Phytochemistry, Vol 24, No 8, pp 1867–1868, 1985
Printed in Great Britain

0031-9422/85 $3.00+0.00

NEOLIGNANS FROM *VIROLA CALOPHYLLOIDEA**

JUAN C. MARTINEZ V., LUIS E. CUCA S., MASSAYOSHI YOSHIDA† and OTTO R. GOTTLIEB†

Departamento de Química, Universidad Nacional de Colombia, Bogotá, Colombia; †Instituto de Química, Universidade de São Paulo, 05508, São Paulo, SP, Brazil

(*Received* 15 *November* 1984)

Key Word Index—*Virola calophylloidea*; Myristicaceae; neolignans; 4-aryltetralins; 2,3-dibenzylbutane.

Abstract—Extraction of *Virola calophylloidea* furnished, besides the known (−)-dihydroguaiaretic acid, two epimeric methoxyhydroxyotobains and a methoxyotobaene.

INTRODUCTION

Virola calophylloidea, a large Myristicaceous tree, occurs in the Amazonian region of Colombia. Designated kó-ga by the Kubeo tribe of Indians, its bark resin is used in the preparation of a narcotic snuff [2]. Material for the present study was collected from a specimen growing on the margin of the river Piraparaná, near Sonaña, Comisária del Vaupés, Colombia. Three novel compounds **1a**, **2** and **3a** were isolated from leaf and bark extracts. (−)-Dihydroguaiaretic acid (**4**), previously found in other Myristicaceae species [3], was also isolated from the leaf extract.

RESULTS AND DISCUSSION

Compounds **1a** and **2** have identical molecular formulae, $C_{21}H_{22}O_6$, determined by HR mass spectrometry, and very similar UV, IR and mass spectra. The NMR spectra reveal these isomers to be 5-methoxy (δ_H 3.8, δ_C 56) substituted derivatives of hydroxyotobain (**1b**), previously isolated from other Myristicaceae species [3–5]. Indeed, in **1a** and **2** as in **1b**, the characteristic non-equivalence of O_2CH_2-signals places one of the methylenedioxy groups at C-3 and C-4. In contrast to **1b**, however, a methoxyl must also be sustained by the tetralin, since only one aromatic proton occurs on this system. Its signal, a broad singlet (δ6.45), is consistent with the position at C-6. Here coupling with the benzylic protons (δ2.8–3.2) can take place and this was ascertained by double resonance experiments.

Apart from the spectral consequences of the methoxyl substitution, the ^1H NMR spectra of **1a** and **1b** [4–6] are practically superimposable. Hence, in **1b** as well as **1a** the aryl and methyl substituents must all be equatorial. Furthermore, since the compounds also show comparable CD curves, the absolute configuration of **1a** must be identical with that attributed to **1b** [7]. In contrast, the CD curves of **1a** and **2** show opposite signs and the compounds must possess opposite chiralities at the benzylic carbon. Dehydration of **2** into **3a** occurs in chloroform solution in the presence of a trace of acid. The ease of the reaction is evidence for the *trans*-elimination of water and hence for the *trans*-relation of the piperonyl at C-7′ and the methyl at C-8′. The dehydration product is identical with compound **3a**, an additional constituent of the plant extract. The optical rotations of **3a**, $[\alpha]_D = +52°$, and of otobaene (**3b**), $[\alpha]_D = +47°$ [5], of known absolute configuration [7], are evidence for identical stereochemistries. Compounds **2** and **3** must, of course, have identical chiralities at C-8.

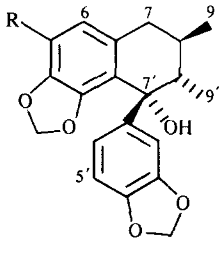
In contrast to **1a** with the piperonyl and methyl groups all equatorial, in **2** only the piperonyl at C-7′ and the methyl at C-8′ can be equatorial, the methyl at C-8 must be axial. Indeed, as is to be expected, the only conspicuous difference of the ^1H NMR spectra of **1a** and **2** refers to one of the methyl-signals of **2**, which occurs at slightly higher field than the corresponding signal of **1a** ($\Delta\delta = 0.1$). Otobaene (**3b**) is considered to be an artifact [5, 8] and the same may be true for **3a**.

EXPERIMENTAL

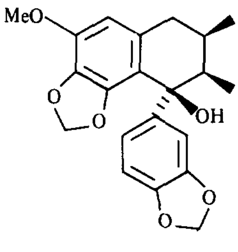
Isolation of constituents. Dried and powdered leaves (0.9 kg) and bark (0.7 kg) of *V. calophylloidea* Markgraf (voucher Herb. Nac. Colombiano No Col. 231562) were extracted with C_6H_6 (room temp). The solvent was evapd The residue of the leaf extract (25 g) was submitted to CC (350 g silica gel). Elution was performed with C_6H_6–EtOAc (9:1). The 65 × 100 ml fractions were examined by TLC and combined into seven groups. The residue of group 2 (1.3 g) was separated by repeated prep. TLC (silica gel, cyclohexane–MeOH, 9:1) into the more polar **1a** (90 mg), **2** (30 mg) and the least polar **3a** (95 mg). The residue of group 4 (1.2 g) was separated, by successive CC and TLC (silica gel, C_6H_6–EtOAc, 4:1), into a mixture of steroids (95 mg) and impure **4**. The residue of group 6 (1.1 g), submitted to chromatographic techniques, gave an additional quantity of impure **4**. The **4**-containing residues were combined and gave, by repeated prep. TLC (silica gel, petrol–EtOAc, 7:3) pure **4** (290 mg). The residue of the bark extract (8 g), treated in an analogous manner, gave **1a**

