Phytochemistry, 1980, Vol. 19, pp. 1523–1525. © Pergamon Press Ltd. Printed in England. 0031-9422/80/0701-1523 $02.00/0

EUSIDERINS AND 1,3-DIARYLPROPANES FROM *VIROLA* SPECIES*

JOÃO B. FERNANDES, M. NILCE DE S. RIBEIRO,†
OTTO R. GOTTLIEB‡ and HUGO E. GOTTLIEB§

Centro de Ciências e Tecnologia, Universidade Federal de São Carlos, 13560-São Carlos, SP, Brazil

(*Received* 16 *August* 1979)

Key Word Index—*Virola divergens*; *V. guggenheimii*; *V. pavonis*; Myristicaceae; virolane; virolanol; eusiderins-A, -C, -D.

Abstract—Trunk wood of *Virola divergens* Ducke and *V. guggenheimii* W. Rodrigues (Myristicaceae) contains the 1,3-diarylpropanes virolane and (2*S*)-virolanol. The latter species contains in addition the benzodioxane-type neolignan eusiderin. Bark of *V. pavonis* (A. DC.) A.C. Smith contains two novel representatives of this group, *rel*-(2*S*, 3*R*)-7-allyl-5-methoxy-2-(3′, 4′, 5′-trimethoxyphenyl- and *rel*-(2*S*, 3*R*)-7-allyl-5-methoxy-2-(3′,4′-dimethoxyphenyl)-3-methyl-benzodioxane, designated eusiderin-C and eusiderin-D, respectively.

INTRODUCTION

Since the discovery of the ethnopharmacologic relevance of *Virola* (Myristicaceae) [2, 3], 12 out of 35 Brazilian species of this genus were submitted to chemical scrutiny. The present paper reports data on 3 additional species, *V. divergens* Ducke, *V. guggenheimii* W. Rodrigues [4] and *V. pavonis* (A.DC.) A. C. Smith.

RESULTS

The benzene extracts of trunk wood of *V. divergens* and *V. guggenheimii* both contained 1-(2-hydroxy-4 methoxyphenyl)-3-(3′,4′-methylenedioxyphenyl)-propane (virolane) and (2*S*)-2-hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(3′,4′-methylenedioxyphenyl)-propane (virolanol). Virolane and virolanol, together with other 1,3-diarylpropanes, had been isolated previously from other *Virola* species [3, 5] and were identified by direct comparison with authentic samples. The stereochemistry of virolanol is revealed by the similarity of the ORD curves of this compound (**1a**, peak at 277 nm, $[\alpha]_D^{25} - 9.5°$) and of the (+)-catechin derivative **1b** (peak at 268 nm, $[\alpha]_D^{21} - 2.5°$) [6], as opposed to the antipodal curve of the peltogynol derivative **2** ($[\alpha]_D^{27} + 86°$) [6].

The benzene extract of *V. guggenheimii* wood yielded *rel*-(2*R*, 3*R*)-7-allyl-5-methoxy-3-methyl-2-(3′, 4′, 5′-trimethoxyphenyl)-benzodioxane (**3a**, eusiderin), which, together with eusiderin-B (**3b**), belongs to the benzodioxane-type neolignans [7], and was again identified by direct comparison with an authentic sample [8]. The chloroform extract of bark from *V. pavonis* yielded two further and novel benzodioxane-type neolignans, eusiderin-C (**3c**) and eusiderin-D (**3d**).

Determination of the MW by MS, together with hydrogen, carbon and methoxyl counts by NMR, revealed the formulae $C_{18}H_{14}O_2(OMe)_4$ and $C_{18}H_{15}O_2(OMe)_3$, respectively, for **3c** and **3d**. Since NMR data, confirmed by double resonance experiments, indicated also the existance, in both, of ArCH(O)CH(O)Me and $ArCH_2CH{=}CH_2$ moieties, the compounds were immediately classified as eusiderins, and tentatively formulated as shown.

