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GERMACRANOLIDES RELATED TO CHAPLIATRIN FROM *CALEA HARLEYI*

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Key Word Index—*Calea harleyi*; Compositae; sesquiterpene lactones; *p*-hydroxyacetophenone derivatives.

Abstract—The roots of *Calea harleyi* afforded four germacranolides closely related to chapliatrin and two derivatives of *p*-hydroxyacetophenone related to the acyloxycalefoliones.

The aerial parts of *Calea harleyi* H. Robins. afforded in addition to thymol methyl ether, thymohydroquinone dimethyl ether and euparin, the germacranolides **1**, **3**, **4** and **5** and the two *p*-hydroxyacetophenone derivatives **7** and **8**.

The ^{1}H NMR spectral data (Table 1) of **1** were close to those of acetylchapliatrin [1]. However, the signals of the ester residue were replaced by those of an angelate. Careful spin decoupling in deuteriochloroform as well as in deuteriobenzene allowed the assignment of all signals. The stereochemistry at C-6–C-8 followed from the typical couplings while that at C-3, C-4, C-5 and C-13 could be deduced from the W-couplings between H-1β and H-14 and between H-3 and H-5 and H-1α. Inspection of models showed that these couplings required the proposed configuration. In agreement with this stereochemistry NOE difference spectra showed a strong effect at H-6 after irradiation of H-1β. In agreement with the resulting stereochemistry the down field shift of the H-6 signal can be explained as the result of a strong deshielding effect of the quasi-axial 3β-acetoxy group which is, as expected, even stronger in chapliatrin itself. Accordingly, the proposed stereochemistry of the chapliatrins [1] also should be changed to **2a–c**.

The ^{1}H NMR spectra of **3**, **4** and **5** (Table 1) differed mainly in the signals of the ester residue. While the corresponding signals of **3** and **4** clearly indicated that the compounds were epimeric epoxy angelates, the ester signals of **5** showed that an ester of 2-hydroxy-2-methylbut-3-enoic acid was present. A methyl singlet at δ3.78 indicated a methyl ester group while a broadened double doublet at δ7.05 most likely was due to an olefinic proton which was in β-position to the ester carbonyl. Spin decoupling showed that this proton had a neighbouring methylene group. Further decouplings allowed the assignment of all signals and determination of the whole sequence as an allylic coupling was present between H-3 and H-5. The W-coupling between H-14 and H-1β allowed closure of the sequence in a ten-membered ring. Again a strong NOE was visible between H-1β and H-6 indicating that the stereochemistry in **3–5** was the same as that of **1**. In the MS m/z 169 most likely is **6**, formed by α-splitting of the ether bonds. The 8-desacyl compounds **3–5** we have named caleharloide.

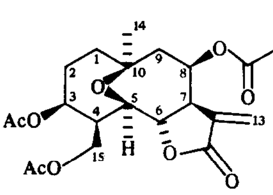
The ^{1}H NMR spectral data of **7** and **8** (Table 2) were close to those of the acyloxycalefoliones from *Calea teucriifolia* [2]. The altered nature of the C-7 substituent clearly followed from the ^{1}H NMR spectra. The spectrum of **7** showed the typical signals of a 1-hydroxyethyl placed on an aromatic ring (5.04 *q* and 1.45 *d*, $J = 7$ Hz). In the spectrum of **8**, the presence of the corresponding angelate was deduced from the typical angelate signals and the downfield shift of the H-9 signal if compared with the shift in the spectrum of **7**.

The aerial parts only gave germacrene D and squalene. While so far nearly all *Calea* species afforded heliangolides (see ref. [3]), lactones like **1** never have been reported from *Calea* species. Further investigations may show whether the lactones of type **1–5** are present in other *Calea* species too.

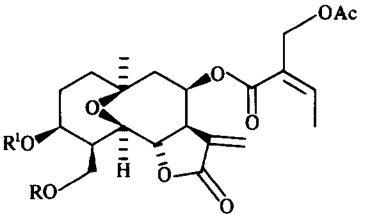
EXPERIMENTAL

The air dried plant material (collected in the province Bahia, Brazil, voucher Nr. RMK 8628) was extracted with Et_2O–petrol, 1:2 (24 hr room temp), and the extract obtained was first separated by CC on silica gel. The aerial parts (140 g) gave CC fractions (100 ml) as follows: 1 (Et_2O–petrol, 1:10), 2 (Et_2O–petrol, 1:1) and 3 (Et_2O and Et_2O–MeOH, 20:1). TLC of fractions 1 (silica gel PF 254, Et_2O–petrol, 1:10) gave 20 mg thymol methyl ether and 10 mg thymohydroquinone dimethyl ether. TLC of fraction 2 (Et_2O–petrol, 1:3) gave 20 mg euparin (R_f 0.62), 6 mg **8** (R_f 0.57) and 9 mg **7** (R_f 0.50), while TLC of fraction 3 (Et_2O) gave 3 mg **1** (R_f 0.42) and 9 mg of a mixture of **3–5** (R_f 0.35) which after HPLC (RP 8, MeOH–H_2O, 3:2) and TLC (Et_2O–C_6H_6–CH_2Cl_2, 1:1:1) afforded 5 mg **3** (R_f 0.45), 1 mg **4** (R_f 0.40) still containing **3** and 1.5 mg **5** (R_f 0.35). The lactones **1**, **4** and **5** were homogeneous by TLC in different solvent mixtures, but could not be induced to crystallize. Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic material. TLC zones were detected by UV light (255 nm) and quantities were determined by weighing.

