Available online at www.sciencedirect.com
SCIENCE DIRECT®
Phytochemistry 65 (2004) 377–380
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

Quivisianthone, an evodulone limonoid from the Madagascan Meliaceae *Quivisia papinae*

Philip H. Coombes[a,*], Dulcie A. Mulholland[a], Milijaona Randrianarivelojosia[a,b]

[a] *Natural Products Research Group, School of Pure and Applied Chemistry, University of Natal, Durban 4041, South Africa*
[b] *Malaria Research Group, BP 1274, Antananarivo (101), Institut Pasteur de Madagascar, Madagascar*

Received in revised form 1 September 2003; accepted 12 September 2003

Abstract

An investigation of the seeds of the Madagascan Meliaceae *Quivisia papinae* has yielded quivisianthone, a novel evodulone group limonoid, together with the known azadiradione and two novel derivatives: 6α-hydroxyazadiradione and 7-deacetyl-7-angeloyl-6α-hydroxyazadiradione. Quivisianthone is the first reported evodulone group limonoid possessing both a ring A lactone and an azadiradione-type ring D.

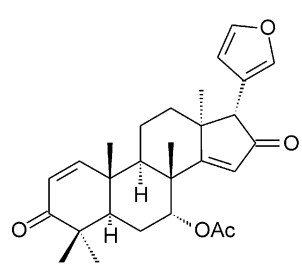
Keywords: *Quivisia papinae*; Meliaceae; Madagascar; Seeds; Isolation; Limonoids; Azadiradone; 6α-Hydroxyazadiradione; 7-Deacetyl-7-angeloyl-6α-hydroxyazadiradione; Evodulone; Quivisianthone

1. Introduction

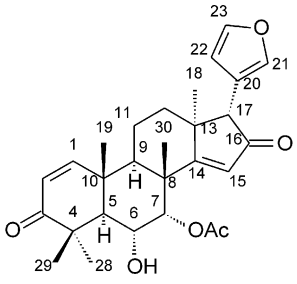
Quivisia papinae Baillon ex Grandidier is an endemic Madagascan species originally placed in the genus *Trichilia,* tribe Trichilieae, subfamily Melioideae by Harms (1940). Pennington and Styles (1975) subsequently considered the fruit and seed sufficiently distinctive to warrant the creation of a new subfamily, the Quivisianthiodeae, in which it is the sole species. It is known locally in Southern Madagascar as "hompy"; no information is available about its medicinal properties.

In the only previous study on the wood and stembark of this species (Mulholland and Taylor, 1988), a limonoid tentatively identified as the 3-keto analogue of *Ekebergia pterophylla* compound 1 (Taylor and Taylor, 1984), was obtained from the bark, and the coumarin 5-methoxy-6,7-methylenedioxycoumarin from the wood.

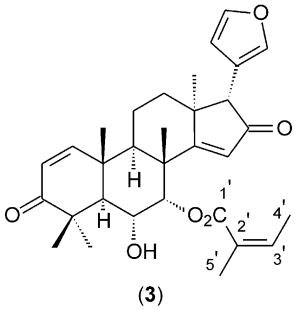
In a continuation of previous studies on the Madagascan Meliaceae, we have isolated from the seed of *Q. papinae* the well known azadiradione, two novel azadiradione analogues and a novel evodulone group limonoid.



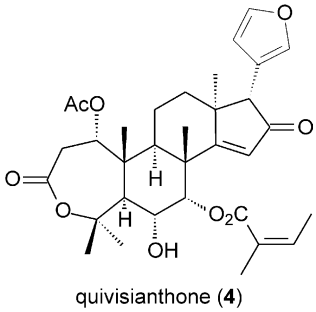
azadiradione (**1**)



6α-hydroxyazadiradione (**2**)



(**3**)



quivisianthone (**4**)

* Corresponding author. Tel.: +27-31-260-1395; fax +27-31-260-3091.
E-mail addresses: coombesp@nu.ac.za (P.H. Coombes), mulholld@nu.ac.za (D.A. Mulholland), milijaon@pasteur.mg (M. Randrianarivelojosia).

0031-9422/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2003.09.012

2. Results and discussion

Compound **1** was identified, by comparison with literature data (Kraus and Cramer, 1978), as the havanensin group limonoid azadiradione (**1**). Azadiradione was first isolated (Lavie et al., 1971) from *Melia azadirachta* L., the closely related species *Azadirachta indica* A.Juss has subsequently afforded both the 7-benzoyl analogue (Kraus et al., 1981) and the parent alcohol nimbocinol (Siddiqui et al., 1986).

