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MONOTERPENES AND LIGNANS FROM *MIKANIA SALTENSIS*

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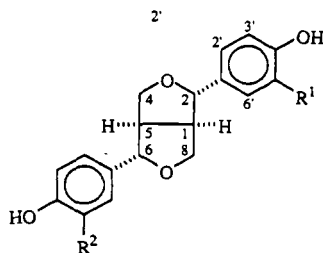
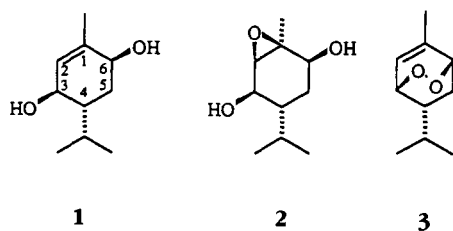
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ABSTRACT.—The aerial parts of *Mikania saltensis* yielded, in addition to common plant constituents, two menthane derivatives **1** and **2** new as natural products, pinosresinol, and a new lignan, (1*R**,2*S**,5*R**,6*S**)-2-(4-hydroxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane [**5**].

In continuation of our work on Argentine *Mikania* species (1–4) we have examined *Mikania saltensis* Hieron. (Compositae), a species limited to the provinces of Tucumán, Salta and probably Jujuy of northwestern Argentina (5). In contrast to almost all other *Mikania* species studied so far (6–13) *M. saltensis* yielded no sesquiterpene lactones or diterpenoids and contained only small amounts of other secondary metabolites. Isolated in addition to common plant sterols were the norsesterpene lactone loliolide and two optically active menthane derivatives **1** and **2** which are new as natural products but which one of us

has reported previously as transformation products of the *trans*-epidioxide **3** of *R*-(-)- α -phellandrene (14), although the rotations of the synthetic substances were not recorded. As **3** is also a natural product (15), it and its β -epoxide are probably the precursors of **1** and **2** in *M. saltensis*.

Two lignans of the 2,6-diaryl-3,7-dioxobicyclo[3.3.0]octane type were also found. The first was pinosresinol [**4**], identified by mass, uv, ir, and ¹H-nmr spectrometry. The second, isolated only in minute amount (less than 1 mg), was identified as the previously unreported pinosresinol analogue **5**. The ms showed that the formula was C₁₉H₂₀O₅, one methoxy unit less than **4**, but exhibited strong peaks (see Experimental) characteristic (16) of fragments containing both the 4-hydroxy-3-methoxyphenyl groups of pinosresinol and the 4-hydroxyphenyl groups of ligballinol [**6**] (17,18). Comparison of the 500 MHz ¹H-nmr spectra of pinosresinol and the new substance in C₆D₆ solution, which allowed for improved separation of the signals in the aromatic region, and decoupling experiments showed the presence in the new substance of both a *p*-hydroxyphenyl and an *m*-methoxy-*p*-hydroxyphenyl unit in equal amounts; in addition the doublet of H-2, -6, the dd of H-4_{eq}, H-8_{eq}, the dd of H-4_{ax}, H-8_{ax} and the multiplet of H-1, H-5 were doubled although the coupling constants remained the same as in



- 4** R¹, R² = OMe
5 R¹ = H, R² = OMe
6 R¹, R² = H

pinoresinol. Hence the two aryl substituents were diequatorial and the new substance was (1R*,2S*,5R*,6S*)-2-(4-hydroxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane [5]. Scarcity of material prevented determination of the absolute stereochemistry.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—For separation of mixtures, Waters hplc equipment (M45 pump, U6K injector with a 2 ml loop and R-401 differential refractometer) was used. Columns employed were a Phenomenex Maxsil 10 μ C8 (10 \times 500 mm) and a Phenomenex Ultramax 5 μ C18 (10 \times 250 mm). Retention times were measured from the solvent peak. The peaks were collected separately and rechromatographed if necessary to obtain samples pure by hplc criteria (single peak). Nmr spectra were obtained on Varian 300 and 500 MHz spectrometers and mass spectra on a Finnigan 6C/MS System Model 4510 at 70 eV.

