# PANAMA FLORA. II. NEW SESQUITERPENE LACTONES FROM *NEUROLAENA LOBATA*

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Abstract.—Three germacranolides were isolated from the leaves and stems of *Neurolaena lobata* (*L.*)*R.Br.* One was found to be neurolenin-B (**2**). The two remaining compounds were new. Their structures were elucidated by spectroscopic methods. They have been named lobatin-A (**3**) and lobatin-B (**4**).

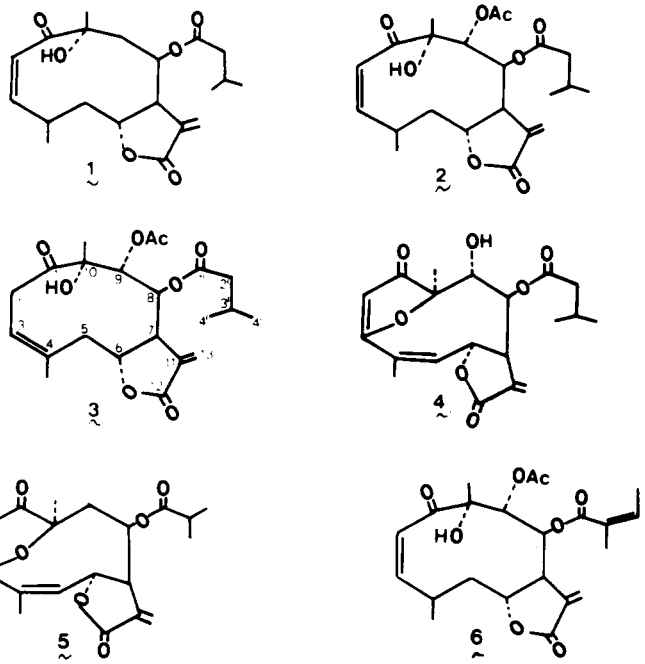
*Neurolaena lobata* (*L.*)*R.Br.* (Compositae, tribe Heliantheae, subtribe Neurolaeninae) is a herbaceous plant of 1 to 3 m. This species is found all around Central America and the Caribbean islands. It is known by various common names such as "gavilana" and "capitana". The plant is said to have several medicinal properties and has been cited as a tonic and an antipyretic (1,2). In Panama, where it is known as "contragavilana" and as "inaciabi" by Cuna natives, it is a popular folk remedy in the form of an infusion of the leaves for diabetes, hypertension and hepatic ailments; in the province of Darien it is also used for malaria and as an insect repellent.

Manchand and Blount isolated two sesquiterpene lactones, which they named neurolenin-A (**1**) and neurolenin-B (**2**) (3), from specimens collected in Trinidad, West Indies.

## DISCUSSION

In this communication, we report the results obtained from the study of a sample of *Neurolaena lobata* (*L.*)*R.Br.* collected in September 1980 in the Republic of Panama. This specimen was treated as explained in the experimental section. The chloroform extract was chromatographed. The first compound isolated, **2**, had mp, 162–63° (hexane) and $[\alpha]^{20}D - 350°$. Its physical constants and spectroscopic data coincided with those of neurolenin-B (**2**), a compound whose stereoestructure was established by spectral data and X-ray crystallographic analyses (3). Two compounds new to scientific literature were isolated from the remaining chromatographic fraction. Considering their origin, we assigned to them the names lobatin-A (**3**) and lobatin B (**4**), respectively. Lobatin-A (**3**), an isomer of the above mentioned compound, is interesting from the biogenetic point of view because of the position of the double bond $\Delta^3$, which had not been found in nature until now. Lobatin-B (**4**) is correlated with the heliangolides ciliarin (**5**) and woodhousin (5–7).

Lobatin-A (**3**) is a crystalline product ($C_{22}H_{30}O_8$): mp, 154–5° (hexane); $[\alpha]^{20}D - 304°$. Its uv spectrum showed an absorption at 219 nm (2320). The ir spectrum showed the following bands: a hydroxyl at 3485 $cm^{-1}$, carbonyl of $\alpha,\beta'$-unsaturated-$\gamma$-lactone at 1765 $cm^{-1}$, carbonyls of the ester groups at 1745 $cm^{-1}$, carbonyl of ketone at 1710 $cm^{-1}$ and olefinic bonds at 1660 $cm^{-1}$. Its $^1H$-nmr ($CDCl_3$) exhibited the $\alpha,\beta'$-unsaturated-$\gamma$-lactone group: at 4.94 ppm (1H, m,

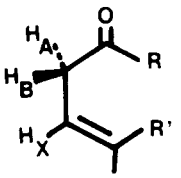


H–6), a similar value to that of *caleines* (**6**) (4); two bands at 5.7 ppm (1H, d, $J_{7,13}=3$ Hz) and 6.33 (1H, d, $J_{7,13}=3$ Hz) which correspond to exocyclic methylene and are coupled to H–7. These signals are simplified by irradiation on H–7; H–7 appears at 2.65 ppm (1H, m).