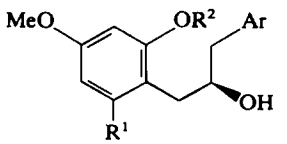
Indeed, comparison of ^1H and ^{13}C NMR data showed clearly that the B-rings of all four eusiderins are identically substituted. Again, as already shown, for **3a** and **3b** by LIS of the *meta*-split ^1H NMR doublets of H-6 and H-8 [8], $Pr(fod)_3$ complexes strongly with a site on ring B of **3c**. Since neither *ortho* diethers in which the oxy-functions are part of a ring, nor isolated methoxyls, associate strongly with the reagent [8], both functions must occupy vicinal positions. Among two alternatives the one shown in **3** was selected. The considerable difference in Δ values for the H-3 and H-2 signals (31 vs 2 ppm) favoured closer proximity of the association site with H-3 than with H-2. Although LIS data for **3d** were not obtained, relevant ^{13}C NMR data for 3c and 3d are identical and

* Part 13 in the series "The Chemistry of Brazilian Myristicaceae". For Part 12 see ref. [1]. Based on the M. S. thesis submitted by M. N. de S. R. to Universidade de São Paulo (1979).

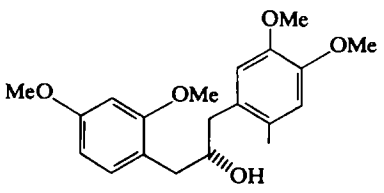
† Instituto Nacional de Pesquisas da Amazônia, Conselho Nacional de Desenvolvimento Científico e Tecnológico, 69000-Manaus, AM.

‡ Instituto de Quimica, Universidade de São Paulo, 05508-São Paulo, Brazil.

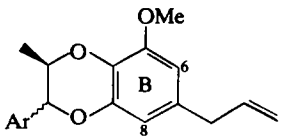
§ Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel.



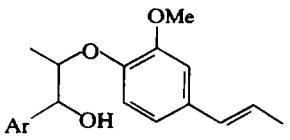
1a $R^1 = R^2 = H$, Ar = Pi*
1b R^1 = OMe, R^2 = Me, Ar = Ve



2



3a Ar = α-Tp
3b Ar = α-Pi
3c Ar = β-Tp
3d Ar = β-Ve



4a Ar = Tp
4b Ar = Ve

thus revealed not only the constitutional but also the configurational identity of the benzodioxane units of **3c** and **3d**.

^{1}H and ^{13}C NMR evidence clarified two further points: the structure of the aryl substituents and, by comparison with analogous data for eusiderin (**3a**), the relative configuration of the Ar-2/Me-3 groups. Indeed, **3a** contrasts with **3c** and **3d** by a trans- versus cis-relation of these groups. This is seen in the chemical shifts of Me-3(τ 8.68 vs 8.86) as well as in the values of $J_{H\text{-}2,H\text{-}3}$(8 vs 2 Hz) by ^{1}H NMR, and in the chemical shifts of Me-3(δ 17.1 *vs* 12.7) and C-1′ (δ 131.9 vs 129.6) by ^{13}C NMR. The resonances at higher field of Me-3 in the ^{1}H NMR and ^{13}C NMR spectra suggested this group to suffer anisotropic protection and steric interaction, both emanating from the *cis*-aryl in **3c** and **3d**.

The ORD curves are consistent with these results, showing an antipodal feature (positive, for **3a**, vs negative, for **3c** and **3d**, Cotton effects at *ca* 250 nm) and a coincident feature (positive Cotton effects, for **3a, 3c, 3d,** at *ca* 280 nm).

DISCUSSION

Eusiderins (**3a, 3b**) have previously only been isolated from Lauraceae species [7]. The presence of such benzodioxane-type neolignans also in Myristicaceae, and specially in *Virola*, was nevertheless to be expected since the isolation and characterization of the biosynthetically related surinamensin (**4a**) and virolin (**4b**) from leaves of *V. surinamensis* (Rol.) Warb. [9]. *V. pavonis* is morphologically akin to *V. surinamensis* and to *V. carinata* (Benth.) Warb. [10], the three species being distinguished usually by fruit morphology and habitat (Rodrigues, W. A., personal communication).

