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SESQUITERPENE LACTONES FROM *SERRATULA LATIFOLIA*

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Key Word Index—*Serratula latifolia*; Compositae; sesquiterpene lactones; guaianolides; guaianolide hydroperoxides; eudesmanolides.

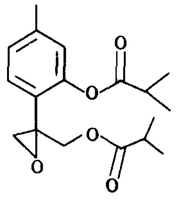
Abstract—The aerial parts of *Serratula latifolia* afforded in addition to costic acid and a thymol derivative, alantolactone, ivalin, carabrone and pseudoivalin, three new guaianolide hydroperoxides all biogenetically derived from pseudoivalin. The structures were elucidated by high field ^{1}H NMR spectroscopy and the stereochemistry was determined by NOE difference spectroscopy.

INTRODUCTION

The genus *Serratula* (tribe Cynareae) with about 70 species is placed in the subtribe *Centaureinea* in the first group together with *Acroptilon, Rhaponticum, Tricholepis* and *Leuzea* [1]. The roots mostly contain acetylenic compounds, especially thiophene acetylenes [2] while from the leaves mainly flavones [3, 4] and some triterpenes are reported. All these constituents are not very characteristic as they are widespread in the family. We have now studied a species from Iran, *Serratula latifolia* Boiss.

RESULTS AND DISCUSSION

The extract of the aerial parts of *S. latifolia* afforded the thymol derivative **1** [5], costic acid (**2**) [6], alantolactone (**3**) [7], ivalin (**4**) [8], carabrone (**5**) [9], pseudoivalin (**6**) [10] and three new sesquiterpene lactones, the guaianolides **7–9**. The structures of the known compounds were elucidated by comparison of the 400 MHz ^{1}H NMR spectra with those of authentic material or by using the sequences obtained by spin decoupling. The data of **4** and **6** are included in Table 1 as no high field NMR data for these compounds is to be found in the literature.



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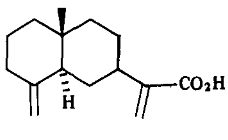

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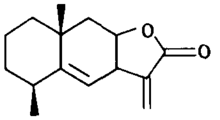

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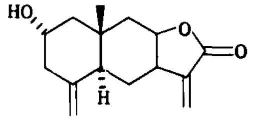

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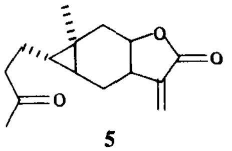

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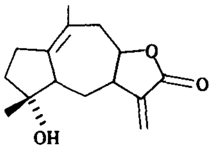

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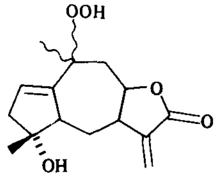
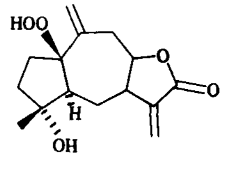


7 10αMe **8** 10βMe



9

Compound **7** gave no molecular ion in the mass spectrum. However, with chemical ionization two strong fragments, *m/z* 263 $[M+1-H_2O]^+$ and *m/z* 247 $[M+1-H_2O_2]^+$, were visible. The presence of a hydroperoxide was supported by the occurrence in the ^{1}H NMR spectrum (Table 1) of a broadened singlet at δ7.81, typical for such derivatives. Furthermore, the presence of a 12,8-guaianolide was indicated by the characteristic signals of H-7 and H-8 (δ3.19 *ddddd* and 4.77 *ddd* respectively). The chemical shifts and the couplings agreed with the presence of a *cis*-lactone. Irradiation of a triplet of doublets at δ5.75 altered the signals at 2.60, 2.48 and 2.41. The protons corresponding to the latter two signals showed a geminal coupling of 16 Hz and homoallylic coupling with the proton which gave the signal at δ2.60. Further spin decoupling indicated that the latter signal was due to H-5 as starting with this signal a sequence H-5, H-6α, H-6β and H-7 could be assigned as irradiation of the signal of the latter proton collapsed the typical H-13 doublets to singlets. Furthermore a triplet of doublets at δ4.77 was altered to a doublet of doublets indicating that this signal

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Table 1. ^{1}H NMR spectral data of compounds **4** and **6**–**9** (400 MHz, $CDCl_3$)

