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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REFERENCES

1. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 1643.
2. Epstein, W. W. and Poulter, C. D. (1973) *Phytochemistry* **12**, 737.
3. Bohlmann, F. and Zdero, C. (1977) *Phytochemistry* **16**, 1065.
4. Baruah, N. C., Sharma, R. P., Madhusudanan, K. P. Thyagarajan, G., Herz, W. and Murari, R. (1979) *J. Org. Chem.* **44**, 1831.

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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 $\Delta 12,13$-isomer of lupeol and its acetate, haageanolide (**1**) [4] and three further lactones. From the mass spectra and the ^1H 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 $\delta 1.15$ 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 ($\delta 2.66$) 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 $\delta 4.60$ 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 ^1H NMR spectrum followed from the additional exomethylene signals and the methyl singlet at $\delta 0.92$. 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 ^1H 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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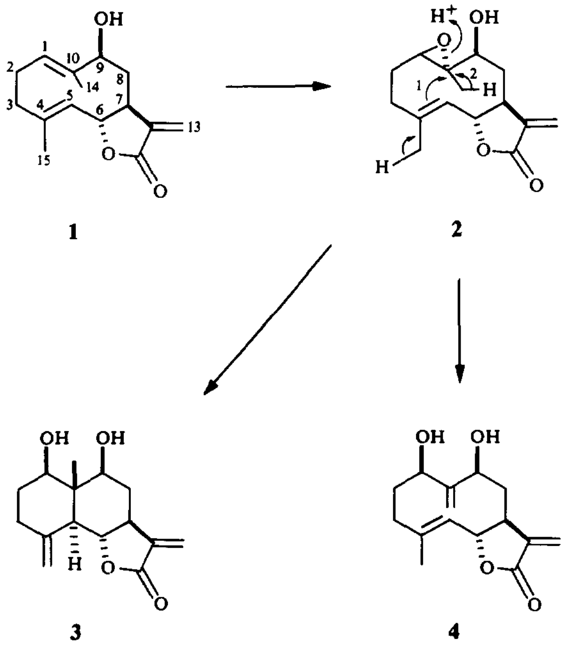
*Part 405 in the series "Naturally Occurring Terpene Derivatives". For Part 404 see Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1982) *Phytochemistry* **21**, 1045.

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

	2	**3**	**4**
H-1α	2.86 *dd*	3.97 *dd*	4.20 *br d*
H-2α	2.11 *dddd*	not detected	2.05 *br d*
H-2β	1.46 *dddd*		1.97 *m*
H-3α	2.41 *dd*	2.27 *m*	2.26 *m*
H-3β	2.29 *ddd*	2.35 *br d*	
H-5	5.19 *d*(*br*)	2.17 *br d*	5.19 *br d*
H-6β	4.60 *dd*	3.99 *dd*	4.26 *dd*
H-7α	2.66 *ddddd*	2.59 *ddddd*	2.78 *m*
H-8α	2.25 *br d*	not detected	2.78 *m*
H-8β	2.76 *ddd*		1.90 *ddd*
H-9α	3.21 *d*	3.89 *dd*	4.00 *br d*
H-13	6.29 *d*	6.11 *d*	6.23 *d*
H-13′	5.58 *d*	5.49 *d*	5.54 *d*
H-14	1.15 *s*	0.92 *s*	5.50 *br s* 5.37 *br s*
H-15	1.84 *d*	5.06 *br s* 4.91 *br s*	1.58 *d*

J (Hz): Compound **2**: 1α, 2α = 2.5; 1α, 2β = 11; 2α, 2β = 14; 2α, 3β = 2.5; 2α, 3α = 5; 2β, 3α = 13; 2β, 3β = 4.5; 5, 6β = 10; 5, 15 = 1; 6β, 7α = 10; 7α, 8α ~ 1.5; 7α, 8β = 10; 7, 13 = 3.5; 7, 13′ = 3; 8α, 8β = 15; 8β, 9α = 10; compound **3**: 1α, 2α = 4; 1α, 2β = 10; 3α, 3β = 14; 5, 6 = 11; 6,7 = 10; 7, 8α = 3;7, 8β = 10; 7, 13 = 3.5; 7, 13′ = 3; compound **4**: 1,2 β = 10; 2α, 2β = 13; 5, 6 = 10; 5, 15 = 1.5; 6, 7 = 10; 7, 8 β = 10; 7, 13 = 3.5; 7, 13′ = 3; 8α, 8β = 14; 8β, 9α = 10.



