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SESQUITERPENE LACTONES FROM *MIKANIA* SPECIES

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Key Word Index—*Mikania guaco*; *M. vitifolia*; Compositae; sesquiterpene lactones; guaianolides; pycnolide derivative; eudesmanolides.

Abstract—The aerial parts of *Mikania guaco* afforded in addition to a known eudesmanolide three new ones. The aerial parts of *M. vitifolia* gave two guaianolides, both being 3-chlorodehydroleudocin derivatives and a seco-germacranolide related to pycnolide. The structures were elucidated by highfield NMR techniques. The proposed position of the hydroxyl group in a chloroguaianolide from a *Lasiolaena* species has to be revised.

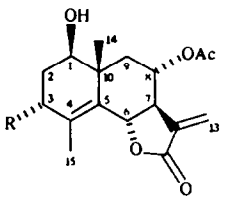
INTRODUCTION

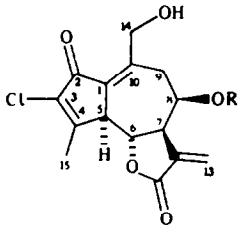
The large genus *Mikania* (Compositae, tribe Eupatorieae, subtribe Mikaniinae) with about 300 species is distributed over the tropical parts of America, Africa and Asia. So far 20 species have been investigated chemically. While several species contain sesquiterpene lactones, mostly germacranolides [1–9] but also some unusual lactones [1, 3, 4, 7], others lack these compounds and high concentrations of diterpenes, mostly kaurene derivatives, are present [5]. We have now studied two further species from Costa Rica. Again there are two groups, those containing lactones and those affording diterpenes. The results will be discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of *Mikania guaco* Hum. et Bonpl., which have been used for many years in folk medicine against snake and scorpion bites, afforded in addition to widespread compounds (Experimental) four eudesmanolides, namely rothin B acetate (**4**) [10] and three new compounds identified as the hydroxy acetates **1** and **3** and dihydroxy acetate **2**. The structure of **1** followed from the ^{1}H NMR spectrum (Table 1) in which all signals could be assigned by spin decoupling. The relative positions of the oxygen functions were deduced from the chemical shifts and the stereochemistry followed from the couplings observed. The ^{1}H NMR spectrum of **2** was similar to that of **1** but the H-3 signals were replaced by a broadened singlet at δ4.32 indicating the presence of an axial hydroxyl group at C-3. Spin decoupling established this proposal. Thus compound **2** was 3α-hydroxy-8α-acetoxybalchanine. The ^{1}H NMR spectrum (Table 1) of lactone **3** differed more significantly from that of **1**. The changed position of the double bond followed from the presence of a triplet for H-6 and that of a broadened singlet at δ5.37 for H-3. Spin decoupling showed that compound **3** was the Δ^3 isomer of **1** and the epimer of ludalbin [11].

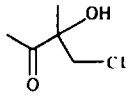
The aerial parts of *Mikania vitifolia* DC. afforded *ent*-kaurenic acid and three sesquiterpene lactones, the 3-chloro-dehydroleucodin derivatives **5** and **6** and the seco-germacranolide **8**. The ^{1}H NMR spectra of **5** and **6** (Table 1) were similar to that of guaianolide isolated from a *Trichogonia* species where the structure was established by X-ray analysis [12]. However, the tiglate residue at C-8 was replaced by a methacryloyl group in **5** and a 2-hydroxy-3-chloroisobutyryloxy residue in **6**. Furthermore, the data showed that the 9-hydroxyl group was missing in **5** and **6**. Spin decoupling allowed the assignment of all signals and the relative





	1	2	3	4
R	H	OH	H	H
			Δ^3,5αH	$\Delta^{4(15)}$,5αH

5 R = Meacr

6 R = 

7 R = Δ9βOH

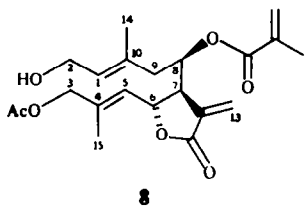


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Table 1. ^{1}H NMR spectral data of compounds 1–3, 5 and 6 (400 MHz, $CDCl_3$, TMS as internal standard)

