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SESQUITERPENE LACTONES FROM *ARTEMISIA HERBA ALBA**

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Key Word Index—*Artemisia herba alba*; Compositae; herbolides E, F, G, H and I; germacranolide; eudesmanolide; ^{1}H and ^{13}C NMR.

Abstract—A new chemotype of *Artemisia herba alba* has been analysed and been shown to contain two known sesquiterpene lactones, herbolides E and F, and three new ones, herbolides G, H and I.

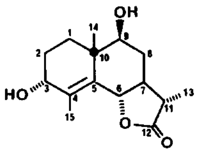
Artemisia herba alba which grows abundantly in the Middle East is a well known medicinal plant. Six different chemotypes have already been collected from the arid zones of Egypt and Israel [1–7] and have been discerned on the basis of their sesquiterpene lactone constitution. We wish to report now the identification of a further chemotype growing in the northern Judean desert.

The dichloromethane extract of the inflorescences, small stems and leaves yielded on column chromatography (CC) five fractions in which the existence of sesquiterpene lactones was indicated by a strong IR absorption band in the 1750 cm^{-1} region. From the two most polar fractions herbolide E (1) and herbolide F (2) were isolated. These compounds have previously been described by us [7] as the only sesquiterpene lactones present in a different population growing also in the Judean desert. From the three less-polar fractions three novel sesquiterpene lactones were isolated, herbolide G (3), herbolide H (4) and herbolide I (5). The structure elucidation of these was based on extensive use of spectroscopic methods.

Herbolide G (3) which emerged first on CC has an empirical formula of $C_{15}H_{22}O_3$ (HRMS). Its IR spectrum shows bands for a hydroxyl function (3440 cm^{-1}) and a γ lactone group (1750 cm^{-1}); no further carbonyl band was observed. The eudesmanolide structure was inferred from the H-14 NMR signal which is a sharp three-proton singlet at δ 0.88 indicating the angular position of the C-14 methyl group. Further confirmation resulted from the inspection of the multiplicities of the 'off-resonance' ^{13}C NMR signals (Table 1). The ^{1}H signal of the C-15 methyl group appears as a slim multiplet at δ 1.79 and turns to singlet on irradiation of the olefinic H-3 at δ5.34 (multiplet with $\Delta\nu_{1/2}$ 8–8.5 Hz). The shape of the H-6 signal (triplet at δ4.18; J = 10.5 Hz) is in accordance with the proposed structure 3. The 9β-position of the hydroxyl group is indicated by the H-9α signal at δ3.65 (double doublet) with total coupling constants of 16.5 Hz suggesting an antiperiplanar orientation of H-9α and H-8β. The H-11 signal is a double quartet centred at δ2.61 and that of the three H-13 atoms is a doublet at δ1.19 ($J_{11,13}$ = 7.5 Hz).

The second lactone eluted by CC was herbolide H (4). Its structure was deduced as the 3-deoxy-derivative of herbolide F (2) from the following spectroscopic evidence: The empirical formula is $C_{15}H_{22}O_3$ (HRMS); the IR spectrum indicated the presence of a γ lactone ring (1763 cm^{-1}) and a hydroxyl group (3472 cm^{-1}). Selective ^{1}H decoupling led to the identification of the following ^{1}H signals which are very similar in their chemical shifts and coupling patterns to the corresponding signals in the ^{1}H spectrum of 2 [7]: two H-14 signals at δ5.19 (J = 1.8 Hz) and 4.85 (J = 1.7 Hz); H-5, doublet at δ5.18 ($J_{5,6}$ = 9.9 Hz); H-6, triplet at δ4.59 ($J_{5,6} \approx J_{6,7}$ = 9.8–10.0 Hz); H-9, multiplet at δ3.89 ($\Delta\nu_{1/2} \approx$ 15 Hz); H-11, double quartet at δ2.65; H-13, doublet at δ1.20 ($J_{11,13}$ = 7.5 Hz); H-15, doublet at δ1.68 ($J_{5,15}$ = 1.4 Hz). The ^{13}C NMR data (Table 1) also support the structure proposed for herbolide H (4). Most of the chemical shifts of 4 are in good agreement with the corresponding signals for herbolide F (2) [7]. The only exception is the C-15 signal the δ value of which is shifted downfield by 5.7 ppm in herbolide H (4). This is consistent with a lack of a γ-gauche substituent effect in 4 which is operating in 2.

