

PRENYLATED 4-HYDROXYBENZOIC ACID DERIVATIVES FROM
*PIPER MARGINATUM*¹

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Members of the Piperaceae from both the Old and the New World have been widely used medicinally (1,2). This has led to their intensive chemical investigation and to the isolation of a wide range of natural products including alkaloids (1,3,4), terpenes (5), flavonoids (1,6,7), lactones (8,9), phenylpropanoids (1,10), and 4-hydroxybenzoic acid derivatives (11,12).

Piper marginatum Jacq. (Piperaceae) is an important medicinal plant to the natives of the Amazon (10). Previous work has shown the presence of phenylpropanoids (10) and flavonoids (13). In addition, several terpenes in the essential oil have been identified (10). There has, however, been no reported work on *P. marginatum* from Trinidad, where the plant is also utilized in the practice of folk medicine (14).

We report here the isolation of the known 3-farnesyl-4-hydroxybenzoic acid (15) and its previously unreported methylated derivative **2** from the aerial parts of *P. marginatum*.

The phenolic acid **1** was obtained as a clear, viscous oil that was unstable when kept at room temperature. Compound **1** gave a band in the uv spectrum at 289 nm and showed significant ir absorptions at 3300, 1680, and 1605 cm⁻¹. These data coupled with the ¹H-nmr spectrum (Table 1) suggested the structure **1**. Indeed, our ¹H-nmr data matched quite closely those reported (15) for compound **1**. The previously unreported ¹³C-nmr data presented in Table 2 agree with the assigned structure **1**.

Acid **1** was monomethylated with CH₂N₂ to give the stable ester **3**. Eims

TABLE 1. ¹H-nmr (80 MHz) Data of Compounds **1-4** in CDCl₃.^a

Proton	Compound			
	1	2	3	4
2-H	7.90(brs)	7.91(brs)	7.90(brs)	7.88(brs)
5-H	6.85(d, J _{5,6} = 9) ^b	6.85(d, J _{5,6} = 9)	6.85(d, J _{5,6} = 9)	6.85(d, J _{5,6} = 9)
6-H	7.85(d, J _{6,5} = 9) ^b	7.98(d, J _{6,5} = 9)	7.85(d, J _{6,5} = 9)	7.92(d, J _{6,5} = 9)
1'-H	3.40(d, J _{1',2'} = 7) ^c	3.34(d, J _{1',2'} = 7)	3.40(d, J _{1',2'} = 7)	3.34(d, J _{1',2'} = 7)
2'-H	5.35(t, J _{2',1'} = 7) ^c	5.32(t, J _{2',1'} = 7)	5.35(t, J _{2',1'} = 7)	5.32(t, J _{2',1'} = 7)
4', 5', 8', 9'-H	2.06(m)	2.06(m)	2.06(m)	2.06(m)
6', 10'-H	5.10(m)	5.10(m)	5.10(m)	5.10(m)
12'-H	1.68(brs)	1.68(brs)	1.68(brs)	1.68(brs)
13'-H	1.78(brs)	1.75(brs)	1.78(brs)	1.71(brs)
14'-H	1.60(brs)	1.60(brs)	1.60(brs)	1.60(brs)
15'-H	1.60(brs)	1.60(brs)	1.60(brs)	1.60(brs)
1-OMe	—	—	3.90(s)	3.90(s)
4-OMe	—	3.90(s)	—	3.90(s)

^aAll chemical shifts (relative to TMS) are given in δ (ppm) and coupling constants in Hz. Assignment of the signals was based on comparison with the published data (15) for **1** as well as with data (16, 17) for compounds with the farnesyl side chain.

^bWhen 5-H was irradiated, the signal due to 6-H collapsed to a singlet (and vice versa).

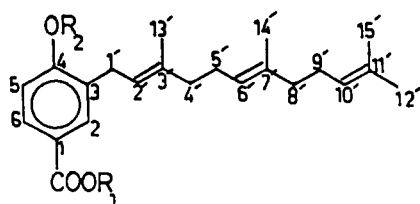
^cWhen 1'-H was irradiated, the signal due to 2'-H collapsed to a singlet (and vice versa).

