
5 X = βOH,H



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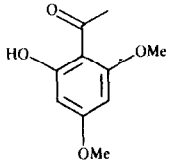

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those of artemorin and the coupling $J_{7,11}$ required an 11α-methyl group. Accordingly, the stereochemistry was settled. A lactone where no stereochemistry was presented, may be identical with **4** [5].

The ^{1}H NMR spectrum of **5** resembles that of anhydroverlotorin [4]. However, again the exomethylene proton signals were replaced by those of 11,13-dihydro derivative [δ2.67 *dq*, 1.41 *d* (3H)]. The couplings of H-8 were slightly different from those of **4**. Inspection of a model showed that still an 8α-hydroxy group has to be proposed, the differences only being due to small changes in the preferred conformation.

The chemistry of this *Artemisia* species is typical for a large number of species, the isolated compounds are all closely related to 11,13-dihydrocostunolide. The lactones **1** and **2** most likely are formed from the corresponding 1,10-epoxide and **3**–**5** by allylic oxidation at C-1 or C-15.

EXPERIMENTAL

The air-dried aerial parts (400 g, collected in province Khorrassan, 50 km W of Mashed, Iran, voucher deposited in the Herbarium of the Dept. of Botany, Shahid Beheshty University, Tehran, Iran) were extracted with Et_2O–MeOH–petrol (1:1:1). The more polar part of the extract was taken into methanol and the soluble part was first separated by CC (silica gel) into four fractions. While the first one gave no definitive compounds, fraction 2 (Et_2O–petrol, 1:1) afforded by HPLC (MeOH–H_2O, 7:3, always RP 8, *ca* 120 bar, flow rate 3 ml/min) 35 mg **7** and 30 mg **6** (R_t 5.0 min). The third CC fraction (Et_2O) gave by HPLC (MeOH–H_2O, 1:1) 10 mg **3** (R_t 9.2 min) and 18 mg **5** (R_t 7.8 min). The most polar CC fraction (Et_2O–MeOH, 9:1) gave by HPLC (MeOH–H_2O, 1:1) 15 mg **1** its ^{1}H NMR data being identical with those reported in ref. [3], 20 mg **2** and 32 mg **4** (R_t 4.3 min). Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material and/or with the lit. data.

8α,14-*Dihydroxy*-11,13-*dihydromelampolide* (**3**). Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1765 (γ-lactone); MS *m/z* (rel. int.): 266.152 [M]$^+$ (1.3) (calc. for $C_{15}H_{22}O_4$: 266.152), 248 [M − H_2O]$^+$ (10), 230 [248 − H_2O]$^+$ (11), 121 (51), 93 (71), 71 (80), 55 (100); $[\alpha]_D^{24}$ + 16 ($CHCl_3$; *c* 0.2).

11β,13-*Dihydroartemorin* (**4**). Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 266 [M]$^+$ (0.8), 248.141 [M − H_2O]$^+$ (14) (calc. for $C_{15}H_{20}O_3$: 248.141), 230 [248 − H_2O]$^+$ (5), 121 (48), 93 (86), 69 (100), 55 (82); $[\alpha]_D^{24}$ + 48 ($CHCl_3$; *c* 0.3).

11β,13-*Dihydroanhydroverlotorin* (**5**). Colourless gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone), 1680 (C=CC=O); MS *m/z* (rel. int.): 264.136 [M]$^+$ (7.5) (calc. for $C_{15}H_{20}O_4$: 264.136), 246 [M − H_2O]$^+$ (5), 222 [M − ketene]$^+$ (10), 207 [222 − Me]$^+$ (12), 97 (83), 71 (92), 69 (100), 55 (88); $[\alpha]_D^{24}$ + 83 ($CHCl_3$; *c* 0.45).

2β-*Hydroxy*-5-*keto*-β-*pinene* (**6**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1790 (C=O); MS *m/z* (rel. int.): 166. 099 [M]$^+$ (10) (calc. for $C_{10}H_{14}O_2$: 166.099), 148 [M − H_2O]$^+$ (7), 98 (32), 69 (100); ^{1}H NMR ($CDCl_3$): 4.29 (*br d*, H-2, *J* = 5 Hz), 2.47 (*ddd*, H-3, *J* = 15, 5, 1), 2.19 (*dd*, H-3β, *J* = 15, 5), 2.62 (*ddd*, H-4, *J* = 6, 6, 1), 3.19 (*d*, H-6, *J* = 5), 5.12 (*s*, H-7), 4.84 (*s*, H-7′), 1.20 (*s*, H-9), 1.03 (*s*, H-10); ^{13}C NMR ($CDCl_3$, C-1 − C-10): 152.3, 72.3, 35.1, 50.8, 205.9, 66.9, 114.0, 33.0, 26.8, 18.0; $[\alpha]_D^{24}$ − 24 ($CHCl_3$; *c* 1.2).

Acknowledgements—A. R. thanks Prof. Dr F. Bohlmann (Technical University of Berlin) for giving the opportunity to work in his Institute and Dr J. Jakupovic (Technical University of Berlin) for his help in structure elucidation.

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