As in neurolenin-B (**2**), at 5.85 ppm (1H, dd, $J_{8,9}=9$ Hz and $J_{7,8}=1.5$ Hz), it showed signals corresponding to a methine proton on a carbon atom with an ester group, H–8. When H–7 was irradiated, the signal at 5.85 ppm appeared as a doublet with $J_{8,9}=9$ Hz. The signal at 5.6 ppm (1H, d, $J_{8,9}=9$ Hz) corresponded to H–9. The signals of the ester groups at C–8 and C–9 appeared at 2.07 ppm (2H, d, $J=4.5$ Hz, H–2'), 1.66 ppm (1H, m, H–3') and 0.90 ppm (6H, d, $J=6$ Hz, H–4' and H–4'') corresponding to the isovalerate group, and at 2.15 ppm (3H, s) corresponding to the acetate group. The presence of these esters was seen by the fragmentation in ms: 379 ($M^+$–43) (4%), 337 ($M^+$–85) (9%), 85 (100%) and 43 (94%).

The main difference with the neurolenin-B (**2**) is the presence of the following signals:

a) This spectrum showed an ABX system formed by the cluster



$\delta_A$: 3.58 ppm ($J_{AB}=15$ and $J_{AX}=8.4$ Hz)

$\delta_B$: 3.08 ppm ($J_{AB}=15$ and $J_{BX}=7.2$ Hz)

$\delta_X$: 5.91 ppm ($J_{AX}=8.4$ and $J_{BX}=7.2$ Hz)

When $H_A$ was irradiated, $H_X$, which is olefinic, appeared as a doublet; in the same way, when $H_B$ was irradiated, the olefinic proton was simplified.

b) The signal from protons at C–5 appeared at 2.8 ppm (2H, dd, $J_{5,6}=3.1$ Hz and $J_{5,14}=1.0$ Hz). When H–6 was irradiated, the signals of the protons at C–5 were simplified.

c) The C–4 methyl group was seen in a three-proton signal at 1.85 ppm (s, br). When this methyl group was irradiated, the signals at C–5 and C–6

were simplified. And the C–10 methyl group was 1.35 ppm (3H, s). This value is similar to that of the caleines (**6**) (4).

Lobatin-B (**4**) ($C_{20}H_{24}O_7$) was isolated as an oil, $[\alpha]^{20}D-11.54°$. Its uv spectrum showed a band at 219 nm (5920). The ir spectrum had the following absorptions: a hydroxyl band at 3450 $cm^{-1}$, carbonyl of $\alpha,\beta'$-unsaturated-$\gamma$-lactone at 1775 $cm^{-1}$, carbonyl ester at 1740 $cm^{-1}$, carbonyl of furanone at 1715 $cm^{-1}$, and at 1665 and 1600 $cm^{-1}$ two absorptions of olefinic bonds, the second of which is very strong owing to the enolic double bond $\Delta^2$.

The $^1$H-nmr spectrum ($CDCl_3$) contained the signals which follow: $\alpha,\beta'$-unsaturated-$\gamma$-lactone at 5.3 ppm (H, m, H–6). This was simplified when H–5, H–7 and H–14 were irradiated; at 6.33 (1H, d, $J=3$ Hz) and 5.75 ppm (1H, d, $J=3$ Hz) corresponding to exocyclic methylene at C–13 ,and at 3.83 ppm (1H, m) of H–7. When H–7 was irradiated, the signals of H–13 became two singlets and H–6 and H–8 were simplified.

