Pergamon

PII: S0031-9422(96)00295-6

Phytochemistry, Vol. 43, No. 4, pp. 863–865, 1996

0031-9422/96 $15.00 + 0.00

PRENYLATED HYDROXYBENZOIC ACID DERIVATIVES FROM *PIPER MURRAYANUM*

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(*Received* 22 *February* 1996)

Key Word Index—*Piper murrayanum*; Piperaceae; leaves; prenylated hydroxybenzoic acid derivatives; chalcone; flavokawain C.

Abstract—The leaves of *Piper murrayanum* have yielded the (*E*) and (*Z*) isomers of 4-hydroxy-3-(3,7-dimethyl-1-oxo)-2,6-octadienylbenzoic acid, together with the known (*E*)-4-hydroxy-3-(3,7-dimethyl)-2,6-octadienylbenzoic acid and the chalcone, 1-(2-hydroxy-4,6-dimethoxy)phenyl-3-(4-hydroxy)phenyl-2-propen-1-one. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

In continuation of our studies on the phytochemistry of selected species of the endemic Jamaican flora [1–3], we now report the isolation and structural elucidation of compounds from *Piper murrayanum*, a shrub of fairly common occurrence throughout the island [4].

RESULTS AND DISCUSSION

Dried ground leaves were exhaustively extracted by cold percolation with hexanes followed by acetone. The residues were subjected to normal-phase silica gel column chromatography in various solvent systems. This procedure gave the crystalline oxo-isoprenylated hydroxybenzoic acid derivatives **1** and **2** from the hexane extract, while the acetone extract yielded the known compounds, 3-geranyl-4-hydroxybenzoic acid **3** [5, 6] and 2,4′-dihydroxy-4,6-dimethoxychalcone **4** [7].

Compound **1** was obtained as plates. The high-resolution mass spectrum showed a $[M]^+$ at *m/z* 288.1356, corresponding to the molecular formula $C_{17}H_{20}O_4$ (calculated 288.1362). Compound **2** was also isolated as a solid which gave high- and low-resolution mass spectra that were almost identical to those of **1**.

The presence of a cross-conjugated carbonyl, an aromatic carboxylic acid and a chelated phenolic group in compound **1** was indicated by the major IR absorption bands (1645, 1686, 3358 cm^{-1}) and confirmed by ^{13}C and ^{1}H NMR signals at δ 195.7, 171.3, 10.50 and 13.47. UV absorptions at 252, 268 and 330 nm, with a bathochromic shift after addition of potassium hydroxide, also suggested a phenolic structure.

The splitting pattern in the ^{1}H NMR spectrum of the three aromatic protons established that the aromatic ring was 1,3,4-trisubstituted; the signals for the protonated carbons were assigned on the basis of HMQC spectra. Connectivities obtained from HMBC spectra, optimized for $J_{CH} = 8$ Hz, enabled the correct placement of the substituents. Interpretation relies on the knowledge that $^{2}J_{CH} \cong 0$ Hz and $^{3}J_{CH} \cong 8$ Hz for aromatic derivatives, with the result that three-bond connectivity peaks are usually intense, while two-bond peaks are usually very weak and often not observed [8]. H-2 (δ 8.59, *d*, $J = 2.2$ Hz), therefore, showed cross-peaks to both carbonyls, in keeping with their 1,3-relationship, to the hydroxyl-bearing quaternary carbon C-4 at δ 167.7 and to the protonated carbon C-6 at δ 137.0. Three-bond connectivities were observed from the phenolic hydrogen (δ 13.47) to the protonated carbon C-5 at δ 118.9 and to the carbonyl-bearing quaternary C-3 at δ 119.5. Finally, H-6 (*dd*, $J = 8.0$, 2.2 Hz) displayed a cross-peak to the carboxyl carbon at δ 171.3. The ^{13}C and ^{1}H spectra of compound **2** contained signals very similar to those for the aromatic portion of compound **1**, indicating that compound **2** was also a 3-substituted-4-hydroxybenzoic acid derivative (Table 1).

