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FURANOHELIANGOLIDES AND FARNESOL DERIVATIVES FROM *CALEA HISPIDA**

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Key Word Index—*Calea hispida*; Compositae; sesquiterpene lactones; furanoheliangolides; myrtenyl substituted sesquiterpene lactone; farnesol derivatives; dihydroxy dehydromenthone.

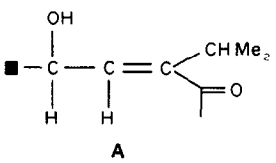
Abstract—From *Calea hispida*, in addition to known compounds, two new furanoheliangolides, one substituted with a myrtenyl residue, two further farnesol derivatives and a dihydroxy dehydromenthone were isolated. The structures were elucidated by high field ^{1}H NMR spectroscopy and by comparison of the data with those of similar compounds. The chemotaxonomic situation is discussed briefly.

INTRODUCTION

Several species of the large genus *Calea* (tribe Heliantheae) with *ca* 100 taxa have already been investigated chemically. Most of them afforded sesquiterpene lactones, especially furanoheliangolides [1–8], but also other germacranolides [1, 2, 4, 9–12] and a few eudesmanolides [4, 7] were found. Furthermore, several species gave prenylated *p*-hydroxyacetophenone derivatives [3, 5–7, 13, 14]. We now have studied the constituents of *Calea hispida* (DC.) Baker. The results are discussed in this paper.

RESULTS AND DISCUSSION

The roots of *C. hispida* afforded the thymol derivatives **1–4**, the eudesmene derivative **9** [15] and the chromenes **5–8** [16–18], while the aerial parts gave germacrene D, caryopyhllene, α-humulene, bicyclogermacrene, **2**, **4**, the furanoheliangolides **12** [3] and **13** [1], the heliangolide **11** [19], two further heliangolides, the myrtenyl substituted angelate **14** and the hydrated furanoheliangolide **15**, the farnesol derivatives **16** and **17** as well as the dihydroxy dehydromenthone **10**. The structure of the latter followed from the molecular formula and the ^{1}H NMR spectral data (see Experimental). Spin decoupling showed that the isopropyl proton was allylic to the olefinic proton. The chemical shift of the latter showed that it must be in a β-position to the keto group. The presence of an unsaturated keto group also was evident from the corresponding IR band (1690 cm^{-1}). The olefinic proton was further coupled with a proton, which displayed a double doublet at δ 4.30. The latter was further coupled with a hydroxy doublet at δ 2.41. Accordingly, the sequence **A** was established.



