

NOVEL PRENYLATED HYDROXYBENZOIC ACID DERIVATIVES
FROM *PIPER SALTUUM*

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ABSTRACT.—The acetone extract of the aerial parts of *Piper saltuum* yielded three new prenylated hydroxybenzoic acids, **1**, **2** and **3**, the structures of which were determined principally by spectroscopic methods.

Piper saltuum C. DC (Piperaceae) is a relatively rare species in the New World (1) and has not been previously studied. We examined the aerial parts of *P. saltuum* occurring in Trinidad and wish to report the isolation of three new prenylated hydroxybenzoic acid derivatives. Despite extensive study of Piperaceae, this class of compounds has only very recently been isolated from *Piper* species (2-5).

Compound **1** was obtained as a yellow, viscous oil. Its uv spectrum showed bands at 217 and 258 nm and its ir spectrum exhibited absorptions at 3400 (br), 1675, and 1601 cm^{-1} , which suggested an aromatic carboxylic acid. Indeed, the ^1H -nmr spectrum of **1** (Table 1) was very similar to that of the previously reported compound **6** (4-6). However, in the case of **1** five vinyl methyl groups, rather than the four that would be expected for **6**, were indicated. The signal

at δ 1.60 accounted for three of these while the other two appeared at δ 1.68 and 1.78. Seven allylic methylene groups were also indicated for **1** (as opposed to five in **6**). Six of these methylene groups comprised the multiplet at δ 2.06 and the seventh occurred as a doublet at δ 3.40. Additionally, the signals at δ 5.12 and δ 5.36 integrated for four olefinic protons and not three as would be the case for **6**. The presence of a geranylgeranyl chain in **1** rather than the farnesyl group as in **6** was therefore clearly established.

Further, the aromatic region of the ^1H -nmr spectrum indicated that **1** contained a 1,3,4-trisubstituted benzene ring moiety. ^{13}C nmr (Table 2) fully supported the geranylgeranyl moiety and, significantly, showed quaternary carbons at δ 160.8 and δ 173.1. These data led us to the structure indicated for **1**. Eims gave $[\text{M}]^+$ at m/z 410, which is

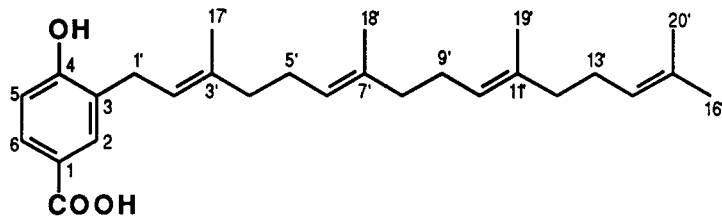
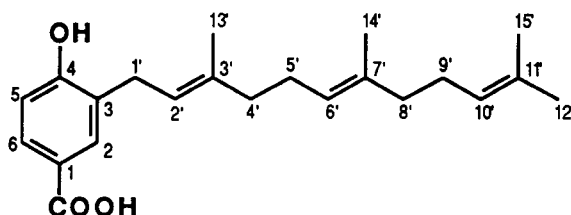
**1****6**

