Phytochemistry, Vol. 31, No. 4, pp. 1375–1377, 1992
Printed in Great Britain.

0031-9422/92 $5.00+0.00

NEOLIGNANS AND A PHENYLPROPANOID FROM *VIROLA PAVONIS* LEAVES*

PEDRO H. FERRI and LAURO E. S. BARATA

Instituto de Química, Universidade Estadual de Campinas, C.P. 6154, (13081) Campinas, SP, Brazil

(*Received* 29 *July* 1991)

Key Word Index—*Virola pavonis*; Myristicaceae; eusiderin-E; 8,4′-oxyneolignan; phenylpropanoid; pavonisol.

Abstract—Pavonisol, a new C-1/C-2 oxygenated phenylpropanoid, together with the known eusiderin-E and an 8,4′-oxyneolignan, were isolated from *Virola pavonis* leaves. Their structures were established by spectroscopic methods and chemical transformations.

INTRODUCTION

Virola pavonis grows in the mainland region of the Amazonian forest, known by the Karijona Indian name '*Veri-que*' [1]. *Virola pavonis* is morphologically akin to *V. carinata* (Benth.) Warb. The two species can only be distinguished by their habitat and fruit morphology (Rodrigues, W. A., personal communication). Previous chemical investigations have shown the presence of 1,3-diarylpropanoids in the trunk wood [2]; two 3′,7-epoxy-8,4′-oxyneolignans, eusiderin-C and eusiderin-D, in the bark [3] and an 8,4′-oxyneolignan (**1**) in the fruits [4]. We have recently reported the isolation of the 7,7′-epoxylignan, (−)-*di-de-O*-methylgrandisin from this little known species restricted to the Guaporé river region in Rondônia, Brazil [5]. The chlorophyll-free dichloromethane extract of the same plant material was further investigated leading to the isolation of the known 8,4′-oxyneolignan (**1**) and eusiderin-E (**2**), previously isolated from the fruit pericarps of *V. carinata* [6] together with the new phenylpropanoid (**3**) for which the name pavonisol is proposed.

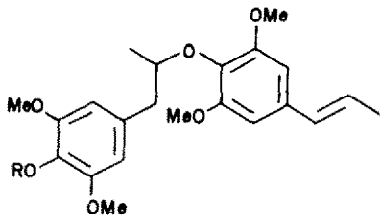
RESULTS AND DISCUSSION

Compound **1**, $C_{22}H_{28}O_6$, $[\alpha]_D^{25}+7.5°$ ($CHCl_3$; *c* 1.13) was phenolic and the most abundant neolignan of *V. pavonis*. Its ^1H and ^{13}C NMR spectra presented signals which corresponded to those exhibited by a known constituent of *V. carinata* [6]. The ^1H NMR of the acetate (**1b**) showed one singlet peak for aromatic acetoxyl (δ2.28), thus confirming the presence of a phenolic group. The data for its methylated derivative, $C_{23}H_{30}O_6$, $[\alpha]_D^{25}-7.8°$ ($CHCl_3$; *c* 0.95), were consistent with structure **1b** and agreed well with the data given for (−)-virolongin, isolated from the bark of *V. elongata* (Benth.) Warb. [7]. Additionally, a direct comparison was also made with a total synthetic sample of the (±)-(**1**), prepared from self-oxidative coupling of 2,6-dimethoxy-4-(*E*)-propenylphenol [8] (see Experimental).

