Pergamon

Phytochemistry, Vol. 46, No. 4, pp. 745–749, 1997

Printed in Great Britain
0031-9422/97 $17.00+0.00

PII: S0031-9422(97)00199-4

LIGNOIDS, FLAVONOIDS AND POLYKETIDES OF *VIROLA SURINAMENSIS*

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(*Received* 10 *December* 1996)

Key Word Index—*Virola surinamensis*; Myristicaceae; seeds; lignoids; flavonoids; polyketides.

Abstract—From the seeds of *Virola surinamensis*, which were collected near Altamira and near Marabá, Pará State, Brazil, the following substances were isolated by chromatographic techniques: two dibenzylbutanediol lignans, dihydrocubebin and the new dihydrocubebin monolaurate, two furofuran lignans, sesamin and asarinin, three dibenzylbutyrolactol lignans, cubebin, β-*O*-methylcubebin and α-*O*-methylcubebin, one dibenzylbutyrolactone lignan, hinokinin, one aryltetralin neolignan, galbulin, two tetrahydrofuran neolignans, galgravin and the new 4′-hydroxy-3′-methoxy-3,4-methylenedioxy-8.8′,7.*O*.7′-neolignan, one flavone, tithonine, one isoflavone, irisolidone, and two new polyketides, 3-hydroxy-1-(15-phenylpentadecanoyl)-2,6-cyclohexanedione and 1-(5-phenylpentanoyl)-2,6-cyclohexanedione. Different chemical constitutions of the fruits from the two localities were observed. © 1997 Published by Elsevier Science Ltd

INTRODUCTION

Previous studies on *Virola* species describe the occurrence of the lignans dihydrocubebin (**1a**) [1, 2], sesamin (**2a**) [1–5], asarinin (**2b**) [1, 2, 6], cubebin (**3b**) [1, 2, 6], hinokinin (**3e**) [1, 2, 3, 6], the neolignans, galbulin (**4**) [3] and galgravin (**5a**) [7], and the flavone tithonine (**6**) [2]. Leaves of *V. surinamensis* collected at Aurá Forest Reserve, Belém, Pará State, Brazil, contain virolin and surinamensin which showed activity against penetration of cercaria of *Schistosoma mansoni* [8]. More recently, 11 lignans, three propiophenone derivatives and two γ-lactones were isolated from leaves and seeds of *V. surinamensis* collected at Combu Island, Pará State, Brazil [9].

The chemical variability observed in specimens of *V. surinamensis* from different localities stimulated the analysis of fruits collected at Xingu river-bank (Altamira-PA) and Tocantins river-bank (Marabá-PA). These fruits contain two dibenzylbutanediol lignans, two furofuran lignans, three dibenzylbutyrolactol lignans, one dibenzylbutyrolactone lignan, one aryltetralin neolignan, two tetrahydrofuran neolignans, one flavone, one isoflavone and two polyketides. The nomenclature and the numbering of lignans and neolignans follow the rules outlined in a review [10].

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RESULTS AND DISCUSSION

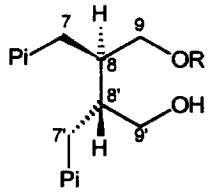
Hexane extracts of teguments and kernels from fruits of *V. surinamensis* collected near Altamira, Pará State, Brazil, were submitted to chromatographic fractionation affording dihydrocubebin (**1a**) [11], dihydrocubebin monolaurate (**1b**), sesamin (**2a**) [12, 13], asarinin (**2b**) [14], β and α-cubebin (**3a** and **3b**) [15, 16], hinokinin (**3e**) [17], galbulin (**4**) [18, 19], **8b** and **8c**. The chloroform extract gave β-*O*-methylcubebin (**3c**) [20] and α-*O*-methylcubebin (**3d**) [20], besides **1a** and **3e**.

Chromatographic fractionation of the chloroform extract of kernels from fruits of *V. surinamensis* collected near Marabá, Pará State, Brazil, afforded galgravin (**5a**) [21, 22], **5c** and tithonine (**6**) [23], besides **2a** and **3b**. The chloroform extract from pericarps yielded irisolidone (**7**) [24].

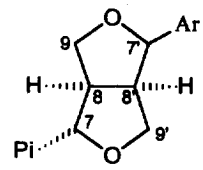
The lignans **3c**, **3d** and isoflavone **7** in *Virola* and polyketides in *V. surinamensis* were isolated for the first time. Compounds **3c** and **3d** can be artifacts [20]. The lignan **1b**, neolignan **5c** and polyketides **8b** and **8c** are unknown compounds.

