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11,13-DEHYDRODESACETYLMATRICARIN AND OTHER SESQUITERPENE LACTONES FROM *ARTEMISIA LUDOVICIANA* VAR. *LUDOVICIANA* AND THE IDENTITY OF ARTECANIN AND CHYRSARTEMIN B

NOBUO OHNO, JONATHAN GERSHENZON, CATHERINE ROANE and TOM J. MABRY

The Department of Botany, The University of Texas at Austin, Austin, TX 78712, U.S.A.

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Key Word Index—*Artemisia ludoviciana* var. *ludoviciana*; Anthemideae; Compositae; *Hypochlora alba*; grasshopper; sesquiterpene lactones; 11,13-dehydrodesacetylmatricarin; achillin; parishin-C; vulgarin; artecanin; chrysartemin-B.

Abstract—11,13-Dehydrodesacetylmatricarin, achillin, parishin-C, vulgarin and artecanin were isolated from *A. ludoviciana* var. *ludoviciana*. The identity of artecanin and chrysartemin-B was confirmed and ^{13}C NMR and ^{1}H NMR data are described.

INTRODUCTION

Artemisia ludoviciana var. *ludoviciana* Nutt. (Compositae: Anthemidae) serves as the primary host for the grasshopper *Hypochlora alba*, but closely related grasshoppers almost completely avoid this plant [1]. In connection with a determination of the chemical and physical bases of these feeding preferences (a joint project with Professors H. Knutson and T. L. Hopkins, Kansas State University), six sesquiterpene lactones were isolated from a $CHCl_3$ extract of *A. ludoviciana* var. *ludoviciana*: a new guaianolide (**1**), three known guaianolides (**3–5**), a known eudesmanolide (**6**) and an incompletely characterized isomer of **6**. The identity of artecanin and chrysartemin-B (**5**) was established by direct comparison of their IR spectra. The structure of the latter has been recently revised as shown by an X-ray diffraction study [2]. Previous collections of *Artemisia ludoviciana* from Oklahoma, New Mexico, and Mexico have yielded thirteen other sesquiterpene lactones including eight eudesmanolides [3–7], four guaianolides [8, 9] and a germacranolide [4], as well as one of the compounds reported here, namely **3** (Table 1).

Although testing of the isolated sesquiterpene lactones with grasshoppers has not yet begun, two of the compounds (**3**, **6**) were shown to have antifeedant activity against larvae of *Spodoptera eridania* (the southern armyworm) in preliminary testing.

RESULTS AND DISCUSSION

Air-dried and ground leaves and stems of *A. ludoviciana* var. *ludoviciana* were extracted with $CHCl_3$. The extract was purified by standard procedures [10]. Chromatographic separations (Si gel and PLC) of the purified syrup gave five sesquiterpene lactones (**1** and **3–6**). A small amount of a sixth compound was isolated and partially characterized as an isomer of **6**. All the known compounds were identified by comparison of their IR and NMR spectra with those of authentic specimens.

Lactone **5** was identified as artecanin [11, 12] by direct comparison of its IR spectrum to that of an authentic specimen. Both of these spectra were also identical to that of an authentic specimen of chrysartemin-B [3, 13]. In 1975, Bhadane and Shafizadeh [12] revised the structures of canin and artecanin proposing structure **5** for canin and the corresponding α-(1,2)-α-(3,4)-diepoxide for artecanin. However, more recently, Osawa *et al.* [2] established by X-ray diffraction that structure **5** corresponds to chrysartemin-B. Since the present investigation has shown that artecanin is equivalent to chrysartemin-B, artecanin, not canin, is also represented by **5**.*

Lactone **1** (mp 224–226°, M^+ 260.105 (obs.), calc. for $C_{15}H_{16}O_4$: 260.105) is an α-methylene-γ-lactone as indicated by an IR absorbance at 1750 cm^{-1}. A set of ^{1}H NMR double doublets at δ 6.40 and 6.62 (in pyridine-d_5) is diagnostic for sesquiterpene lactones with either an 8α or 6α-hydroxyl group [14]. Lactone **1** gave the monoacetate **2** (mp 144–145°, $M^+ = m/e$ 302 = $C_{17}H_{18}O_5$) on treatment with Ac_2O/Py. Examination of the ^{1}H NMR couplings of **1** and double

* That canin and chrysartemin-A are the same compound has also been established in this laboratory (IR comparison of both crystalline samples). An X-ray diffraction study of canin is now in progress at the University of Montana (personal communication from Dr. R. Kelsey). Once the structure of canin is established by X-ray analysis, the nomenclatural matter can be resolved.