TABLE I. ¹H-nmr (80 MHz) Data of Compounds 1-5 in CDCl₃.^a

Proton	Compound				
	1	2	3	4	5
H-2	7.93 (brs)	—	7.51 (brs)	—	7.48 (d, $J_{2,6} = 2$ Hz)
H-5	6.85 (d, $J_{5,6} = 9$ Hz)	6.85 (d, $J_{5,6} = 9$ Hz)	—	6.78 (d, $J_{5,6} = 9$ Hz)	—
H-6	7.86 (br d, $J_{6,5} = 9$ Hz)	7.68 (d, $J_{6,5} = 9$ Hz)	7.51 (brs)	7.68 (d, $J_{6,5} = 9$ Hz)	7.55 (d, $J_{6,2} = 2$ Hz)
H-1'	3.40 (d, $J_{1',2'} = 7$ Hz)	3.92 (d, $J_{1',2'} = 7$ Hz)	3.38 (d, $J_{1',2'} = 7$ Hz)	3.78 (obscured d)	3.38 (d, $J_{1',2'} = 7$ Hz)
H-2'	5.36 (t, $J_{2',1'} = 7$ Hz)	5.30 (t, $J_{2',1'} = 7$ Hz)	5.35 (t, $J_{2',1'} = 7$ Hz)	5.16 (m)	5.30 (t, $J_{2',1'} = 7$ Hz)
H-4', 5', 8', 9', 12', 13'	2.06 (m)	2.06 (m)	2.05 (m)	2.02 (m)	2.05 (m)
H-6', 10', 14'	5.12 (m)	5.10 (m)	5.11 (m)	5.16 (m)	5.12 (m)
H-16'	1.68 (brs)	1.68 (brs)	1.68 (brs)	1.68 (brs)	1.70 (brs)
H-17'	1.78 (brs)	1.86 (brs)	1.76 (brs)	1.79 (brs)	1.76 (brs)
H-18', 19', 20'	1.60 (brs)	1.60 (brs)	1.61 (brs)	1.60 (brs)	1.61 (brs)
3-OH	—	— ^b	6.02 (brs)	—	—
4-OH	7.56 (brs)	— ^b	6.02 (brs)	—	—
1-CO ₂ Me	—	—	—	3.79 (s), 3.85 (s)	3.88 (s), 3.91 (s)
3-OMe	—	—	—	and 3.89 (s)	and 3.93 (s)
4-OMe	—	—	—	—	—

^aAll chemical shifts (relative to TMS) are given in δ (ppm) and coupling constants in Hz.

^bSignal not observed.

consistent with the molecular formula $C_{27}H_{38}O_3$, and diagnostically important fragments at, for example, m/z 69 (base peak), 91, 123, and 151. The stereochemistry within the geranylgeranyl residue was established as all (*E*) on the basis of the ^{13}C -nmr chemical shifts of the vinyl methyl groups (C-17', C-18', C-19', and C-20'). These all lie between 16 and 18 ppm as a result of the shielding γ -*cis* interactions (7,8). No such interaction exists for the Me-16'; therefore, it resonates at lower field, i.e., 25.4 ppm.

Compound **2** was also isolated as a yellow oil and gave bands in the uv spectrum at 217, 258, and 286 nm. Its ir spectrum exhibited major absorptions at 3300 (br), 1675 and 1600 cm^{-1} . Consideration of the 1H -nmr data (Table 1) indicated that **2** contained a geranylgeranyl moiety and a 1,2,3,4-tetrasubstituted benzene ring. ^{13}C nmr confirmed the presence of the geranylgeranyl moiety and pointed to the presence of two oxygen-bearing aromatic carbons (δ 143.9 and δ 150.0). All the data suggested that **2** must be assigned the structure indicated. Eims gave an $[M]^+$ at m/z 426, consistent with the molecular formula $C_{27}H_{38}O_4$, and fragments in accord with the structure. Further, comparison of both the 1H - and ^{13}C -nmr data of **2** with those reported (9, 10) for the several dihydroxybenzoic acid isomers showed that our data corresponded most closely with those of the 3,4-dihydroxybenzoic acid isomer.

Treatment of **2** with excess $Me_2SO_4/$

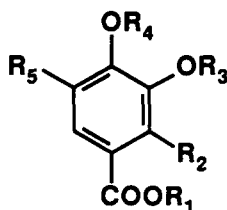
K_2CO_3 in Me_2CO gave the trimethylated derivative **4**. Eims (m/z $[M]^+$ 468), ir (carbonyl stretch at 1710 cm^{-1}), 1H -nmr (Table 1), and ^{13}C -nmr (Table 2) data fully support the structure of compound **4**.

Compound **3**, also a yellow oil, was clearly closely related to **2**. For example, eims of **3** gave an $[M]^+$ at m/z 426, which is consistent with the molecular formula $C_{27}H_{38}O_4$; the ir spectrum showed absorptions at 3300 (br), 1675, and 1603 cm^{-1} , and 1H nmr (Table 1) indicated the presence of the geranylgeranyl moiety. However, the aromatic region of the 1H -nmr spectrum revealed the presence of two meta coupled protons rather than two protons ortho to each other as in **2**. These spectral data, considered along with those obtained for **2**, clearly pointed to the structure we have indicated for **3**. The ^{13}C -nmr data (Table 2) and fragment ions of the eims confirm the assigned structure of **3**.

