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NEW HELIANGOLIDES FROM *CALEA OXYLEPIS**

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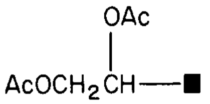
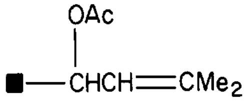
Key Word Index—*Calea oxylepis*; Compositae; roots; aerial parts; sesquiterpene lactones; heliangolides; unusual monoterpene.

Abstract—An investigation of the roots and aerial parts of *Calea oxylepis* afforded, in addition to known compounds, three new heliangolides and an unusual monoterpene triacetate.

The roots of *Calea oxylepis* Baker afforded the chromene derivatives **1** and **2**, the thymol derivatives **3–6** and the triacetate **10**. The structure of this unusual monoterpene derivative followed from the ^1H NMR, the IR spectrum and the molecular formula (see Experimental). In the mass spectrum only one elimination of acetic acid was visible, while an α-splitting (C-3/C-4) led to the prominent fragment *m/z* ($C_7H_{11}O_2$) followed by loss of ketene leading to the base peak *m/z* 85 (C_5H_9O). The ^1H NMR spectrum clearly showed the presence of a triacetate, while the substitution pattern was assigned from the downfield signals. A pair of double doublets were coupled with a double doublet at δ 5.16, while an olefinic proton was coupled with two olefinic methyl groups and a proton, which displayed a doublet at δ 5.38. Furthermore two methyl singlets at δ 1.03 and 0.89 were present. These observations led to the sequences **A** and **B**:


$\mathrm{AcOCH_2\overset{\overset{\displaystyle OAc}{|}}{C}H{-}\blacksquare}$

A


$\mathrm{\blacksquare{-}\overset{\overset{\displaystyle OAc}{|}}{C}HCH{=}CMe_2}$

B

Accordingly, the structure could only be **10**. The absolute configuration, however, was not determined. **10** is a derivative of artemisia alcohol [2].

The aerial parts afforded small amounts of sesquiterpene lactones, the heliangolides **7–9**. The structures were deduced from the characteristic ^1H NMR spectra (Table 1), which were similar to those of known heliangolides. The spectra of **7–9** showed the presence of 2-methyl butyrates, while the presence of heliangolides followed from the chemical shifts and the typical splitting of the signals of H-5 through H-8 and H-13. As the irradiation of the fourfold doublet at δ 4.02 in the spectrum of **8** collapsed the signals of the exomethylene protons to singlets, its assignment as H-7 was obvious. Simultaneously the overlapping signals at δ 5.57 and 5.55 were altered in the expected

Table 1. ^1H NMR spectral data of compounds **7–9** (400 MHz, $CDCl_3$, TMS as int. standard)

	7	**8**		**9**
		$CDCl_3$	C_6D_6	
H-1	4.31 *br d*	5.56 *br d*	5.37 *br d*	—
H-2α	2.30 *dd*	2.14 *br d*	1.63 *br d*	3.18 *d*
H-2β	2.09 *br d*	2.85 *dd*	1.98 *dd*	2.65 *d*
H-5	5.92 *dq*	5.74 *dq*	5.63 *dq*	5.68 *dq*
H-6	5.66 *br s*	5.57 *br s*	5.71 *ddq*	5.07 *ddq*
H-7	4.13 *dddd*	4.02 *dddd*	3.94 *dddd*	3.60 *dddd*
H-8	5.56 *ddd*	5.55 *ddd*	5.68 *ddd*	5.29 *dd*
H-9α	1.85 *dd*	1.94 *dd*	1.82 *dd*	2.27 *dd*
H-9β	2.63 *dd*	2.82 *dd*	2.43 *dd*	2.32 *dd*
H-13	6.24 *d*	6.26 *d*	6.35 *d*	6.34 *d*
H-13′	5.59 *d*	5.61 *d*	5.27 *d*	5.74 *d*
H-14	1.51 *s*	1.51 *s*	1.13 *s*	1.48 *s*
H-15	1.85 *dd*	1.78 *dd*	1.68 *dd*	1.93 *dd*
OCOR	2.27 *tq*	2.27 *tq*	2.19 *tq*	2.32 *tq*
	1.58 *m*	1.58 *ddq*	1.6 *m*	1.58 *m*
	1.40 *ddq*	1.39 *ddq*	1.23 *ddq*	1.36 *ddq*
	1.01 *d*	1.04 *d*	1.08 *d*	1.08 *d*
	0.86 *t*	0.86 *t*	0.83 *t*	0.84 *t*
OAc	—	2.12 *s*	1.67 *s*	—

J(Hz): Compound **7**: 1,2α = 5; 2α, 2β = 13.5; 5, 6 = 3.5; 5, 15 = 6, 15 = 1.5; 6, 7 = 3.5; 7, 13 = 2.5; 7, 13′ = 2; 7, 8 = 5; 8, 9α = 5; 8, 9β = 10; 9α, 9β = 14; compound **8**: 1, 2α = 6; 2α, 2β = 14; 5, 6 = 3.5; 5, 15 = 6, 15 = 1.5; 7, 8 = 5; 7, 13 = 2.5; 7, 13′ = 2; 8, 9α = 5; 8, 9β = 10; 9α, 9β = 14; compound **9**: 2α, 2β = 19; 5, 6 = 6; 5, 15 = 6, 15 = 1.5; 6, 7 = 2.5; 7, 13 = 2.5; 7, 13′ = 2; 8, 9α = 8, 9β = 3.5; 9α, 9β = 14.