Table 1. Sesquiterpene lactones from *Artemisia ludoviciana*

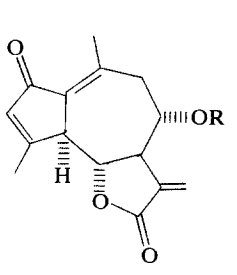
Taxon	Collection site	Sesquiterpene lactones			Ref.
		Eudesmanolides	Guaianolides	Germacranolides	
A. ludoviciana Nutt.	Nuevo Leon, Mexico		desacetylmatricarin, achillin (**3**)		8
A. ludoviciana var. *ludoviciana* Nutt.	Kansas, U.S.A.	vulgarin (**6**)	achillin (**3**), parishin-C (**4**), 11,13-dehydrodes-acetylmatricarin (**1**), artecanin (**5**) (chrysartemin-B)		This work
A. ludoviciana ssp. *albula* (Woot.) Keck.	Oklahoma, U.S.A.	ludalbin			7
A. ludoviciana ssp. *mexicana*	Arizona, U.S.A.	douglanine, ludovicin-A, ludovicin-B, ludovicin-C			6
A. mexicana Willd (syn. *A. ludoviciana* ssp. *mexicana* (Willd) Keck)	Mexico City, Mexico	arglanine, douglanine, armexine,	estafiatin, chrysartemin-A	artemolin	3 9 4
	New Mexico, U.S.A.	santonin			5

resonance experiments on the acetate **2** (Table 2) clearly indicated partial structure **7** for **1** and **2** (including the stereochemistry shown). In the acetate **2**, the H-13b resonance became a doublet with a chemical shift (δ 5.68) as predicted on the basis of an empirical rule [14]. The presence of two more degrees of unsaturation in the molecule as shown by the molecular formula, together with the presence of an additional vinyl methyl group (^{1}H NMR and UV data (λ_{max} 252 and 211 nm)), indicated the guaianolide structure **1**.

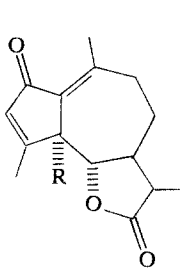
Recently, Bohlmann [15] isolated 11,13-dehydromatricarin from *Athanasia coraropifolia*. This substance is identical in all respects to the present acetate **2**. Thus, the structure of **1** was confirmed as 11,13-dehydrodesacetylmatricarin. ^{13}C NMR data for **1**, **3**, **5** and **6** are given in Table 3.

EXPERIMENTAL

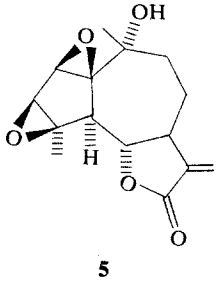
^{1}H NMR and ^{13}C NMR spectra were measured at 100 and 22.6 MHz, respectively. Mps were determined on a Fischer–Johns mp block and are uncorr. Analytical TLC and PLC



1 R = H
2 R = Ac



3 R = H
4 R = OH



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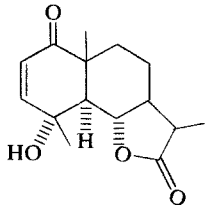

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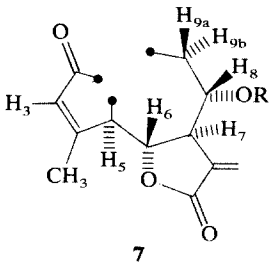

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Table 2. ^{1}H NMR data for **1** and **2***

	1 (Py-d_5)	**1** (Me_2CO-d_6)	**2** ($CDCl_3$)
H-3	6.30 *q*	6.15 *q*	6.23 *q*
H-5	3.52 *bd*	3.70 *bd*	3.52 *bd*
H-6	3.68 *t*	3.78 *t*	3.75 *t*
H-7	3.27 *tt*	3.22 *m*	3.27 *tt*
H-8	4.00 *dt*	3.98 *dt*	4.95 *dt*
H-9a	2.98 *dd*	2.92 *dd*	2.76 *dd*
H-9b	2.60 *dd*	2.43 *dd*	2.48 *dd*
H-13a	6.62 *dd*	6.27 *dd*	6.28 *d*
H-13b	6.40 *dd*	6.15 *dd*	5.68 *d*
C-4Me	2.22 *bs*	2.31 *bs*	2.36 *bs*
C-10Me	2.50 *bs*	2.40 *bs*	2.48 *bs*
C-8 OAc			2.17 *s*

* Run on a 100 MHz instrument in the solvents specified with TMS as internal standard. *J* values (Hz) for protons are essentially the same in all spectra: 3,15 = 1; 5,6 = 10; 6,7 = 10; 7,8 = 10; 7,13a,b = 3; 8,9a = 10; 8,9b = 2.5; 13a,13b = 2 (only in **1**).