¹After submission of this manuscript for publication, the occurrence of compound **1** in *Piper auritum* was reported: S.A. Ampofo, V. Roussis, and D.F. Wiemer, *Phytochemistry*, **26**, 2367 (1987).

of the latter showed a molecular ion at m/z 356, which is consistent with the molecular formula C₂₃H₃₂O₃, and diagnostically useful peaks at m/z 69 (base peak), 81, 136, 165, and 191. The ¹H-

nmr spectrum of **3** (Table 1) was essentially identical to that of **1** except that a new signal, a three-proton singlet, appeared at δ 3.90. The ^{13}C -nmr spectra of **1** and **3** were also quite similar, the significant difference between the two being the appearance of a signal at δ 51.8 in the spectrum of **3**.

The previously unreported methoxy acid **2** was obtained as a white solid, mp 56–57°. Eims gave a molecular ion at m/z 356, which is consistent with a molecular formula $\text{C}_{23}\text{H}_{32}\text{O}_3$, and diagnostic fragments (cf. compound **1**) at m/z 69, 81, 136, 165, and 191. The uv spectrum showed a band at 260 nm, and the ir spectrum showed important absorptions at 3400, 1680, and 1601 cm^{-1} . The ^1H -nmr spectrum (Table 1) of **2**



- 1 $R_1 = R_2 = \text{H}$
- 2 $R_1 = \text{H}, R_2 = \text{Me}$
- 3 $R_1 = \text{Me}, R_2 = \text{H}$
- 4 $R_1 = R_2 = \text{Me}$

clearly revealed its close similarity to **1**. The three-proton singlet at δ 3.90 suggested that **2** is a methylated derivative of **1**. Because **2** was unlike the methyl ester **3**, both chromatographically and spectrally, it seemed clear that it was the methyl ether of **1**. To establish this, we prepared **2** by the alkaline hy-

TABLE 2. ^{13}C -nmr Data of Compounds **1–3** in CDCl_3 .^a

Carbon	Compound		
	1	2	3
1	121.4	122.6	122.0
2	132.3	132.5	131.7
3	126.9	132.1	127.3
4	159.3	163.0	159.0
5	115.4	110.4	115.3
6	130.2	131.3	129.5
1'	29.2	28.7	29.0
2'	120.8	122.6	121.2
3'	138.8	138.0	138.4
4'	39.5	40.2	39.6
5'	26.2 ^b	27.0	26.5 ^b
6'	123.5	125.2	123.8
7'	135.4	136.2	135.4
8'	39.5	40.2	39.6
9'	26.5 ^b	27.0	26.7 ^b
10'	124.2	125.5	124.4
11'	131.1	131.6	131.2
12'	25.4	26.0	25.6
13'	16.1 ^c	16.2	16.2 ^c
14'	15.8 ^c	16.2	15.9 ^c
15'	17.5	18.0	17.6
1-C=O	171.1	173.0	167.5
1-CO ₂ Me	—	—	51.8
4-OMe	—	55.9	—

^aChemical shifts, relative to TMS, are given in δ (ppm). Assignment of the signals was based on the *J*-Modulated Spin Echo ^{13}C -nmr spectra, careful comparison of ^{13}C -nmr data of similar compounds (15–17), and on calculations of chemical shifts from empirical rules.

^{b,c}Assignments of the signals in the same column with the same letter may be interchanged.

drolisis of the dimethylated derivative **4** of the phenolic acid **1**. The methoxy acid thus obtained was identical to the natural compound **2**.

Compound **1** was previously isolated (15) from the shrub *Turricula parryi* (Gray) MacBr., a member of the family Hydrophyllaceae. To the best of our knowledge, ours is the first report of the occurrence of either 3-farnesyl-4-hydroxybenzoic acid or its derivative **2** in any member of the Piperaceae. However, reports have appeared recently of prenylated 4-hydroxybenzoic acid derivatives occurring in *Piper hispidum* and *Piper aduncum* from Jamaica (11) and in *Piper hostmannianum* from Colombia (12). It is interesting that there appears to be no report of prenylated 4-hydroxybenzoic acid derivatives from Old World *Piper* species.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Reichert micro melting point apparatus and are uncorrected. Uv spectra were recorded on a Perkin-Elmer 552A uv-vis spectrophotometer, and ir spectra were run on Nujol mulls (solids) or on neat liquids with a Pye Unicam SP3-200 instrument. ^1H - (80 MHz) and ^{13}C - (20 MHz) nmr spectra were run on a Bruker WP 80 SY FT nmr spectrometer with TMS as internal standard. Eims were obtained at 70 eV using an HP5985 gc-ms system. Si gel 60 PF-254 & 366 (Merck) was used for analytical (0.25 mm) and preparative (1 mm) tlc.