Compound **2**, assigned the molecular formula $C_{26}H_{34}O_6$ on the basis of HREIMS data, had a difference, relative to **1**, of a single oxygen atom. Comparison of the ^{1}H and ^{13}C NMR spectra of **2** with those of **1** revealed them to be very similar, with the only difference being the appearance of a double doublet at δ_H 4.41 (J = 11.5, 2.8 Hz) in the ^{1}H NMR spectrum, coupled in the HSQC spectrum to a newly appeared oxymethine resonance at δ_C 68.2, while the C-6 methylene signal at δ_C 23.4 had disappeared. Couplings in the COSY spectrum to a doublet at δ_H 5.45 (J = 2.8 Hz), ascribed to H-7, and to a doublet at δ_H 2.28 (J = 11.5 Hz), ascribed to H-5, established this as H-6. HMBC correlations to C-7 at δ_C 78.0 and C-5 at δ_C 50.1 confirmed this placing, and NOESY correlations to 3H-19 and 3H-30 that H-6 is β. Compound **2** is thus the novel 6α-hydroxyazadiradione and the 6-deacetyl analogue of mahonin recently reported from *Swietenia mahogani* C.DC (Kadota et al., 1990).

The molecular formula of compound **3** was determined by HREIMS to be $C_{31}H_{38}O_6$, with a difference, relative to compound **2**, of C_3H_4. Inspection of the ^{1}H NMR spectrum revealed the characteristic signal at δ_H 6.02 attributable to H-3′ of an angelate ester, which was then assigned by analysis of the COSY, HSQC and HMBC spectra [δ_C 168.4(*s*), C-1′; δ_C 127.3(*s*), C-2′; δ_H 6.02qq J = 6.1, 1.1 Hz, δ_C 139.2(*d*), H-3′; δ_H 1.92m, 16.2(*q*), 3H-4′; δ_H 1.80s, H δ_C *20.8*(*q*), 3H-5′]. Further correlation in the HMBC spectrum between C-1′ and H-7β, and between C-1′ and both 3H-4′ and 3H-5′ confirmed the ester location at H-7α. The remaining ^{1}H and ^{13}C NMR signals were virtually identical to those of **2**. Compound **3** is thus the novel 7-deacetyl-7-angeloyl analogue of **2**.

The molecular formula of compound **4** was assigned by HRFABMS as $C_{33}H_{42}O_9$. Inspection of the ^{1}H and ^{13}C NMR spectra revealed the presence, in addition to a furan ring and an angelate ester, of an acetate ester [δ_H 2.00s, δ_C 21.4(*q*) and 169.2(*s*)], an additional ester carbonyl signal at δ_C 169.6, and a fully substituted C–O resonance at δ_C 86.7. That **4** has the same D ring as that present in **1–3** was inferred by comparison of the relevant signals, as was that of the B ring 6α-hydroxy,7α-angeloyloxy substitution pattern; HMBC correlations between C-1′ and H-7β, and between C-1′ and both 3H-4′ and 3H-5′ placed the angeloyl ester, as before, at C-7. HMBC correlations between C-17 and a quaternary methyl proton singlet signal at δ_H 0.93, and between C-14 and another at δ_H 1.38, established these as 3H-18 and 3H-30, respectively. Further correlation from 3H-30 to a methine resonance at δ_C 32.8 designated this as C-9, which, in turn, is correlated to a third quaternary methyl singlet signal at δ_H 1.25, ascribed to 3H-19. The 3H-19 resonance correlates to a methine signal at δ_C 48.6, assigned to C-5, and to an oxymethine resonance at δ_C 74.3, ascribed to C-1.

A doublet of doublets (J = 9.3, 6.4 Hz) at δ_H 4.84, attributed to H-1, were seen to be coupled in the COSY spectrum to two pairs of double doublets at δ_H 2.62 (J = 12.8, 9.3 Hz; H-2α, by NOESY coupling to H-5) and δ_H 3.00 (J = 12.8, 6.4 Hz; H-2β). The H-2α and H-2β resonances both displayed correlations in the HMBC spectrum to the remaining carbonyl signal at δ_C 169.6, ascribed to C-3 in a seven-membered lactone ring. The fully substituted C–O resonance at δ_C 86.7, correlating to both H-5 and two superimposed quaternary methyl singlet signals at δ_H 1.70 in the HMBC spectrum, which must be 3H-28 and 3H-29, were then assigned to C-4. Final confirmation is provided by an HMBC correlation between the 3H-28/29 resonances and that of C-3. The acetate ester is placed at C-1 by HMBC correlation between C-1″ and H-1. NOESY correlations to both 3H-19 and 3H-30 establish H-1 as β and hence the acetate as α.

