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LEPTOCARPIN AND 17,18-DIHYDROLEPTOCARPIN, TWO NEW HELIANGOLIDES FROM *LEPTOCARPHA RIVULARIS*

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Key Word Index—*Leptocarpha rivularis*; Compositae; leptocarpin; 17,18-dihydroleptocarpin; heliangolides.

Abstract—The isolation and structure determination of two new sesquiterpene lactones of the heliangolide type, leptocarpin and 17,18-dihydroleptocarpin from *Leptocarpha rivularis*, are described. The structure of leptocarpin was established as the 8β-angeloyl ester of 3β,8β-dihydroxy germacra-4,11(13)-dien-1(10)-oxido-6α,12-olide. The second component was the 17,18-dihydro derivative of leptocarpin.

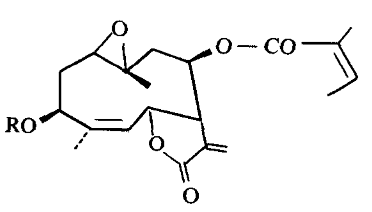
INTRODUCTION

In connection with a general phytochemical investigation of the native vegetation of southern Chile, we studied *Leptocarpha rivularis* (Compositae) [1] collected in the Botanical Garden at the University Austral de Chile, Valdivia in April, 1975. This study resulted in the isolation [2] of two closely related new heliangolides [3], leptocarpin (**1a**) and 17,18-dihydroleptocarpin (**4**).

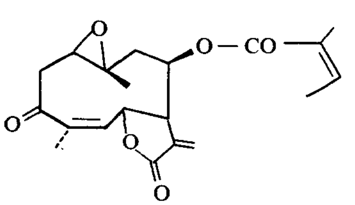
RESULTS AND DISCUSSION

Leptocarpin, $C_{20}H_{26}O_6$, mp 192–195°, $[\alpha]_D$ −99° ($CHCl_3$) contained a γ-lactone, conjugated with an exocyclic methylene group as indicated by its IR bands (1750 and 1660 cm^{-1}) and by the characteristic low field doublets in its ^1H NMR spectrum (δ 5.70 and 6.30, $J = 2$ Hz) which did not appear in the dihydro derivative (**2**). An ester group was indicated by an IR band at 1720 cm^{-1} (UV absorption, λ_{max} 209 nm, ε 16600, lactone and ester groups). In the MS, leptocarpin exhibited M^+ at m/e 362 and the typical fragments of tiglic or angelic esters at m/e 83 (99.5 %) and 55 (100 %). That the ester was angelic rather than tiglic was indicated by the signal of its vinylic proton which appeared as a multiplet at δ 6.08, a chemical shift characteristic of angelates [4]. The presence of a OH group was indicated by an IR band at 3430 cm^{-1} and by the formation of an acetate (**1b**), and the 3-dehydro leptocarpin (**3**) prepared on oxidation of **1a**.

Characteristic features of the ^1H NMR spectrum of leptocarpin are given in the Experimental. The assignment of the spectrum was carried out by frequency swept decoupling experiments. The observation of the chemical shifts and the vicinal and long range coupling constants of leptocarpin and some of its derivatives in the ^1H NMR spectra indicated the typical stereochemistry of heliangolides with a C-6 *trans* lactone and a *cis* double bond between C-4 and C-5. The coupling constants $J_{7,13} = 2$ and $J_{6,7} = 2$ Hz [5] are characteristic. On the other hand, the comparison of leptocarpin and epoxinobilin [5] spectral data revealed the relationship between both compounds. Based on this evidence leptocarpin must be the C-8 epimer of epoxinobilin.



1a R = H **1b** R = Ac



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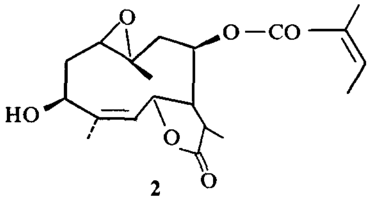

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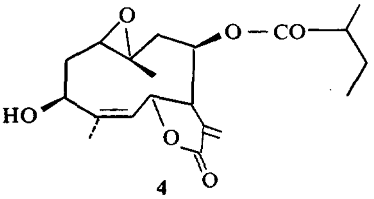