---

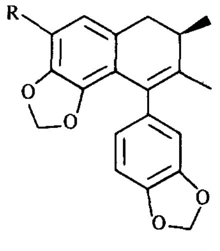
*Part 4 in the series "Chemistry of Colombian Myristicaceae". For Part 3 see ref. [1].



1a R = OMe
1b R = H



2



3a R = OMe
3b R = H

(100 mg), **2** (20 mg) and **3a** (215 mg).

(7'R, 8R, 8'S)-7'-*Hydroxy*-5-*methoxy*-3,4,3',4'-*dimethylenedioxy*-2.7',8.8'-*neolignan* (**1a**). Oil; [[M]$^+$ found 370.1686; $C_{21}H_{22}O_6$ requires 370.1417]. UV λ_{max}^{MeOH} nm (ε): 239 (7300), 292 (4500), 308 (3450). IR ν_{max}^{film} cm^{-1}: 3545, 1608, 1465, 1240, 1195, 1140, 935, 795, 750, 690. ^{1}H NMR (80 MHz, $CDCl_3$). δ0.82 (*d*, *J* = 6 Hz, 3H-9), 1.05 (*d*, *J* = 6 Hz, 3H-9'), 1.42 (*s*, HO-7'), 1.5–2.5 (*m*, H-8, H-8'), 2.8–3.3 (*m*, 2H-7), 3.78 (*s*, MeO-5), 5.50 and 5.68 (2*d*, *J* = 2 Hz, CH_2O_2-3,4), 5.93 (*s*, CH_2O_2-3',4'), 6.45 (*s*, H-6), 6.6–6.9 (*m*, H-2', H-5', H-6'). ^{13}C NMR (20 MHz, $CDCl_3$): δ118.6 (C-1), 126.4 (C-2), 145.5 (C-3), 142.2 (C-4), 150.9 (C-5), 93.6 (C-6), 33.2 (C-7), 30.5 (C-8), 19.5 (C-9), 138.2 (C-1'), 106.7 (C-2'), 145.8 (C-3'), 146.7 (C-4'), 106.8 (C-5'), 118.7 (C-6'), 75.7 (C-7'), 48.7 (C-8'), 10.1 (C-9'), 100.5 (2 CH_2O_2), 56.0 (MeO). MS *m/z* (rel. int.): 372 [M + 2]$^+$ (4), 371 [M + 1]$^+$ (25), 370 [M]$^+$ (100), 352 [M − H_2O]$^+$ (7), 314 (39), 313 (98), 284 (32), 283 (15), 282 (14), 269 (10), 241 (10), 215 (11), 149 (27), 137 (31), 128 (10), 121 (13), 111 (18), 109 (14). CD (*c* 0.013 g/100 ml; MeOH): $[\theta]_{300}^{max}$ −7800, $[\theta]_{242}^{max}$ −6400; CD (MeOH) (**1b**) [7] $[\theta]_{284}^{max}$ −3140, $[\theta]_{234}^{max}$ −9450.

(7'S,8R,8'R)-7'-*Hydroxy*-5-*methoxy*-3,4,3',4'- *dimethylenedioxy*-2.7',8.8'-*neolignan* (**2**). Mp 66–67° (MeOH) [[M]$^+$ found 370.1450; $C_{21}H_{22}O_6$ requires 370.1417]. UV λ_{max}^{MeOH} nm (ε): 240 (7150), 290 (5500), 308 (3500). IR ν_{max}^{film} cm^{-1}: 3530, 1610, 1465, 1345, 1240, 1195, 1095, 985, 880, 815, 755, 662. ^{1}H NMR (80 MHz, $CDCl_3$): δ0.85 (*d*, *J* = 6 Hz, 3H-9), 0.95 (*d*, *J* = 6 Hz, 3H-9'). 1.45 (*s*, HO-7'), 1.5–2.5 (*m*, H-8, H-8'), 2.8–3.3 (*m*, 2H-7), 3.82 (*s*, MeO-5), 5.73 and 5.80 (2*d*, *J* = 2 Hz, CH_2O_2-3,4), 5.94 (*s*, CH_2O_2-3',4'), 6.47 (*s*, H-6), 6.6–6.9 (*m*, H-2', H-5', H-6'). ^{13}C NMR (20 MHz, $CDCl_3$): δ118.1 (C-1), 121.3 (C-2), 145.7 (C-3), 138.3 (C-4), 151.5 (C-5), 93.4 (C-6), 32.8 (C-7), 30.1 (C-8), 19.6 (C-9), 138.3 (C-1'), 108.8 (C-2'), 146.4 (C-3'), 146.8 (C-4'), 106.9 (C-5'), 121.3 (C-6'), 77.8 (C-7'), 45.4 (C-8'), 12.1 (C-9'), 100.9 (2 CH_2O_2), 56.1 (MeO). MS *m/z* (rel. int.). 372 [M + 2]$^+$ (4), 371 [M + 1]$^+$ (23), 370 [M]$^+$ (100), 352 [M − H_2O]$^+$ (25), 314 (23), 313 (66), 284 (22), 282 (12), 269 (10), 149 (12). CD (*c* 0.009 g/100 ml; MeOH): $[\theta]_{297}^{max}$ +4100, $[\theta]_{237}^{max}$ +7100