The compounds **1a**, **2a**–**5a**, **6** and **7**, previously isolated, were identified by comparison with reported spectroscopic data.

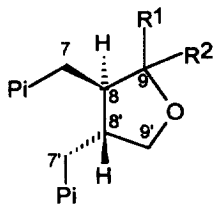
Compound **1b** showed many spectral features in common with dihydrocubebin (**1a**) [11]. The IR spectrum showed hydroxyl and carbonyl absorptions at 3498 and 1733 cm^{-1}. The mass spectrum did not exhi-



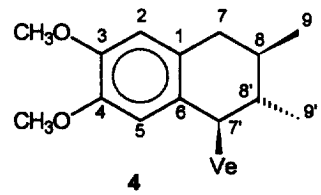
1a - R=H
1b - R=CO(CH$_2$)$_{10}$CH$_3$



2a - Ar=α-Pi
2b - Ar=β-Pi



3a - R^1 = β-OH ; R^2=H
3b - R^1 = α-OH; R^2=H
3c - R^1 = β-OCH$_3$; R^2=H
3d - R^1 = α-OCH$_3$; R^2=H
3e - R^1=R^2=O



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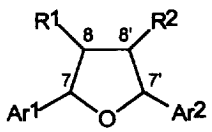
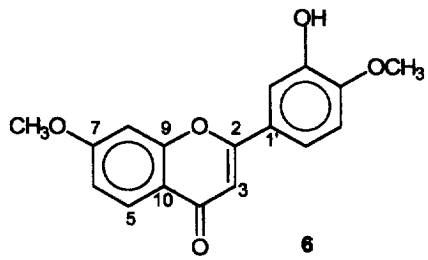


5a - R^1=R^2=β-CH$_3$; Ar1=Ar2=α-Ve
5b - R^1=β-CH$_3$; R^2=α-CH$_3$; Ar1=α-Ve; Ar2=β-Ve
5c - R^1=β-CH$_3$; R^2=α-CH$_3$; Ar1=α-Pi; Ar2=β-Gu



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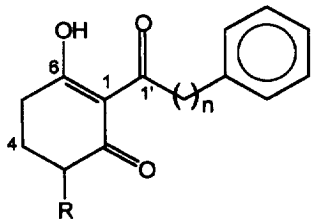
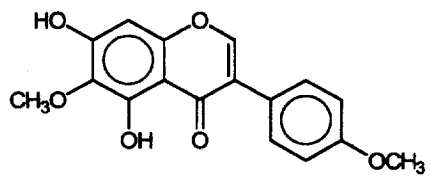


8a - R=OH; n=10
8b - R=OH; n=14
8c - R=H; n=4



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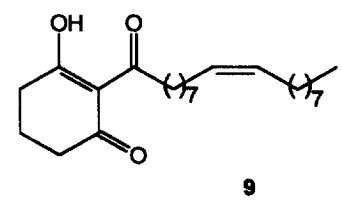
Pi = 3,4-methylenedioxyphenyl
Ve =3,4-dimethoxyphenyl
Gu =4-hydroxy-3-methoxyphenyl



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bit a $[M]^+$ at *m/z* 540. Elemental analysis, carbon counts of the ^{13}C NMR spectrum and proton integration of the ^1H NMR spectrum confirmed the linear chain with 12 carbons. The mass spectrum showed fragmentation at *m/z* 340 corresponding with $[M-CH_3(CH_2)_{10}COOH]^+$.

The ^{1}H NMR spectrum of **5c** showed an all *trans*-configuration of the tetrahydrofuran ring as in galbelgin (**5b**) [25]. These compounds differ only in the pattern of the aromatic rings: the veratryl groups of **5b** were replaced by piperonyl and guaiacyl groups in **5c**. Compounds **5b** and **5c** showed the same $[\alpha]_D$ value and the structure (7*S*, 8*S*, 7′*S*, 8′*S*)-4′-hydroxy-3′-methoxy-3,4-methylenedioxy-8.8′,7.*O*.7′-neolignan-Δ:1,3,5,1′,3′,5′ can be depicted for compound **5c**.

The IR absorptions and ^{1}H NMR spectra of compounds **8a** [26] and **8b** are closely comparable. The mass spectrum of **8b** exhibited a $[M]^+$ at *m/z* 428 supporting the presence of four additional methylene groups in the aliphatic chain. The structure of **8c** was established on the basis of ^{1}H and ^{13}C NMR of the cyclohexyl moiety of **9** [27] and the *w*-phenylacyl moiety of **8a**. The methylenic chain length was established from the $[M]^+$ at *m/z* 272.