H	1	2	3	5*	6*
1	3.55 *dd*	3.81 *dd*	3.68 *dd*	—	—
2	1.74 *m*	2.36 *ddd*	2.38 *m*	—	—
2′		1.77 *ddd*	1.95 *m*	—	—
3	2.23 *br ddd*	4.32 *br d*	5.37 *br s*	—	—
3′	2.06 *br d*				—
5	—	—	2.39 *br d*	3.65 *br d*	3.65 *br d*
6	4.62 *ddq*	4.65 *ddq*	4.03 *t*	4.12 *t*	4.13 *t*
7	2.86 *dddd*	2.92 *dddd*	2.79 *dddd*	3.22 *br ddd*	3.26 *br ddd*
8	5.19 *ddd*	5.19 *ddd*	5.27 *ddd*	5.80 *br d*	5.87 *br d*
9	2.49 *dd*	2.54 *dd*	2.48 *dd*	3.34 *dd*	3.29 *dd*
9′	1.30 *dd*	1.30 *dd*	1.25 *dd*	2.71 *br d*	2.71 *br d*
13	6.22 *d*	6.24 *d*	6.13 *d*	6.23 *d*	6.27 *d*
13′	5.63 *d*	5.65 *d*	5.53 *d*	5.61 *d*	5.63 *d*
14	1.17 *s*	1.16 *s*	0.94 *s*	4.63 *br dd* 4.55 *br dd*	4.96 *d* 4.31 *d*
15	1.89 *br s*	2.05 *t*	1.85 *br s*	2.44 *d*	2.39 *br s*
OAc	2.12 *s*	2.12 *s*	2.10 *s*	—	—

*OMeacr: 5.97 *br s*, 5.58 *br s*, 1.86 *dd*; 3.66 and 3.49 *d* (J = 11 Hz), 1.38 *s*.

J (Hz): Compounds 1 and 2: 1,2 = 4; 1,2′ = 12; 3,6 = 6, 15 = 1.5; 6,7 = 7,8 = 11; 7,13 = 3.5; 7,13′ = 3; 8,9 = 4.5; 8,9′ = 11; 9,9′ = 13; (compound 1: 2,3 = 2′,3 ~ 8; 3,3′ = 17; compound 2: 2,2′ = 14; 2,3 = 2; 2,3′ = 4); compound 3: 1,2 = 10; 1,2′ = 6.5; 5,6 = 6,7 = 7,8 = 8,9′ = 11; 7,13 = 3; 7,13′ = 2.7; 8,9 = 4.5; 9,9′ = 13; compounds 5 and 6: 5,6 = 6,7 = 10; 7,13 = 3; 7,13′ = 2.6; 8,9 = 6; 9,9′ = 15; 14,14′ = 14; (compound 5: 14, OH = 6).

position of the hydroxy group was established by NOE difference spectroscopy. Clear effects were obtained between H-15, H-6 and H-5 indicating that no hydroxyl was at C-15. Also, the ^{13}C NMR data of **5** were close to those of the 8β-tigloyloxy derivative [12]. Accordingly, the structures of the two new guaianolides were settled. The structure of a similar lactone isolated from a *Lasiolaena* species [13] has to be revised. NOE difference spectroscopy indicated that here the hydroxyl group was also at C-14 as in **7** and not at C-15. Accordingly, **7** is a desacetyl derivative of the lactone from *Trichogonia gardneri* [12]. The third lactone showed a ^{1}H NMR spectrum (Experimental) which was in part close to that of pycnolide, a seco-germacranolide from *Liatris pycnostachya* [14]. However, the tiglate residue was replaced by a methacrylate and a singlet at δ2.11 indicating an acetate group. Furthermore the H-3 singlet of pycnolide was replaced by a pair of doublets at δ4.56 and 4.50. The downfield shift of these signals and the unchanged chemical shift of H-2 clearly indicated that the 3-hydroxyl group of pycnolide was esterified. All signals were assigned by spin decoupling and the relative position of the ester groups were determined by NOE difference spectroscopy. Irradiation of H-6 caused a clear effect on H-3′ (5.60 *br s*) of the axial orientated ester side chain at C-8. Further NOEs were observed between H-14, H-8 and H-5, between H-15, H-3 and H-6 as well as between H-7, H-8 and H-5. These effects support a fixed conformation which may be due to a hydrogen bridge with the 2-hydroxyl group.

The overall picture of the chemistry of this large genus is still not very uniform as one group of species contain highly oxygenated sesquiterpene lactones and a second group contains only diterpenes, mainly *ent*-kaurene derivatives. Those species which accumulate sesquiterpene lactones produce mainly unusual lactones, but as in the case of *M. guaco* also simple sesquiterpene lactones are present [3, 8, 9]. Further investigations, including taxonomic ones, may show whether the genus can be subdivided into sections or subgenera.

EXPERIMENTAL

The air dried plant material (collected near San Carlos, Costa Rica, in February 1985, vouchers deposited in the National Herbarium of Costa Rica) was extracted with Et_2O–petrol–MeOH (1:1:1) and the extracts obtained were first separated by CC (silica gel). Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material.

Mikania guaco (185 g, voucher 108542). Four CC fractions were collected: Fr. 1: petrol; Fr. 2: Et_2O–petrol (1:10); Fr. 3: Et_2O–petrol (1:1) and Fr. 4: Et_2O and Et_2O–MeOH (9:1). TLC of fraction 1 (petrol) gave 20 mg bisabolene. Fraction 2 gave 800 mg lupeyl acetate and fraction 3 gave 1 g lupeol. TLC of fraction 4 (Et_2O–petrol, 1:1, three developments) gave 26 mg **3** (R_f 0.58 always in Et_2O), 5 mg **1** (R_f 0.57), 27 mg **4** (R_f 0.50) and 1 mg **2** (R_f 0.39).

