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CHEMICAL STUDIES ON MEXICAN PLANTS USED IN TRADITIONAL MEDICINE, XVIII.[1] NEW SECONDARY METABOLITES FROM *DODONAEA VISCOSA*

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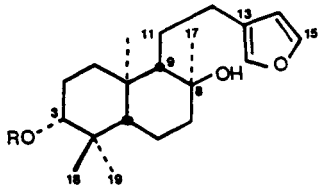
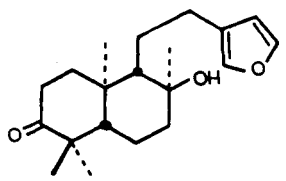
ABSTRACT.—Investigation of the aerial parts of *Dodonaea viscosa* led to the isolation of a new *ent*-labdane **1** [*ent*-15,16-epoxy-9αH-labda-13(16),14-diene-3β,8α-diol] and a novel *p*-coumaric acid ester **4** of 1-L-*myo*-inositol [1-L-1-*O*-methyl-2-acetyl-3-*p*-coumaryl-*myo*-inositol], along with other known compounds. The structures were determined by spectroscopic analysis and chemical reactions.

In the central valley of Oaxaca, México, *Dodonaea viscosa* (L.) Jacq. (Sapindaceae), locally known as "cacho venado," "cuerno de cabra," and "chapuliztle," is used as an herbal remedy for human inflammations, swelling, rheumatism, and pain (1). Previous chemical studies on this species resulted in the isolation and characterization of several flavonoids (2–6), two diterpenoid acids (7,8), some biologically active saponins (9,10) and plant acids (2). In the course of our continuing research on Mexican plants used in traditional medicine, we now report on the isolation and structure elucidation of a new diterpene **1** and a novel *p*-coumaric acid ester **5** of 1-L-*myo*-inositol together with other known compounds from the aerial parts of *D. viscosa*.

Compound **1**, $C_{20}H_{32}O_3$, was obtained as an oil. On acetylation it formed the monoacetate **2**, and on treatment with Collins reagent it yielded the ketone **3**. The presence of the furan moiety in **1** was indicated by the uv, ir, and mass spectra (11). The nmr data clearly demonstrated that **1** had a labdane-type skeleton with a β-substituted furan ring and two carbinol functionalities. The ^{1}H-nmr spectrum (see Experimental) showed resonances due to the furan moiety (δ 7.40, 7.29, and 6.36), an axially oriented proton geminal to a secondary hydroxyl group (δ 3.29, dd, $J = 11$, 5 Hz), and the four methyl groups of the parent structure; the downfield shift (δ 1.15) of H-17 was consistent with the presence of a tertiary hydroxyl group at C-8. The ^{13}C-nmr data of **1**–**3** (Table 1), when compared with those values of appropriate models (12,13), allowed assignment of the secondary hydroxyl group to C-3. This comparison showed the predictable α and β paramagnetic shifts caused by the acetylation in **2**, and



1 R=H
2 R=Ac



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[1]Taken in part from the B.S. theses of D. Crisanto and J.L. Contreras and M.S. thesis of P. Castañeda. For Part XVII, see P. Castañeda, C. Albor, E. Linares, R. Bye, and R. Mata, *Fitoterapia*, in press (1991).

TABLE 1. ^{13}C-nmr Spectral Data of Compounds **1–3**.[a]

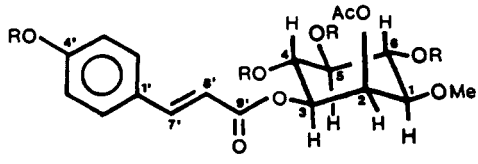
Carbon	1	2	3
C-1	37.85	37.58	38.51
C-2	26.96	23.35	33.85
C-3	78.60	80.57	216.50
C-4	38.74	37.71	47.43
C-5	54.90	55.07	54.96
C-6	20.14	20.08	21.30
C-7	44.33	44.35	43.87
C-8	73.85	73.79	73.72
C-9	61.00	60.89	60.02
C-10	38.74	38.70	38.28
C-11	25.97	25.94	26.20
C-12	27.90	27.81	27.71
C-13	125.44	125.36	125.25
C-14	110.95	110.99	110.94
C-15	142.62	142.75	142.75
C-16	138.57	138.81	138.78
C-17	23.73	23.75	23.65
C-18	28.04	28.03	26.27
C-19	15.30	16.44	21.30
C-20	15.48	15.62	14.87