(1.0 mm) were done on Si gel 60 GF254. Si gel 60 (70–230 mesh, Merck) was used for CC separations. MS were recorded by direct inlets at 70 eV ionization.

Extraction and isolation. Ground dried leaves and stems (1.23 kg) of *Artemisia ludoviciana* var. *ludoviciana* Nutt. (collected June 1977 near Manhattan, Kansas, Herbert Knutson Voucher No. 1, deposited at the Department of Entomology, Kansas State University) were extracted with petrol (3.9 l. × 2). The petrol extract was concd *in vacuo* affording 18.9 g of dark syrup (syrup-A). The plant material was extracted further with $CHCl_3$ (1.2 l. × 3). The $CHCl_3$ extract was concd *in vacuo* to give 21.3 g of dark syrup, which was purified by standard procedures [10] to give 16.6 g of a yellow syrup (syrup-B).

Table 3. ^{13}C NMR data for **1**, **3**, **5** and **6***

Carbon Nos.	**1** (Me_2CO-d_6)	**3** ($CDCl_3$)	**5** (DMSO-d_6)	**6** ($CDCl_3$)
1	134.2	131.8	81.8	201.8
2	195.5	195.9	86.4 *d*	125.7 *d*
3	136.0 *d*†	135.5 *d*	61.1 *d*	151.9 *d*
4	170.7	170.3	74.4	70.1
5	52.0 *d*	52.9 *d*	48.1 *d*	54.6 *d*
6	82.5 *d*	83.6 *d*	10.0 *d*	79.6 *d*
7	58.3 *d*	51.8 *d*	46.6 *d*	52.4 *d*
8	68.2 *d*	23.5 *t*	26.3 *t*	22.7 *t*
9	49.4 *t*	37.6 *t*	40.7 *t*	34.3 *t*
10	146.2	152.4	74.3	46.3
11	139.2	39.3 *d*	143.7	40.6 *d*
12	169.5	179.6	173.9	178.4
13	121.8 *t*	10.0 *q*	122.8 *t*	12.4 *q*
14	21.3 q^a	21.5 q^b	23.6 q^c	22.7 *q*
15	19.8 q^a	19.8 q^b	30.9 q^c	23.8 *q*

* Run on a 22.6 MHz instrument in the specified solvent with TMS as internal standard. Signals were assigned by means of off-resonance decoupled spectra.

† Indicates multiplicity on off-resonance partially decoupled spectra, signals without indication appeared as singlets.

^{a,b,c} : Assignments may be interchanged.

Syrup-A was chromatographed through a Si gel column (450 g) using a hexane–C_6H_6–EtOAc gradient solvent system, initiated with C_6H_6–hexane (1:1). Eighteen 500 ml fractions were collected. Fractions eluted with C_6H_6–EtOAc (1:1; Nos. 14–18) gave oily crystals which were recrystallized from an EtOAc–*iso*-Pr_2O mixture to give 305 mg achillin (**1**), mp 144° (lit. 144–145° [16]). Fractions 11–13 and the mother liquor of the above recrystallization were combined and purified on a smaller column to give an additional 250 mg of **1**.

