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ENT-NORLABDANES AND OTHER CONSTITUENTS OF FOUR VENEZUELAN SPECIES PREVIOUSLY CLASSIFIED IN THE GENUS *EUPATORIUM*

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ABSTRACT.—The investigation of four Venezuelan species previously classified in the genus *Eupatorium*, but which are now placed in the genera *Chromolaena, Lourteigia, Ageratina,* and *Austroeupatorium*, led to the isolation of several known flavonoids, diterpenes, and a chromene derivative. Austroeupatol [**3**], a novel *ent*-norlabdane, was obtained from *Austroeupatorium inulaefolium*. Its structure was established by spectroscopic methods.

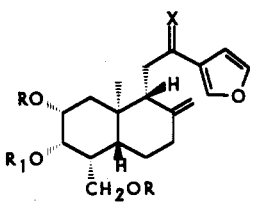
In an earlier paper (1), one of us (J.T.) reported a chemical study of *Lourteigia ballotaefolia* (HBK.) K. et R. (*Eupatorium ballotaefolium* HBK.) (2). We now describe isolation of the major components of the aerial parts of four members of the family Asteraceae, namely, *Chromolaena farinosa* (Rob) K. et R. (*E. farinosum* Rob) (3), *Lourteigia stoechadifolia* (L. f.) K. et R. (*E. stoechadifolium* L. f.) (4), *Ageratina ibaguensis* (Sch. Bip. ex Hieron.) K. et R. (*E. ibaguense* Sch. Bip. ex Hieron.) (5) and *Austroeupatorium inulaefolium* (HBK.) K. et R. (*E. inulaefolium* HBK.) (6), all collected in the Venezuelan Andes. *A. inulaefolium* from different locations has been chemically investigated previously (7–10), leading to the isolation of kauranes and norlabdanes in addition to common representatives of other classes of compounds.

Chromolaena farinosa afforded the following flavonoids: 5,7-dihydroxy-4′-methoxyflavone (acacetin) (11); 5,7-dihydroxy-3′,4′-dimethoxyflavone (12); 5,3′-dihydroxy-7,4′-dimethoxyflavone (pilloin) (13); 5,7,3′-trihydroxy-4′-methoxyflavone (diosmetin) (14); 3,5,3′-trihydroxy-7,4′-dimethoxyflavone (ombuin) (15); 5,3′-dihydroxy-7,4′-dimethoxyflavanone (persicogenin) (16), and 5,3′,4′-trihydroxy-7-methoxyflavanone (17). Their identifications were determined by spectroscopic procedures (18).

Likewise, *L. stoechadifolia* afforded the known flavonoids 5,3′-dihydroxy-6,7,4′-trimethoxyflavone (eupatorin) (19) and 5-hydroxy-6,7,3′,4′-tetramethoxyflavone (20), as well as the diterpene jhanidiol (21).

From *A. ibaguensis*, ripariochromene A (22) and the flavonoid 3,5,4′-trihydroxy-6,7-dimethoxyflavone 3-galactoside (eupalitin-3-*O*-galactoside) (23) were isolated and identified.

The aerial parts of *A. inulaefolium* afforded, in addition to the flavonoid 5,7,3′,4′-tetrahydroxy-6-methoxyflavone (eupafolin) (19), the three *ent*-norlabdanes **1**, **2**, and austroeupatol [**3**]. Compound **1** was previously isolated from this same species collected in Argentina (9). Compound **2** (24) was identified by comparison of its uv, ir, ^{1}H- and ^{13}C-nmr spectra with literature values (24). Compound **2** differs from **1** in the presence of two acetyl groups located at C-2 and C-



