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FURTHER HELIANGOLIDES AND GUAIANOLIDES FROM *EUPATORIUM ALTISSIMUM*

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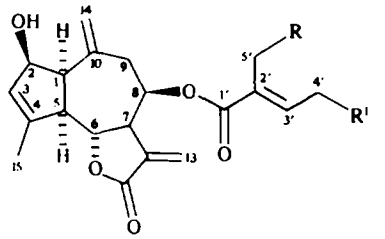
Key Word Index—*Eupatorium altissimum*; Compositae; sesquiterpene lactones; heliangolides; guaianolides.

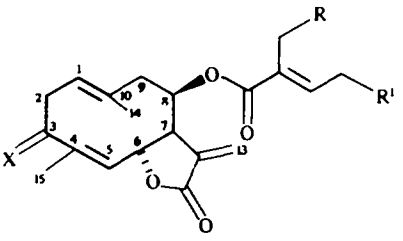
Abstract—The investigation of the aerial parts of *Eupatorium altissimum* from a collection in West Virginia gave three new guaianolides, six heliangolides and a costunolide all closely related to lactones isolated previously from the tribe Eupatorieae.

Eupatorium altissimum L. (tribe Eupatorieae, subtribe Eupatoriinae) has been investigated previously. In addition to flavones a sesquiterpene lactone glucoside [1] and two pyrrolizidine alkaloids [2] were reported. We now have investigated a sample collected in West Virginia. The aerial parts afforded the guaianolides **1** [3], **2**–**4**, **5** [4] and **6** [3], the heliangolides **7**–**10** and **12**–**14** [5] and **15** [6] as well as the germacranolide **11**. The structure of **2** could be deduced easily from the ^{1}H NMR spectrum (Table 1) which was close to that of **1** [3]. The presence of a tiglate followed from the typical signals. Similarly the presence of a 5′-hydroxy derivative of **1** could be deduced from the ^{1}H NMR spectrum (Table 1) of **3** as the broadened methyl singlet in the spectrum of **1** was replaced by a two-proton signal at δ4.20. Also the structure of **4** directly followed from the ^{1}H NMR spectrum (Table 1). The spectrum only



	1	2	3	4	5	6
R	H	H	OH	OH	H	H
R¹	OH	H	OH	OH	H	OH

10α,14-epoxide



	7	8	9	10	11	12	13	14	15
R	H	H	OH	H	H	H	H	H	OH
R¹	H	OH	OH	OH	OAc	H	OH	OH	OH
X	αOH,H	αOH,H	αOH,H	βOH,H	βOH,H (4*E*)	O	O	βOAc,H	βOAc,H

Table 1. ^{1}H NMR spectral data of **2–4** and **7–13** (400 MHz, $CDCl_3$, TMS as internal standard)