[a]Recorded in $CDCl_3$. Chemical shift values are reported as δ values (ppm) from internal TMS at 75.4 MHz; multiplicities were confirmed by APT and DEPT spectra.

the shift effects, attributable to the oxidation, on C-2 ($\Delta\delta = 11.5$), C-3 (δ 216.5), C-4 ($\Delta\delta = 9.7$), C-18 ($\Delta\delta = -1.7$), and C-19 ($\Delta\delta = 4.8$) in **3**. The negative Cotton effect of the CD curve of **3** ($\Delta\epsilon_{287} = -0.31$) indicated the *ent*-type absolute configuration (15). Therefore, the structure of the new natural product was formulated as *ent*-15,16-epoxy-9αH-labda-13(16),14-diene-3β,8α-diol. Assignments of individual nmr signals were based on 2D heteronuclear chemical shift correlation, APT, and DEPT spectra (Table 1 and Experimental).

Compound **4** was obtained as a white crystalline solid, and the molecular formula $C_{18}H_{22}O_9$ was indicated by elemental analysis. Its ir spectrum showed absorptions for hydroxyl (3100–3500 cm^{-1}), conjugated ester (1710 and 1630 cm^{-1}), acetate (1730 cm^{-1}), and aromatic groups (1610 cm^{-1}). Evidence that **4** has four hydroxyl groups came from its complete acetylation, which gave a crystalline solid **5**, $C_{26}H_{30}O_{13}$. Alkaline hydrolysis of **4** with NH_4OH afforded *p*-coumaric acid and 1-L-1-*O*-methyl-*myo*-inositol [(+)-bornesitol], identical with standard samples. The nmr data (Table 2) further established that **4** was a *myo*-inositol derivative trisubstituted with methyl, acetyl, and *trans*-*p*-coumaryl groups. The signals for the two ester residues and the non-aromatic methoxyl group were readily identified in the spectra and assigned as indicated in Table 2. The resonances for the cyclitol portion appeared between δ 3.25 and 5.75 in the ^{1}H-nmr spectrum, and the 2D COSY experiment elucidated the homonuclear proton couplings summarized in Table 2. Based on the coupling pattern and chemical shift exhibited by the methine protons of the cyclitol moiety in **4** and **5**, it was found that the acetyl group was located on C-2 and was axially oriented, and the *p*-coumaryl residue on C-3 was equatorially disposed. The ^{13}C-nmr assignments of the cyclitol portion of **5** were confirmed by the heteronuclear ^{1}H-^{13}C correlation (Table 2). On the basis of these results the structure of compound **4** was elucidated as 1-L-1-*O*-methyl-2-acetyl-3-*p*-coumaryl-*myo*-inositol (15).

The known flavonoids sakuranetin, 6-hydroxykaempferyl-3,7-dimethyl ether, not previously described in the plant, and hautriwaic acid were also isolated. Their physical and spectral properties



4 R=H
5 R=Ac

TABLE 2. ^{13}C- (75.4 MHz) and ^{1}H-nmr (300 MHz) Chemical Shifts of Compounds **4**[a] and **5**[b] (coupling constants, in Hz, in parentheses).

Position	^{13}C		^{1}H	
	4	**5**[c]	**4**[d]	**5**[c,d]
1	79.72 d	77.16 d	3.25 dd (10,4)	3.48 dd (10,4)
2	66.65 d	66.11 d	5.75 dd (4)[e]	5.84 dd (4)[e]
3	71.52 d[f]	69.27 d	4.90 dd (10,4)	5.10 dd (10,4)
4	71.11 d[f]	69.50 d	3.92 dd (10)[e]	5.60 dd (10)[e]
5	74.52 d	71.03 d	3.44 dd (10)[e]	5.20 dd (10)[e]
6	70.32 d[f]	70.95 d	3.75 dd (10)[e]	5.39 dd (10)[e]
7	57.32 s	58.24 s	3.40 s	3.45 s
8	169.52 s	169.09 s	—	—
9	20.32 s	20.53 s	2.10 s	2.18 s
1′	125.09 s	131.53 s	—	—
2′,6′	129.56 d	129.45 d	7.38 d (8)	7.55 d (8)
3′,5′	115.62 d	122.13 d	6.82 d (8)	7.15 d (8)
4′	159.56 s	152.35 s	—	—
7′	145.35 d	145.45 d	7.61 d (15)	7.65 d (15)
8′	113.20 d	116.35 d	6.22 (15)	6.22 d (15)
9′	166.37 s	165.45 s	—	—
OH	—	—	2.92 bs	—
4′-OH	—	—	4.70 bs	—
Me*C*O-	—	169.98	—	—
	—	169.95	—	—
	—	169.87	—	—
	—	169.82	—	—
*Me*CO-	—	21.13	—	1.98 s
	—	20.82	—	1.99 s
	—	20.74	—	2.03 s
	—	20.61	—	2.30 s

[a]Recorded in $CDCl_3$/DMSO-d_6.
[b]Recorded in $CDCl_3$.
[c]Assignments confirmed by HETCOR.
[d]Assignments confirmed by 2D COSY.
[e]Triplet-like signal.
[f]Assignments may be interchanged.

were in good agreement with those reported in the literature (8,16,17).