Quivisianthone **4** is a novel evodulone-class limonoid, and the first to be found with both a ring A lactone and the azadiradione (Δ^{14}, 16-keto)-type ring D. Evodulone itself, from *Carapa procera* DC. (Sondengam et al., 1979), possesses a Δ^1 double bond and a 14β, 15β-epoxide ring, and lacks the 1α-acetoxy group, while proceranone, from the same source (Sondengam et al., 1981), has the same A ring, and a Δ^{14} double bond, yet lacks the keto group at C-16. Carapolides H and I, from the related species *Carapa grandiflora* Sprague (Ayafor et al., 1994), are their 1α-acetoxy A ring analogues, while rubralin C, from *Trichilia rubra* C.DC. (Musza et al., 1995) is the 12α-acetoxy-7-tigloyl derivative of carapolide 1/kihadalactone A (Kishi et al., 1992).

3. Experimental

3.1. General

NMR spectra were recorded at room temperature on a 400 MHz Varian UNITY-INOVA spectrophotometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as internal standard and coupling constants are given in Hz. ^{1}H NMR spectra were referenced against the C<u>H</u>Cl$_3$ signal at δ_H 7.27, and ^{13}C NMR spectra to the corresponding signal at δ_C 77.0. IR spectra were recorded on a Nicolet Impact 400D Fourier-Transform Infrared (FT–IR) spectro-

meter, using NaCl windows with $CHCl_3$ as solvent against an air background. Melting points were determined on a Kofler micro-hot stage melting point apparatus and are uncorrected. HREIMS and HRFABMS were acquired on a Kratos 9/50 HRMS instrument. Optical rotations were measured at room temperature in $CHCl_3$ on an Optical Activity AA-5 Polarimeter, using a series A2 (4×200 mm) stainless steel unjacketed flow tube.

3.2. Plant material

Q. papinae was collected in April 1999 in the Bezaha Mahafaly area in southern Madagascar. A voucher specimen (02/99-Mj/Mdul, TAN) is deposited at the Department of Botany of the University of Antananarivo. Plant identification was confirmed by Dr. Hanson Rabarison of the Department of Botany at the Parc Zoologique et Botanique de Tsimbazaza.

3.3. Extraction and isolation of compounds

The air-dried, milled seed (701 g) was extracted successively for 24 h in a Soxhlet apparatus with hexane, CH_2Cl_2, EtOAc and MeOH, yielding extracts of masses 19.47, 27.99, 20.28 and 189.15 g, respectively. Only the hexane and CH_2Cl_2 extracts were examined during the course of this investigation, while the EtOAc and MeOH extracts have been stored for future study. Azadiradione **1** (7.1 mg) and quivisianthone **4** (14.5 mg) were isolated from the CH_2Cl_2 extract, and 6α-hydroxyazadiradione **2** (18.1 mg) and 7-deacetyl-7-angeloyl-6a-hydroxyazadiradione **3** (35.0 mg) from both extracts.

3.3.1. 6α-Hydroxyazadiradione (*2*)

Pale yellow gum. $[\alpha]_D = +23^\circ$ (*c*, 0.312 in $CHCl_3$); ν_{max} (NaCl) cm^{-1} 3462, 2924, 1730, 1700, 1666, 1602, 1379, 1233, 1151; HREIMS (70 eV) *m/z* (rel. int.) 466.2355 (100) (calc. for $C_{28}H_{34}O_6$ 466.2355), 451.2110 (29) $[M-CH_3]+$, 406.2116 (15) $[M-HOAc]+$, 381.1690 (18) $[M-HOAc-CH_3]+$, 299.1273 (8), 227.1079 (7), 174.0685 (17), 121.0652 (28), 83.0493 (30); ^1H NMR spectral data (400 MHz, $CDCl_3$) δ_H 7.46 (1H, *br s,* H-21), 7.41 (1H, *br s*, H-23), 7.07 (1H, *d, J* = 10.1 Hz, H-1), 6.25 (1H, *br s*, H-22), 5.91 (1H, *d, J* = 10.1 Hz, H-2), 5.86 (1H, *s*, H-15), 5.45 (1H, *d, J* = 2.8 Hz, H-7), 4.41 (1H, *dd, J* = 11.5, 2.8 Hz, H-6), 3.41 (1H, *s*, H-17), 2.44 (1H, *br m,* H-9), 2.28 (1H, *d, J* = 11.5 Hz, H-5), 2.10 (2H, *m*, H-11α, H-12α), 2.01 (3H, *s*, 3H-2′), 1.87 (1H, *m*, H-12β), 1.82 (1H, *m*, H-11β), 1.40 (3H, *s*, 3H-29), 1.36 (3H, *s*, 3H-30), 1.30 (3H, *s*, 3H-28), 1.17 (3H, *s*, 3H-19), 1.02 (3H, *s*, 3H-18); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