PLANT MATERIAL.—Aerial parts of *M. salten-sis* were collected at the flowering stage on April 14, 1988, at La Quebradita, Tafí del Valle, Tucumán province, Argentina. A voucher specimen (Legname 9275) is on deposit in the herbarium of the Instituto Miguel Lillo, Tucumán.

EXTRACTION AND ISOLATION.—Flowers and leaves (505 g) were extracted with CHCl₃ (2 \times 6 liters) at room temperature for 6 days to give 37.4 g (7.41%) of crude extract which was suspended in EtOH (520 ml) at 55°, diluted with H₂O (390 ml), and extracted successively with *n*-hexane (3 \times 500) and CHCl₃ (3 \times 400 ml). The CHCl₃ extract on evaporation at reduced pressure furnished a residue (5.5 g), which was chromatographed over Si gel (250 g) using CHCl₃ containing increasing amounts of EtOAc (10–40%); 48 fractions were collected and monitored by tlc.

Fractions 7–14 (170 mg) were combined and decolorized with charcoal using hexane-EtOAc (3:1). After filtration and evaporation the residue was processed by hplc (C-18 column, MeOH, 1.5 ml/min) to yield fractions containing mixtures of alkanes, alkanolic acids, pure stigmaterol (33 mg), and pure sitosterol (18 mg). Fractions 17–24 (134 mg) were rechromatographed over Si gel using CHCl₃ containing increasing amounts of EtOAc (0–15%), and 49 fractions were collected. Fractions 24–33 (23 mg) of the rechromatography were combined and processed by reversed-phase-hplc [C8 column, MeOH-H₂O (7:6), 2 ml/min] to give loliolide (3 mg, Rt 9 min) and pinoresinol [4] (5.1 mg, Rt 13 min) as well as un-

defined material. Hplc of fractions 34–40 furnished an additional 0.5 mg of 4 and 0.8 mg of 5. Combination of fractions 41–49 (15 mg) and hplc [C8 column, MeOH-H₂O (7:5), 1.7 ml/min] gave 2 (8 mg, Rt 5 min) and 1 (16 mg, Rt 10 min).

(3R,4R,6S)-3,6-Dihydroxy-1-menthene [1]: mp 166–168° [lit. (14) mp 166–168]; [α]_D²⁰ + 114° (c = 0.119, MeOH); ir (film) 3572 (s), 3248 (vs), 1255 (w), 1165 (w), 1130 (w), 1072 (w), 1028 (m), 988 (w), 937 (w), 866 (w), 666 (s) cm⁻¹; ¹H nmr (300 MHz, CD₃OD) δ 5.46 (brs, H-2), 3.90 (t, J = 3 Hz, H-6), 3.84 (brd, J = 10 Hz, H-3), 2.10 (seprd, J = 7, 3 Hz, H-8), 1.76 (brs, 3p, H-7), 1.71 (ddd, J = 13.5, 3, 2.7 Hz, H-5a), 1.58 (dddd, J = 13.5, 10, 3, 2.7 Hz, H-4), 1.37 (ddd, J = 13.5, 13.5, 3, H-5b), 0.97 (d, J = 7, 3p, H-9) and 0.82 (d, J = 7, 3p, H-10). Comparison with the nmr spectrum of synthetic material (14) confirmed the identity.

(1S,2R,3R,4R,6S)-3,6-Dihydroxy-1,2-epoxymenthane [2]: mp 124–126° [lit. (14) mp 115–117]; [α]_D²⁰ - 380° (c = 0.065, MeOH); ir (film) 3573 (s), 3308 (vs), 1644 (m), 1244 (w), 1204 (w), 1132 (w), 1090 (w), 1066 (m), 1032 (s), 996 (m), 666 (vs); ¹H nmr (300 MHz, CD₃OD) 3.89 (dd, J = 5, 2.7 Hz, H-6), 3.67 (dd, J = 10, 2 Hz, H-3), 3.14 (d, J = 2 Hz, H-2), 2.04 (seprd, J = 7, 3 Hz, H-8), 1.58 (dddd, J = 12, 10, 3, 2.7 Hz, H-4), 1.47 (ddd, J = 14.5, 2.7, 2.7 Hz, H-5a), 1.37 (s, 3p, H-7), 1.21 (ddd, J = 14.5, 12, 5 Hz, H-5b), 0.91 (d, J = 7; 3p, H-9), 0.77 (d, J = 7 Hz, H-10). Comparison with the nmr spectrum of synthetic material (14) established identity.