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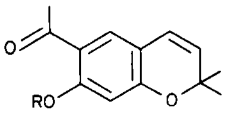
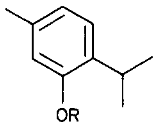
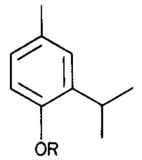
*Part 421 in the series "Naturally Occurring Terpene Derivatives". For Part 420 see Bohlmann F. and Wegner, P. (1982) *Phytochemistry* **21**, (in press).



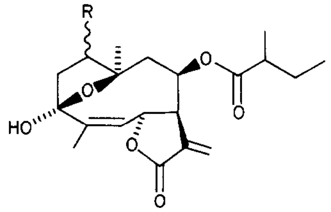
1 R=H
2 R=Me



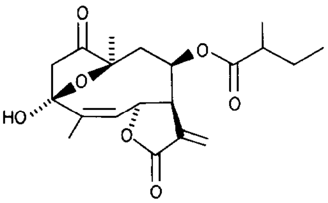
3 R=H
4 R=Me



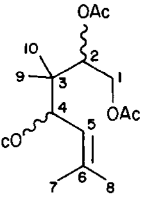
5 R=H
6 R=Me



7 R=βOH
8 R=αOAc



9



10

way. These signals were separated more clearly in deuteriobenzene. Further decoupling allowed the assignment of the signals of H-5 and H-9. The remaining downfield signal at δ 5.56 was coupled with a double doublet at δ 2.85 which itself showed geminal coupling with a doublet at δ 2.14. These data were in agreement with the presence of a 1α-acetoxy group in a heliangolide similar to zexbrevin B acetate, only the ester group at C-8 being different. The ^{1}H NMR spectral data of **7** were similar to those of **8**. However, some clear differences were visible, indicating a different stereochemistry of the hydroxyl group at C-1. Though the coupling $J_{1,2}$ was very similar, the differences in the chemical shifts of several signals could only be explained, if a 1β-hydroxy derivative was proposed. Accordingly, the ^{1}H NMR spectral data were similar to those of a corresponding 8β-methacryloyloxy derivative isolated from another *Calea* species [3], but different from those of zexbrevin B [4]. The third lactone (**9**) was the corresponding ketone, as was deduced from the pair of doublets at δ 3.18 and 2.65. All data were also similar to those of a methacrylate isolated from a *Calea* species [3]. In the spectrum of the latter a drastic change of the couplings of $J_{8,9}$ were visible, indicating a different conformation, which also followed from the differences in the chemical shifts of H-7 in the spectra of **7** and **9**. This could be explained with a conformation of **9** where the ester group at C-8 was quasi-axial, while for **7** and **9** a conformation with a quasi-equatorial ester group was proposed. This assumption was further supported by the differences in chemical shifts of H-9α, which in the case of **8** was deshielded by the 1α-acetoxy group. The chemistry of *C. oxylepis* shows that it should be placed in the Neurolinae [1].

EXPERIMENTAL

The air-dried plant material, collected in north-eastern Brazil (voucher RMK 8560, deposited in the U.S. National Herbarium, Washington) was extracted with Et_2O–petrol, 1:2 and the resulting extracts separated first by CC (Si gel) and further by repeated TLC (Si gel). Known compounds were identified by comparing the ^{1}H NMR spectra with those of authentic material. The roots (320 g) afforded 80 mg **1**, 110 mg **2**, 80 mg **3**, 30 mg **4**, 80 mg **5**, 30 mg **6** and 20 mg **10** (Et_2O–petrol, 1:3), while the aerial parts (180 g) gave 2 mg **7** and 2 mg **9**, which could not be separated completely, and 2.5 mg **8**. The lactones were separated by TLC using Et_2O–petrol, (3:2), several developments.

1β-Hydroxy-8-desacylzacatechinolide-(2-methyl butyrate) (**7**). Colourless gum, not free from **9**, IR$\nu^{CCl_4}_{max}$, cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1740 (CO_2R); MS *m/z* (rel. int.): 278 $[M-RCO_2H]^+$ (1.5), 260 $[278-H_2O]^+$ (5), 85 $[C_4H_9CO]^+$ (48), 57 $[85-CO]^+$ (100).