PLANT MATERIAL.—Aerial parts of the plant *P. marginatum* were collected near the eight-mile post along Blanchisseuse Road, Arima, Trinidad. A voucher specimen is on deposit at the National Herbarium of Trinidad and Tobago. The material was air dried (ca. 35°) for 1 week.

EXTRACTION, SEPARATION, AND ISOLATION.—The dried, ground plant material (1.3 kg) was extracted with cold Me_2CO (5 liters) for 24 h. Evaporation of the Me_2CO gave the crude extract (68 g). A portion (25 g) of this crude extract was dissolved in CHCl_3 and extracted twice with dilute NaOH (1 M, 2 × 250 ml). The combined aqueous layers were acidified with HCl (6 M), and the mixture was extracted with EtOAc. Removal of the EtOAc from the dried (Na_2SO_4) solution gave a green residue that was decolorized

in Me_2CO solution with powdered charcoal. After filtration and evaporation of solvent there was obtained a yellow, viscous oil (8.1 g), a portion (1.5 g) of which was subjected to preparative tlc (petroleum ether- Me_2CO , 3:1) to yield **1** and **2**. The major and most polar component, phenolic acid **1**, was obtained as a clear oil (700 mg). Compound **1** gave uv (MeOH) λ max 289 nm (ϵ 2350); ir ν max 3300 (br), 3020, 1680, 1605, 1440, 1280, 1045 cm^{-1} ; ^1H nmr see Table 1 [cf. Reynolds *et al.* (15)]; ^{13}C nmr see Table 2. The component **2** of lower polarity was first obtained as a slightly impure solid (350 mg). Further purification by preparative layer chromatography yielded pure **2** as a white amorphous solid (250 mg), mp 56–57°; uv (MeOH) λ max 260 nm (ϵ 10400); ir ν max 3400, 3010, 1680, 1603, 1440, 1255, 1030 cm^{-1} ; eims m/z (%) [$\text{M}]^+$ 356 (1.7), 191 (12), 175 (15), 165 (34), 136 (31), 121 (15), 109 (10), 107 (8), 95 (10), 93 (9), 81 (36), 69 (100); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

MONOMETHYLATION OF 1.—An ethereal solution of **1** (100 mg) was treated with CH_2N_2 (0.15 g Diazald[®]) and left at room temperature for 20 min. The usual work-up followed by preparative tlc (petroleum ether- Me_2CO , 3:1) gave methyl ester **3** (96 mg) as a colorless oil, ir ν max 3370, 3010, 1685, 1601, 1435, 1280 cm^{-1} ; eims m/z (%) [$\text{M}]^+$ 356 (1.6), 203 (11), 191 (14), 187 (11), 165 (33), 145 (12), 136 (32), 121 (13), 109 (15), 107 (10), 95 (13), 93 (11), 81 (37), 69 (100); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

DIMETHYLATION OF 1.—To a mixture of **1** (405 mg) and K_2CO_3 (100 mg) in Me_2CO (50 ml) was added Me_2SO_4 (2 ml). The reaction mixture was refluxed for 15 h. Work-up followed by preparative tlc (petroleum ether- Me_2CO , 3:1) gave **3** (102 mg) and the dimethylated compound **4** (240 mg), ir ν max 3020, 1710, 1605, 1440, 1260, 1030 cm^{-1} ; ^1H nmr see Table 1.

ALKALINE HYDROLYSIS OF 4.—A mixture of **4** (50 mg), MeOH (2 ml), and dilute NaOH (1 M, 3 ml) was refluxed for 24 h. The usual work-up followed by preparative tlc (petroleum ether- Me_2CO , 3:1) gave a white solid (40 mg), mp 56–57°, mp with **2** 56–57°, which was chromatographically and spectrally identical with **2**.

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