1 R=R$_1$=H, X=O
2 R=Ac, R$_1$=H, X=O
2a R=R$_1$=Ac , X=O
3 R=R$_1$=H, X=H$_2$
3a R=R$_1$=Ac, X=H$_2$

19. Acetylation of **2** led to **2a**, identical with the compound obtained by total acetylation of **1** (9). The structure of compound **2** has previously been confirmed by means of X-ray diffraction analysis (24). Its ^{1}H- and ^{13}C-nmr spectral data are being presented here for the first time. Austroeupatol [**3**] has the empirical formula $C_{19}H_{28}O_4$ as deduced from its high-resolution mass spectrum. Its ir and ^{13}C-nmr spectra (see Experimental), together with its ^{1}H-nmr spectrum, pointed to the presence of a side-chain furan ring similar to those of compounds **1** and **2**, although the presence of a vicinal carbonyl group was not observed in the molecule of **3**. The remaining signals in the ^{1}H-nmr spectrum of **3** (Table 1) were analogous to those of compound **1**. Compound **3** was therefore assigned a structure corresponding to the 12-deoxy derivative of **1**.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined with a Fisher-Johns melting-point apparatus and are uncorrected. Ir and uv spectra were recorded on Perkin-Elmer Model 377 and Pye Unicam SP-800 spectrophotometers, respectively. ^{1}H-Nmr spectra were obtained using a Varian T-60A or a Nicolet NT-360 instrument. ^{13}C-Nmr spectra were recorded on a Bruker WP-80 spectrometer at 20.1 MHz and ms were provided by Shrader Analytical and Consulting Laboratories, Inc. (Detroit, MI). Optical rotations were measured with an Autopol III automatic digital polarimeter.

PLANT MATERIAL.—The aerial parts of the plants were collected as follows: *Chromolaena farinosa*, in November 1977 at Pueblo Nuevo del Sur; *Lourteigia stoechadifolia*, in July 1976 at Bailadores; *Ageratina ibaguensis*, in September 1979

TABLE 1. ^{1}H-Nmr Spectral Data of Compounds **2**, **3**, and **3a** (360 MHz, $CDCl_3$, TMS as internal standard).[a]

Proton	Compound		
	2	**3**	**3a**
1α	2.03 dd (14, 2.5)	2.03 dd (14, 2.5)	2.0 m
1β	1.52 dd (14, 2.5)	1.25 dd (14, 2.5)	1.50 dd (14, 2.5)
2	5.27 q (2.5)	4.14 q (2.5)	5.33 q (2.5)
3	3.91 dd (6, 3)	3.84 dd (6, 3)	4.96 dd (6, 3)
4	2.25 m	2.20 m	2.25 m
5	1.80 m	1.65 m	1.70 m
6α	1.80 m	1.65 m	1.70 m
6β	1.57 m	1.55 m	1.50 m
7α	2.44 ddd (13, 4, 2)	2.43 ddd (13, 4, 2)	2.40 m
7β	2.25 m	2.20 m	2.25 m
9	2.64 dd (10, 3)	2.56 m	2.50 m
11a	3.00 dd (17, 10)	1.55 m	1.60 m
11b	2.70 dd (17, 3)		
12a	—	2.54 m	2.50 m
12b	—	2.20 m	2.25 m
14	6.75 dd (1.5, 1)	6.25 br	6.22 br
15	7.45 dd (1.5, 1.5)	7.30 dd (1.5, 1.5)	7.33 dd (1.5, 1.5)
16	8.10 dd (1.5, 1)	7.17 br	7.17 br
17a	4.81 br	4.93 br	4.97 br
17b	4.39 br	4.61 br	4.63 br
19a	4.80 dd (10, 10)	4.55 dd (10, 10)	4.80 dd (10, 10)
19b	4.26 dd (10, 2)	3.72 dd (10, 2)	4.26 dd (10, 2)
20	0.85 s	0.78 s	0.80 s
OAc	2.12 s		2.10 s
	2.06 s		2.03 s
			1.97 s

[a]Values in parentheses are coupling constants in Hz.

in Valle Grande; and *Austroeupatorium inulaefolium*, in September 1977 in Urb. Santa Ana. All of these areas are in the vicinity of Mérida, Venezuela, and the plants were identified by Prof. Anselmo Quintero of the Facultad de Ciencias Forestales, Universidad de Los Andes, where voucher specimens are deposited.