The dihydroxy acid **3** was converted into its trimethylated derivative **5** in a manner similar to that described for **2**. Compound **5** in its eims gave an $[M]^+$ at m/z 468 ($C_{30}H_{44}O_4$), and its ir spectrum showed a carbonyl absorption at 1710 cm^{-1} . Moreover, the 1H - and ^{13}C -nmr data were fully in accord with its proposed structure.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were recorded on a Perkin-Elmer 552A uv-vis spectrophotometer, and ir spectra were run on the neat liquids with a Pye Unicam SP3-200 instrument. 1H - (80 MHz) and ^{13}C - (20



- 2** $R_1=R_3=R_4=R_5=H$, $R_2=geranylgeranyl$
4 $R_5=H$, $R_1=R_3=R_4=Me$, $R_2=geranylgeranyl$
3 $R_1=R_2=R_3=R_4=H$, $R_5=geranylgeranyl$
5 $R_2=H$, $R_1=R_3=R_4=Me$, $R_5=geranylgeranyl$

TABLE 2. ^{13}C -nmr Data of Compounds 1-5 in CDCl_3 ,^a

Carbon	Compound				
	1	2	3	4	5
1	122.5	121.7	121.5	123.0	126.6
2	133.6	132.4	115.7	134.8	112.5
3	128.3	143.9	144.2	147.4	152.7
4	160.8	150.0	148.8	155.7	154.0
5	116.3	113.3	132.0	109.1	132.4
6	131.3	122.8	122.0	123.4	123.3
1'	29.5	29.9	29.0	26.9	28.9
2'	122.0	124.7	124.8	124.3	125.0
3'	140.0	140.0	139.5	138.2	137.8
4'	40.1	40.0	40.1	39.9	40.2
5'	26.9	26.8	26.8	26.0	27.0
6'	124.9	125.3	125.0	124.3	125.3
7'	136.8	136.9	136.7	135.0	136.9
8'	40.1	40.0	40.1	39.9	40.2
9'	27.0	26.9	26.8	26.9	27.0
10'	125.4	125.5	125.0	124.5	125.4
11'	135.9	136.1	136.0	134.8	136.4
12'	40.1	40.0	40.1	40.0	40.2
13'	27.2	27.0	27.0	26.9	27.0
14'	125.5	126.8	125.3	127.3	125.6
15'	132.2	131.6	128.5	131.1	136.3
16'	25.4	26.0	26.0	25.7	26.0
17'	16.4	16.5	16.4	16.4	16.5
18'	16.2	16.3	16.1	16.1	16.2
19'	16.2	16.3	16.1	16.1	16.2
20'	17.9	17.8	17.9	17.8	17.9
1-C=O	173.1	173.5	127.7	167.9	169.0
1-CO ₂ Me	—	—	—	51.7 ^b	52.6 ^b
3-OMe	—	—	—	60.5 ^b	56.5 ^b
4-OMe	—	—	—	55.7 ^b	61.0 ^b

^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 and reference to ^{13}C -nmr data of related compounds (5, 8, 10).

^bAssignments of the signals in the same column with the same letter may be interchanged.

MHz) nmr spectra were run on a Bruker WP80 SY FT nmr spectrometer with TMS as internal standard. Eims were obtained at 70 eV using a Finnegan 4000 mass spectrometer. Si gel 60 PF-254 + 366 (Merck) was used for analytical (0.25 mm) and preparative (1 mm) tlc and for vacuum liquid chromatography (vlc) (11).

PLANT MATERIAL.—Aerial parts of the plant *P. saltuum* were collected in August 1987, near the 10.5 mile post along the Blanchisseuse Road, Arima, Trinidad. A voucher specimen is on deposit at the National Herbarium of Trinidad and Tobago. The material was oven dried at 40° for 5 days.

