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GLAUCOLIDE-LIKE SESQUITERPENE LACTONES FROM *ARTEMISIA JUDAICA*

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Key Word Index—*Artemisia judaica*, Compositae, sesquiterpene lactones, eudesmanolides, germacranolides, seco-eudesmanolides, glaucolide-like lactones

Abstract—The aerial parts of *Artemisia judaica* afforded, in addition to known compounds, eight new sesquiterpene lactones, two eudesmanolides, two seco-eudesmanolides and four glaucolide-like lactones The structures were elucidated by high field NMR techniques.

INTRODUCTION

Artemisia judaica L. (arabic name: Shih-Balady) is widespread in Egypt in the coastal areas but also in the desert near the Nile and in the Sinai peninsula As this species has long been used as a medical herb it has been studied chemically by different groups. In addition to eudesmanolides [1–4] some monoterpenes [4, 5] and some aromatic compounds [4, 5] are reported. The main constituent is vulgarin (=judaicin) (**1**) [2–4] A reinvestigation of the polar parts of the extract from aerial parts gave several new sesquiterpene lactones In addition to vulgarin the eudesmanolides **2** and **3**, the glaucolides **4–7** and the epimeric seco derivatives **8a/b** were present

RESULTS AND DISCUSSION

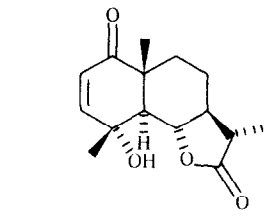
The structure of **2** could be easily deduced from the ^{1}H NMR spectrum (Table 1) which was close to that of erivanin [6]. However, the splitting of H-1 indicated a changed configuration. The relative position of the equatorial hydroxy group followed from the results of spin decoupling in deuteriobenzene which allowed the assignment of all signals Similarly, the ^{1}H NMR spectrum of **3** (Table 1) showed that an isomer of isoerivanin [7] was present Again the 1-hydroxy group was equatorial as followed from the couplings.

The ^{1}H NMR spectral data of **4** (Table 1) differed from those of **2** and **3** Especially, the H-13 doublet was missing and the signal of H-6 was a doublet (δ5 02 *br d*). The chemical shift of the latter and a long range coupling with a broadened singlet at δ4.38 indicated the presence of a glaucolide type lactone with a 7 11-double bond and an oxygen function at C-13. The remaining signals were assigned by spin decoupling and the observed couplings of H-1 and H-3 established the stereochemistry at the corresponding carbons Thus lactone **4** was the 13-*O*-desacetyl derivative of artemisia glaucolide which was isolated from *Artemisia afra* [8]. A related eudesmanolide, arbusculin D, has been reported from a further *Artemisia* species [9]

The separation of the epimeric lactones **5** and **6** was extremely difficult and the ^{1}H NMR spectra were highly broadened at room temperature. However, at elevated temperature most signals could be assigned by spin decoupling (Table 1). The results clearly showed that again glaucolides were present This was further supported by the ^{13}C NMR spectra (Table 2) NOE difference spectroscopy further allowed the assignment of the configuration at C-1. Thus lactone **5** showed a NOE between H-15, H-1 (5%) and H-6 (12%) while in the case of **6** NOE's between H-1 and H-3 (5%) as well as between H-15 and H-6 (15%) were observed. Inspection of models indicated that these effects and the couplings required conformations differing in the orientation of C-14 which was below the plane in the case of **5** while C-15 was above the plane in the preferred conformations of the lactones The ^{1}H NMR data of **5** and **6** were close to those of a pair of isomeric lactones [8] which, however, again were 13-*O*-acetates. Similarly, the ^{1}H NMR spectrum of **7** was close to the corresponding 13-*O*-acetate [8] which also could be interpreted only at elevated temperature. Surely, the precursor of the lactones **5–7** is the corresponding 1(10),4-germacradiene which was not isolated. However, the 13-*O*-acetate was present in *Artemisia afra* [8]

The structures of the epimers **8a/b**, which could not be separated, were deduced from the structure of **9b**, the single methyl ester obtained by reaction of the epimers with diazomethane. Together with the molecular formula therefore the natural compounds must be the C-1 epimers **8a/b** The relative position of the oxygen functions followed from the shift differences of H-14 in the epimers which are surely due to the neighbouring hydroxy group which deshields H-14 in the main epimer **8a**. Most likely they are formed by fragmentation of the hydroxy ketone **10** followed by oxidation of the resulting conjugated aldehyde leading to **9a** which is in equilibrium with the epimeric pseudo acids **8a/b** (Scheme 1). We have named the latter *seco*-isoerivanin pseudo acid.