3.3.2. 7-Deacetyl-7-angeloyl-6α-hydroxyazadiradione (*3*)

Pale yellow solid. Mp 91–94 °C; $[\alpha]_D = +69^\circ$ (*c*, 0.658 in $CHCl_3$); ν_{max} (NaCl) cm^{-1} 3485, 2959, 1707, 1678, 1602, 1461, 1391, 1233, 1151; HREIMS (70 eV) *m/z* (rel. int.) 506.2672 (30) (calc. for $C_{31}H_{38}O_6$ 506.2668), 423.2176 (2), 407.2232 (4) $[M-HOAng\}+$, 174.0672 (4), 121.0653 (6), 83.0484 (100); ^1H NMR spectral data (400 MHz, $CDCl_3$) δ_H 7.43 (1H, *br s*, H-21), 7.39 (1H, *br s*, H-23), 7.06 (1H, *d, J* = 10.1 Hz, H-2), 6.22 (1H, *br s*, H-22), 6.02 (1H, *qq*, *J* = 6.1, 1.1 Hz, H-3′), 5.90 (1H, *d, J* = 10.1 Hz, H-2), 5.93 (1H, *s*, H-15), 5.61 (1H, *d, J* = 2.2 Hz, H-7), 4.46 (1H, *dd, J* = 11.5, 2.2 Hz, H-6), 3.39 (1H, *s*, H-17), 2.46 (1H, *br m*, H-9), 2.26 (1H, *d, J* = 11.5 Hz, H-5), 2.10 (2H, *m*, H-11α, H-12α), 1.92 (3H, *m*, 3H-4′), 1.88 (1H, *m*, H-11β), 1.87 (1H, *m*, H-12β), 1.80 (3H, *s*, 3H-5′), 1.40 (3H, *s*, 3H-29), 1.38 (3H, *s*, 3H-30), 1.28 (3H, *s*, 3H-28), 1.18 (3H, *s*, 3H-19), 1.02 (3H, *s*, 3H-18); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

3.3.3. 7-Deacetyl-7-angeloyl-16-ketokihadalactone A, quivisianthone (*4*)

Pale yellow gum. $[\alpha]_D = +0.0$ (too small to be measured); ν_{max} (NaCl) cm^{-1} 3468, 2947, 1730, 1707, 1607,

Table 1
^{13}C NMR spectral data for compounds **2**–**4** ($CDCl_3$, 100 MHz)