H	**4***	**6**	**7**	**8**	**9**
2	3.84 *dddd*	2.49 *br dd* 2.17 *m*	5.75 *ddd*	5.73 *br t*	2.00 *m* 1.83 *m*
3	2.69 *ddd*	1.80 *m*	2.41 *ddd*	2.44 *br s*	2.33 *m*
3′	2.01 *br dd*	1.73 *m*	2.48 *ddd*		2.00 *m*
5	1.84 *br d*	2.40 *br d*	2.60 *ddddd*	2.65 *br d*	2.00 *br d*
6α	1.81 *ddd*	2.22 *ddd*	1.90 *ddd*	2.07 *ddd*	1.64 *ddd*
6β	1.37 *ddd*	1.48 *ddd*	1.61 *ddd*	1.35 *ddd*	1.41 *ddd*
7	3.00 *br ddd*	3.25 *ddddd*	3.19 *ddddd*	3.38 *ddddd*	3.05 *ddddd*
8	4.52 *ddd*	4.80 *ddd*	4.77 *ddd*	5.03 *ddd*	4.69 *ddd*
9	2.27 *dd*	2.32 *br dd*	2.31 *dd*	2.44 *dd*	2.90 *ddd*
9′	1.54 *dd*	2.17 *dd*	2.37 *dd*	1.81 *dd*	2.67 *br dd*
13	6.15 *d*	6.30 *d*	6.31 *d*	6.27 *d*	6.21 *d*
13′	5.61 *d*	5.63 *d*	5.69 *d*	5.61 *d*	5.62 *d*
14 14′	0.84 *s*	1.63 *br s*	1.39 *s*	1.59 *s*	5.35 *br s* 5.31 *br s*
15	4.89 *br s* 4.56 *br s*	1.05 *s*	1.28 *s*	1.37 *s*	1.24 *s*
OOH	—	—	7.81 *br s*	7.98 *br s*	7.75 *br s*

*H-1 1.92 *ddd*; H-1′ 1.21 *dd*.

J(Hz): Compound **4**: 1,1′ = 3,3′ = 12; 1,2 = 2,3 = 4; 1,3 = 2; 1′,2 = 2,3′ = 11; 5,6β = 6α,6β = 6β,7 ≈ 12.5; 5,6α = 2; 6α,7 = 7; 7,8 = 8,9′ = 4.5; 7,13 = 8,9 ≈ 1; compounds **6**–**9**: 5,6β = 6α,6: = 6β,7α ≈ 12.5; compound **6**: 2,2′ = 15; 2,3′ = 13; 5,6α = 1.5; 6α,7 = 5; 7,8 = 8.5; 7,13 = 3.5; 7,13′ = 3; 8,9 = 11; 8,9′ = 2.5; 9,9′ = 15; compound **7**: 2,3 = 2,3′ = 2,5 = 3′,5 = 5,6α = 2; 3,3′ = 15; 3,5 = 1.5; 6α,7 = 4; 7,8 = 8; 7,13 = 2.5; 7.13′ = 2; 8,9 = 5; 8,9′ = 11; 9,9′ = 14; compound **8**: 2,3 = 2; 5,6α = 1.5; 6α,7 = 5; 7,8 = 8; 7,13 = 2.8; 7,13′ = 2.5; 8,9 = 4; 8,9′ = 12; 9,9′ = 14; compound **9**: 5,6α = 2; 6α,7 = 4; 7,8 = 8,9′ = 6; 7,13 = 2; 7,13′ = 1.8; 8,9 = 4.5; 9,9′ = 14.5; 9,14 = 0.8.

was due to H-8 which also was coupled with the protons showing a doublet of doublets at δ2.37 and 2.31 which therefore must be due to H-9. The chemical shift of two singlets (δ1.39 and 1.28) required methyl groups on carbons bearing an oxygen function. Thus the presence of a guaian-12,8α-olide with 1.2- and 11.13-double bonds and oxygen functions at C-4 and C-10 was very likely. The relative position of the oxygen functions and the stereochemistry was determined by NOE difference spectroscopy. Saturation of H-15 (δ1.28 *s*) gave clear effects with H-6α (9%) and H-6β (5%) but not with H-5. Further NOE's were observed between H-14, H-8 (16%), H-7 (3%), H-5 (8%), H-9α (8%) and H-2 (7%), between H-7 and H-5 (10%) and H-8 (12%) as well as between OOH and H-2 (3%).

The ^{1}H NMR spectrum of **8** (Table 1) was very close to that of **7**. However, several signals were slightly shifted and also the couplings were in part not completely the same. All data therefore agreed with the presence of an epimer of **7**. The downfield shifts of H-9α, H-8 and H-7 indicated a 10α-orientation of the hydroperoxide group. As the shift of H-5 was nearly identical in the spectra of **7** and **8** a changed stereochemistry at C-4 could be excluded.