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17,18-Dihydroleptocarpin (**4**) $C_{20}H_{28}O_6$, mp 178–180° was also isolated from *Leptocarpha rivularis* in very low yield. It showed IR absorptions similar to those of leptocarpin, indicating the presence of a hydroxyl group (3460 cm^{-1}) and an α,β-unsaturated γ-lactone (1760 and 1660 cm^{-1}). The MS of **4** gave the parent peak at *m/e* 364 and the base peak at *m/e* 57 which differed from the parent and base peaks of leptocarpin by two mass units, thus strongly suggesting that **4** represented a dihydro derivative of leptocarpin. Further evidence supporting the structure of **4** was provided by its ^{1}H NMR spectrum. It showed a pair of low field doublets at δ 6.30 and 5.68 ($J = 2$ Hz) characteristic of H-13$_a$ and H-13$_b$. The coupling constants for H-7 and H-13 were identical with those of leptocarpin indicating that **4** was also a heliangolide. The major ^{1}H NMR spectral differences between **1a** and **4** were observed in the C-18 and C-17 methyl groups. In leptocarpin these signals were typical of an angeloyl group while the C-18 methyl signal in **4** appeared as a sharp triplet at δ 0.9 ($J = 7$ Hz) and the C-17 methyl protons appeared as a doublet ($J = 7$ Hz) at 1.18 ppm, indicating the presence of a *sec*-butyl group in the side chain (**4**).

EXPERIMENTAL

Isolation of leptocarpin (**1a**) *and* 17,18-*dihydroleptocarpin* (**4**). A collection of *Leptocarpha rivularis* D.C. was made on April, 1975 in the Botanical Garden at the University Austral de Chile in Valdivia, Chile. Ground, dried leaves (2 kg) of the plant were extracted with cold $CHCl_3$ and the extract was worked-up in the usual way [2]. The crude gum obtained (9.0 g) was chromatographed over a Si gel column, 200 ml fractions being collected in the following order: 1–90 (petrol), 91–158 (C_6H_6), 159–184 (C_6H_6–$CHCl_3$, 1:1), 185–195 ($CHCl_3$), 196–204 ($CHCl_3$–MeOH, 2:1), 205–207 (MeOH–$CHCl_3$, 2:1). Fractions 192–196 gave crude leptocarpin which crystallized from BuOH and then was recrystallized from cyclohexane–EtOAc as white plates, yield 0.20 g; mp 192–195°; $[\alpha]_D = -99°$ ($CHCl_3$); UV $\lambda_{\max}$ nm: 209, ε 16600; IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3430, 1750, 1720, 1660, 820; ^{1}H NMR: δ 2.80 (*dd*, $J = 5, 9$ Hz, H-1); 1.75 (*m*, $J = 2, 9, 15$ Hz) and 2.45 (*dt*, $J = 5, 5, 15$ Hz) (two H-2); 4.50 (*dd*, $J = 2, 5$ Hz, H-3); 5.31 (*dd*, $J = 2, 11$ Hz, H-5); 6.70 (*dd*, $J = 2, 11$ Hz, H-6); 3.00 (*m*, H-7); 5.25 (*m*, H-8); 6.30 (*d*, $J = 2$ Hz, H-13$_a$); 5.70 (*d*, $J = 2$ Hz, H-13$_b$); 1.80 (*s*, C-4 Me); 1.50 (*s*, C-10 Me); 6.08 (*m*, H-18); 2.00 (*m*, C-17 Me); 1.93 (*m*, C-18 Me). Low resolution MS *m/e* (rel. int.): 362 (M$^+$, 16.2), 344 (9.2), 300 (7.1), 245 (58.9), 83 (99.5), 55 (100). (Found: C, 65.41; H, 7.32, $C_{20}H_{26}O_6$ requires: C, 66.35; H, 7.24%). Fraction 197 provided a syrup which by successive crystallization from *n*-BuOH afforded 0.04 g of white crystals of 17,18-dihydrodroleptocarpin (**4a**), mp 178–180°; UV $\lambda_{\max}$ nm: 213, ε 9000; IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3460, 1760, 1730, 1660, 840; ^{1}H NMR: δ 5.10–5.40 (*br*, H-5 and H-8); 4.12 (*br*, H-3); 6.05 (*dd*, $J = 2, 11$ Hz, H-6); 2.75 (*m*, H-7); 6.30 (*d*, $J = 2$ Hz, H-13$_a$); 5.68 (*d*, $J = 2$ Hz, H-13$_b$); 1.88 (*d*, $J = 1.5$ Hz, C-4 Me); 1.60 (*s*, C-10 Me); 1.18 (*d*, $J = 7$ Hz, C-17 Me); 0.90 (*t*, $J = 7$ Hz, C-18 Me). Low resolution MS *m/e*: 364, 57 (base peak). (Found: C, 65.65; H, 7.75. $C_{20}H_{28}O_6$ requires: C, 65.99; H, 7.75%).