The lignan cubebin was isolated as a mixture of β-(**3a**) and α-(**3b**) anomers. We are including ^{13}C NMR data for β-cubebin whose ^{1}H NMR data were previously described [15].

EXPERIMENTAL

General. Prep. TLC, flash CC and CC were carried out on silica gel PF-254, 60H and 60 (Merck), respectively. Mps are uncorr. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ with TMS as int. standard. EIMS were obtained at 70 eV.

Plant material. Ripening fruits were collected near Altamira and near Marabá, Pará State, Brazil, by Dr Hipolito F. Paulino Filho (Universidade Estadual Paulista, Araraquara, São Paulo State, Brazil). The specimens were identified by Dr William A. Rodrigues (Instituto Nacional de Pesquisas da Amazonia, Manaus, Amazonas State, Brazil).

Isolation of constituents. Seeds from both fruits were removed and air-dried. Teguments and kernels (200 g) from seeds collected near Altamira were milled and extracted in a Soxhlet apparatus successively with hexane and $CHCl_3$. The hexane extract (11.3 g) was suspended in hot MeOH and kept overnight at 0°. The insoluble portion (0.9 g) was sepd by filtration, submitted to silica gel CC and elution with hexane–EtOAc mixts of increasing polarities; recrystallization from Me_2CO–hexane afforded polyketide **8b** (0.4 g). The mother liquor was concd under vacuum and the residue (8.5 g) partitioned between hexane and MeOH (1:9). The MeOH layer (2.5 g) was submitted to flash CC (silica gel, hexane–EtOAc, 4:1) providing frs A (173 mg), B (1.2 g) and C (466 mg). Fr. A was submitted to CC (silica gel, benzene), followed by prep. TLC (silica gel, hexane–EtOAc) and finally recrystallization from Me_2CO–hexane giving sesamin (**2a**, 12 mg) asarinin (**2b**, 24 mg) and **8c** (19 mg). Fr. B was submitted to CC (silica gel, hexane–$CHCl_3$, 1:1), followed by prep. TLC (silica gel, benzene–MeOH, hexane–EtOAc, $CHCl_3$) yielding dihydrocubebin monolaurate (**1b**, 6 mg), hinokinin (**3e**, 815 mg) and galbulin (**4**, 6 mg). Fr. C was submitted to flash CC (silica gel, hexane–EtOAc, 7:3), followed by prep. TLC (silica gel, hexane–EtOAc, $CHCl_3$–EtOAc) and recrystallization from Me_2CO–hexane giving dihydrocubebin (**1a**, 11 mg) and cubebin (**3a** and **3b**, 123 mg).

The $CHCl_3$ extract (7.4 g) was submitted to CC (silica gel, hexane–EtOAc, 9:1, EtOAc) furnishing initially frs D (223 mg) and E (4.4 g). Fr. D was submitted to prep. TLC (silica gel, hexane–EtOAc), followed by recrystallization from MeOH, yielding dihydrocubebin (**1a**, 60 mg), β-*O*-methylcubebin (**3c**, 23 mg) and α-*O*-methylcubebin (**3d**, 25 mg). Fr. E consisted essentially of a mixt. of **1a**, **3c**, **3d** and **3e**; it was not fractionated.

From seeds of fruits collected near Marabá, kernels (300 g) and pericarps (200 g) were sepd, milled and extracted with $CHCl_3$ at room temp. The $CHCl_3$ extract (18 g) of kernels was crystallized from EtOH. Fatty material was filtered off and the mother liquor concd under vacuum to yield 6 g. This residue was submitted to silica gel CC eluting with hexane and hexane–EtOAc mixts of increasing polarity providing frs F (2.2 g), G (1.8 g) and H (1.1 g). Part of fr. F (220 mg) was submitted to prep. TLC (silica gel, benzene–EtOAc) and recrystallization from hexane, affording galgravin (**5a**, 25 mg), cubebin (**3b**, 45 mg) and **5c** (15 mg). Part of fr. G (200 mg) was submitted to prep. TLC (silica gel, benzene–EtOAc) affording **5c** (13 mg), tithonine (**6**, 12 mg) and cubebin (**3b**, 65 mg). Fr. H was recrystallized from MeOH yielding sesamin (**2a**, 350 mg).

The $CHCl_3$ extract (3.8 g) of pericarps was submitted to recrystallization from EtOH and filtration of fatty material. The concd mother liquor (2.4 g) was submitted to prep. TLC (silica gel, benzene–EtOAc), followed by recrystallization from Me_2CO, affording irisolidone (**7**, 14 mg).