The ^{1}H NMR spectral data of **9** (Table 1) were more different from those of **7** and **8**. A broadened singlet at δ7.75 indicated that again a hydroperoxide was present, obviously a further isomer of **7** as CIMS showed again *m*/*z* 247 $[M+1-H_2O_2]^+$. The most striking difference in the NMR spectrum was the replacement of one methyl singlet by two signals for exomethylene protons. Furthermore, the olefinic proton (H-2) was absent and the H-5 signal was shifted upfield. All data therefore agreed with the presence of a 4α-hydroxyguaia-10(14), 11(13)-dien-12,8β-olide with a hydroperoxide group at C-1. Comparison of the chemical shifts of **9** with those of the corresponding guaianolide with no oxygen function at C-1 indicated that the hydroperoxide was most likely β-orientated. This was supported by the chemical shifts of H-14 which should not be influenced so much by an α-hydroperoxide group.

Thus all these hydroperoxides are derived from pseudoivalin by reaction with oxygen. The remaining possible isomer, the 1-*epi* derivative of **9**, was not detected.

The constituents of *S. latifolia* are typically different from those of *Acroptilon*, *Tricholepis*, *Leuzea* and *Rhaponticum* placed together in the first group of subtribe Centaureinea [1]. From the first two genera guaianolides have been reported [11–13] but of different substitution pattern, closely related to those of the genus *Centaureae*. So far from *Rhaponticum* and *Leuzea* no sesquiterpene lactones have been isolated, but from all genera thiopene acetylenes have been isolated.

EXPERIMENTAL

The air-dried, aerial parts (300 g, collected 70 km N of Tehran, Iran, voucher deposited in the Herbarium of the Department of Botany, Shahid Beheshty University, Tehran) were extracted at room temp. with MeOH–Et_2O–petrol, 1:1:1). After evapn of the solvent the residue was treated with MeOH to remove longchain saturated compounds. The soluble part was separated by CC (silica gel). The fractions obtained with Et_2O–petrol (1:3) were further separated by TLC (silica gel PF 254, Et_2O–petrol, 3:7) affording 25 mg **1** (R_f 0.55) and 30 mg **3** (R_f 0.45). The polar CC fractions (Et_2O–petrol, 1:1, Et_2O and Et_2O–MeOH, 9:1) gave by TLC (Et_2O–petrol, 3:2) 50 mg **2** (R_f 0.85), 60 mg **5** (R_f 0.75), 30 mg **6** (R_f 0.50), 100 mg **4** (R_f 0.42) and a mixture which was further separated by HPLC (RP 8, MeOH–H_2O, 1:1, *ca* 100 bar, flow rate, 3 ml/min), 12 mg **7** (R_t 4.7 min), 8 mg **9** (R_t 5.9 min), 15 mg **8** (R_t 7.0 min), 10 mg **4** (R_t 9.2 min) and 6 mg **6** (R_t 12.6 min). Compounds **1–3** and **5** were identified by comparing the 400 MHz ^1H NMR spectra with those of authentic material. The structures **4** and **6** were elucidated by their spectroscopic data including mass spectra and 400 MHz ^1H NMR spectra with spin decoupling.

4α-Hydroxy-10β-hydroperoxyguaia-1,11(13)-*dien*-12,8*β-olide* (**7**). Colourless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1770 (γ-lactone); CIMS *m/z* (rel. int.). 263 $[M+1-H_2O]^+$ (22), 247 $[M+1-H_2O_2]^+$ (41), 245 $[263-H_2O]^+$ (24), 229 $[263-H_2O_2]^+$ (44), 157 (100); $[\alpha]_D^{24°}+23$ ($CHCl_3$; *c* 0.19).

4α-Hydroxy-10α-hydroperoxyguaia-1,11(13)-*dien*-12,8*β-olide* (**8**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1770 (γ-lactone); CIMS *m/z* (rel. int.): 263 $[M+1-H_2O]^+$ (74), 247 $[M+1-H_2O_2]^+$ (70), 245 $[263-H_2O]^+$ (100), 229 $[263-H_2O_2]^+$ (88); $[\alpha]_D^{24°}-21$ ($CHCl_3$; *c* 0.23).

4α-Hydroxy-1β-hydroperoxyguaia-10(14),11(13)-*dien*-12, 8*β-olide* (**9**). Colourless oil; IR $\nu_{max}^{CHCl_3}$, cm^{-1}: 3600 (OH), 1770 (γ-lactone); CIMS *m/s* (rel. int.): 263 $[M+1-H_2O]^+$ (20), 247 $[M+1-H_2O_2]^+$ (26), 229 $[263-H_2O_2]^+$ (25), 197 (54), 170 (100); $[\alpha]_D^{24°}+20$ ($CHCl_3$; *c* 0.33).

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