However, as the H-7 signal was overlapped with that of H-8α the signal of H-8β was changed to a double doublet. Obviously all the lactones were derived from **1**. Epoxidation of the 1(10)-double bond led to **2**, which can be transformed by proton attack to **3** or to **4**.

Although some of the characteristic ^{1}H NMR signals were visible in the crude fraction of **2–4**, it cannot be excluded that **3** and **4** were artefacts formed by interaction of **2** with acidic compounds in the extracts. *I. heterolepis*, therefore, does not contain the usual 8,12-eudesmanolides widespread in the genus. However, germacranolides have been reported from this genus [1].

EXPERIMENTAL

The air-dried aerial parts (500 g), collected in the Çetikbeli (Mugla) region in the south of Turkey (voucher ISTE 45787, deposited in the Herbarium of the Faculty of Pharmacy, Istanbul) were extracted with Et_2O–petrol (1:2) and the resulting extract was treated with MeOH to remove long chain saturated hydrocarbons. Separation by CC (Si gel) afforded 7 mg squalene, 100 mg Δ-12,13-isomer of lupeol and 200 mg of its acetate, 35 mg **1**, 7 mg **2**, 2 mg **3**, and 3.9 mg **4** (**2–4** separated by HPLC, reversed phase, MeOH–H_2O, 3:7).

1β,10α-*Epoxyhaageanolide* (**2**). Colourless gum, IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3600 (OH), 1788 (γ-lactone); MS *m/z* (rel. int.): 246.126 $[M]^+$(2)($C_{15}H_{18}O_3$), 228$[M-H_2O]^+$(2), 213$[228-Me]^+$(3), 149(58), 81$[C_6H_9]^+$(100), 55$[C_4H_7]$ (94);

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \qquad 578 \qquad 546 \qquad 436\ \mathrm{nm}}{+7.5 \qquad +9.6 \qquad +10.8 \qquad +22.1} (\mathrm{CDCl_3};\ c0.24).$$

9β-*Hydroxyreynosin* (**3**). Colourless gum, IR(CCl_4/νmax), cm^{-1}: 3500 (OH), 1780 (γ-lactone); MS *m/z* (rel. int.): 246.126 $[M]^+$(4)($C_{15}H_{18}O_3$), 228 $[246-H_2O]^+$ (5), 213 $[228-Me]^+$ (2), 149 (75), 57 (100):

$$[\alpha]_{24^\circ}^{\lambda} = \frac{589 \qquad 578 \qquad 546 \qquad 436\ \mathrm{nm}}{+19 \qquad +20 \qquad +20 \qquad +28} (\mathrm{CHCl_3};\ c0.1).$$

9β-*Hydroxyartemorin* (**4**). Colourless gum, IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3540 (OH), 1780 (lactone); MS *m/z* (rel. int.): 264.136 $[M]^+$ (1) ($C_{15}H_{20}O_4$), 236$[M-CO]^+$ (3), 218$[236-H_2O]^+$ (2), 203 $[218-Me]^+$ (1), 57 (100).

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REFERENCES

1. Fischer, N. H., Olivier, E. J. and Fischer, H. D. (1979) *The Biogenesis and Chemistry of Sesquiterpene Lactones*, Progress in the Chemistry of Organic Natural Products Vol. **38**, p. 47. Springer, Vienna.
2. Bohlmann, F. and Zdero, C. (1977) *Phytochemistry* **16**, 1243.
3. Bohlmann, F., Mahanta, P. K., Jakupovic, J., Rastogi, R. C. and Natu, A. A. (1978) *Phytochemistry* **17**, 1165.
4. Kisiel, W. (1978) *Phytochemistry* **17**, 1059.