(8*R*,8′*R*)-9-*Dodecanoyl*-9′-*hydroxy*-3,4,3′,4′-*dimethylenedioxy*-8.8′-*lignan*-Δ: 1,3,5,1′,3′,5′ (**1b**). Oil. $[\alpha]_D$ −13.3° ($CHCl_3$; *c* 0.075). IR ν_{max}^{KBr} cm^{-1}: 3498, 2926, 2855, 2776, 1733, 1609, 1490, 1443, 1362, 1247, 1189, 1041, 930. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (*t*, *J* = 6.3 Hz, 3H-12″), 1.23 (*br s*, 2H-3″ to 2H-11″), 1.88–1.97 (*m*, H-8, H-8′), 2.28 (*t*, *J* = 7.5 Hz; 2H-2″), 2.53 (*dd*, *J* = 7.8, 13.8 Hz; 2H-7, 2H-7′), 2.70 (*dd*, *J* = 6.8, 13.8 Hz; 2H-7, 2H-7′), 3.59 (*d*, *J* = 5.4 Hz; 2H-9′), 4.01 (*dd*, *J* = 5.4, 11.3 Hz; 2H-9), 4.12 (*dd*, *J* = 6.0, 11.3 Hz; 2H-9), 5.90 (*s*, 2 OCH_2O), 6.50–6.71 (*m*, 6ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7 (C-12″), 22.3 (C-11″), 24.6 (C-3″), 28.9–29.3 (C-4″ to C-9″), 31.6 (C-10″), 34.1 (C-2″), 35.1 (C-7), 35.3 (C-7′), 40.4 (C-8), 43.6 (C-8′), 62.6 (C-9′), 64.6 (C-9), 101.1 (OCH_2O), 108.4 (C-2, C-2′), 109.5 (C-5, C-5′), 122.1 (C-6, C-6′), 145.8 (C-4, C-4′), 147.6 (C-3, C-3′), 173.7 (C-1″). MS *m/z* (rel. int.): 340 (9), 135 (100). (Found: C, 71.54; H, 8.33. $C_{32}H_{44}O_7$ requires: C, 71.11; H, 8.15%).

(8*R*,8′*R*,9*S*)-9-*Hydroxy*-3,4,3′,4′-*dimethylenedioxy*-8.8′,9.*O*.9′-lignan-Δ: 1,3,5,1′,3′,5′ (**3a**). ^{13}C NMR (50

MHz, $CDCl_3$): δ 33.5 (C-7), 38.8 (C-7′), 42.8 (C-8′), 51.9 (C-8), 72.4 (C-9′), 98.7 (C-9), 100.8 (OCH_2O), 108.1 (C-2, C-2′), 109.1 (C-5, C-5′), 121.4 (C-6′), 121.7 (C-6), 133.8 (C-1′), 134.5 (C-1), 145.7 (C-4, C-4′), 147.6 (C-3, C-3′).

(8*R*,8′*R*,9*S*)-9β-*Methoxy*-3,4,3′,4′-*dimethylenedioxy*-8.8′.9.*O*.9′-lignan-Δ: 1,3,5,1′,3′,5′ (**3c**). Amorphous solid. $[\alpha]_D$ −2.2° ($CHCl_3$, *c* 0.2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.6 (C-7), 39.3 (C-7′), 43.2 (C-8′), 52.1 (C-8), 54.5 (OCH_3), 72.2 (C-9′), 100.8 (OCH_2O), 105.4 (C-9), 108.1 (C-2, C-2′), 108.9 (C-5′), 109.2 (C-5), 121.4 (C-6′), 121.6 (C-6), 134.0 (C-1′), 134.8 (C-1), 145.6 (C-4′), 145.9 (C-4), 147.5 (C-3′), 147.7 (C-3).

(8*R*,8′*R*,9*R*)-9α-*Methoxy*-3,4,3′,4′-*dimethylenedioxy*-8.8′,9.*O*.9′-lignan-Δ: 1,3,5,1′,3′,5′ (**3d**). Oil. $[\alpha]_D$ −17.9° ($CHCl_3$; *c* 0.2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.7 (C-7′), 39.2 (C-7), 45.8 (C-8′), 52.4 (C-8), 54.7 (OCH_3), 72.0 (C-9′), 100.8 (OCH_2O), 108.0 (C-2, C-2′), 108.9 (C-5′), 109.1 (C-5), 109.9 (C-9), 121.4 (C-6′), 121.7 (C-6), 133.4 (C-1′), 134.2 (C-1), 145.7 (C-4′), 145.8 (C-4), 147.5 (C-3′), 147.6 (C-3).