H	2	3	4	7	8	9	10	11	12	13
1	3.18 *br dd*	3.12 *br dd*	2.07 *dd*	5.10 *br t*	5.08 *br t*	5.07 *br t*	5.21 *m*	4.92 *dd*	5.36 *br t*	5.36 *br t*
2	4.72 *dr d*	4.66 *br d*	4.77 *br d*	2.66 *m* 2.14 *m*	2.68 *m* 2.11 *m*	2.61 *m* 2.05 *m*	2.67 *m* 2.19 *m*	2.50 *m* 2.33 *m*	3.22 *d*(2H)	3.22 d (2H)
3	5.72 *br s*	5.69 *br s*	5.70 *br s*	4.72 *dd*	4.69 *dd*	4.67 *dd*	4.52 *t*	4.36 *br dd*	—	—
5	2.67 *br dd*	2.60 *br dd*	2.59 *br dd*	5.27 *br d*	5.26 *br d*	5.28 *br d*	5.23 *br d*	4.84 *br d*	5.20 *dq*	5.20 *dq*
6	4.65 *dd*	4.66 *dd*	4.74 *dd*	5.21 *br d*	5.18 *br d*	5.16 *br d*	6.38 *br d*	5.18 *d*	4.71 *dd*	4.72 *dd*
7	3.18 *m*	3.17 *dddd*	3.19 *dddd*	2.97 *br d*	2.96 *br s*	2.97 *br s*	2.95 *br s*	2.91 *ddd*	3.01 *dddd*	3.02 *dddd*
8	5.52 *br dd*	5.50 *br dd*	5.55 *br dd*	5.24 *br dd*	5.23 *br dd*	5.23 *br dd*	5.23 *br dd*	5.77 *br d*	5.23 *br t*	5.24 *br t*
9	2.85 *dd*	2.84 *dd*	2.87 *dd*	2.72 *dd*	2.68 *dd*	2.70 *br d*	2.73 *br dd*	2.83 *dd*	2.73 *dd*	2.73 *dd*
9′	2.72 *dd*	2.77 *dd*	2.05 *dd*	2.39 *dd*	2.38 *dd*	2.38 *br d*	2.39 *br d*	2.29 *br d*	2.47 *dd*	2.49 *dd*
13	6.28 *d*	6.24 *d*	6.31 *d*	6.28 *d*	6.35 *d*	6.35 *d*	6.32 *d*	6.32 *d*	6.35 *d*	6.36 *d*
13′	5.55 *d*	5.46 *d*	5.51 *d*	5.77 *d*	5.74 *d*	5.75 *d*	5.72 *d*	5.62 *d*	5.75 *d*	5.76 *d*
14	5.11 *br s*	5.10 *br s*	2.74 *d*	1.82 *br s*	1.76 *br s*	1.76 *br s*	1.70 *br s*	1.48 *br s*	1.70 *br s*	1.70 *br s*
14′	5.09 *br s*	5.07 *br s*	2.71 *dd*							
15	1.98 *br s*	1.94 *br s*	1.99 *br s*				1.76 *br s*	1.85 *d*	1.89 *d*	1.87 *d*
OCOR	6.73 *qq*	6.82 *t*	6.84 *t*	6.84 *qq*	6.77 *br t*	6.90 *br t*	6.77 *br t*	6.69 *br t*	6.79 *qq*	6.75 *tq*
	1.74 *br d*	4.29 *br d*	4.35 *br d*	1.82 *br s*	4.32 *br d*	4.42 *br d*	4.29 *br d*	4.73 *dq*	1.75 *dq*	4.31 *br d*
	1.73 *br s*	4.20 *br s*	4.25 *br d*		1.76 *br s*	4.33 *br s*	1.76 *br s*	1.78 *br s*	1.74 *dq*	1.75 *dt*
Ac	—	—	—	—	—	—	—	2.07 *s*	—	—

J (Hz): compounds **2–4**: 1,2 = 6; 1,5 = 8; 5,6 = 11; 6,7 = 9; 7,8 = 4; 7,13 = 3.5; 7,13′ = 3; 8,9 = 7; 8,9′ = 8; 9,9′ = 14 (compound **4**: 9,14 = 1; 14,14′ = 5); compounds **7–13**: 1,2 ~ 7; 2,3 = 5; 2,3′ = 11; 5,6 ~ 10; 6,7 ~ 2; 7,8 ~ 1; 7,13 = 2.5; 7,13′ = 2; 8,9 = 8,9′ ~ 3; 9,9′ = 14; (compounds **10** and **11**: 2,3 ~ 3; compounds **11–13**: 1,2 = 8.5; 5,6 = 11; 5,15 = 1.5; 6,7 = 1.7; 7,13 = 2; 7,13′ = 1.7; 8,9 = 8,9′ = 3).

differed from that of **6** [2] by the signals of the ester group which were typical for a 4',5'-dihydroxytiglate.

The structures of **7–9** could be deduced from the ^{1}H NMR spectra (Table 1) as they were close to that of the 3-*O*-acetate of **8** [7]. The presence of a free 3-hydroxyl group was indicated by the expected upfield shift of the H-3 signal. The stereochemistry at C-3 followed from the couplings, and the broadened singlet around δ2.97 was typical for a heliangolide with an 8β-oxygen function. Comparison of the ^{1}H NMR spectrum of **10** (Table 1) with that of **14** [5] showed that **10** was the corresponding free 3β-hydroxy derivative. Accordingly, the H-3 signal was a triplet with a 3 Hz coupling. The ^{1}H NMR spectrum of **11** (Table 1) was similar to that of the corresponding 4'-desacetoxy derivative [8]. The nature of the ester group of **11** followed from the typical signals of a 4-acetoxy tiglate.