EXTRACTION, SEPARATION, AND ISOLATION.—The dried, ground plant material (800 g) was extracted with cold Me_2CO (9 liters) over 5

days. Evaporation of the Me_2CO gave the crude extract (106 g), which tlc [petroleum ether- Me_2CO (85:15)] showed to consist of three major uv-active components. A portion of the crude extract (11 g), subjected to vlc eluting initially with petroleum ether and then with increasing quantities of Me_2CO , yielded the three somewhat impure components. These were individually purified by preparative tlc [petroleum ether- Me_2CO (4:1)]. The least polar compound, the hydroxy acid **1**, was obtained as a viscous, yellow oil (824 mg). Compound **1** gave uv (MeOH) λ max 258, 217 nm (ϵ 5900, 9800); ir ν max 3400 (br), 1675, 1601, 1273, 905, 730 cm^{-1} ; eims *m/z* (%) [M^+ 410 (0.3), 189 (10), 151 (25), 136 (15), 135 (13), 123 (16), 121 (12), 109 (15), 107 (13), 95 (15), 93 (15), 91 (12), 81 (41), 69 (100)]; ^1H nmr see Table 1; ^{13}C nmr see Table 2. The compound of intermediate polarity, dihydroxyben-

zoic acid **2**, was also a viscous, yellow oil (875 mg). Compound **2** gave uv (MeOH) λ max 286, 258, 217 nm (ϵ 4400, 7600, 21000); ir ν max 3300 (br), 1675, 1600, 1290, 1210, 755 cm^{-1} ; eims m/z (%) $[M]^+$ 426 (0.3), 205 (38), 167 (20), 151 (18), 149 (25), 135 (35), 123 (30), 121 (33), 109 (35), 107 (40), 105 (23), 95 (33), 93 (45), 91 (28), 81 (55), 69 (100), 55 (44); ^1H nmr see Table 1; ^{13}C nmr see Table 2. The most polar component, also obtained as a yellow oil (882 mg), was the dihydroxybenzoic acid **3**. This compound gave uv (MeOH) λ max 296, 264, 221 nm (ϵ 2300, 3300, 7500); ir ν max 3300 (br), 1675, 1603, 1440, 1300, 907, 730 cm^{-1} ; eims m/z (%) $[M]^+$ 426 (0.2), 205 (12), 167 (24), 137 (8), 136 (11), 135 (13), 123 (16), 121 (13), 109 (16), 107 (14), 105 (5), 95 (18), 93 (18), 91 (11), 81 (46), 69 (100), 67 (29), 55 (20); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

METHYLATION OF 2.—A mixture of **2** (1.4 g), K_2CO_3 (1.5 g) and Me_2SO_4 (3 ml) in Me_2CO (25 ml) was refluxed for 20 h. The reaction mixture was then neutralized with aqueous NH_3 and extracted with EtOAc, and the organic extract was washed with H_2O and dried over anhydrous Na_2SO_4 . Preparative tlc [petroleum ether- Me_2CO (4:1)] on the crude isolated material yielded the trimethylated derivative **4** as a yellow oil (624 mg) uv (MeOH) λ max 254, 221 nm (ϵ 7200, 9500); ir ν max 1710, 1595, 1445, 1430, 1280, 1260, 908, 730 cm^{-1} ; eims m/z (%) $[M]^+$ 468 (0.1), 231 (16), 209 (21), 203 (23), 189 (13), 179 (15), 151 (27), 136 (15), 135 (17), 123 (16), 121 (19), 109 (21), 107 (17), 95 (21), 83 (19), 91 (17), 81 (43), 69 (100), 67 (17), 59 (17), 55 (25); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

METHYLATION OF 3.—A sample of **3** (230 mg) was methylated (0.30 g K_2CO_3 , 0.50 ml Me_2SO_4 in 15 ml Me_2CO) as described above for **2**. Workup followed by preparative tlc [petroleum ether- Me_2CO (4:1)] gave, as a light yellow oil (61 mg), the trimethylated derivative **5**: uv (MeOH) λ max 293, 253, 211 nm (ϵ 2500, 7600, 26800); ir ν max 1710, 1590, 1435, 1335, 1305, 1215, 1085, 1000, 750 cm^{-1} ; eims m/z (%) $[M]^+$ 468 (2), 399 (3.5), 231 (14), 209 (50), 135 (16), 123 (14), 121 (14), 109 (16), 107

(10), 95 (14), 93 (12), 91 (9), 81 (43), 69 (100), 55 (16), 41 (46); ^1H nmr see Table 1; ^{13}C nmr see Table 2.

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