The side-chain residue at C-3 of compound **1** was 1′-oxogeranyl from the ^{1}H and ^{13}C NMR shifts and the signals were again assigned with the aid of HMQC and HMBC spectra. The relatively shielded position of the C-9′ methyl group (δ 20.4), which is attached to the β-carbon of an enone, suggested that this group is γ-*cis* to the carbonyl and that the stereochemistry of the C-2′-C-3′ double bond is (*Z*). This was borne out by the chemical shift of C-4′ (δ 41.9), which correlates closely with that of C-4 in geraniol (δ 40.6) [9]. Comparison of these shifts with those of the corre-

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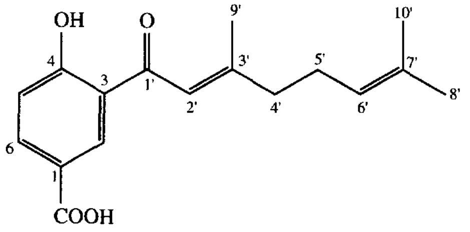

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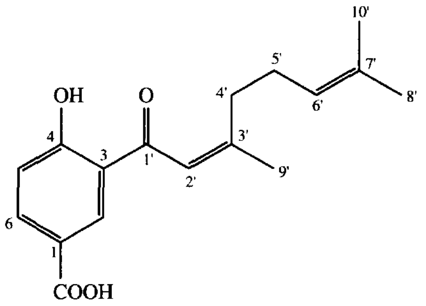

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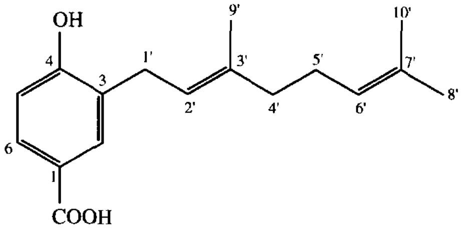

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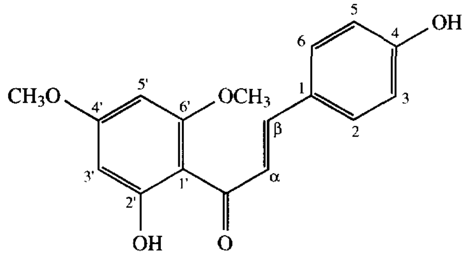

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sponding positions in compound **2** corroborated the (*Z*) assignment to C-2′-C-3′ of compound **1** and established the stereochemistry of this bond in compound **2** as (*E*) and the side-chain as 1′-oxoneryl. Thus, C-9′ of compound **2** was deshielded to δ 25.7 and C-4′ resonated at δ 34.7, in keeping with its γ-*cis* relationship to the C-1′ carbonyl and showing close similarity to C-4 of nerol (δ 33.0) [9].

Compounds **3** and **4** were identified as (*E*)-4-hydroxy-3-(3,7-dimethyl)-2,6-octadienylbenzoic acid and 2,4′-dihydroxy-4,6-dimethoxychalcone, respectively, from their spectral data and by comparison of these and physical data with literature values [5–7]. The ^{13}C NMR shifts of compounds **3** and **4** are reported here for the first time.

While dihydrochalcones and flavanoids are of widespread and relatively frequent occurrence in *Piper* species [10–13], the related chalcones are rare in the genus. Compound **4** and its 4-methyl derivative, 2′-hydroxy-4,4′,6′-trimethoxychalcone, both isolated from

Table 1. NMR data for compounds **1** and **2** ($CDCl_3$, *J* values, in Hz, are given in parentheses)

Position	**1**			**2**	
	^{13}C	^{1}H	HMBC*	^{13}C	^{1}H
1	120.1			120.1	
2	133.0	8.59, *d* (2.2)	6	133.0	8.60, *d* (2.1)
3	119.5		5,4-OH	119.4	
4	167.7		2, 5, 6, 4-OH	167.8	
5	118.8	7.04, *d* (8.0)	4-OH	118.9	7.04, *d* (8.8)
6	137.0	8.17, *dd* (8.0, 2.2)	2	137.0	8.16, *dd* (8.8, 2.1)
1′	195.7		2, 2′	195.3	
2′	118.7	6.86, 2	4′, 9′	119.5	6.85, *s*
3′	163.8		2′, 4′, 5′, 9′	164.1	
4′	41.9	2.37, *t* (7.5)	2′, 5′, 6′, 9′	34.7	2.66, *t* (9.0)
5′	26.2	2.29, *q* (7.5)	4′, 6′	26.8	2.24, *q* (9.0)
6′	122.6	5.15, *t* (6.7)	4′, 5′, 8′	123.3	5.15, *t* (7.6)
7′	132.9		5, 8′	132.7	
8′	25.7	1.73, *s*	5′, 6′	26.5	1.64, *s*†
9′	20.4	2.25, *d* (1.0)	2′, 4′	25.7	2.09, *d* (1.0)
10′	17.8	1.66, *s*	6′, 8′	17.7	1.65, *s*†
COOH	171.3	10.50, *bs*	2	170.7	
4-OH		13.47, *s*			13.43, *s*

*Protons correlating with carbon resonance.

†Interchangeable.

the roots of *P. methysticum* from India [7, 14], are among the few examples of this structural type in *Piper*.