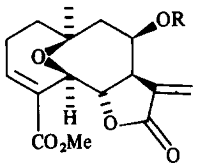
8-*Desacylacetylchapliatrin angelate* (**1**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775 (γ-lactone), 1750 (OAc), 1720 (C=CCO$_2$R); MS m/z (rel. int.): 422.194 $[M - \text{ketene}]^+$ (2) ($C_{22}H_{30}O_8$), 404 $[M - \text{HOAc}]^+$ (1.5), 364 $[M - \text{AngOH}]^+$ (1.5), 322 $[422 - \text{AngOH}]^+$ (6), 304 $[364 - \text{HOAc}]^+$ (2), 262 $[322 - \text{HOAc}]^+$ (2), 244 $[304 - \text{HOAc}]^+$ (6), 83 $[C_4H_7CO]^+$ (91), 55 $[83 - CO]^+$ (100); CD (MeCN): $\Delta\varepsilon_{270} = -0.58$.



1

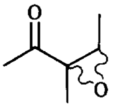


2a R = Ac, R¹ = H
2b R = H, R¹ = Ac
2c R = R¹ = Ac



R

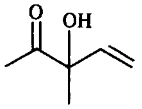
3

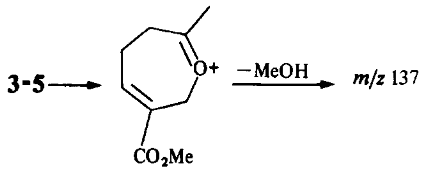


4

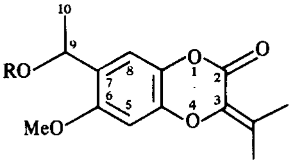
2′,3′epi

5





6 *m/z* 169



7 R = H
8 R = Ang

Caleharloide-8-O-[2′,3′-*epoxy*-2′-*methylbutyrate*] (**3**). Colourless crystals, mp 135°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1785 (γ-lactone), 1730 (CO_2R, $C{=}CCO_2R$); MS *m/z* (rel. int.): 406 $[M]^+$ (0.5), 375.144 $[M - OMe]^+$ (7) ($C_{20}H_{23}O_7$), 290 $[M - RCO_2H]^+$ (20), 259 $[290 - OMe]^+$ (14), 258 $[290 - MeOH]^+$ (20), 230 $[258 - CO]^+$ (19), 169 $[C_9H_{13}O_3, \mathbf{6}]^+$ (28), 137 $[169 - MeOH]^+$ (19), 109 $[137 - CO]^+$ (35), 99 $[RCO]^+$ (10), 71 $[99 - CO]^+$ (48), 55 $[C_4H_7]^+$ (100); CI (isobutane): 407 $[M + 1]^+$ (23).

Caleharloide-8-O-[*ent*-2′,3′-*epoxy*-2′-*methylbutyrate*] (**4**). Not free from **3**, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1730 (CO_2R, $C{=}CCO_2R$); MS *m/z* (rel. int.): 406 $[M]^+$ (0.5), 375.144 $[M - OMe]^+$ (6) ($C_{20}H_{23}O_7$), 290 $[M - RCO_2H]^+$ (18), 169 $[\mathbf{6}]^+$ (27), 137 $[169 - MeOH]^+$ (20), 109 $[137 - CO]^+$ (33), 55 (100).

Caleharloide-8-O-[2′-*hydroxy*-2′-*methyl*-*but*-3′-*enoate*] (**5**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1735 (CO_2R, $C{=}CCO_2R$); MS *m/z* (rel. int.): 406.163 $[M]^+$ (0.9) ($C_{21}H_{26}O_8$), 375.144 $[M - OMe]^+$ (8), 290 $[M - RCO_2H]^+$ (11), 169 $[\mathbf{6}]^+$ (37), 137 $[169 - MeOH]^+$ (22), 109 $[137 - CO]^+$ (38), 71 $[C_4H_7O]^+$ (100).