The third polar constituent is herbolide I (5) which proved to possess an eudesmanolide structure with an



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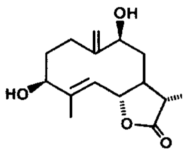

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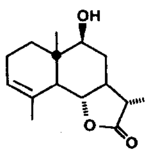

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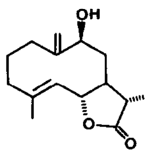

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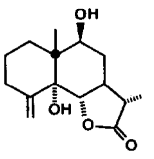

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*Part IV in the series 'Sesquiterpene Lactones from *Artemisia herba alba*'; for Part III, see ref. [7]; for Part II, ref. [5] and Part I, ref. [2].

Table 1. ^{13}C chemical shifts of herbolide E (**1**), F (**2**), G (**3**), H(**4**), and I (**5**)*

	1†	2†‡	3	4	5‡	5§
1	21.2 *t*	—¶	20.2 *t*	33.0 *t*	20.2 *t*	21.0
2	29.8 *t*	—¶	34.6 *t*‖	24.8 *t*	—¶	31.4‖
3	72.9 *d*‖	75.4 *d*‖	121.1 *d*	36.4 *t*	—¶	31.1‖
4	126.9 *s*	—**	137.8 *s*	144.4 *s*	147.3 *s*	—**
5	134.3 *s*	122.9 *d*	51.2 *d*	123.1 *d*	76.8 *s*	78.1
6	81.6 *d*	79.9 *d*	80.2 *d*	79.8 *d*	80.7 *d*	82.8
7	48.1 *d*	48.5 *d*	49.6 *d*	48.0 *d*	—¶	30.9‖
8	42.3 *t*	42.7 *t*	32.9 *t*‖	40.1 *t*	40.9 *t*	42.0
9	71.8 *d*‖	75.9 *d*‖	—¶	—¶	71.0 *d*	72.6
10	38.2 *s*	152.0 *s*	40.7 *s*	151.9 *s*	44.9 *s*	—¶
11	37.9 *d*	40.7 *d*	38.2 *d*	40.1 *d*	38.7 *d*	39.9
12	179.5 *s*	179.9 *s*	180.1 *s*	179.7 *s*	179.6 *s*	—**
13	9.9 *q*	10.6 *q*	9.7 *q*	10.5 *q*	9.2 *q*	9.6
14	17.4 *q*‖	110.6 *t*	11.1 *q*	110.2 *t*	12.8 *q*	13.6
15	18.0 *q*‖	11.8 *q*	23.3 *q*	17.5 *q*	110.6 *t*	111.8

*In $CDCl_3$ if not otherwise noted; downfield from internal TMS ($\delta 0$); letters in parentheses indicate signal multiplicities in the off-resonance spectra.

†Data taken from ref. 7.

‡In $(CD_3)_2CO$.

§In CD_3OD.

¶Overlapped by solvent signals.

‖May be interchanged.