Compound **2**, $C_{21}H_{24}O_6$, showed in its ^1H NMR spectrum a characteristic signal pattern of the 3′,7-epoxy-8,4′-oxyneolignans, eusiderin [3, 6]. Its structure and relative configuration have been established by LIS data [9] and an X-ray analysis [10]. The chemical shift of Me-9 (δ 1.26, *d*, $J=6.0$ Hz) and the value for $J_{H\text{-}7,H\text{-}8}=8.0$ Hz are evidence for the *trans*-relationship of the Ar-7/Me-9 [3]. This, combined with one signal for the two equivalent aromatic protons (δ6.55; H-2, 6), the propenyl derived signals (δ1.88, *d*, $J=5.6$ Hz, 3H; δ5.91–6.45, *m*, 2H), three methoxyls (δ3.93, *s*, 9H) and one hydroxyl group (δ5.55, *sl*), is in agreement with those of eusiderin-E [6]. Acetylation with acetic anhydride–pyridine afforded the monoacetate (**2a**), $C_{23}H_{26}O_7$, $[\alpha]_D^{25}-22.5°$ ($CHCl_3$; *c* 1.13). Its ^1H NMR spectrum showed one singlet peak (δ2.30) for aromatic acetoxyl and clear splitting of the methoxyl signals (δ3.80, *s*, OMe-3, 5; δ3.88, *s*, OMe-5′). In another experiment, **2** was methylated to yield eusiderin-E methyl ether (**2b**) as an oil, $C_{22}H_{26}O_6$, with similar ^1H NMR data to **2** (see Experimental). Compound **2a** was wrongly reported as a known derivative [13] but is a hitherto undescribed compound. Eusiderins have been reported from *V. guggenheimii*, *V. pavonis* [3] and *V. carinata* [6] and various genera of the Lauraceae [11, 12].

Pavonisol (**3**) was obtained as crystals, $C_{12}H_{18}O_5$, showing IR bands corresponding to phenolic and aliphatic hydroxyls (3450, 3240 cm^{-1}) and an aromatic ring (1610, 1510 cm^{-1}). The ^1H NMR spectrum clearly showed the presence of two equivalent protons (δ6.50, *s*), one hydroxyl (δ5.50, *s*) and two methoxyl groups (δ3.85, *s*), on a symmetrically substituted aromatic ring, with alkoxyl groups at C-3′, C-5′ and a hydroxyl group at C-4′. The remaining signals were in agreement with the arrangement Ar–CH(OR^1)–CH(OR^2)–Me [δ3.75 (*d*, $J=5.2$ Hz, H-1); 3.65 (*m*, H-2); 0.96 (*d*, $J=6.3$ Hz, Me-3) and δ3.25 (*s*, aliphatic OMe)] with $R^1=H$, $R^2=Me$ or $R^1=Me$, $R^2=H$. Furthermore, double reasonance experiments supported this framework. The ^1H NMR spectrum of the diacetate (**3a**), $[\alpha]_D^{25}+86.7°$ ($CHCl_3$; *c* 0.85), showed two singlet peaks for aliphatic and aromatic acetoxyls (δ2.00 and 2.30, respectively). The multiplet signal ascribed for H-2 in **3** was shifted from δ3.65 to 5.01

*In memoriam of Dr Hipolito F. Paulino Filho.



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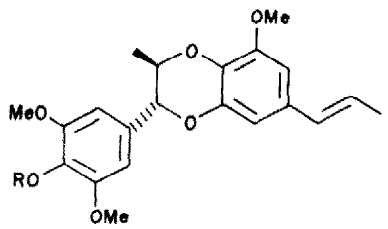

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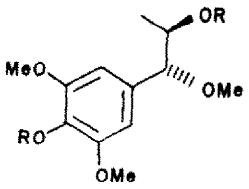

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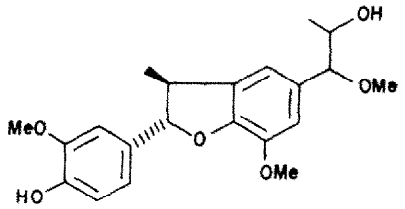

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on acetylation, indicating that the aliphatic hydroxyl group is attached to C-2. Accordingly, the aliphatic methoxyl group was considered to be attached to C-1. Otherwise, the presence of the mass fragment (base peak) at *m/z* 197 $[M-Me-CH_2O]^+$ for **3** and its diacetate and the mass fragment at *m/z* 239 $[M-Me-CH_2O-CH_2CO]^+$ for **3a** showed that the aliphatic methoxyl group must be attached at the benzylic position and the hydroxyl group has to be linked to the C-2. The double resonance experiments on the diacetate showed that on irradiation at δ5.01 (H-2), the doublet at δ4.08 (H-1) and also the doublet at δ1.06 (Me-3) each became a singlet.