The ^{1}H NMR spectra of **12** and **13** (Table 1) only differed in the signals of the ester residues. While **12** obviously was a tiglate, **13** was a 4-hydroxytiglate. The remaining ^{1}H NMR signals differed mainly from those of **7** and **8** in shifts of H-1 and H-2 while H-3 was obviously missing in the spectra of **12** and **13**. The downfield shifted H-2 doublet (δ3.22, 2H) was coupled with H-1 as followed from spin decoupling. Accordingly, in agreement with the molecular formulae, **12** and **13** were 3-oxo-derivatives of desacetoxyeupaformin tiglate and desacetoxychromolaenide.

All the isolated sesquiterpene lactones from this collection are very similar to those which have been isolated from other genera of the subtribe Eupatoriinae. Characteristic are the presence of heliangolides with 8β-tigloyloxy residues containing a variety of oxygen functions as well as an oxygen function at C-3; however, guaianolides related to euparotin are also common in this tribe.

EXPERIMENTAL

The air dried aerial parts (580 g, voucher deposited in the U.S. National Herbarium as well as that of a repeated investigation which gave the same compounds) were extracted with Et_2O–petrol (1:2) and the extract obtained (15.5 g) was first separated by CC (300 g, SiO_2). The nonpolar fractions (petrol and Et_2O–petrol, 1:9) gave germacrene D, taraxasteryl acetate and caryophyllene epoxide. The next fractions (Et_2O–petrol, 1:3 and 1:1) afforded bisabolol, taraxasterol, lupeol, phytol, stigmasterol and sitosterol (all identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material). The CC fractions obtained with Et_2O (5/1 and 5/2) and with Et_2O–MeOH, 9:1) (6/1 and 6/2) were further separated by TLC (Et_2O–petrol, 4:1). Fraction 5/1 gave 9 mg **1** (R_f 0.6), 4 mg **7** (R_f 0.5) and 28 mg **4** (R_f 0.4). TLC of 5/2 ($CHCl_3$–MeOH, 500:1) gave 4.6 mg **12** (R_f 0.6) and 26 mg **4** (R_f 0.3). Fraction 6/1 was separated again by medium pressure CC (SiO_2) affording with Et_2O–MeOH (100:1–100:3) four fractions (6/1/1–6/1/4). Repeated HPLC (MeOH–H_2O, 1:1) of one tenth of 6/1/1 gave 7 mg **5**, 3 mg **13**, 3 mg **8**, 4 mg **1**, 7 mg **10**, 5 mg **14** and 10 mg **11**. HPLC (MeOH–H_2O, 1:1) of 6/1/2 (one tenth) gave 20 mg **6** and HPLC of 6/1/3 (one tenth, MeOH–H_2O, 1:1) afforded 8.5 mg **6** and 8.5 mg **15**. HPLC of 6/1/4 (one third) gave 30 mg **6** (R_t 6.7 min) and 6 mg **5** (R_t 13.6 min). HPLC of one fifth of 6/2 (MeOH–H_2O, 1:1) gave 8 mg **3** (R_t 5.0 min), 24 mg **9** (R_t 6.3 min), 20 mg **2** (R_t 8.0 min) and 48 mg **15** (R_t 9.7 min). Compounds **1**, **5**, **6**, **14** and **15** were identified by comparing with authentic material (400 MHz ^{1}H NMR).

8β-Tigloyloxypreeupatundin (**2**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1760 (γ-lactone), 1710, 1650 (C=CCO_2R); MS *m/z* (rel. int.): 344.162 [M]$^+$ (0.8) (calc. for $C_{20}H_{24}O_5$: 344.162), 326 [M – H_2O]$^+$ (1.5), 314 [M – CH_2O]$^+$ (1), 244 [M – RCO_2H]$^+$ (8), 226 [244 – H_2O]$^+$ (7), 83 [C_4H_7CO]$^+$ (100), 55 [83 – CO]$^+$ (62); $[\alpha]_D^{24°}$ = –52 (MeOH; *c* 0.8).

8β-[4',5'-Dihydroxytigloyloxy]-preeupatundin (**3**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1710 (C=CCO_2R); MS *m/z* (rel. int.): 376.152 [M]$^+$ (0.1) (calc. for $C_{20}H_{24}O_7$: 376.152), 358 [M – H_2O]$^+$ (1.3), 328 [M – CO]$^+$ (0.8), 244 [M – RCO_2H]$^+$ (14), 115 [RCO]$^+$ (30), 97 [115 – H_2O]$^+$ (63), 69 [97 – CO]$^+$ (100); $[\alpha]_D^{24°}$ = –54 (MeOH; *c* 0.55).