EXPERIMENTAL

General. EIMS: 70 eV. IR: KBr pellets. UV: EtOH solns. NMR: 200, 400 and 500 MHz for ^{1}H and 125 MHz for ^{13}C; samples run in $CDCl_3$ with TMS as int. standard. Adsorption CC was performed with silica gel 60 (230–400 mesh), TLC with pre-coated silica gel 60 F_{254} plates. Spots were visualized under UV and by spraying with 4% phosphomolybdic acid in 5% H_2SO_4 followed by heating.

Plant material. Leaves of *P. murrayanum* were collected in Balaclava, St Elizabeth, Jamaica, in June 1995. A voucher specimen is deposited in the herbarium, Department of Botany, University of the West Indies, Mona.

Extraction and isolation. Dried ground leaves (950 g) were exhaustively extracted by cold percolation with hexanes followed by Me_2CO. Evapn of the hexanes *in vacuo* gave a gum (41 g), a portion (10 g) of which was chromatographed using a hexane–EtOAc gradient. Early frs eluted with 18% EtOAc–hexane afforded **1** (130 mg). The residue (730 mg) from evapn of the latter frs obtained in this mixt. was rechromatographed in a hexane–Me_2CO gradient to give compound **2** (67 mg) in the 15% Me_2CO–hexane eluant.

Evapn of the Me_2CO soln gave a gum (50 g) of which a portion (10 g) was chromatographed in a Me_2CO–hexane gradient. The oily residue (2 g) obtained after evapn of the 17% Me_2CO–hexane eluant was rechromatographed in a EtOAc–hexane gradient to give compound **3** (112 mg) in the 25% EtOAc–hexane eluant and compound **4** (122 mg) eluted with 30% EtOAc–hexane.

Compound **1**. Plates (hexane–EtOAc), mp 133–134°. IR v_{max}^{KBr} 3380, 1695, 1643, 1615, 1585 cm^{-1}. UV λ_{max} nm (log ε): 252 (4.09), 268 (3.82), 330 (3.52) + (KOH) nm (log ε) 252 (4.09), 280 (3.77), 380 (3.52). EI-MS *m/z* (rel. int.): 288 $[M]^+$ (12), 270 (19), 255 (16), 245 (21), 220 (18), 205 (100), 175 (29), 165 (65), 60 (96). ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR: Table 1.

Compound **2**. Plates (hexane–Me_2CO), mp 137–139°. IR v_{max}^{KBr} 2855, 1692, 1640, 1573 cm^{-1}. UV λ_{max} nm (log ε): 228 (3.67), 276 (3.26), 340 (2.82) + (KOH) nm (log ε) 248 (3.58), 276 (3.42), 380 (2.92). EIMS *m/z* (rel. int.): 288 $[M]^+$ (12), 273 (12), 270 (56), 255 (46), 245 (12), 227 (25), 205 (96), 175 (26), 165 (100), 123 (16), 119 (12), 69 (81). ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR: Table 1.

Compound **3**. Plates (hexane–Me_2CO), mp 74–76°, lit. [5] 67–69°. HR-MS, *m/z* 274.1553 (calcd for $C_{17}H_{22}O_3$ 274.1569). IR, UV, ^{1}H NMR and LREI-MS, in agreement with lit. values [5, 6]. ^{13}C NMR ($CDCl_3$): δ 172.0 (COOH), 159.5 (C-4), 139.4 (C-3′), 132.5 (C-2), 132.1 (C-7′), 130.5 (C-6), 126.8 (C-3), 123.6 (C-2′), 121.6 (C-1), 120.8 (C-6′), 115.7 (C-5), 39.7 (C-1′), 29.7 (C-5′), 26.4 (C-4′), 25.7 (C-8′), 17.7 (C-9′), 16.3 (C-10′).

Compound **4**. Yellow prisms (hexane–EtOAc), mp 185–187°, lit. [7] 194–195°. HRMS, *m/z* 300.0990 (calcd. for $C_{17}H_{16}O_5$ 300.0998). IR, UV, ^{1}H NMR and LR EIMS in agreement with lit. values [7]. ^{13}C NMR ($CDCl_3$): δ 192.5 (CO), 168.1 (C-2′), 165.9 (C-4′), 162.4 (C-6′), 159.8 (C-4), 143.1 (C-β), 130.3 (C-2, C-6), 126.8 (C-1), 124.0 (C-α), 116.1 (C-3, C-5), 106.2 (C-1′), 93.8 (C-3′), 91.1 (C-5′), 55.8 (C-6′OMe), 55.5 (C-4′OMe).

Acknowledgements—We thank Mr Patrick Lewis for identifying plant material. Financial support from the University of the West Indies Research and Publications Fund Committee and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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