The assignment of the relative stereochemistry for pavonisol was established when the ^{1}H NMR data were compared with those described for *erythro-threo* isomers of 1,2-disubstituted arylpropanes [14]. The relatively large coupling constant for H-1 in **3** (δ3.75, *d*, J=5.2 Hz) and its diacetate (δ4.08, *d*, J=6.4 Hz) led us to propose the *threo* configuration. Furthermore, the high field chemical shift for the methyls [(δ0.96, *d*, J=6.3 Hz) in **3** and (δ 1.06, *d*, J=6.3 Hz) for **3a**] was also in agreement with those described for other *threo* isomers [14, 16].

These findings consequently led us to characterize pavonisol as *threo*-1-(4'-hydroxy-3',5'-dimethoxyphenyl)-1-methoxy-2-propanol. Recently a 4',7-epoxy-8,3'-neolignan, fragransol A (**4**) [17], was obtained from the phenolic fraction of *Myristica fragrans* Houtt. The structure of **4** has the same side-chain substitution pattern present in pavonisol (**3**).

Phenylpropanoids with C-1/C-2 oxygenation, e.g. laserines [16, 18] and helmanticines [19], although structurally unrelated to pavonisol (**3**), have only been reported recently [20]. Up to now, they have been isolated only from the Umbelliferae; this is the first report of these compounds in Myristicaceae.

EXPERIMENTAL

General. Mps: uncorr. Chemical shifts are in ppm (δ) from TMS as int. standard.

Isolation of constituents. Performed as described in ref. [5]. The least polar fraction from the chlorophyll-free CH_2Cl_2 extract ($CHCl_3$–EtOAc, 8:1, 3.9 g), after rechromatography in the same system, yielded **1** (1.5 g). The chlorophyll-free hexane extract (7.1 g) as described in ref. [5] was chromatographed on a silica gel column with hexane–EtOAc (0–50%). The frs in hexane–EtOAc (4:1) (1.7 g) after rechromatography in the same system gave **1** (840 mg), **2** (7 mg) and **3** (14 mg).

(7'E)-4-Hydroxy-3,3',5,5'-tetramethoxy-8,4'-oxyneolignan (**1**). Oil. Yield 0.094% w/w. $[\alpha]_D^{25}$ +7.5° ($CHCl_3$; *c* 1.13). UV λ_{max}^{MeOH} nm (log ε): +NaOH: 264 (4.3). ^{1}H NMR, ^{13}C NMR, IR, UV and EIMS were identical with those described in ref. [6].

Acetate of compound **1**. Oil. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.20 (*d*, J=6.0 Hz, Me-9), 1.85 (*d*, J=5.5 Hz, Me-9'), 2.28 (*s*, OAc-4), 2.80 (*dd*, J=8.0, 14 Hz, H-7a), 3.03 (*dd*, J=6.0, 14 Hz, H-7b), 4.15–4.45 (*m*, H-8), 6.05–6.50 (*m*, H-7', H-8'), 6.45 (*s*, H-2, H-6), 6.50 (*s*, H-2', H-6'), 3.75 (*s*, 4 × OMe). EIMS *m/z* (rel. int.): 430 $[M]^+$ (22), 429 (16), 220 (3), 196 (9), 195 (6), 194 (100), 192 (4), 191 (2), 179 (2), 177 (3), 165 (5), 164 (2), 162 (2), 150 (1), 134 (3).