EXTRACTION AND ISOLATION.—The material was air-dried and extracted with hot EtOH. The extract was concentrated under reduced pressure and diluted with H_2O to obtain a 90% aqueous EtOH solution. This solution was extracted with petroleum ether and the aqueous alcoholic layer was concentrated, and extracted with EtOAc. The resultant EtOAc extracts were separated by cc (Si gel) using as eluent the solvent mixtures indicated in each case. *Chromolaena farinosa* (7 kg) gave 112 g of EtOAc extract which, upon cc with petroleum ether-EtOAc (8:2) afforded persicogenin (950 mg) and pilloin (130 mg) and with (petroleum ether-EtOAc (7:3) acacetin (960 mg) and 5,7-dihydroxy-3′,4′-dimethoxyflavone (620 mg), and with petroleum ether-EtOAc (6:4) diosmetin (200 mg), ombuin (80 mg), and 5,3′,4′-trihydroxy-7-methoxyflavanone (115 mg). *Lourteigia stoechadifolia* (5.7 kg) afforded 67 g of an EtOAc extract which were chromatographed with C_6H_6-EtOAc (8:2) to give eupatorin (510 mg), 5-hydroxy-6,7,3′,4′-tetramethoxyflavone (150 mg), and jhanidiol (45 mg). *Ageratina ibaguensis* (2.4 kg) gave, after extraction with EtOAc, a residue (77 g) that, when chromatographed with petroleum ether-EtOAc (8:2), afforded ripariochromene A (850 mg) and with petroleum ether-EtOAc (2:8) eupalitin-3-*O*-galactoside (55 mg), purified by cc (Polyclar) using as eluent the mixture $CHCl_3$-MeOH-2-butanone (9:4:1). *Austroeupatorium inulaefolium* (5 kg), afforded upon extraction with EtOAc, 195 g of residue that was chromatographed with C_6H_6-EtOAc (9:1) to give **2** (815 mg); with C_6H_6-EtOAc (8:2) austroeupatol **3** (3.9 g); C_6H_6-EtOAc (6:4) eupafolin (4.85 g) and with C_6H_6-EtOAc (3:7) **1** (1.15 g).

Compound **2**.—Colorless crystals, mp 75–77° (Me_2CO-petroleum ether); ir and uv as reported (24); ^{13}C nmr (80 MHz, $CDCl_3$) (C-1-C-20) δ 40.4, 71.3, 73.6, 45.1, 47.1, 28.8, 37.3, 146.0, 50.2, 37.2, 36.5, 193.6, 127.1, 108.3, 144.9, 147.6, 108.2, 62.1, 15.9, (OAc) 170.9, 21.4, (OAc) 171.3, 21.2 (some signals may be interchangeable); ^1H-nmr data, see Table 1. This substance (120 mg) was acetylated with Ac_2O-pyridine (1:1) by refluxing for 6 h with work up in the usual manner affording 45 mg of **2a**, which was found to be identical with the product obtained by acetylation of **1** (mp, tlc, ir, nmr, and mass spectra).

Austroeupatol [**3**].—Colorless crystals, mp 116–118° (EtOAc-petroleum ether); $[\alpha]_D$ −78.9° (c=0.99, MeOH); ir (KBr) ν max 3260, 1640, 1440, 1350, 1160, 1090, 1055, 1020, 890, 870 cm^{-1}; uv λ max (MeOH) (log ε) 221 (3.77) nm; hreims *m/z* $[M]^+$ 320.1996 (calcd for $C_{19}H_{28}O_4$, 320.1988); eims *m/z* 320 (100), 302 (12), 284 (26), 271 (6), 202 (9), 162 (11), 161 (15), 149 (18), 148 (15), 135 (16), 123 (27), 121 (23), 107 (13), 105 (32), 95 (17), 94 (17), 93 (28), 81 (21); ^{13}C nmr [80 MHz, $(CD_3)_2CO$] (C-1-C-20) δ 43.9, 72.2, 75.8, 48.9, 48.7, 25.7, 39.3, 149.2, 57.1, 38.9, 30.6, 24.6, 126.8, 112.2, 144.1, 140.2, 108.3, 62.4, 16.6 (some signals may be interchangeable); ^1H-nmr data, see Table 1. A sample (150 mg) of **3** was acetylated as described for **2**, to afford, after chromatography of the reaction product on a Si gel column with C_6H_6-EtOAc (6:4), 50 mg of **3a**, colorless crystals, mp 112–114° (EtOAc-petroleum ether); ir (KBr) ν max 1725, 1640, 1440, 1340, 1230, 1160, 1030, 920, 890, 870 cm^{-1}; ^1H-nmr data, see Table 1.

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