EXPERIMENTAL

Isolation of constituents from V. divergens. The C_6H_6 extract of a small sample of trunk wood, collected near the Manaus–Itacoatiara highway, km 60, voucher INPA herbarium No. 53.126, was submitted to dry column chromatography (Si gel, C_6H_6—Me_2CO, 9:1). The fractions were purified, yielding sitosterol, virolane and virolanol [11].

Isolation of constituents from V. guggenheimii. Trunk wood was collected from a specimen, voucher INPA herbarium No. 9.255, growing in the park around INPA, Manaus, AM. A sample (8 kg) was percolated with C_6H_6 at room temp. The extract (5.5 g) was separated into crystals (0.5 g) and oil (5 g) by filtration. The crystals were chromatographed on Si gel (25 g), C_6H_6—$CHCl_3$ (1:1) and $CHCl_3$—MeOH (99:1) eluting fractions which gave by several recrystallizations, respectively, sitosterol, mp 132–134° (MeOH), and virolanol (**1a**, 10 mg), mp and lit. [11] mp 114–116° (EtOH + petrol). The oil was chromatographed on a dry column (200 g Si gel deactivated by 10% H_2O, C_6H_6—Me_2CO) which was extruded and cut into 5 equal portions. Portion 1 contained fatty material (0.6 g). The eluate of portion 2 (0.6 g) was chromatographed on Si gel (30 g). Elution with C_6H_6, C_6H_6—$CHCl_3$ (99:1) and $CHCl_3$ gave fractions A_1, A_2 and A_3. A_1 crystallized from C_6H_6—MeOH to virolane (20 mg), mp and lit. [11] mp 102–104°; A_2, purified by TLC, gave a mixture of virolane and virolanol; A_3 crystallized from hexane—$CHCl_3$ to eusiderin (**3a**, 110 mg), mp and lit. [12] mp 93–94°. The eluate of portion 3 (1.5 g) was separated by TLC (Si gel, C_6H_6—EtOAc, 9:1) into virolanol (**1a**, 15 mg) and oil. The eluate of portion 4 (1 g), chromatographed on Si gel, gave virolane and virolanol in the middle fractions. The eluate of portion 5 (1.2 g) was a complex mixture of compounds.

Isolation of constituents from V. pavonis. Bark was collected from a specimen, growing near the Manaus–Itacoatiara highway, km 165, AM, voucher INPA herbarium No. 47.280. A sample (2 kg) was percolated with $CHCl_3$ at room temp. The extract (6 g) was chromatographed on Si gel (300 g). C_6H_6 eluted an oil of aliphatic nature. C_6H_6—EtOH (99:1) eluted a mixture (0.6 g) which was separated by repeated TLC (Si gel, $CHCl_3$–Et_2O, 19:1) into eusiderin-C (**3c**, 80 mg) and eusiderin-D (**3d**, 60 mg).

(2*S*)-2-*Hydroxy*-1-(2-*hydroxy*-4-*methoxyphenyl*)-3-(3′,4′-*methylenedioxyphenyl*)-*propane* (**1a**, *virolanol*). ORD (7 mg/10 ml MeOH): $[\phi]_{240} - 3950$, $[\phi]_{255} - 150$, $[\phi]_{265} - 270$, $[\phi]_{270}0$, $[\phi]^{pk}_{277} + 5500$, $[\phi]_{300} + 400$.

rel-(2R,3R)-7-*Allyl*-5-*methoxy*-2-(3′,4′,5′)-*trimethoxy*-*phenyl*-3-*methylbenzodioxane* (**3a**, *eusiderin*). ORD (3.2 mg/25

* Tp = Tri-*O*-methylpyrogallyl, Pi = piperonyl, Ve = veratryl.

ml MeOH): $[\phi]_{245}-7200$, $[\phi]^{tr}_{248}-12550$, $[\phi]^{sh}_{250}-8400$, $[\phi]^{sh}_{260}-4050$, $[\phi]_{285-300}0$, $[\phi]_{365-400}+2050$.

