Phytochemistry, Vol. 33, No. 5, pp. 1113–1115, 1993
Printed in Great Britain.

0031-9422/93 $6.00+0.00

SESQUITERPENE LACTONES AND FLAVONOIDS FROM *ARTEMISIA LUDOVICIANA* SSP. *MEXICANA**

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(*Received in revised form* 13 *October* 1992)

Key Word Index—*Artemisia mexicana* ssp. *mexicana*; Anthemideae; Asteraceae; sesquiterpene lactones, eudesmanolides, flavonoids.

Abstract—From the aerial parts of the medicinal plant *Artemisia ludoviciana* spp. *mexicana* were isolated douglanin, ludovicin A, 1α,3α-dihydroxyarbusculin B, santamarin, arglanin, artemorin, chrysartemin B, armefolin, ridentin, the new eudesmanolide 3α-hydroxyreynosin, and the flavonoids eupatilin and jaceosidin.

INTRODUCTION

The genus *Artemisia* is a fairly abundant genus located mainly in the northern hemisphere which includes many species used in the flavour industry and for medicinal purposes [1]. The accumulated chemical information indicates that the structural diversity of the major sesquiterpenes and other secondary metabolites isolated from this group of plants is in agreement with its morphological variation [1, 2]. *Artemisia ludoviciana* ssp. *mexicana* (syn: *A. mexicana*; common name: estafiate) is widely utilized in Mexican traditional medicine as an antihelmintic, to alleviate intestinal pain and for other ailments [3, 4]. This species has been previously investigated [5–8], as well as its variety (*A. mexicana* var. *angustifolia*) [9, 10]. Continuing the phytochemical investigation of Mexican *Artemisia* species [5–7, 9–13], we report here the constituents of a population of this plant.

RESULTS AND DISCUSSION

From the methylene dichloride extract of the aerial parts of *A. ludoviciana* ssp. *mexicana* were isolated sitosterol, douglanin [6, 14], ludovicin A [8], 1α,3α-dihydro xyarbusculin B [15], santamarin [9, 10, 16], arglanine [9, 10, 17], artemorin [7, 18], chrysartemin B [19], armefolin [10], ridentin [20] and the flavonoids eupatilin [21] and jaceosidin [22]. The structures were confirmed by direct comparison with authentic samples and comparing physical and spectroscopic data with those reported in the literature.

An additional constituent, hitherto unreported, has been established as 3α-hydroxyreynosin **1a**. This compound showed IR bands at 3607 cm^{-1} (hydroxyl) and 1767 cm^{-1} (γ-lactone). In the ^1H NMR spectrum the following groups were evident (Table 1): an exocyclic methylene conjugated with the γ-lactone (δ6.06 and 5.38, *d*, $J = 3$ Hz), an additional exocyclic methylene (δ5.14 and 4.98), a tertiary methyl group (δ0.76), a hydrogen geminal to the lactone (δ3.98, *t*, $J = 11$ Hz) and two secondary alcohols (carbinolic hydrogens at δ4.32 and 3.92); these last two signals shifted downfield in the acetyl derivative **1b**.

The observed coupling constants for H-1 ($J_{1\alpha,2\alpha} = 5$ Hz; $J_{1\alpha,2\beta} = 11$ Hz), H-3 ($J_{2\alpha,3\beta} = J_{2\beta,3\beta} = 4$ Hz), and H-6 ($J_{5\alpha,6\beta} = J_{6\beta,7\alpha} = 11$ Hz) of the natural compound are in agreement with the stereochemistry showed

Table 1. ^1H NMR spectral data of **1a**, **1b** and **3** (80 MHz, $CDCl_3$)

H	1a	1b	3
1	3.92 *dd*	5.12 *t*	3.44 *dd*
3	4.32 *t*	5.45 *t*	3.01 *dd*
5	2.72 *d*	2.70 *d*	1.80 *d*
6	3.98 *t*	3.99 *t*	3.80 *t*
7	2.50 *m*	2.50 *m*	2.45 *m*
13a	6.06 *d*	6.10 *d*	6.09 *d*
13b	5.38 *d*	5.42 *d*	5.41 *d*
14	0.76 *s*	0.92 *s*	0.91 *s*
15a	5.14 *br s*	5.34 *br s*	–
15b	4.98 *br s*	5.15 *br s*	1.49 *s*

J(Hz) **1a**, **1b**: 1α,2α = 5; 1α,2β = 11; 2α, 3β = 2β,3β = 4; 5α,6β = 6β,7α = 11; 7α,13*a* = 7α,13*b* = 3. **3**: 1α,2α = 5; 1α,2β = 12; 2α,3β = 1; 2β,3β = 2.8; 5α,6β = 6β,7α = 11; 7α,13*a* = 7α,13*b* = 3.