**Not observed.

exomethylene group at C-4 and hydroxyl groups at C-5 and C-9: The empirical formula is $C_{15}H_{22}O_4$ (HRMS, MS); the IR spectrum exhibits a γ lactone band at 1760 cm^{-1}. The tricyclic system is revealed by the typical H-14 singlet at $\delta 0.88$ and the 'off-resonance' ^{13}C signal multiplicities (Table 1). Except for the H-13 doublet at $\delta 1.21$ ($J_{11,13} = 7.5$ Hz) no further methyl signal appears in the ^1H NMR spectrum. The H-15 atoms resonate at $\delta 5.03$ and 4.98 (two *br d* signals) typical for an exocyclic methylene group; this is also confirmed by the ^{13}C NMR spectrum (Table 1). One hydroxyl group is in the 9β-position because of the 9α hydrogen signal ($\delta 4.16$, $J_{8\beta,9\alpha} = 11.0$ Hz, $J_{8\alpha,9\alpha} = 5.2$ Hz) (cf. the H-9 signal in **1** [7] and **3**). The second hydroxyl group was assigned to the 5α-position because of the following arguments: The ^{13}C signal at $\delta 76.8$ appears as a singlet in the 'off-resonance' spectrum indicating the presence of a tertiary alcohol. The H-6 signal is a doublet at $\delta 4.48$ ($J_{6\beta,7\alpha} = 10.8$ Hz), thus there cannot be an axial hydrogen atom at C-5. A *cis*-A/B ring junction is biogenetically implausible and can be excluded because of the C-14 chemical shift ($\delta 12.8$) which is nearly identical with that in **3** ($\delta 11.1$). If the A and B rings were *cis*-fused the C-14 δ value would be expected to be *ca* 17–18 because the two γ effects from C-2 and C-4 in the *trans*-form would be replaced by only one from the 5β-hydroxyl group in the *cis*-form. The H-7 signal is at $\delta 2.87$, its shape ($\Delta\nu_{1/2} \approx 36$–$37$ Hz) indicating at least two antiperiplanar interactions (H-6 and H-11). H-11 resonates at $\delta 2.64$ (double quartet) overlapped by a broad multiplet ($\Delta\nu_{1/2} \approx 38$–$40$ Hz) which was assigned to H-3α because double irradiation experiments proved a long-range coupling with the H-15 signal at $\delta 5.03$. The three H-13 protons give rise to a doublet at $\delta 1.21$ ($J_{11,13} = 7.5$ Hz). It should be noted that 5α-hydroxylactones of related structure have been reported before [8, 9] and their ^1H NMR spectral data correspond nicely with those of **5**.

EXPERIMENTAL

Plant material. Stems including leaves and heads (capitulae) of *Artemisia herba alba* Asso. were harvested in the northern Judean desert 13 km northeast of Jerusalem, 2 km north of Ein-El-Fawar, Voucher No. Danin 15.6.83. Voucher specimens were deposited in the Herbarium of the Hebrew University of Jerusalem. The air-dried flowers, leaves and small stems (160 g) were processed and extracted as described previously [6]. The crude extract was separated on a Florisil column, eluting first with CH_2Cl_2 and then with CH_2Cl_2–MeOH. The first lactone-containing fraction (0.5 g) was purified by chromatography on silica gel with Me_2CO (20 %) in petrol. Crystallization from ether yielded 35 mg pure herbolide G (**3**), mp 126–128°; $[\alpha]_D^{22}$ 111° [$CHCl_3$, *c* 0.7]; HRMS *m/z* 250.1584 (calc. for $C_{15}H_{22}O_3$: 250.1569); EIMS (probe) 70 eV *m/z* (rel. int.): 250 (78) $[M]^+$; 235 (2) $[M-Me]^+$; 232 (9) $[M-H_2O]^+$; 217 (9) $[M-H_2O-Me]^+$. The second lactone fraction (0.45 g) was purified by silica gel chromatography with Me_2CO (25 %) in petrol to yield 25 mg of chromatographically pure herbolide G (**4**) which could not be crystallized; $[\alpha]_D^{22}$ 179° [$CHCl_3$, *c* 0.69]; HRMS *m/z* 232.1432 $[M-18]^+$ (calc. for $C_{15}H_{20}O_2$: 232.1435); MS 70 eV *m/z* (rel. int.): 250 (2) $[M]^+$; 232 (27) $[M-H_2O]^+$; 217 (17) $[M-H_2O-Me]^+$. The third lactone fraction (0.8 g) was chromatographed on silica gel with Me_2CO (25 %) in petrol. Crystallization from ether yielded 38 mg pure herbolide I (**5**), mp 213–215°; $[\alpha]_D^{22}$ 170° [MeOH, *c* 0.11]; HRMS *m/z*: 266.1499 (calc. for $C_{15}H_{22}O_4$: 266.1518); EIMS (probe) 70 eV *m/z* (rel. int.): 266 (100) $[M]^+$; 248 (7) $[M-H_2O]^+$; 233 (17) $[M-H_2O-Me]^+$. The fourth fraction (0.8 g) was chromatographed on silica gel with Me_2CO (20 %) in petrol to yield 800 mg herbolide E (**1**); TLC, NMR and MS were identical with an authentic sample. The most polar lactone fraction from the Florisil column was crystallized from $CHCl_3$ to yield 80 mg herbolide F (**2**); TLC, NMR and MS again being identical with an authentic sample.

All NMR spectra were measured in $CDCl_3$ if not otherwise noted; the chemical shifts are referenced to internal TMS ($\delta 0$).

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