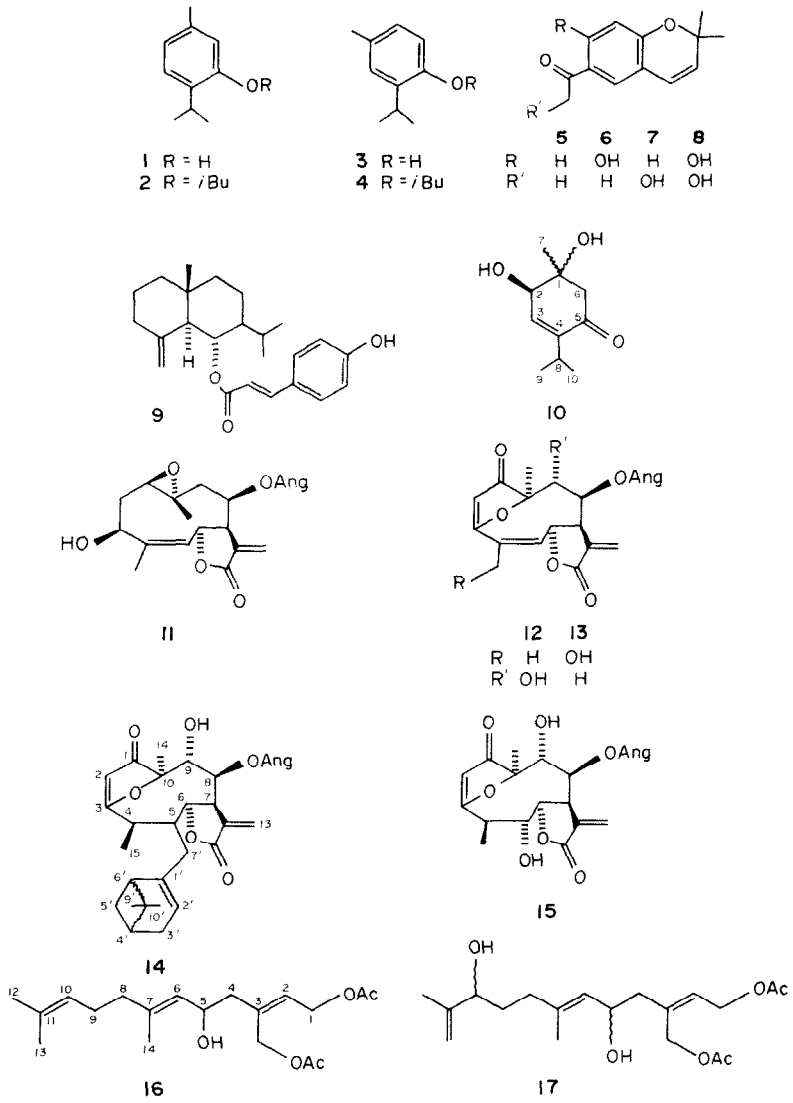
A

A downfield methyl singlet at δ 1.36 indicated the presence of a tertiary hydroxyl group, while a pair of doublets at δ 2.74 and 2.50 obviously were the signals of a methylene group α to the carbonyl. Thus the structure of **10** was established, but the stereochemistry at C-1 could not be determined. Probably **10** was formed by hydroxylation of 1,2,3,4-tetradehydromenthone, an intermediate in the biogenesis of thymol.

The diacetate **16** gave no molecular ion in the mass spectrum, similarly chemical ionization produced an ion by loss of acetic acid. The ^{1}H NMR spectrum, however, showed (Table 1) that a diacetate was present. A three-fold doublet at δ 4.49 indicated an additional hydroxyl group. Spin decoupling showed that the corresponding proton was coupled with an olefinic proton, which displayed a broadened double quartet at δ 5.19. Further couplings with two pairs of double doublets at δ 2.45 and 2.24 showed that the allylic hydroxyl group was at C-5 or C-9 of a farnesol with an acetoxyl group at C-15. The position of the latter followed from the chemical shifts of the olefinic protons and methyl groups. Spin decoupling further indicated that the broadened triplet at δ 5.06 showed allylic couplings with two olefinic methyls.

Accordingly, the hydroxyl group was at C-5. In addition **17** showed no molecular ion in the mass spectrum even under CI conditions where, however,

* Part 453 in the series "Naturally Occurring Terpene Derivatives". For Part 452 see Bohlmann, F. and Zdero, C. (1982) *Phytochemistry* **21**, 2263.



an ion formed by loss of water and acetic acid could be detected. The presence in **17** of the end group of **16** with acetoxyl groups at C-1 and C-15 and a hydroxyl group at C-5 clearly followed from the ^{1}H NMR spectral data (Table 1) as the corresponding signals were nearly identical with those of **16**. An additional hydroxyl and an exomethylene group was revealed in the ^{1}H NMR spectrum by a broadened triplet at δ 4.04 and a pair of narrowly split double quartets at δ 4.94 and 4.84. The position of the second hydroxyl followed from the chemical shifts of the methylene protons. The relative configuration at C-5 and C-10, however, could not be determined.

The structure of **14** followed from the molecular formula ($C_{30}H_{38}O_7$), the fragmentation pattern in the mass spectrum and from the ^{1}H NMR spectrum (Table 2), which was close to that of a similarly modified furanoheliangolide isolated from *Calea morii* and *C. pilosa* [3]. The H-9 signals, however, were replaced by a broadened double doublet at δ 4.21. Accordingly, a 9-hydroxyl group was present. Consequently, most signals were similar to those of **12** [3]. Spin decoupling allowed the assignment of all signals, thus confirming the structure of **14** as 5β - myrtenyl - 9α - hydroxy - 4,5 - dihydroatripliciolide - 8 - *O* - angelate. The stereochemistry of **14** at C-4, C-5 and C-8 was obviously the same as that of the myrtenyl derivative from *C. pilosa* [3]. Accordingly, the H-4 signal showed no allylic coupling with H-2 and $J_{4,5}$ and $J_{5,6}$ were nearly equal. Inspection of a model showed that this was more likely with a 5α-proton. **14** is the third example of a heliangolide combined with a monoterpene [3, 7].