rel-(2S,3R)-7-*Allyl*-5-*methoxy*-2-(3′,4′,5′-*trimethoxy*-*phenyl*)-3-*methylbenzodioxane* (**3c**, *eusiderin*-C). Viscous oil. ν^{Film}_{max}, cm^{-1}: 1590, 1500, 1460, 1420, 1360, 1340, 1240, 1210, 1125. λ^{MeOH}_{max} nm: 219, 270 (log ε 4.47, 3.23). MS (*m/e*): 386 (17%) M^+, 209 (19), 208 (84), 205 (16), 194 (10), 193 (69), 191 (29), 179 (17), 167 (45), 149 (15), 148 (100), 113 (17), 112 (11), 105 (10). LIS data ($\Delta\tau$): 5.1 (OMe-4′), 4.0 (MeO-3′,5′,5), 6.4 (H-2′,6′), 2.0 (H-2), 31.0 (H-3), 10.5 (Me-3), 6.0 (H-6), 5.7 (H-8). Shift studies were carried out by stepwise addition of known amounts of $Pr(fod)_3$ to *ca* 0.25 M solns of substrate in $CDCl_3$. The LIS data were obtained by graphic extrapolation of observed shifts to 1:1 shift reagent-substrate ratio. ORD (3.8 mg/25 ml MeOH): $[\phi]_{250}+2800$, $[\phi]_{253}0$, $[\phi]^{tr}_{256}-1200$, $[\phi]_{262}0$, $[\phi]^{pk}_{270}+650$, $[\phi]^{tr}_{280}+250$, $[\phi]_{288}+2050$, $[\phi]_{295}+2200$, $[\phi]_{370-400}+1400$.

rel-(2S,3R)-7-*Allyl*-5-*methoxy*-2-(3′,4′-*dimethoxyphenyl*)-3-*methylbenzodioxane* (**3d**, *eusiderin*-D). Viscous oil. ν^{Film}_{max} cm^{-1}: 1600, 1500, 1460, 1360, 1260, 1120, 1020. λ^{MeOH}_{max} nm: 219, 232 infl., 276 (log ε 4.53, 4.39, 3.73). MS (*m/e*): 356 (10%) M^+, 191 (13), 179 (12), 178 (100), 167 (20), 163 (17), 149 (55), 107 (10). ORD (3.9 mg/25 ml MeOH): $[\phi]_{245}+1050$, $[\phi]_{248}0$, $[\phi]^{tr}_{252}-4500$, $[\phi]^{pk}_{268}-1500$, $[\phi]^{tr}_{275}-1800$, $[\phi]_{282}0$, $[\phi]^{pk}_{288}+2350$, $[\phi]_{365-400}+900$.

^{1}H *NMR spectra* (τ,$CDCl_3$) *of* **3a** (60 MHz) [13]/**3c** (270 MHz)/**3d** (270 MHz): 5.4/4.9/4.9 (*d*, 8Hz/*d*, 2 Hz/*idem*; H-2); 5.7–6.3/5.39/5.41 (*m/dq*, 2.5, 6.5 Hz/*idem*; H-3), 3.63/3.6/3.62 (*d*, 1.5 Hz; H-6), 3.51/3.48/3.49 (*d*, 1.5 Hz; H-8), 8.68/8.85/8.85 (*d*, 6.5 Hz; Me-3), 6.09/6.12/6.11 (*s*, MeO-5), 6.67/6.69/6.69 (*d*, 7 Hz; CH_2-7), 3.8–4.3/4.02/4.03 (*m/ddt*, 17, 10.6, 6.5 Hz/*idem*; CH═), 4.7–5.1/4.8–4.9/4.8–4.9 (*m*, CH_2═), 3.4/3.38/3.06 (*s/s/d*, 1.5 Hz; H-2′), —/—/3.13 (—/—/*d*, 8.5 Hz; H-5′), 3.4/3.38/3.07 (*s/s/dd*, 8.5, 1.5 Hz; H-6′), 6.09/6.13/6.12 (*s*; MeO-3′), 6.09/6.15/6.12 (*s*; MeO-4′), 6.09/613/— (*s*; MeO-5′).