9-O-*Dihydrocalefolione* (**7**). Colourless crystals, mp 135°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3540 (OH), 1750, 1715 (CO_2R); MS *m/z* (rel. int.):

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

	1	C_6D_6*	**3**	**4**	**3** (C_6D_6)	**5**
H-1α	1.42 *br dd*	1.00	1.59 *br dd*		1.07 *dddd*	1.60 *br dd*
H-1β	2.52 *br dd*	2.36	2.60 *br dd*	2.62 *br dd*	2.45 *br dd*	2.48 *br dd*
H-2α	1.90 *br dd*	1.48	2.76 *br dd*		2.21 *br dddd*	2.75 *br dd*
H-2β	2.09 *br dd*	1.85	2.49 *dddd*		1.78 *dddd*	2.47 *br ddd*
H-3	5.36 *br s*	5.42	7.05 *br dd*		6.87 *ddd*	7.05 *br dd*
H-4	2.47 *dddd*	2.32	—		—	—
H-5	4.04 *ddd*	3.82	5.08 *br d*		5.27 *br d*	5.08 *br d*
H-6	5.40 *dd*	5.36	4.94 *dd*		4.90 *dd*	4.86 *dd*
H-7	3.39 *dddd*	2.73	3.50 *dddd*		2.75 *dddd*	3.50 *dddd*
H-8	5.77 *ddd*	5.49	5.80 *ddd*	5.85 *ddd*	5.35 *ddd*	5.75 *ddd*
H-9α	2.09 *dd*	1.70	2.09 *dd*	2.11 *dd*	1.65 *dd*	2.07 *d*
H-9β	2.02 *dd*	1.46	2.04 *dd*	2.06 *dd*	1.43 *dd*	
H-13	6.32 *d*	6.21	6.34 *d*	6.30 *d*	6.17 *d*	6.33 *d*
H-13′	5.60 *d*	5.21	5.61 *d*	5.58 *d*	5.11 *d*	5.58 *d*
H-14	1.24 *s*	1.03	1.32 *s*	1.33 *s*	0.98 *s*	1.31 *s*
H-15	4.34 *dd*	4.61	—	—	—	—
H-15′	4.10 *dd*	4.22	—	—	—	—
OCOR	6.14 *qq*	5.75	3.03 *q*	3.02 *q*	2.45 *q*	5.87 *dd*
	1.99 *dq*	2.02	1.23 *d*	1.20 *d*	0.93 *d*	5.46 *dd*
	1.84 *dq*	1.67	1.47 *s*	1.50 *s*	1.24 *s*	5.20 *dd*, 1.37 *s*
OMe	—	—	3.78 *s*	3.78 *s*	3.49 *s*	3.78 *s*
OAc	2.03 *s* (6H)	1.77 *s* 1.63 *s*	—	—	—	—

*Identical multiplicity.

J (Hz): Compound **1**: 1α, 1β = 16; 1α, 2β = 7; 1α, 3α = 1; 1β, 2α = 13; 1β, 2β = 5; 2α, 2β = 15; 2α, 3 = 2β, 3 ~ 1.5; 3, 4 = 3; 3, 5 = 0.7; 4, 5 = 4; 4, 15 = 9; 4, 15′ = 6.5; 5, 6 = 6, 7 = 10; 7, 8 ~ 2; 7, 13 = 3.5; 7, 13′ = 3; 8, 9α = 2.5; 8, 9β = 4.5; 9α, 9β = 16; 15, 15′ = 11.5; 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5; compounds **3**/**4**: 1α, 1β = 16; 1α, 2α = 1β, 2β ~ 1.5; 1α, 2β = 5; 1α, 3 = 1; 1β, 2α = 13; 2α, 2β = 19; 2α, 3 ~ 1.5; 2β, 3 = 6; 5, 6 = 6, 7 = 9.5; 7, 8 ~ 1.5; 7, 13 = 3.5; 7, 13′ = 3; 8, 9α = 2.5; 8, 9β = 4.5; 9α, 9β = 16; epang: 3′, 4′ = 5; vinylhydroxypropyl: 3′, 4t′ = 17; 3′, 4c′ = 10.5; 4t′, 4c′ = 1.

264.100 $[M]^+$ (9) ($C_{14}H_{16}O_5$), 249 $[M-Me]^+$ (22), 246 $[M-H_2O]^+$ (12), 217 $[249-MeOH]^+$ (3), 69 (100).

9-O-*Dihydrocalefolione angelate* (**8**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1750, 1720 (CO_2R); MS *m/z* (rel. int.): 346.142 $[M]^+$ (23) ($C_{19}H_{22}O_6$), 247 $[M-OCOR]^+$ (100), 246 $[M-RCO_2H]^+$ (20), 232 $[247-Me]^+$ (6), 231 $[246-Me]^+$ (9), 83 $[RCO]^+$ (41), 55 $[83-CO]^+$ (86).

Table 2. ^{1}H NMR spectral data of **7** and **8** (400 MHz, $CDCl_3$, TMS as int. standard)

	7	**8**
H-5	6.55 *s*	6.55 *s*
H-8	7.05 *s*	7.03 *s*
H-9	5.04 *q*	6.19 *q*
H-10	1.45 *d*	1.46 *d*
H-12	2.25 *s*	2.25 *s*
H-13	2.01 *s*	2.01 *s*
OMe	3.83 *s*	3.82 *s*
OCOR	—	6.08 *qq*
		1.98 *dq*
		1.91 *dq*

J (Hz): 9, 10 = 7; 3′, 4′ = 7; 3′, 5′ = 4′, 5′ = 1.5.

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