The ^{1}H NMR spectrum of **15** was again in part similar to that of **12**. However, that the situation at C-4 and C-5 was changed was obvious as the olefinic methyl signal was replaced by a doublet at δ 1.29. Spin decoupling showed that the corresponding methyl group was coupled with a proton, which gave rise to a broadened double quartet. The latter was

Table 1. ^{1}H NMR spectral data of compounds **16** and **17** (400 MHz, $CDCl_3$, TMS as int. standard)

	16	**17**
H-1	4.68 *br dd*	4.70 *br dd*
H-1′	4.64 *br dd*	4.65 *br dd*
H-2	5.73 *br t*	5.75 *br t*
H-4	2.45 *dd*	2.44 *dd*
H-4′	2.24 *dd*	2.24 *dd*
H-5	4.49 *ddd*	4.52 *br ddd*
H-6	5.19 *br dq*	5.23 *br dq*
H-8	2.07 *m*	2.07 *m*
H-9 }	2.02 *m*	2.00 *m*
H-9′ }		1.64 *m*
H-10	5.06 *br t*	4.04 *br t*
H-12	1.67 *br s*	1.72 *br s*
H-13 }	1.60 *br s*	4.94 *dq*
H-13′ }		4.85 *dq*
H-14	1.68 *br s*	1.68 *br s*
H-15	4.61 *br d*	4.62 *br d*
H-15′	4.54 *br d*	4.55 *br d*
OAc	2.09 *s*	2.09 *s*
	2.06 *s*	2.06 *s*

J (Hz): 1,1′ = 4,4′ = 15,15′ = 14; 1,2 = 7; 1,2′ = 6; 4,5 = 8; 4′,5 = 4; 5,6 = 8; 6,14 = 1; 9,10 = 7; 10,12 = 10,13 ~ 1 (compound **17**: 9,10 = 6.5; 10,13 = 10,13′ ~ 1.5).

Table 2. ^{1}H NMR spectral data of compounds **14** and **15** (400 MHz, $CDCl_3$, TMS as int. standard)

	14	**15**
H-2	5.62 *d*	5.63 *d*
H-4	2.82 *br dq*	3.36 *br dq*
H-5	2.98 *ddt*	4.44 *br dd*
H-6	4.51 *dd*	4.40 *dd*
H-7	3.55 *m*	3.73 *m*
H-8	5.04 *br d*	5.04 *br d*
H-9	4.21 *br dd*	4.16 *br dd*
H-13	6.33 *d*	6.41 *d*
H-13′	5.74 *d*	5.81 *d*
H-14	1.50 *s*	1.48 *s*
H-15	1.21 *d*	1.29 *d*
H-2′	5.31 *br s*	—
H-5$_1^1$	0.99 *d*	—
H-5$_2^1$	2.35 *dt*	—
H-3′,7′	2.05 *m*	—
H-9′	0.82 *s*	—
H-10′	1.27 *s*	—
OAng	6.15 *qq*	6.16 *qq*
	1.94 *dq*	1.94 *dq*
	1.81 *dq*	1.81 *dq*

J (Hz): Compound **14**: 2,4 = 1.5; 4,5 = 5; 4,15 = 7; 5,6 = 6,7 = 5; 5,7′ = 6; 7,8 ~ 2; 7,13 = 3; 7,13′ = 2.5; 8,9 = 6; 9,OH = 5; 4′,5′ = 5′,6′ = 5; 5$_1^1$,5$_2^1$ = 9; compound **15**: 2,4 = 1.5; 4,5 = 4,15 = 7; 5,6 = 9; 6,7 = 4; 7,8 ~ 2; 7,13 = 3; 7,13′ = 2.5; 8,9 = 5; 9,OH = 4; OAng: 3,4 = 7; 3,5 = 4,5 = 1.5.

Table 3. Distribution of typical constituents in *Calea* species

	Prenylated *p*-hydroxyaceto-phenones	Thymol derivatives	Furanoheliangolides	Germacranolides (precursor of furanoheliangolides)	Eudesmanolides	Farnesyl derivatives
C. cuneifolia DC.[14]	+		?	?		
C. hispida (DC.) Baker	+	+	+	+	(+)*	+
C. hymenolepis Baker[7]	+		+	+	+	
C. morii H. Rob.[3]	+		+			
C. oxylepis Baker[6]	+	+	+			
C. pilosa Baker[3]		+	+	+		+
C. pinnatifida Baker[11]				+		
C. reticulata Gardn.[15]					(+)*	‡
C. rotundifolia (Less) Baker[4]	+			+	+	
C. teucrifolia (Gardn.) Baker[5]	+	+	+		(+)†	+
C. urticifolia (Müller) DC.[1, 2, 11, 12]		+	+	+		
C. zacatechichi Schlecht.[1, 9–11]	+		+	+		
C. species[5]	+	+	+			

* Eudesmene **9**.
†Isocostic acid.
‡ Ichthyotherol.

further coupled with a narrowly split doublet at δ 5.63 and a broadened double doublet at 4.44. As the latter was coupled with H-7, whose identity followed from spin decoupling, sequence H-4–H-7 was established. While the missing allylic coupling of H-4 again required a 4β-methyl, the changed couplings of H-5 supported a 5β-proton if a model was considered, though the flexibility in such a ring system does not allow a definite assignment.