1α-Acetoxy-8-desacylzacatechinolide-(2-methyl butyrate) (**8**). Colourless gum, IR$\nu^{CCl_4}_{max}$, cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1740 (CO_2R, OAc); MS *m/z* (rel. int.): 404 $[M-H_2O]^+$ (0.2), 320.126 $[M-RCO_2H]^+$ (2) ($C_{17}H_{20}O_6$), 278 $[320-\text{ketene}]^+$ (11), 260 $[320-HOAc]^+$ (18), 242 $[260-H_2O]^+$ (4), 85 $[C_4H_9CO]^+$ (57), 57 $[85-CO]^+$ (100).

$$[\alpha]^{\lambda}_{24°} = \frac{589}{-161}\;\frac{578}{-164}\;\frac{546}{-192}\;\frac{436\,\text{nm}}{-340}\;(CHCl_3;\; c = 0.09).$$

1-Oxo-8-desacetylzacatechinolide-(2-methyl butyrate) (**9**). Colourless gum, IR$\nu^{CCl_4}_{max}$, cm^{-1}: 3600 (OH), 1780 (γ-lactone), 1740 (CO_2R, C=O); MS *m/z* (rel. int.): 378 $[M]^+$ (0.1), 276 $[M-RCO_2H]^+$ (2), 258 $[276-H_2O]^+$ (1), 85 $[C_4H_9CO]^+$ (50), 57 $[85-CO]^+$ (100).

1,2-Diacetoxy-1,2-dihydroartemisia alcohol acetate (**10**). Colourless oil, IR$\nu^{CCl_4}_{max}$, cm^{-1}: 1750, 1250 (OAc), 1470, 1440, 1380, 1065, 1040, 1020, 980, 950; MS m/z (rel. int.): 314.173 $[M]^+$ (0.2) ($C_{16}H_{26}O_6$), 254 $[M-HOAc]^+$ (6), 127 $[Me_2C{=}CH{-}CHOAc]^+$ (71), 85 $[127-\text{ketene}]^+$ (100), 68 $[C_5H_8]^+$ (72).

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NEW GERMACRANOLIDES FROM *INULA HETEROLEPIS**

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Key Word Index—*Inula heterolepis*; Compositae; sesquiterpene lactones; germacranolides; eudesmanolide.

Abstract—The aerial parts of *Inula heterolepis* afforded two new germacranolides and a new eudesmanolide, all closely related to haageanolide, which was also isolated.

Already about one-third of the species of the large genus *Inula* (tribe Inuleae) have been investigated chemically. Most contain sesquiterpene lactones which with few exceptions are 8, 12-lactones [1]. While eudesmanolides are most widespread, germacranolides, guaianolides, pseudoguaianolides and xanthanolides are frequently found. So far, only six species have been found to contain no lactones. From this group several thymol derivatives have been isolated [2, 3]. We have now investigated *Inula heterolepis* Boiss. (*I. verbascifolia* (Willd.) Hausskn. subsp. *heterolepis* (Boiss.) Tutin).

The aerial parts afforded squalene, the Δ12,13-isomer of lupeol and its acetate, haageanolide (**1**) [4] and three further lactones. From the mass spectra and the ^{1}H NMR spectral data (Table 1) the structures **2**–**4** were determined. The signals in the spectrum of **2** were similar to those of **1**. However, the absence of the second olefinic double bond followed from the presence of a singlet at δ1.15 and a double doublet at 2.86, the latter indicating an epoxide proton. Spin decoupling allowed the assignment of all signals. Irradiation of the typical H-7 signal (δ2.66) collapsed the signals at 6.29 and 5.58 to singlets, that at 4.60 to a doublet, the three-fold doublet at 1.76 to a double doublet and sharpened the signal at 2.25. As the double doublet at δ4.60 was further coupled with a broadened doublet at 5.19 which itself was coupled with the olefinic methyl, the presence of a 6,12-germacranolide was established. The stereochemistry at C-1 and C-9 followed from the couplings observed, if a model was inspected. Consequently, **2** was haageanolide-1β,10α-epoxide. The ^{1}H NMR spectrum followed from the additional exomethylene signals and the methyl singlet at δ0.92. Spin decoupling allowed the assignment of H-5 through H-7, while irradiation of H-5 showed that the exomethylene protons were at C-15. The protons at the hydroxyl bearing carbons displayed double doublets and their couplings indicated equatorial orientations of the hydroxyls. Their chemical shifts and the couplings showed that the hydroxyls were at C-1 and C-9, as both signals were double doublets and the chemical shifts indicated a non-allylic position. Consequently, **3** was 9β-hydroxyreynosin. The last lactone was obviously 9β-hydroxyartemorin (**4**). The ^{1}H NMR spectral data (Table 1) showed that both protons at the hydroxyl-bearing carbons were coupled with the exomethylene protons, while spin decoupling indicated that a 6,12-*trans*-germacranolide was present. Irradiation of the H-7 signal collapsed the signals of the neighbouring protons in the expected way, thus allowing the assignment of H-6, H-7, H-8 and H-13.

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*Part 405 in the series "Naturally Occurring Terpene Derivatives". For Part 404 see Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 1045.