Lolliolide, mp 149–150°, was identical with an authentic sample. Pinoresinol [4], obtained only as a gum, was identified by its mass, uv, and ¹H-nmr spectrum, which showed that it was 2,6-diequatorially substituted di-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (16): ir (film) 3573 (m), 3385 (vs), 2060 (w), 1703 (w), 1659 (w), 1605 (m), 1274 (vs), 1239 (vs), 1160 (s), 1126 (m), 1035 (s), 963 (m), 903 (w), 820 (m), 666 cm⁻¹; uv λ max (MeOH) 209, 230, 260 nm; ms m/z (rel. int. %) [M]⁺ 358 (48.5), 205 (23.6), 196 (11.2), 190 (12.5), 180 (11.6), 163 (36.9), 162 (11.1), 152 (24.1), 151 (100), 150 (32.5), 137 (58.2), 133 (10.6), 131 (32.8); ¹H nmr (500 MHz, CDCl₃) δ 6.89 (d, J = 2 Hz, 2p, H-2'), 6.88 (d, J = 8 Hz, 2p, H-5), 6.82 (dd, J = 8, 2 Hz, 2p, H-6'), 5.59 (s, 2p, exchanges with D₂O, OH), 4.73 (d, J = 4 Hz, 2H, H-2, -6), 4.25 (dd, J = 9, 6.5 Hz, 2H, H-4eq, H-8eq), 3.91 (s, 6p, OMe), 3.87 (dd, J = 9, 4 Hz, 2p, H-4ax, H-8ax), 3.1 (m, 2p, H-1, H-5); ¹H nmr (500 MHz, C₆D₆ for comparison with 5) δ 7.01 (d, H-5'), 6.84 (d, H-2'), 6.64 (dd, H-6'), 5.43 (-OH), 4.68 (d, H-2, 6), 4.03 (dd, H-4eq, H-8eq), 3.75 (dd, H-4ax, H-8ax), 3.16 (OMe), 2.86 (m, H-1, H-5). To distinguish 4 from the

di-4'-methoxy-3-hydroxyphenyl analogue, the location of the OMe group on C-3' was established by an nOe experiment; irradiation at the frequency of the OMe signal increased the intensity of the H-2' signal by 5.7%.

(1R*,2S*,5R*,6S*)-2-(4-Hydroxyphenyl)-6-(3-methoxy-4-hydroxyphenyl)-3,7-dioxabicyclo [3.3.0]octane **5** was a gum: ms *m/z* (rel. int. %) 328 (62.6), 297 (12.5), 205 (13.1), 178 (11), 175 (22.5), 163 (17.7), 162 (12.9), 161 (12.2), 153 (11.6), 152 (33.3), 151 (70.1), 150 (29.4), 147 (14.0), 145 (16.5), 137 (44.9), 135 (14.0), 133 (38.5), 132 (13.7), 131 (33.6), 124 (15.2), 123 (16.4), 122 (24.8), 121 (100), 107 (41.9); ¹H nmr (500 MHz, C₆D₆) 7.10 (d, *J* = 8 Hz, 2p, H-3', H-6'), 6.99 (d, *J* = 8 Hz, H-5"), 6.81 (d, *J* = 2 Hz, H-2"), 6.64 (dd, *J* = 8, 2-Hz, H-6'), 6.52 (d, *J* = 8 Hz, 2p, H-2', H-6'), 5.42 (s, OH), 4.65 and 4.64 (both d, *J* = 4 Hz, each 1p, H-2, H-6), 4.04 (s, OH), 3.98 (two nearly superimposed dd, *J* = 9, 6.5 Hz, each 1p, H-4eq, H-8eq), 3.73 and 3.70 (both dd, *J* = 9, 4 Hz, each 1p, H-4ax, H-8ax), 3.16 (3p, OMe), 2.71 (two nearly superimposed m's, 2p, H-1, H-5).

NOTE ADDED IN PROOF: A 3-*O*-β-D-glucoside of **1** or its enantiomer has been reported from *Ageratina anisochroma* (19).

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