To our knowledge this is the first report of a *myo*-inositol derivative in a member of the Sapindaceae family.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were taken on a Beckman DU-7; ir spectra were obtained in KBr or neat on a Perkin-Elmer 599 B spectrophotometer; nmr spectra were registered in a Varian VXR-300 S apparatus. Optical rotations were measured with a JASCO DIP 360 digital polarimeter; mass spectra were determined on a Hewlett-Packard 5985-B spectrometer. Si gel 60 (70–230 mesh) Merck was used for cc; tlc was done on Si gel 60 GF_{254} plates (Merck).

PLANT MATERIAL.—The plant material (aerial parts) was collected by Biologist Alejandro Cisneros in Oaxaca, on the route to Jayacatlan (17 km), in March 1989. Reference samples have been deposited at the Herbarium of the Department of Botany, School of Chemistry, Universidad Autónoma Benito Juarez de Oaxaca, Oaxaca, México (voucher no. Cisneros 368).

ISOLATION PROCEDURES.—The air-dried, shredded plant material (1.5 kg) was macerated four times with a mixture of $CHCl_3$-MeOH (1:1) at room temperature for 2 days. The combined extracts were evaporated to dryness to yield 164 g of a dark residue, which was chromatographed on Si gel (1.64 kg); elution was accomplished with a solvent gradient of increasing polarity (hexane gradually enriched with $CHCl_3$, and $CHCl_3$ with increasing amounts of Me_2CO). Fractions dis-

playing similar composition on tlc were combined and further fractionated by cc. Final purification of the compounds was achieved by ptlc. The following compounds were obtained, in order of elution from the initial chromatographic column: *ent*-15,16-epoxy-9αH-labda-13(16),14-diene-3β,8α-diol (920 mg), sakuranetine (523.3 mg), 6-hydroxykaempferyl 3,7-dimethyl ether (8.52 g), hautriwaic acid (1.96 g) and 1-L-1-*O*-methyl-2-acetyl-3-*p*-coumaryl-*myo*-inositol (35 mg).

Ent-*15,16-epoxy-9αH-labda-13(16),14-diene-3β,8α-diol* [**1**].—Oil: $[\alpha]_D$ −4.16° (*c* = 0.24, MeOH); uv λ max (MeOH) 282 nm (log ε 3.96); ir (neat) ν max 3460, 2950, 2875, 1500, 1460, 1385, 1260, 1160, 1110, 1050, 1020, 1000, 930, 875, 790 cm^{-1}; eims *m/z* (rel. int.) $[M]^+$ 320 (0.4), $[M-H_2O]^+$ 302 (8.1), $[M-H_2O-15]^+$ 287 (3.7), $[M-2H_2O]^+$ 284 (1.5), 208 (18.5), 207 (11), 190 (25), 175 (40), 147 (30), 135 (20), 95 (42), 94 (58), 81 (100), 71 (41.6). *Anal.* calcd for $C_{20}H_{32}O_3$, C 72.91, H 10.10; found C 73.15, H 9.90. ^1H nmr (300 MHz, $CDCl_3$, δ) 0.76 (s, H-19), 0.82 (s, H-20), 0.93 (m, H-5), 0.99 (s, H-18), 1.09 (m, H-9), 1.15 (m, H-1ax), 1.16 (s, H-17), 1.37 (m, H-6ax), 1.42 (m, H-7ax), 1.53 (m, H-11), 1.64 (m, H-2), 1.70 (m, H-6eq), 1.75 (m, H-1eq, H-11′), 1.92 (m, H-7eq), 2.52 (t, H-12), 3.29 (dd, *J* = 11, 5 Hz, H-3), 6.36, 7.29 (each br s, H-14, H-16), 7.40 (t, *J* = 1.8 Hz, H-15).