The constituents of this *Calea* species again show that furanoheliangolides and related germacranolides are typical for this genus (see Table 3). The only exceptions so far are *C. cuneifolia*, which only was investigated for compounds like **5–8**[14] and *C. reticulata* [15]. However, prenylated *p*-hydroxyacetophenone and thymol derivatives are widespread in this genus. Only two species have so far afforded eudesmanolides, while three others contain eudesmene derivatives. Farnesyl derivatives, so far isolated from three species, also may be of interest. The placement of *Calea* in the Neurolaeninae [Robinson, H., unpublished] is supported by the presence of similar germacranolides in *Neurolaena* [20], which also contains several thymol derivatives. Furanoheliangolides, and related lactones, however, are also reported from several other genera, which belong to the tribes Heliantheae (*Helianthus, Tithonia, Zexmenia, Viguiera, Eriophyllum, Podanthus, Bahia* and *Leptocarpha*), Eupatorieae (*Eupatorium, Liatris, Trichogonia, Bejaranoa, Disynaphia, Conocliniopsis, Isocarpha* and *Hartwrightia*) and Vernonieae (*Eremanthus, Chresta, Piptolepis, Alcantara* and *Lychnophora*). As in other cases, therefore, only the combination of different types of constituents can be regarded as characteristic for a genus.

EXPERIMENTAL

The air-dried plant material, collected in N.E. Brazil (voucher RMK 8434, deposited in the U.S. National Herbarium, Washington) was extracted with Et_2O-petrol (1:2), and the resulting extracts were separated by CC (SiO_2) and further by repeated TLC (SiO_2). Known compounds were identified by their high field ^1H NMR spectra, which were compared with those of authentic material, and by their R_f-values on TLC. Crystalline compounds were further compared by mmp's. The roots (20 g) afforded 10 mg **1**, 10 mg **2**, 10 mg **3**, 10 mg **4**, 5 mg **5**, 5 mg **6**, 20 mg **7**, 10 mg **8** and 10 mg **9**, while the aerial parts (120 g) gave 100 mg germacrene D, 100 mg caryophyllene, 50 mg α-humulene, 20 mg bicyclogermacrene, 10 mg **2**, 10 mg **4**, 50 mg **5**, 20 mg **6**, 20 mg **9**, 2 mg **10** (TLC: C_6H_6–CH_2Cl_2–Et_2O, 10:10:1, several times), 150 mg **11**, 300 mg **12**, 50 mg **13**, 5 mg **14** (Et_2O–petrol, 1:1, several times), 2 mg **15** (Et_2O, several times), 2 mg **16** (Et_2O–petrol, 9:1, several times) and 2 mg **17** (C_6H_6–CH_2Cl_2–Et_2O, 10:10:1, several times).

1,2 - *Dihydroxy* - 3,4 - *dehydromenthone* (**10**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 *br* (OH), 1690 (C=CCO); MS *m/z* (rel. int.): 166.099 $[M-H_2O]^+$ (17) ($C_{10}H_{14}O_2$), 151 $[166-Me]^+$ (11), 149 $[166-OH]^+$ (10), 126 (100) $[M-C_3H_6O]^+$ (100) (RDA), 111 $[126-Me]^+$ (20), 83 $[C_5H_7O]^+$ (31); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.30 (*dd*, H-2), 6.41 (*dd*, H-3), 2.74 (*d*, H-6), 2.50 (*d*, H-6'), 1.36 (*s*, H-7), 2.89 (*dqq*, H-8), 1.04 (*d*, H-9), 1.01 (*d*, H-10), 2.41 (*d*, OH) [*J* (Hz): 2,3 = 4; 2,OH = 8; 3,8 = 1; 6,6' = 16; 8,9 = 8,10 = 7];

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+10 \quad +14 \quad +18 \quad +24} (CHCl_3;\ c\ 0.1).$$

5β - *Myrtenyl* - 9α - *hydroxy* - 4,5 - *dihydroatripliciolide* - 8 - O - *angelate* (**14**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1720 (C=CCO_2R), 1600 (C=COR); MS *m/z* (rel. int.): 510.262 $[M]^+$ (1) ($C_{30}H_{38}O_7$), 492 $[M-H_2O]^+$ (0.1), 410 $[M-RCO_2H]^+$ (1), 392 $[410-H_2O]^+$ (0.3), 382 $[410-CO]^+$ (0.4), 375 $[M-C_{10}H_{15}]^+$ (2.5), 135 $[C_{10}H_{15}]^+$ (12), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (40);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+42 \quad +37 \quad +34 \quad -143} (CHCl_3;\ c\ 0.4).$$