(7*S*,8*S*,7′*S*,8′*S*)-4′-*Hydroxy*-3′-*methoxy*-3,4-*methylenedioxy*-8.8′,7.*O*.7′-neolignan-Δ: 1,3,5,1′,3′,5′ (**5c**). Oil. $[\alpha]_D$ −17.9° ($CHCl_3$; *c* 0.125) ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (*d*, *J* = 5.8 Hz; 3H-9, 3H-9′), 1.02 (*d*, *J* = 5.7 Hz; 3H-9, 3H-9′), 1.66–1.79 (*m*, H-8, H-8′), 3.89 (*s*, OCH_3), 4.59 (*d*, *J* = 9.2 Hz; H-7, H-7′), 5.56 (*s*, OH), 5.92 (*s*, OCH_2O), 6.73–7.01 (*m*, 6ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8 (C-9, C-9′), 50.8 (C-8′), 51.1 (C-8), 55.9 (OCH_3), 88.2 (C-7), 88.4 (C-7′), 100.9 (OCH_2O), 106.6 (C-2), 107.9 (C-5), 108.6 (C-2′), 114.0 (C-5′), 119.4 (C-6′), 119.7 (C-6), 134.1 (C-1′), 136.6 (C-1), 145.1 (C-4′), 146.6 (C-3′), 146.9 (C-4), 147.8 (C-3). MS *m*/*z* (rel. int.): 342 $[M]^+$ (43), 192 (66), 190 (100), 180 (13), 178 (25), 177 (26), 175 (55), 164 (20), 162 (27), 152 (17), 151 (91), 150 (18), 149 (49).

3-*Hydroxy*-1-(15-*phenylpentadecanoyl*)-2,6-*cyclohexanedione* (**8b**). Colorless crystals. Mp 69–70° (Me_2CO–hexane). $[\alpha]_D$ −5.0° ($CHCl_3$; *c* 0.2). IR ν_{max}^{KBr} cm^{-1}: 3424, 2919, 2848, 1666, 1544, 1495, 1467, 1405, 1114, 755, 704. ^1H NMR (200 MHz, $CDCl_3$): δ 1.19 (*br s*, $9CH_2$), 1.54 (*m*, $3CH_2$), 1.62–1.85 (*m*, $H\text{-}4_{ax}$), 2.24–2.37 (*m*, $H\text{-}4_{eq}$), 2.53 (*t*, *J* = 7.7 Hz; 2H-15′), 2.68–2.76 (*m*, 2H-5), 2.80–3.08 (*m*, 2H-2′), 3.88 (*s*, OH), 4.03 (*dd*, *J* = 4.4, 13.2 Hz; H-3), 7.04–7.24 (*m*, 5ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.5 (C-3′), 27.1 (C-5), 29.3–29.6 (C-4′ to C-13′), 31.3 (C-4), 31.5 (C-14′), 36.0 (C-15′), 40.2 (C-2′), 71.6 (C-3), 110.3 (C-1), 125.5 (C-19′), 128.2 (C-17′, C-21′), 128.4 (C-18′, C-20′), 142.9 (C-16′), 195.6 (C-6), 197.9 (C-2), 206.1 (C-1′). MS *m*/*z* (rel. int.): 428 $[M]^+$ (100), 183 (19), 155 (3), 91 (33).

1-(5-*Phenylpentanoyl*)-2,6-*cyclohexanedione* (**8c**). Oil. IR ν_{max}^{KBr} cm^{-1}: 3026, 2941, 2860, 1667, 1557, 1497, 1454, 1421, 1190, 751, 701. ^1H NMR (200 MHz, $CDCl_3$): δ 1.66–1.70 (*m*, 2H-3′, 2H-4′), 1.90–1.99 (*m*, 2H-4), 2.48 (*t*, *J* = 6.5 Hz; 2H-3, 2H-5′), 2.65 (*t*, *J* = 6.2 Hz; 2H-5), 3.05 (*t*, *J* = 6.7 Hz; 2H-2′), 7.13–7.31 (*m*, 5ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0 (C-4), 24.2 (C-3′), 31.1 (C-4′), 33.2 (C-5), 35.7 (C-5′), 38.8 (C-3), 40.4 (C-2′), 113.0 (C-1), 125.7 (C-9′), 128.3 (C-7′, C-11′), 128.4 (C-8′, C-10′), 142.3 (C-6′), 195.3 (C-6), 198.6 (C-2), 206.1 (C-1′). MS *m*/*z* (rel. int.): 272 $[M]^+$ (1), 167 (63), 139 (100), 91 (48).

Acknowledgements—We are grateful to CNPq, CAPES, PADCT, FAPESP and FEDIB for financial aid.

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