ACETYLATION OF **1**.—Compound **1** (85 mg) was dissolved in 1 ml of Ac_2O and 1 ml of pyridine. The reaction mixture was worked up as usual to yield 76 mg of an oily residue, compound **2**: eims *m/z* (rel. int.) $[M]^+$ 362 (1), $[M-60]^+$ 300 (5), 285 (1), 95 (40), 94 (35), 81 (70), 43 (100); ir (neat) ν max 3430, 2950, 2870, 1720, 1450, 1370, 1260, 1115, 1060, 1010, 735; ^1H nmr (300 MHz, $CDCl_3$, δ) 0.84 (6H, s, H-19 and H-20), 0.88 (s, H-18), 1.15 (s, H-17), 2.04 (s, *Me*-CO-), 4.48 (dd, *J* = 11, 4.5 Hz, H-3), 6.29, 7.23 (each br s, H-14 and H-16), 7.35 (t, *J* = 1.8 Hz, H-15).

OXIDATION OF **1**.—Compound **1** (106 mg) in pyridine (1.5 ml) was treated with a solution of CrO_3 (112 mg in 1.5 ml of pyridine) at room temperature for 18 h. Workup followed by tlc furnished 31.5 mg of an amorphous solid, compound **3**: ir ($CHCl_3$) ν max 3460, 2935, 2858, 1703, 1501, 1455, 1385, 1267, 1123, 1079, 1022, 925, 873, 789; eims *m/z* (rel. int.) $[M]^+$ 318 (0.5), $[M-15]^+$ 303 (1), $[M-H_2O]^+$ 300 (3), 285 (2), 206 (10), 205 (11), 139 (30), 98 (55), 95 (46), 94 (100), 81 (97), 43 (67); ^1H nmr (300 MHz, $CDCl_3$, δ) 0.96 (s, H-20), 1.02 (s, H-19), 1.10 (s, H-17), 1.22 (s, H-18), 6.30, 7.24, and 7.36 (each br s, H-14, H-16, and H-15, respectively); cd (*c* = 0.05, MeOH) Δε (*nm*) −0.06 (260), −0.168 (270), −0.271 (280), −0.310 (287), −0.1810 (300), 0 (308), +0.06 (320), +0.02 (310).

1-L-O-Methyl-2-acetyl-3-p-coumaryl-myo-*inositol* [**4**].—White crystals: mp 173–176°; $[\alpha]_D$ +32.2 (*c* = 1.8, MeOH); uv λ max (MeOH) 314.5 nm; ir (KBr) ν max 3350–3100, 2995, 1730, 1710, 1630, 1610, 1440, 1380, 1260, 1200, 1100, 1030, 1070, 990, 960, 870 cm^{-1}. *Anal.* calcd for $C_{18}H_{22}O_9$, C 56.50, H 5.70; found C 56.39, H 5.68%.

ACETYLATION OF **4**.—Compound **4** (10 mg) was treated overnight with Ac_2O and pyridine at room temperature. The reaction mixture was worked up as usual to give compound **5** as a white powder: mp 60–62°; ir (KBr) ν max 2950, 1760, 1640, 1610, 1510, 1370, 1320, 1240, 1980, 1060, 950, 840, 760. *Anal.* calcd for $C_{22}H_{30}O_{13}$, C 52.58, H 5.97; found C 52.60, H 6.01%.

HYDROLYSIS OF **4**.—To 10 mg of **4** were added 6 ml of MeOH and 1 ml of a solution of NH_4OH (33%). The mixture was refluxed for 1 h, diluted with distilled H_2O, and neutralized with 1 N HCl. Extraction with $CHCl_3$ yielded *p*-coumaric acid (3 mg) identical to a standard commercial sample (Sigma). The aqueous phase was concentrated in vacuo and extracted with anhydrous MeOH. Upon concentration a crystalline residue (2 mg) of (+)-bornesitol was obtained, mp 204°, $[\alpha]_D$ +63 (0.09, MeOH), identical to a reference compound (ir, tlc).

Sakuranetin.—White needles, mp 135–138°. The methyl derivative obtained by treatment with an ethereal solution of CH_2N_2 was identical (ir, nmr, uv, ms) to the methyl derivative of isosakuranetin, previously obtained from *Salvia nicolsoniana* (16).

6-Hydroxykaempferyl 3,7-dimethyl ether.—Yellow powder, mp 226° [lit. (17) mp 228–230°]. ^1H-nmr, ir, ms, and uv data were identical to those previously described (18).

Hautriwaic acid.—White crystals, mp 185° [lit. (7) mp 188°]. Spectral properties (ir, ^1H nmr, uv, and ms) comparable to those previously reported (7).

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