The isolation of **4–7** from an *Artemisia* species from the Northern hemisphere surely is of interest as these lactones are very close to those from the only South African species, *A afra*, where, however, in addition to the glaucolides guaianolides were isolated [8]. Further investi-



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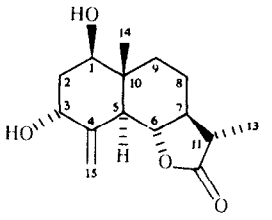

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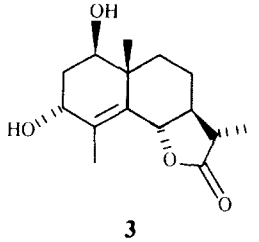

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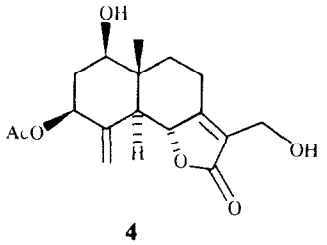

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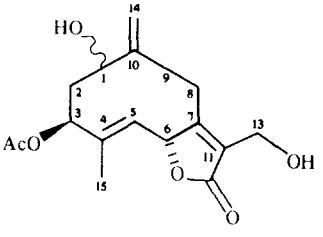
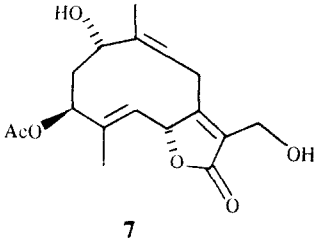


5 1α OH
6 1β OH



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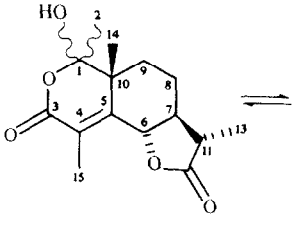
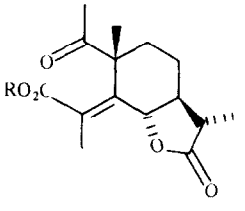
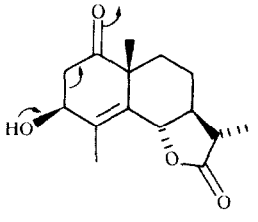


8a 1β OH
8b 1α OH



9a R = H
9b R = Me



10

gations may show whether these lactones are more widespread in the tribe Anthemideae So far, in addition to *Artemisia*, such glaucolides have only been reported from a *Cotula* species [10] where, however, 8α-oxygen functions are present which otherwise are only very common in the tribe Vernonieae [11]

EXPERIMENTAL

The air-dried aerial parts (1 5 kg, collected from Wadi-Hof, Egypt, in March 1986, voucher deposited in the Herbarium of the University of Alexandria) were extracted with 95% EtOH at room temp After concn HOAc was added After 3 hr the dark green deposit was filtered and the soln was successively shaken with petrol, Et_2O, $CHCl_3$, EtOAc and *n*-BuOH The bitter tasting fractions (Et_2O, $CHCl_3$ and EtOAc) were combined and concentrated affording 33 g extract which was separated by CC (Al_2O_3) The fractions obtained with CCl_4–$CHCl_3$ (9 1) gave 2.5 g crystalline judaicin (**1**) The fractions obtained with increasing amounts of $CHCl_3$ gave 11 g crude material which was separated again by CC (Al_2O_3) With Et_2O 75 mg **2** and with $CHCl_3$–Et_2O and $CHCl_3$–MeOH 7 g of a mixture were obtained which gave by CC (SiO_2) with Et_2O–MeOH, 4 1, a polar fraction affording by TLC (silica gel, PF 254, Et_2O–MeOH, 9 1) three bands (3/1–3/3) The first band gave 2 mg **2** and 3/2 10 mg **3** (R_f 0 50) The last band (3/3) was separated by HPLC (MeOH-H_2O, 1 1, always RP 18, *ca* 100 bar) affording three fractions (3/3/1 3/3/3) TLC of 3/3/1 (R_t 1 7 min) (Et_2O–$CHCl_3$–MeCN, 2 2 1, six developments) gave 4 mg **5** and 9 mg **6** Repeated HPLC of 3/3/2 (MeOH–H_2O, 2 3) gave 3 mg **7** (R_t 5 5 min) Fraction 3/3/3 (R_t 3 0 min) contained 9 mg **4** The less polar CC fraction gave by TLC (Et_2O) 3 mg **8a/b** (R_f 0 65) which could not be separated by TLC or HPLC (*ca* 3 2)