Methyl ether of compound **1**. Oil. $[\alpha]_D^{25}$ −7.8° ($CHCl_3$; *c* 0.95) (lit. [7] $[\alpha]_D^{25}$ −12.4° in $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1590, 1500, 1460, 1330, 1240, 1120, 960, 920, 820. ^{1}H NMR (80 MHz, CCl_4) δ: 1.08 (*d*, J=6.8 Hz, Me-9), 1.85 (*d*, J=4.8 Hz, Me-9'), 2.55 (*dd*, J=8.0, 14.0 Hz, H-7a), 2.90 (*dd*, J=5.4, 14 Hz, H-7b), 3.63 (*s*, OMe), 3.73 (*s*, 4 × OMe), 4.23 (*m*, H-8), 5.85–6.25 (*m*, H-7', H-8'), 6.32 (*s*, H-2, H-6), 6.38 (*s*, H-2', H-6'). ^{1}H NMR (80 MHz, $CDCl_3$), UV and EIMS were identical with those reported for virolongin [7].

Synthesis of (±)-(**1**). Catalytic isomerization of the 4-allyl-2,6-dimethoxyphenol [21] at room temp. with $PdCl_2$ in MeOH afforded, after 48 hr, the *E*-isomer (55% chemical yield, 100%

purity isomeric). The physical and spectral properties of its acetate were identical with those reported [22]. The self-coupling of 2,6-dimethoxy-4-(*E*)-propenylphenol under Merlini's experimental conditions [8] led to (±)-(1). IR, ^{1}H NMR and EI mass spectra of the latter were identical with the natural product.

Compound **2**. Oil. The physical and spectral properties (IR, ^{1}H NMR and EIMS) were identical with those described for eusiderin-E [6].

Acetate of compound **2**. Oil. $[\alpha]_D^{25}$ −22.5° ($CHCl_3$; *c* 1.13). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.25 (*d*, *J* = 6.0 Hz, Me-9), 1.83 (*d*, *J* = 5.5 Hz, Me-9'), 2.30 (*s*, OAc-4), 3.80 (*s*, OMe-3,5), 3.88 (*s*, OMe-5'), 3.95–4.23 (*m*, H-8), 4.57 (*d*, *J* = 8.0 Hz, H-7), 5.91–6.45 (*m*, H-7', H-8'), 6.45–6.55 (*m*, H-2', H-6'), 6.60 (*sl*, H-2, H-6). EIMS *m/z* (rel. int.): 414 $[M]^+$ (42), 373 (1), 371 (5), 330 (1), 329 (3), 297 (2), 205 (4), 196 (2), 195 (4), 194 (100), 193 (18), 192 (4), 191 (23), 179 (6), 151 (2).

Eusiderin-E methyl ether (**2b**). Oil. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.20 (*d*, *J* = 6.0 Hz, Me-9), 1.85 (*d*, *J* = 5.5 Hz, Me-9'), 3.83 (*s*, 3 × OMe), 3.85 (*s*, OMe), 4.05–4.30 (*m*, H-8), 4.53 (*d*, *J* = 8.0 Hz, H-7), 5.91–6.45 (*m*, H-7', H-8'), 6.58 (*sl*, Ar–H). EIMS *m/z* (rel. int.): 386 $[M]^+$ (9), 209 (18), 208 (100), 205 (8), 195 (4), 194 (9), 193 (36), 192 (9), 191 (31), 177 (4), 176 (3), 165 (6), 150 (7), 149 (94), 148 (5), 135 (9), 133 (7).

Pavonisol (**3**). Crystals, mp 138–140° (Et_2O). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 0.96 (*d*, *J* = 6.3 Hz, Me-3), 2.92 (*sl*, OH-2), 3.25 (*s*, OMe-1), 3.75 (*d*, *J* = 5.2 Hz, H-1), 3.65 (*m*, H-2), 3.85 (*s*, OMe-3', OMe-5'), 5.50 (*s*, OH-4'), 6.50 (*s*, H-2', H-6'). EIMS *m/z* (rel. int.): 242 $[M]^+$ (10), 211 (1), 199 (2), 198 (15), 197 (100), 196 (1), 183 (1), 182 (13), 181 (4), 168 (1), 166 (1), 139 (1), 137 (92), 136 (1), 104 (1).