^{13}C *NMR spectra* (δ, $CDCl_3$, 22.6 MHz) *of* **3a** [14]/**3c**/**3d**: 80.6/77.1/77.1 (*d*, C-2), 73.7/73.2/73.2 (*d*, C-3), 130.9/132.3/132.3 (*s*, C-4a), 148.1/149.2 (*s*, C-5), 104.3/105.1/104.9 (*d*, C-6), 132.1/132.5/132.5 (*s*, C-7), 109.1/109.8/109.8 (*d*, C-8), 143.8/143.4/143.5 (*s*, C-8a), 17.1/12.6/12.7 (*q*, Me-3), 55.7/56.1/56.1 (*q*, MeO-5), 39.7/40.0/40.1 (*t*, CH_2-7), 136.9/137.5/137.5 (*d*, CH═), 115.3/115.9/115.9 (*t*, CH_2═), 131.9/129.6/129.5 (*s*, C-1′), 104.1/103.2/111.2 (*d*, C-2′), 153.0/153.5/149.1 (*s*, C-3′), 138.0/137.8/148.9 (*s*, C-4′), 153.0/153.5/109.5 (*s/s/d*, C-5′), 104.1/103.2/118.7 (*d*, C-6′), 55.8/56.2/56.0 (*q*, MeO-3′), 60.4/60.9/56.0 (*q*, MeO-4′), 55.8/56.2/- (*q*, MeO-5′).

Acknowledgements—This work was supported by a grant from the Fundação de Amparo à Pesquisa do Estado de São Paulo. The authors are grateful to Dr. W. A. Rodrigues, INPA, for the classification of all plant species; to Drs. A. K. Schwantes and P. de Luca, Universidade Federal de São Carlos, for the UV spectra; to Dr. R. van Fossen de Bravo, Universidade Estadual de Campinas, for the MS; and to Dr. M. Yoshida, Universidade de São Paulo, for the ORD curves.

REFERENCES

1. Braz Filho, R., Diaz D., P. P. and Gottlieb, O. R. (1980) *Phytochemistry* **19,** 455.
2. Schultes, R. E. (1969) *Bot. Mus. Leafl. Harv. Univ.* **22,** 229.
3. Gottlieb, O. R. (1979) *J. Ethnopharm.* **1,** 309.
4. Rodrigues, W. A. (1977) *Acta Amazonica* **7,** 459.
5. Gottlieb, O. R. (1977) *Isr. J. Chem.* **16,** 45.
6. Hassall, C. H. and Weatherston, J. (1965) *J. Chem. Soc.* 2844.
7. Gottlieb, O. R. (1977) *Progr. Chem. Org. Nat. Prod.* **35,** 1.
8. Braz Filho, R., Mourão, J. C., Gottlieb, O. R. and Maia, J. G. S. (1976) *Tetrahedron Letters* 1157.
9. Barata, L. E. S., Baker, P. M., Gottlieb, O. R. and Rúveda, E. A. (1978) *Phytochemistry* **17,** 783.
10. Gottlieb, O. R., Maia, J. G. S. and Ribeiro, M. N. de S. (1976) *Phytochemistry* **15,** 773.
11. Braz Filho, R., Leite, M. F. F. and Gottlieb, O. R. (1973) *Phytochemistry* **12,** 417.
12. Hobbs, J. J. and King, F. E. (1960) *J. Chem. Soc.* 4732.
13. Gottlieb, O. R., Maia, J. G. S. and Mourão, J. C. (1976) *Phytochemistry* **15,** 1289.
14. Wenkert, E., Gottlieb, H. E., Gottlieb, O. R., Pereira, M. O. da S. and Formiga, M. D. (1976) *Phytochemistry* **15,** 1547.