1-epi-*Eriyanin* (**2**) Colourless crystals, mp 257–259°, MS *m/z* (rel int) 266 152 $[M]^+$ (27) (calc for $C_{15}H_{22}O_4$ 266 152), 251 (10), 248 (19), 233 (8), 230 (8), 57 (100), $[\alpha]_D^{24^0}$ +83 ($CHCl_3$, *c* 0 23)

1-epi-*Isoeriyanin* (**3**) Colourless oil, IR $\nu_{max}^{CHCl_3}$, cm^{-1} 3590 (OH), 1770 (γ-lactone), MS *m/z* (rel int.) 266 152 $[M]^+$ (36)

Table 1 ^{1}H NMR spectral data of **2–7**, **8a/b** and **9b** (400 MHz, $CDCl_3$, δ-values)

H	2(C_6D_6/MeOD)	3	4	5(60°)	6(60°)	7(70°)†	8a/b(C_6D_6)	9b
1	4.02 *dd*	3.83 *dd*	3 52 *br dt*	4.04 *br dd*	4 20 *br t*	4 33 *dd*	—	—
2	2.20 *ddd*	1 89 *m*	2 2 *ddd*	2 20 *ddd*	*	2 19 *ddd*	1 47, 1 44 *s*	2 21 *s*
2′	1 80 *ddd*		1.65 *q*	*	*	1 99 *ddd*	—	—
3	4 29 *t*	4 02 *br s*	5 12 *dd*	5 32 *dd*	5 12 *t*	4 96 *dd*	—	—
5	2 66 *dt*	—	1 77 *br d*	4 99 *br d*	5 09 *br d*	4 97 *br d*	—	—
6	3 63 *t*	4 59 *dt*	5 02 *br d*	5 39 *br d*	5 44 *br d*	5 44 *br d*	3 87, 3 86 *dq*	4.68 *dq*
7	1 20 *dq*	1 79 *dq*	—	—	—	—	1 26 *m*	2 10 *m*
8	1 39 *dq*	1.96 *dq*	2 96 *ddd*	*	*	2 89 *br t*	1 50 *m*	1 99 *m*
8′	1.03 *dq*	1 54 *dq*	2.44 *br dt*	2 99 *ddd*	3 27 *ddd*	3 27 *br dd*	2 07 *dq*	1 80 *m*
9	1.16 *ddd*	1 33 *dt*	1 30 *dt*	*	*	5 13 *dd*	0 85 *m*	1 90 *m*
9′	2.03 *dt*	2 12 *dt*	2 27 *ddd*	2 64 *br dd*	*		1 16 *m*	1 60 *m*
11	1 73 *dq*	2.28 *dq*	—	—	—	—	1 50, 1 43 *m*	2 29 *dq*
13	1 01 *d*	1 25 *d*	4.38 *br s*	4 47 *br s*	4 42 *br s*	4 40 *br s*	0 95, 0 91 *d*	1 28 *d*
14	0.82 *s*	1 09 *s*	0 94 *s*	5 17 *br s* 4.97 *br s*	5 24 *br s* 4.92 *br s*	1 76 *br s*	1 41, 1 13 *s*	1 52 *s*
15	5 09 *t* 4.93 *t*	2.01 *d*	5.26 *br s* 5 13 *br s*	1.87 *br s*	1 86 *br s*	1 92 *br s*	2 14, 2 11 *d*	2 12 *d*
OAc	—	—	2 19 *s*	2 08 *s*	2 07 *s*	2 04 *s*	—	—

*overlapped multiplets, † $CDCl_3$–MeOD, 2 1

J[Hz] Compound **2**. 1,2α = 4.5, 1,2β = 11.5, 2α,2β = 13, 2α,3 = 2β,3 = 3, 5,6 = 6,7 = 10 5, 5,15 = 5,15′ = 15,15′ ~ 1, 7,8β = 7,11 = 8α,8β = 8β,9α ~ 12, 7,8α = 8α,9α = 8α,9β = 3, 9α,9β = 13, 11,13 = 7, compound **3** 1,2α = 6, 1,2β = 10, 3,6 = 6,15 = 1 5, 6,7 = 7,8β = 7,11 = 11, 7,8α = 8α,9α = 8α,9β = 9β,9β′ ~ 3, 8α,8β = 9α,9β = 13, 11,13 = 7; Compound **4** 1,2α = 1,OH = 2α,3 = 4, 1,2β = 2α,2β = 2β,3 = 5,6 = 11, 8α,8β = 8β,9α = 14; 8α,9α = 4, 8α,9β = 1 5, 8β,9β = 5.5, 9α,9β = 13, compound **5** 1,2α = 4, 1,2β = 10, 2α,2β = 13, 2α,3 = 8 5, 2β,3 = 6 5, 5,6 = 10, 8′,9 = 2.5, 8′,9′ = 7, 8,8′ = 14, 9,9′ = 14, compound **6** 1,2 = 1,2′ = 7 5, 2,3 = 2′,3 = 7, 5,6 = 10,8,8′ = 15, 8′,9 = 4.5, 8′,9′ = 11 5, compound **7** 1,2α = 6, 1,2β = 10 5, 2α,2β = 8α,8β = 13; 2α,3 = 5,6 = 8α,9 = 11, 2β,3 = 5, 8β,9 = 3, compounds **8a/b** 6,7 = 11, 6,15 = 1 5, 8 8′ = 13, 7,8′ = 8′,9 = 8′,9′ ~ 2 5, 11,13 = 7; compound **9b** 6,7 = 11, 6,15 = 1 7, 7,11 = 12, 11,13 = 7