Acetate of compound **3**. Crystals, mp 115–116° (Et_2O). $[\alpha]_D^{25}$ +86.7° ($CHCl_3$; *c* 0.85). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.06 (*d*, *J* = 6.3 Hz, Mc-3), 2.00 (*s*, OAc-2), 2.30 (*s*, OAc-4'), 3.25 (*s*, OMe-2), 3.80 (*s*, OMe-3', OMe-5'), 4.08 (*d*, *J* = 6.4 Hz, H-1), 5.01 (*m*, H-2), 6.50 (*s*, H-2', H-6'). EIMS *m/z* (rel. int.): 326 $[M]^+$ (4), 285 (1), 284 (5), 240 (2), 239 (13), 255 (1), 224 (1), 199 (1), 198 (11), 197 (100), 183 (1), 182 (4), 181 (2), 167 (2), 104 (2).

Acknowledgements—We thank the CNPq for a fellowship to PHF. Thanks are also due to Dr William A. Rodrigues (INPA-CNPq) for the botanical identification and Mrs Paula Pilli for the ^{1}H NMR spectra.

REFERENCES

1. Shultes, R. E. and Holmstedt, B. (1971) *Lloydia* **34**, 61.
2. Fernandes, J. B., Ribeiro, M. N. S., Gottlieb, O. R. and Gottlieb, H. E. (1980) *Phytochemistry* **19**, 1523.
3. Gottlieb, O. R., Loureiro, A. A., Carneiro, M. L. and Rocha, A. I. (1973) *Phytochemistry* **12**, 1830.
4. Carneiro, M. O., Yoshida, M. and Gottlieb, O. R. (1983) *35th Congress of Sociedade Brasileira para o Progresso da Ciência*, Abstract 47-D.2.5.
5. Ferri, P. H. and Barata, L. E. S. (1992) *Phytochemistry* (in press).
6. Cavalcante, S. H., Yoshida, M. and Gottlieb, O. R. (1985) *Phytochemistry* **24**, 1051.
7. MacRae, W. D. and Towers, G. H. N. (1985) *Phytochemistry* **24**, 561.
8. Zanaroti, A. (1983) *J. Chem. Res. (S)* 306.
9. Braz Filho, R., Mourão, J. C., Gottlieb, O. R. and Maia, J. G. S. (1976) *Tetrahedron Letters* **15**, 1157.
10. Rodrigues, M. M., Fernandes, J. B., Braz Filho, R., Yoshida, M. and Gottlieb, O. R. (1984) *Phytochemistry* **23**, 667.
11. Barbosa filho, J. M., Silva, M. S., Yoshida, M. and Gottlieb, O. R. (1989) *Phytochemistry* **28**, 2209.
12. Dias, S. M. C., Fernandes, J. B., Maia, J. G. S., Gottlieb, O. R. and Gottlieb, H. E. (1986) *Phytochemistry* **25**, 213.
13. Whiting, D. A. (1987) *Nat. Prod. Rep.* **4**, 499.
14. Schmid, G. H. (1968) *Can. J. Chem.* **46**, 3415.
15. Nishiyama, A., Eto, H., Tereda, Y., Yguchi, M. and Yamamura, S. (1983) *Chem. Pharm. Bull.* **31**, 2834.
16. Pascual Teresa, J. D., Pascual, M., Arias, A., Hernández, J. M., Morán, J. R. and Grande, M. (1985) *Phytochemistry* **24**, 1773.
17. Hada, S., Hattori, M., Tezuka, Y., Kikuchi, T. and Namba, T. (1988) *Phytochemistry* **27**, 563.
18. Miski, M. and Mabry, T. J. (1986) *J. Nat. Prod.* **49**, 657.
19. Miski, M. and Jakupovic, J. (1990) *Phytochemistry* **29**, 173.
20. Bottini, A. T., Dev, V., Garfagnoli, D. J., Mathela, C. S., Melkane, A. B., Miller, A. A. and Sturn, N. S. (1986) *Phytochemistry* **25**, 207.
21. Pearl, I. A. (1948) *J. Am. Chem. Soc.* **70**, 1746.
22. Wallis, A. F. A. (1973) *Aust. J. Chem.* **26**, 585.