5β,9α - *Dihydroxy* - 4,5 - *atripliciolide* - 8 - O - *angelate* (**15**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1720 (C=CCO_2R), 1600 (C=COR); MS *m/z* (rel. int.): 392.147 $[M]^+$ (6) ($C_{20}H_{24}O_8$), 374 $[M-H_2O]^+$ (0.2), 364 $[M-CO]^+$ (1), 293 $[M-OCOR]^+$ (0.5), 292 $[M-RCO_2H]^+$ (0.2), 265 $[293-CO]^+$ (2), 247 $[265-H_2O]^+$ (0.2), 83 $[C_4H_7CO]^+$ (100), 55 $[83-CO]^+$ (67);

$$[\alpha]_{24°}^{\lambda} = \frac{589 \quad 578 \quad 546\,nm}{+8 \quad +10 \quad +12} (CHCl_3;\ c\ 0.1).$$

15 - *Acetoxy* - 5 - *hydroxyfarnesyl acetate* (**16**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3520 (*br* α-OH), 1745, 1245 (OAc); MS *m/z* (rel. int.): 135 $[C_{10}H_{15}]^+$ (16), 69 $[C_5H_9]^+$ (100); CI (isobutane): 279 $[M+1-HOAc)]^+$ (3), 261 $[279-H_2O]^+$ (78), 219 $[261-\text{ketene}]^+$ (30), 201 $[261-HOAc]^+$ (70), 75 (100); $[\alpha]_D = -4°$ ($CHCl_3$; *c* = 0.1).

15 - *Acetoxy* - 5,10 - *dihydroxy* - 12,13 - *dehydro* - 10,11 - *dihydrofarnesyl acetate* (**17**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 *br* (OH), 1760, 1245 (OAc); MS *m/z* (rel. int.) (CI, isobutane): 277 $[M+1-H_2O, HOAc]^+$ (78), 217 $[277-HOAc]^+$ (100), 199 $[217-H_2O]^+$ (30); $[\alpha]_D = -7°$ ($CHCl_3$; *c* 0.1).

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REFERENCES

1. Herz, W. and Kumar, N. (1980) *Phytochemistry* **19**, 593.
2. Bohlmann, F. and Jakupovic, J. (1979) *Phytochemistry* **18**, 119.
3. Bohlmann, F., Fritz, U., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 743.
4. Bohlmann, F., Gupta, R. K., Jakupovic, J., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 1635.
5. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 1643.
6. Bohlmann, F., Bapuji, M., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 1164.
7. Bohlmann, F., Mathur, R., Jakupovic, J., Gupta, R. K., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 2045.
8. Bohlmann, F., Gupta, R. K., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 2117.
9. Quijano, L., Romo de Vivar, A. and Rios, T. (1979) *Phytochemistry* **18**, 1745.

10. Bohlmann, F. and Zdero, C. (1977) *Phytochemistry* **16**, 1065.
11. Ferreira, Z. S., Roque, N. F., Gottlieb, O. R., Oliveira, F. and Gottlieb, H. E. (1980) *Phytochemistry* **19**, 1481.
12. Del Castillo, J. B., Ferrero, M. T. M., Luis, F. R., Bueno, P. V., Leonov, N. G. and Arevolo, S. C. (1981) *J. Nat. Prod.* **44**, 348.
13. Quijano, L., Calderon, J. and Rios, T. (1977) *Rev. Latinoam. Quim.* **8**, 90.
14. Lourenco, T. O., Akisue, G. A. and Roque, N. F. (1981) *Phytochemistry* **20**, 773.
15. Bohlmann, F., Borthakur, N., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 1793.
16. Bohlmann, F. and Grenz, M. (1970) *Chem. Ber.* **103**, 90.
17. Bohlmann, F., Grenz, M., Dhar, A. K., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 281.
18. Bohlmann, F. and Jakupovic, J. (1978) *Phytochemistry* **17**, 1677.
19. Martinez, J. K., Ayamante, B. I. S., Nunez-Alarcon, J. A. and Romo de Vivar, A. (1979) *Phytochemistry* **18**, 1527.
20. Manchand, P. S. and Blount, J. F. (1978) *J. Org. Chem.* **43**, 4352.