*Contribution 1163 from Instituto de Química de la UNAM.
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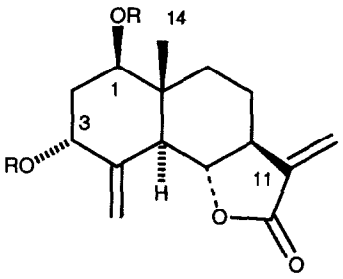
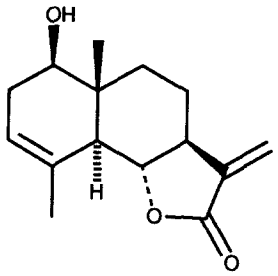


1a R=H
1b R=Ac



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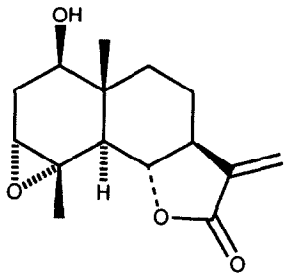

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in **1a**. Analysis of the ^{13}C NMR chemical shifts of this substance (Experimental) provided further support to the stereochemical assignments. Comparison of the ^{13}C NMR spectral data of **1a** with those of reynosin [23] clearly indicated an additional hydroxyl at 3α, due to the upfield of C-1 ($\Delta\delta = -5.8$) and C-5 ($\Delta\delta = -5.6$) and the downfield of C-2 ($\Delta\delta = +7.1$) and C-4 ($\Delta\delta = +3.6$). Finally, compound **1a** was obtained from santamarine **2**, via stereoselective epoxidation (to afford **3**) and acid catalysed regio-selective epoxide opening, affording 3a-hydroxyreynosin **1a**.

The different secondary metabolites isolated from this population of *A. ludoviciana* ssp. *mexicana* with respect to other populations [5–8] may be due to infraspecific variations [24] and are in agreement with the diversity of the constituents present in *Artemisia* [1, 2].

EXPERIMENTAL

Artemisia ludoviciana ssp. *mexicana* (Willd.) Keck (syn: *A. mexicana* Willd) was collected in Milpa Alta, México, D. F., on September 1986. A voucher is deposited at the National Herbarium, Instituto de Biología de la UNAM (MEXU 481869). The air-dried material (11 kg) was extracted with *n*-hexane and then with CH_2Cl_2 at room temp., affording 410 g of extract. This residue (300 g) was extracted with MeCN, to afford 234 g of a gum. This gum (100 g) was chromatographed on vacuum CC (VCC) [25] using *n*-hexane–EtOAc gradient elution system, followed by repetitive prep. TLC. This procedure allowed the isolation in order of increasing polarity of sitosterol (762 mg), douglanin (390 mg) [6, 14], ludovicin A (55 mg) [8], 1α,3α-dihydroxyarbusculin B (60 mg) [15], santamarin (140 mg) [9, 10, 16], arglanine (159 mg) [9, 10, 17], eupatilin (38 mg) [21], artemorin (68 mg) [7, 18], jaceosidin (24 mg) [22], chrysartemin B (59 mg) [19], 3α-hydroxyreynosin (125 mg), armefolin (141 mg) [10] and ridentin (175 mg) [20].

3α-Hydroxyreynosin (**1a**). Crystals from EtOAc–*i*-Pr_2O. Mp 236–237°. $[\alpha]_D$ +73° (Me_2CO; *c* 0.23). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3607, 1767, 1414, 1257, 1230, 1137, 1026, 999. UV λ_{max}^{MeOH} nm (log ε): 203 (3.8). EIMS *m/z* (rel. int.): 246 [M $-H_2O]^+$ (24), 228 (16), 165 (53), 147 (30), 131 (33), 119 (34), 105 (50), 97 (76), 55 (73), 53 (100). ^1H NMR (80 MHz, $CDCl_3$): see Table 1. ^{13}C NMR (20 MHz, $CDCl_3$): δ 72.3 (*d*, C-1 or C-3), 38.5 (*t*, C-2), 72.7 (*d*, C-1 or C-3), 146.1 (*s*, C-4), 47.4 (*d*, C-5), 79.6 (*d*, C-6), 49.6 (*d*, C-7), 21.4 (*t*, C-8), 35.7 (*t*, C-9), 43.3 (*s*, C-10), 139.6 (*s*, C-11), 170.6 (*s*, C-12).

Diacetyl 3α-hydroxyreynosin (**1b**). Compound **1a** (12.4 mg) was acetylated as usual to give 12.2 mg of **1b** as an oil. $[\alpha]_D$ 56.3 ($CHCl_3$; *c* 0.16). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767, 1732, 1373, 1136, 1056, 1021, 966. ^1H NMR (80 MHz, $CDCl_3$): see Table 1. EIMS *m/z* (rel. int.): 228 (6), 183 (5), 120 (8), 105 (22), 91 (15), 88 (9), 87 (12), 70 (13), 43 (100).

3α,4α-Epoxisantamarin (**3**). Compound **2** (57 mg) in CH_2Cl_2 (5 ml) was reacted with *m*-CPBA (102 mg) at 0°. Usual work-up yielded 52 mg of a solid, **3**, mp 241–242° (from Me_2CO–*i*-Pr_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1764. ^1H NMR (80 MHz, $CDCl_3$): see Table 1. EIMS 70 eV *m/z* (rel. int.): 264 $[M]^+$ (3), 249 (10), 189 (38), 147 (60), 119 (49), 91 (33), 79 (33), 77 (32), 53 (50), 43 (100).

Acid treatment of compound **3**. Compound **3** (25 mg) in CH_2Cl_2 (10 ml) was reacted with *p*-TsOH (4 mg) at 0°. Usual work-up and prep. TLC of the reaction mixture yielded 8 mg of **1a**, identified by direct comparison, and 6 mg of starting material **3**.

Acknowledgements—We thank Messrs R. Villena, M. Torres, L. Velasco, F. del Río, J. Espiñeira, R. Gaviño and R. Patiño (Instituto de Química de la UNAM) for running the spectra, and Francisco Ramos (Instituto de Biologia de la UNAM) for identification of plant material.

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