Table 2 ^{13}C NMR spectral data of **5** and **6** (100 6 MHz, $CDCl_3$, δ-values)

C	5*	6*
1	75 2 *d*	75 2 *d*
2	36 6 *t*	37 0 *t*
3	77 2 *d*	77 2 *d*
4	141 3 *s*	137 5 *s*
5	125 2 *d*	123 7 *d*
6	79 7 *d*	79.5 *d*
7	164 2 *s*	163 7 *s*
8	23 8 *t*	24 2 *t*
9	33 9 *t*	26.2 *t*
10	147 9 *s*	149.4 *s*
11	127 1 *s*	127 1 *s*
12	173 8 *s*	173 6 *s*
13	55 1 *t*	54.7 *t*
14	113 1 *t*	114 9 *t*
15	11 7 *q*	11 4 *q*
OAc	169.9 *s*	169 8 *s*
	21 1 *q*	21 1 *q*

*Some signals may be interchangeable

(calc for $C_{15}H_{22}O_4$. 266 152), 251 (18), 248 (54), 233 (38), 55 (100), $[\alpha]_D^{24^0}$ + 39 ($CHCl_3$; *c* 0 93)

13-O-*Desacetyl eudesma-afraglaucolide* (**4**) Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (OH), 1740 (γ-lactone, OAc), MS *m/z* (rel int) 322 142 $[M]^+$ (9) (calc for $C_{17}H_{22}O_6$ 322 142), 280 (28), 279 (36), 262 (24), 244 (42), 216 (50), 60 (100), $[\alpha]_D^{24^0}$ + 82 ($CHCl_3$, *c* 0 88)

13-O-*Desacetyl-1α-hydroxy-afraglaucolide* (**5**) Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3580 (OH), 1740 (γ-lactone, OAc), MS *m/z* (rel int) 322 142 $[M]^+$ (0 2) (calc for $C_{17}H_{22}O_6$ 322 142), 280 (0 6), 262 (1 3), 244 (5), 216 (4), 201 (3), 60 (100)

13-O-*Desacetyl-1β-hydroxy-afraglaucolide* (**6**) Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3580 (OH), 1740 (γ-lactone, OAc), MS *m/z* (rel int) 322 142 $[M]^+$ (0 4) (calc for $C_{17}H_{22}O_6$ 322 142), 280 (1.5), 262 (7 5), 244 (24), 216 (17), 60 (100), $[\alpha]_D^{24^0}$ −9 ($CHCl_3$; *c* 0 85)

13-O-*Desacetyl-1β-hydroxyisoafraglaucolide* (**7**) Colourless crystals, mp 207°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3590 (OH), 1750 (γ-lactone, OAc), Ms *m/z* (rel. int) 322 142 $[M]^+$ (3), 280 (4 5), 262 (7 7), 244 (20), 216 (11), 57 (100), $[\alpha]_D^{24^0}$ + 52 ($CHCl_3$, *c* 0 25)

Seco-isoerivanin pseudo acid (**8a/b**) Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3600 (OH), 1770 (γ-lactone), 1720 (CO_2R), MS *m/z* (rel int) 280 131 $[M]^+$ (6) (calc for $C_{15}H_{20}O_5$ 280 131), 265 (84), 262 (6), 237 (40), 163 (91), 139 (44), 98 (100) To 3 mg **8a/b** in 2 ml Et_2O excess of CH_2N_2 was added After 2 min evaporation and TLC ($CHCl_3$–C_6H_6–Et_2O, 2 2 1) gave 1 5 mg **9b**, colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1770 (γ-lactone), 1720 (CO_2R, CO), MS *m/z* (rel int) 294 157 $[M]^+$ (5) (calc for $C_{16}H_{22}O_5$ 294 157), 251 (24), 220 (18), 192 (25), 57 (100)

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