In the downfield region, four groups of signals appeared: those at 5.95 ppm (1H, dq, $J_{5,6}=4.5$ Hz and $J_{5,14}=2.3$ Hz) corresponded to H–5. When $C_4$-*Me* was irradiated, H–5 was converted into a doublet with $J_{5,6}=4.5$ Hz. Similarly, when H–6 was irradiated, H–5 was converted into a quadruplet with $J_{5,14}=2.3$ Hz. The signal at 5.6 ppm (1H, s) arose from the olefinic H–2. This signal was similar to that ciliarin (**5**) (5). The third group, at 5.10 ppm (1H, dd, $J_{8,9}=4.5$ Hz and $J_{7,8}=2$ Hz), can be ascribed to H–8, a proton on a carbon atom bearing an ester group. The coupling constants have been calculated on the basis of experiments of irradiation on H–7 and H–9. Finally the signal at 4.0 ppm (1H, d, $J_{8,9}=4.5$ Hz) represented H–9. When H–8 was irradiated, H–9 was converted into a singlet.

At 3.1 ppm (1H, s) a signal arose from the hydroxyl group on C–9 but disappeared after shaking with $D_2O$.

The C–4 methyl group was seen in three-proton signal at 2.0 ppm (dd, $J_{5,14}=2.3$ Hz and $J_{6,14}=2$ Hz) and C–10 methyl group at 1.53 ppm (3H, s).

The ester group on C–8 was seen to be isovalerate because of the signals: at 2.14 ppm (2H, d, $J=4.5$ Hz, H–2'), 1.8 ppm (1H, m, H–3') and 0.87 ppm (6H, d, $J=6$ Hz, H–4' and H–4").

From the relation of all this data with the compounds previously mentioned, ciliarin (**5**) and woodhousin (5), we deduced that lobatin-B (**4**) has a stereostructure like them, with a hydroxyl group in 9-$\alpha$-position because $J_{8,9}=4.5$ Hz was assigned by Bohlmann *et al.* for compounds of similar structure (4), and an ester rest isovalerate instead of ester rest isobutyrate in the ciliarin (**5**).

## EXPERIMENTAL[1]

A specimen of *N. lobata* (*L.*) *R. Br.* (aerial parts, 250 g) was collected in September 1980, in the Republic of Panama. The dried plant was extracted with petroleum ether (40–60°, 500 ml) and then with chloroform (500 ml). The chloroform extract (8 g) was filtered, concentrated and chromatographed on Kieselgel with benzene-ethyl acetate in the proportions, first, (8:2) and then (7:3). Neurolenin-B (**2**) (100 mg) was isolated from the first fraction. Lobatin-A (**3**) (28 mg) and lobatin-B (**4**) (21 mg) were eluted with benzene-ethyl acetate (7:3). Lobatines A and B were separated by means of preparative tlc on Kieselgel with benzene-ethyl acetate (7:3).

LOBATIN-A (**3**).—Lobatin-A gave a mp, 154–5° (hexane); $[\alpha]^{20}D-304°$ (0.5, chloroform). Found: C, 62.42%; H, 7.24%. Calc. for $C_{22}H_{30}O_8$: C, 62.55%; H, 7.16%; ms,/*mz* (%) 422 ($M^+$) (2), 404 ($M^+-18$) (8), 394 ($M^+-28$) (2), 379 ($M^+-43$) (4), 363 ($M^+-59$) (8), 337 ($M^+-85$) (9), 321 ($M^+-101$) (30), 292 (8), 283 (3), 250 (87), 232 (9), 217 (3), 207 (5), 190 (13), 189 (11), 181 (12), 176 (7), 165 (4), 139 (5), 127 (4), 121(6), 109(5), 85(100), 59(85), 43 (94).

LOBATIN-B (**4**).—Lobatin-B was an oil; $[\alpha]^{20}D-11.5°$ (1.7, chloroform). Found: C, 62.98%; H, 6.42%. Calc. for $C_{20}H_{24}O_7$: C, 63.83%; H, 6.38%; ms,/*mz* (%) 376 ($M^+$) (1), 358 ($M^+-18$)

[1]Melting points were determined in a *Büchi* apparatus and are uncorrected. Spectra were determined as follows: $^1$H-nmr in a *Varian EM 390* apparatus, in $CDCl_3$ with TMS as internal standard; ir in a *Pye Unicam SP 1100* spectrometer, in nujol; uv in a *Berkman Acta C III* of twice sheaf, in EtOH and ms in a gc/ms *L.K.B. 9000* instrument at 12 and 70 eV.

(1), 348 ($M^+-28$) (0.5), 291 ($M^+-85$) (2), 275 ($M^+-101$) (3), 258 (1), 246 (1), 230 (2), 217 (10), 202 (3), 189 (4), 173 (2), 161 (100), 143 (8), 133 (4), 85 (22), 57 (40), 43 (40).

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