Syrup-B was chromatographed through a Si gel column (320 g) using a $CHCl_3$–EtOAc gradient elution system, beginning with $CHCl_3$–EtOAc (10:1). Thirty-four 500 ml fractions were collected. Fractions 3–5 gave crystals on removal of the solvent; the crystals were recrystallized from EtOAc to afford 910 mg of **1**. Fractions 9–15 showed similar spots on TLC and were combined (2.33 g) and subjected to further CC (Si gel, 93 g). The column was developed with a C_6H_6–EtOAc gradient system, initiated with C_6H_6–EtOAc (6:1). Seventeen 150 ml fractions were collected. Fraction 7 (eluted with C_6H_6–EtOAc (3:2)) gave oily crystals after removal of the solvent. The crude crystals were recrystallized from boiling EtOAc to give 26 mg vulgarin (**6**), mp 172.5–174° (lit. 174–175° [17]). The mother liquor of the above recrystallization gave 353 mg of oily material which was purified by PLC to give 9 mg parishin-C (**4**), mp 247–50° (lit. 241–243° [18]). Fractions 9 and 10 gave a semi-crystalline residue which was recrystallized from EtOAc to give 70 mg artecanin (**5**). A portion of the crystals was recrystallized from Me_2CO to give colorless needles, mp 253–254° (lit. 244–245° [12]; 262–265° [3] and 234–237° [13]). ^{1}H NMR, (DMSO): δ 0.98 (3H, *s*), 1.46 (3H, *s*), 2.88 (1H, *d*, *J* = 10 Hz), 3.37 (1H, *d*, *J* = 2 Hz), 3.61 (1H, *d*, *J* = 2 Hz), 3.96 (1H, *dd*, *J* = 10, 12 Hz), 5.56 (1H, *d*, *J* = 3 Hz) and 6.07 (1H, *d*, *J* = 3.5 Hz); (Py-d_5): δ 1.28 (3H, *s*), 1.51 (3H, *s*), 3.26 (1H, *d*, *J* = 10 Hz), 3.75 (1H, *d*, *J* = 2 Hz), 4.45 (1H, *dd*, *J* = 10, 11 Hz), 5.41 (1H, *d*, *J* = 3 Hz) and 6.05 (1H, *d*, *J* = 3.5 Hz). MS *m/e* (rel. int): M^+ 278.1148 (calc. for $C_{15}H_{18}O_5$: 278.1154, 0.1%), 260.1055 (calc. for $C_{15}H_{18}O_5 - H_2O$: 260.1048, 2%), 217(3), 203(4), 151(2), 111(100). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1745, 1680, 1156, 1000, 860, 820 (superimposable on those of authentic specimens of artecanin and chrysartemin-B).

Fraction 8 and the mother liquor of the above recrystallization were combined (1.12 g) and chromatographed over a Si gel column (38 g, Mallinckrodt 100 mesh, mixed with 7 g of celite) using a C_6H_6–EtOAc solvent system. Twenty-four 50 ml fractions were collected. Crystals of the new lactone **1** (45.5 mg) were obtained after recrystallization from EtOAc of the material from fractions 7–13.

11,13-*Dehydrodesacetylmatricarin* (**1**). Mp 224–226° (EtOAc). MS *m/e* (rel. int.): M^+ 260.1052 (calc. for $C_{15}H_{16}O_4$: 260.1048, 100%), 242(11), 227(22), 199(24), 185(18), 171(23), 147(29), 91(18) and 69(80). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1750, 1685, 1650, 1620, uv λ_{max}^{EtOH} nm (log ε): 252, 211 (4.09, 4.03).

11,13-*Dehydromatricarin* (**2**) *from* **1**. 15 mg of **1** were acetylated with Ac_2O–Py to give 9 mg of the crystalline acetate **2** after PLC purification of the crude product, mp 144–145° (lit. 146° [15]). IR and ^{1}H NMR spectra were identical to spectra obtained from an authentic specimen.

Isolation of isomer of **6**. Similar isolation procedures were employed on another 325 g of dried plant material to give 300 mg of **3** from the petrol extract. The $CHCl_3$ extract gave 23 mg of **1**, 36 mg of **5** and 146 mg of crystals consisting of a *ca* 1:1 mixture of **6** and its isomer. Repeated recrystallizations either from EtOAc or *iso*-Pr_2O–EtOAc did not separate the two isomers. The mixture was finally purified on PLC

(C_6H_6–EtOAc, 5:6; R_f vulgarin = 0.30, the isomer = 0.26) to afford 64 mg of **6** and 42 mg of the isomer as a colorless oil. HRMS *m/e* 264.1365 (calc. for $C_{15}H_{20}O_4$: 264.1361). IR ν_{max}^{Film} cm^{-1}: 3220, 1770, 1675; UV λ_{max}^{EtOH} nm: 215. ^1H NMR ($CDCl_3$): δ 1.26 (3H, *s*), 1.25 (3H, *d*, $J = 7$ Hz), 1.52 (3H, *s*), 2.88 (1H, *d*, $J = 11$ Hz), 4.19 (1H, *dd*, $J = 11$, 10 Hz), 6.05 (1H, *d*, $J = 10$ Hz), 6.80 (1H, *d*, $J = 10$ Hz) and 8.50 (1H, *br*, —OH). All the data were similar to those obtained for **6**.

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