11,13-*Dihydroleptocarpin* (**2**). A soln of 0.100 g **1a** in 50 ml EtOAc was hydrogenated for 4.5 hr over 100 mg 10% Pd/C under atmos. pres. After filtration and evapn, the residue was chromatographed over Si gel. Fractions 5–12 eluted with EtOAc provided an oily residue which after trituration with Et_2O was recrystallized from cyclohexane–Me_2CO, providing 15 mg 11,13-dihydroleptocarpin (**2**), mp 102–105° $[\alpha]_D = 38°$ ($CHCl_3$); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3450, 1750, 1720, 1660; ^{1}H NMR: δ 4.40 (*dd*, $J = 2, 5$ Hz, H-3); 5.50 (*dd*, $J = 2, 11$ Hz, H-5); 6.52 (*dd*, $J = 2, 11$ Hz, H-6); 5.15 (*ddd*, $J = 2, 3, 3$ Hz, H-8); 1.82 (*d*, $J = 1.5$ Hz, C-4 Me); 1.45 (*s*, C-10 Me); 6.15 (*m*, H-18); 1.94 (*m*, C-18 Me); 1.10 (*d*, $J = 7$ Hz, C-11 Me). (Found: C, 65.51: H, 7.25, $C_{20}H_{28}O_6$ requires: C, 65.99; H, 7.75%).

Reduction of **1a** *with* KBH_4. To a soln of 0.345 g of **1a** in 28 ml MeOH was added with stirring 0.240 g KBH_4 in 9 ml MeOH at 0°. Stirring was continued for 1 hr at 0°. The soln was acidified, evapd at red. pres., diluted with 10 ml H_2O and extracted with $CHCl_3$. The washed and dried extract was evapd and the residue was recrystallized from cyclohexane–Me_2CO. Yield 0.178 g, mmp with **2** showed no depression.

3-*Dehydroleptocarpin* (**3**). A soln of 0.2107 g leptocarpin in 10 ml Me_2CO was stirred with 0.2 ml Jones' reagent for 10 min. The excess reagent was eliminated by treatment with MeOH, the solvent was removed *in vacuo*. The residue, following dilution with H_2O and extraction with EtOAc, was dried and crystallized from cyclohexane–EtOAc. Yield 0.140 g **3**: mp 135.5–137° $[\alpha]_D = 13°$ ($CHCl_3$); UV $\lambda_{\max}$ nm: 227 and 243, ε 9600, 8700; IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1760, 1720, 1710, 1660; ^{1}H NMR: δ 5.35 (*dd*, $J = 1.5, 11$ Hz, H-5); 5.12 (*dd*, $J = 2, 11$ Hz, H-6); 3.00 (*m*, H-7); 4.90 (*m*, H-8); 6.28 (*d*, $J = 2$ Hz, H-13$_a$); 5.75 (*d*, $J = 2$ Hz, H-13$_b$); 1.90 (*d*, $J = 1.5$ Hz, C-4 Me); 1.94 (*m*, C-17 Me); 1.45 (*s*, C-10 Me); 6.15 (*m*, H-18); 1.80 (*m*, C-18 Me). (Found: C, 66.62; H, 6.69, $C_{20}H_{24}O_6$ requires: C, 66.72; H, 6.72%).

Oxidation of **1a** *with* MnO_2. A soln of 0.020 g **1a** in 5 ml $CHCl_3$ was stirred with 0.100 g active MnO_2 until TLC indicated disappearance of starting material (20 hr) then filtered, washed, dried and evapd at red. pres. The residue was recrystallized from cyclohexane–EtOAc. Yield 10 mg of white crystals which were identical with **3** by mmp and co-chromatography.

Leptocarpin acetate (**1b**). A soln of 0.180 g **1a** in 2.5 ml Py and 5 ml Ac_2O was stirred at room temp. until TLC indicated disappearance of starting material. After concn *in vacuo*, a solid residue was obtained, which was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$ and then left to dry over Na_2SO_4. The solvent was removed and the residue recrystallized from cyclohexane–EtOAc. Yield 0.08 g **1b**: mp 180–182° $[\alpha]_D = -103$ ($CHCl_3$); IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1750, 1720, 1715, 1660, 1250; ^{1}H NMR: δ 2.75 (*dd*, $J = 4, 10$ Hz; H-1); 1.75 (*m*, $J = 10, 15, 2$ Hz) and 2.50 (*m*, $J = 4, 5, 15$ Hz) (two H-2); 5.1–5.40 (*br*. H-3, H-5 and H-8); 6.12 (*br*, *dd*, $J = 11, 2$ Hz, H-6); 2.98 (*m*, H-7); 6.32 (*d*, $J = 2$ Hz, H-13$_a$); 5.76 (*d*, $J = 2$ Hz, H-13$_b$); 1.90 (*d*, $J = 1.5$ Hz, C-4 Me); 1.50 (*s*, C-10 Me); 6.10 (*m*, H-18); 2.05 (*m*, C-17 Me); 2.10 (*s*, Ac).

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