Mikania vitifolia (1250 g, voucher 108504). Two CC fractions were obtained (Fr. 1: Et_2O–petrol, 1:4; Fr. 2: Et_2O and Et_2O–MeOH, 9:1). Fraction 1 contained 1 g *ent*-kaurenic acid and TLC (Et_2O) of fraction 2 gave 64 mg **6** (R_f 0.23) and a mixture (R_f 0.52) which was separated by HPLC (RP 8,

MeOH–H_2O, 7:3; *ca* 100 bar 3 ml/min) affording 4 mg **8** (*R*, 3.8 min) and 0.5 mg **5** (*R*, 5.5 min).

8α-Acetoxyarbusculin B (**1**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630 (OH), 1780 (γ-lactone), 1750, 1240 (OAc); MS *m/z* (rel. int.): 306.147 (2) $[M]^+$ (calc. for $C_{17}H_{22}O_5$: 306.147), 288 (1.3) $[M-H_2O]^+$, 246 (13) $[M-HOAc]^+$, 228 (30) $[246-H_2O]^+$, 213 (41) $[228-Me]^+$, 202 (100) $[246-C_2H_4O]^+$; $[\alpha]_D^{24} = +55°$ ($CHCl_3$; *c* 0.51).

8α-Acetoxy-3α-hydroxyarbusculin B (**2**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1780 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 322.142 (4) $[M]^+$ (calc. for $C_{17}H_{22}O_6$: 322.142), 304 (12) $[M-H_2O]^+$, 244 (28) $[304-HOAc]^+$, 55 (100).

1-Epiludalbin (**3**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1780 (γ-lactone), 1750 (OAc); MS *m/z* (rel. int.): 306.147 (2) $[M]^+$ (calc. for $C_{17}H_{22}O_5$: 306.147), 288 (18) $[M-H_2O]^+$, 228 (100) $[M-HOAc]^+$, 213 (36) $[228-Me]^+$.

14-Hydroxy-8β-methacryloyloxy-3-chlorodehydroleucodin (**5**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γlactone), 1720 (C=CCO_2R), 1700 (C=CC=O); MS *m/z* (rel. int.): 378.086 (19) $[M]^+$ (calc. for $C_{19}H_{19}O_6Cl_2$: 378.085), 292 (24) $[M-RCO_2H]^+$, 263 (26) $[292-CHO]^+$, 69 (100) $[C_3H_5CO]^+$.

14-Hydroxy-8β-[3-chloro-2-hydroxyisobutyryloxy]-3-chlorodehydroleucodin (**6**). Colourless crystals, mp 180.4°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1740 (CO_2R), 1700 (C=CC=O); MS *m/z* (rel. int.): 430.059 (5) $[M]^+$ (calc. for $C_{19}H_{20}O_7Cl_2$: 430.059), 292 (44) $[M-RCO_2H]^+$, 264 (58) $[292-CO]^+$, 115 (28) $[RCO]^+$, 93 (100) $[115-CO]^+$; ^{13}C NMR ($CDCl_3$, C-1–C-19): δ 131.9, 185.7, 137.4, 147.7, 50.8, 77.9, 52.9, 71.3, 75.1, 162.1, 133.3, 168.1, 121.8, 57.2, 17.6, 172.2, 75.3, 50.3, 23.4; $[\alpha]_D^{24} = +8°$ ($CHCl_3$; *c* 0.64).

8β-Methacryloxyloxy-8-desacyloxy-pycnolide-3-O-acetate (**8**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 1760 (γ-lactone), 1720 br (OAc, C=CCO_2R); CIMS *m/z* (rel. int.): 393 (24) $[M+1]^+$, 375 (100) $[393-H_2O]^+$, 289 (47) $[375-RCO_2H]^+$; $[\alpha]_D^{24} = +88°$ ($CHCl_3$; *c* 0.4); ^1H NMR ($CDCl_3$): δ 5.36 (*br t*, H-1)*, 4.11 (*br d*, H-2), 4.55 and 4.50 (*br d*, H-3), 5.45 (*dt q*, H-5), 5.29 (*dd*, H-6), 3.08 (*dddd*, H-7), 5.36 (*ddd*, H-8)*, 2.38 (*br dd*, H-9), 2.24 (*br dd*, H-9'), 6.38 and 5.74 (*d*, H-13), 1.76 (*br s*, H-14), 1.87 (*br s*, H-15), 6.06 (*br s*), 5.60 (*br s*) and 1.92 (*dd*, *J* = 1, 1 Hz, OMeacr), 2.11 (*s*, OAc). * These ovalapped signals were separated by addition of C_6D_6; (*J* [Hz]: 1,2 = 7; 3,3' = 13.5; 5,6 = 9; 7,8 = 5; 7,13 = 2.8; 7,13' = 2.5; 7,8 = 3; 8,9 = 7.5; 8,9' = 6.5; 9,9' = 14).

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