5-Desoxy-8-deacyleuparotin-8-O-[4',5'-dihydroxytiglate] (**4**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 260 [M – RCO_2H]$^+$ (7), 115 [RCO]$^+$ (21), 97 [115 – H_2O]$^+$ (32), 69 [97 – CO]$^+$ (100); $[\alpha]_D^{24°}$ = –15 (MeOH; *c* 0.6).

Deacetyl eupaformin-8-O-tiglate (**7**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 346.178 [M]$^+$ (0.4) (calc. for $C_{20}H_{26}O_5$: 346.178), 246 [M – RCO_2H]$^+$ (21), 228 [246 – H_2O]$^+$ (3), 83 [C_4H_7CO]$^+$ (100), 55 [83 – CO]$^+$ (88); $[\alpha]_D^{24°}$ = –33 (MeOH; *c* 0.13).

Deacetyl eupaformin-8-O-[4'-hydroxytiglate] (**8**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 362.173 [M]$^+$ (0.4) (calc. for $C_{20}H_{26}O_6$: 362.173), 345 [M – OH]$^+$ (0.7), 246 [M – RCO_2H]$^+$ (22), 99 [RCO]$^+$ (100), 71 [99 – CO]$^+$ (77); $[\alpha]_D^{24°}$ = –25 (MeOH; *c* 0.1).

Deacetyl eupaformin-8-O-[4',5'-dihydroxytiglate] (**9**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1715 (C=CCO_2R); MS *m/z* (rel. int.): 378.168 [M]$^+$ (0.3) (calc. for $C_{20}H_{26}O_7$: 378.168), 360 [M – H_2O]$^+$ (0.6), 246 [M – RCO_2H]$^+$ (25), 228 [246 – H_2O]$^+$ (26), 115 [RCO]$^+$ (20), 97 [115 – H_2O]$^+$ (57), 69 [97 – CO]$^+$ (100); $[\alpha]_D^{24°}$ = –81 (MeOH; *c* 0.93).

Deacetyl chromolaenide (**10**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1765 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 362.173 [M]$^+$ (1.2) (calc. for $C_{20}H_{26}O_6$: 362.173), 345 [M – OH]$^+$ (2), 246 [M – RCO_2H]$^+$ (27), 228 [246 – H_2O]$^+$ (12), 99 [RCO]$^+$ (100), 71 [99 – CO]$^+$ (91).

4E-Deacetyl chromolaenide-4'-O-acetate (**11**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1760 (γ-lactone), 1720 (C=CCO_2R); MS *m/z* (rel. int.): 404.184 [M]$^+$ (3) (calc. for $C_{22}H_{28}O_7$: 404.184), 344 [M – HOAc]$^+$ (1.6), 326 [344 – H_2O]$^+$ (1), 246 [M – RCO_2H]$^+$ (30), 228 [246 – H_2O]$^+$ (32), 99 [RCO]$^+$ (100), 71 [99 – CO]$^+$ (34); $[\alpha]_D^{24°}$ = –10 (MeOH; *c* 0.61).

Deacetoxy-3-oxo-eupaformin tiglate (**12**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (γ-lactone), 1710 (C=CC=O, C=CCO_2R); MS *m/z* (rel. int.): 344.162 [M]$^+$ (2.7) (calc. for $C_{20}H_{24}O_5$: 344.162), 329 [M – Me]$^+$ (2), 244 [M – RCO_2H]$^+$ (2.9), 229 [244 – Me]$^+$ (2), 83 [C_4H_7CO]$^+$ (100), 55 [83 – CO]$^+$ (43); $[\alpha]_D^{24°}$ = –5 (MeOH; *c* 0.19).

Deacetoxy-3-oxo-chromolaenide (**13**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (γ-lactone), 1720 (C=CC=O, C=CCO_2R); MS *m/z* (rel. int.): 360 [M]$^+$ (0.3), 244 [M – RCO_2H]$^+$ (5.5), 99 [RCO]$^+$ (100), 71 [99 – CO]$^+$ (73); $[\alpha]_D^{24°}$ = –5 (MeOH; *c* 0.15).

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