(8R)-5-*Methoxy*-3,4,3',4'-*dimethylenedioxy*-$\Delta^{7',8'}$- 2.7',8.8'-*neolignan* (**3a**). Mp 152° (MeOH), $[\alpha]_D^{20}$ +51.7 (*c* 0.785; $CHCl_3$) [[M]$^+$ found 352.1311, $C_{21}H_{20}O_5$ requires 352.1305]. UV λ_{max}^{MeOH} nm (ε): 279 (1200), 292 (1050), 332 (300). IR ν_{max}^{KBr} cm^{-1}: 1600, 1485, 1440, 1335, 1235, 1195, 1075, 1040, 1081, 935, 915, 890, 865, 805, 775, 760. ^{1}H NMR (60 MHz, $CDCl_3$): δ1.03 (*d*, *J* = 7 Hz, 3H-9), 1.78 (*s*, 3H-9'), 2–2.6 (*m*, H-8), 2.8–3.3 (*m*, 2H-7), 3.79 (*s*, MeO-5), 5.49 and 5.58 (2*d*, *J* = 2 Hz, CH_2O_2-3,4), 5.96 (*s*, CH_2O_2-3',4'), 6.45 (*s*, H-6), 6.5–6.8 (*m*, H-2', H-5', H-6'). ^{13}C NMR (20 MHz, $CDCl_3$): δ119.4 (C-1), 134.6 (C-2), 145.9 (C-3), 141.0 (C-4), 151.2 (C-5), 93.6 (C-6), 34.3 (C-7), 27.9 (C-8), 17.0 (C-9), 137.5 (C-1'), 107.6 (C-2'), 146.5 (C-3'), 147.0 (C-4'), 110.4 (C-5'), 122.9 (C-6'), 128.4 (C-7'), 114.6 (C-8'), 19.2 (C-9'), 100.7 (CH_2O_2), 100.1 (CH_2O_2), 56.8 (MeO). MS *m/z* (rel. int.): 354 [M + 2]$^+$ (6), 353 [M + 1]$^+$ (32), 352 [M]$^+$ (100), 337 (35), 323 (22), 322 (13), 309 (19), 307 (30), 279 (26), 277 (37), 204 (12), 176 (14), 161 (24), 136 (14), 119 (26), 107 (17), 105 (18). CD (*c* 0.007 g/100 ml; MeOH): $[\theta]_{327}^{max}$ +2800, $[\theta]_{291}^{max}$ −5500, $[\theta]_{256}^{max}$ +24 400, $[\theta]_{243}^{max}$ −11 300.

Acknowledgements—We are indebted to the botanist Roberto Jaramillo M., Instituto de Ciências Naturales, Universidad Nacional de Colombia, for collection and identification of plant material. Support by COLCIENCIAS (contract 10000-1-135-81), CINDEC of Universidad Nacional de Colombia and OAS (Multinational Project in Chemistry) is acknowledged by the Colombian authors. Support by CNPq and FAPESP is acknowledged by the Brazilian authors.

REFERENCES

1. Martinez V., J. C., Cuca S., L. E. and Alvarez V., E. (1985) *Rev. Colombiana Quim.* (in press).
2. Schultes, R. E. and Holmstedt, B. (1971) *Lloydia* **34**, 61.
3. Braz Fo., R., Carvalho, M. G. de and Gottlieb, O. R. (1984) *Planta Med.* 53.
4. Wallace, R., Porte, A. L. and Hodges, R. (1963) *J. Chem. Soc.* 1445.
5. Kohen, F., Maclean, I. and Stevenson, R. (1966) *J. Chem. Soc. C* 1775.
6. Klyne, W., Stevenson, R and Swan, R. J. (1966) *J. Chem. Soc. C* 893.
7. Lopes, L. M. X., Yoshida, M. and Gottlieb, O. R. (1982) *Phytochemistry* **21**, 751.
8. Blair, G. E., Cassady, J. M., Robbers, J. E., Tyler, V. E. and Raffauf, R. F. (1969) *Phytochemistry* **8**, 497.