	2	**3**	**4**
C-1	156.1 (CH)	156.2 (CH)	74.3 (CH)
C-2	126.9 (CH)	126.8 (CH)	37.8 (CH_2)
C-3	205.5 (C)	205.5 (C)	169.6 (C)
C-4	45.7 (C)	45.7 (C)	86.7 (C)
C-5	50.1 (CH)	50.4 (CH)	48.6 (CH)
C-6	68.2 (CH)	68.2 (CH)	67.9 (CH)
C-7	78.0 (CH)	77.1 (CH)	76.6 (CH)
C-8	45.1 (C)	45.2 (C)	43.7 (C)[a]
C-9	37.0 (CH)	37.4 (CH)	32.8 (CH)
C-10	40.8 (C)	40.9 (C)	44.0 (C)[a]
C-11	16.1 (CH_2)	16.2 (CH_2)	16.7 (CH_2)
C-12	30.5 (CH_2)	30.4 (CH_2)	30.8 (CH_2)
C-13	48.2 (C)	48.3 (C)	47.8 (C)
C-14	191.6(C)	191.3(C)	190.5(C)
C-15	123.6 (CH)	123.8 (CH)	124.7 (CH)
C-16	205.0 (C)	204.9 (C)	205.0 (C)
C-17	61.1 (CH)	61.1 (CH)	60.8 (CH)
C-18	27.1 (CH_3)	26.9 (CH_3)	26.9 (CH_3)
C-19	21.3 (CH_3)*	21.1 (CH_3)	17.4 (CH_3)
C-20	118.5(C)	118.5(C)	118.4(C)
C-21	141.8 (CH)	141.8 (CH)	141.8 (CH)
C-22	111.3(CH)	11h.3(CH)	111.2(CH)
C-23	143.0 (CH)	142.9 (CH)	143.1 (CH)
C-28	32.2 (CH_3)	32.3 (CH_3)	28.1 (CH_3)[b]
C-29	21.2 (CH_3)*	20.5 (CH_3)	32.7 (CH_3)[b]
C-30	26.4 (CH_3)	26.6 (CH_3)	25.48 (CH_3)
C-1′	171.7 (C)	168.4 (C)	168.2 (C)
C-2′	20.6 (CH_3)	127.3 (C)	127.0 (C)
C-3′		139.2 (CH)	140.2 (CH)
C-4′		16.2 (CH_3)	16.2 (CH_3)
C-5′		20.8 (CH_3)	20.6 (CH_3)
C-1″			169.2 (C)
C-2″			21.4 (CH_3)

[a,b] Values interchangeable within column.

1461, 1391, 1321, 1233, 1157; HRFABMS *m/z* 582.2816 (calc. for $C_{33}H_{42}O_9$ 582.2829); HREIMS (70 eV) *m/z* (rel. int.) 567.2549 (4), 524.2430 (8), 509.2169 (5), 466.2362 (23), 451.2123 (10), 441.1910 (4), 381.1711 (5), 339.1612 (5), 229.1217 (7), 174.0685 (10), 121 .0655 (9), 83.0498 (100); ^{1}H NMR spectral data (400MHz, $CDCl_3$) δ_H 7.42 (1H, *br s*, H-21), 7.39 (1H, *br s*, H-23), 6.19 (1H, *br s*, H-22), 6.07 (1H, *qq*, $J=7.3$, 1.5 Hz, H-3′), 5.99 (1H, *s*, H-15), 5.55 (1H, *d*, $J=2.9$ Hz, H-7), 4.84 (1H, *dd*, $J=9.3$, 6.4 Hz, H-1), 4.42 (1H, *dd*, $J=10.8$, 2.9 Hz, H-6), 3.38 (1H, *s*, H-17), 3.11 (1H, *m*, H-9), 3.00 (1H, *dd*, $J=12.8$, 6.4 Hz, H-2β), 2.62 (1H, *dd*, $J=12.8$, 9.3 Hz, H-2α), 2.41 (1H, *d*, $J=10.8$ Hz, H-5), 2.00 (3H, s, 3H-2″), 1.97 (4H, *m*, H-12β, 3-H-4′), 1.88 (3H, *s*, 3H-5′), 1.80 (2H, *m*, H-11β, H-12α), 1.70 (6H, *s*, 3H-28, 3H-29), 1.39 (1H, *m*, H-11α), 1.38 (3H, *s*, 3H-30), 1.25 (3H, *s*, 3H-19), 0.93 (3H, *s*, 3H-18); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 1.

Acknowledgements

We thank Mr. Dilip Jagjivan and Dr. Philip Boshoff for the running of NMR and mass spectra, respectively, Mr. Bret Parel for his technical assistance, and the University of Natal, the Foundation for Research Development and the Wellcome Trust, under Grant No. 05 2451, for financial support. The general assistance of Mr. Ernest Makhaza is also greatly appreciated.

References

Ayafor, J.F., Kimbu, S.F., Ngadjui, B.T., Akam, T.M., Dongo, E., Sondengam, B.L., Connolly, J.D., Rycroft, D.S., 1994. Limonoids from *Carapa grandiflora* (Meliaceae). Tetrahedron 50, 9343–9354.

Harms, H., 1940. In: Engler, A., Prantl, K. (Eds.), Die NatOrlichen Pflanzenfamilien, second ed. 19bl, pp. 1–172.

Kadota, S., Marpaung, L., Kikuchi, T., Ekimoto, H., 1990. Constituents of the seeds of *Swietenia mahogani* Jacq. III. Chem. Pharm. Bull. 38, 1495–1500.

Kishi, K., Yoshikawa, K., Arihara, S., 1992. Limonoids and protolimonoids from the fruits of *Phellodendron amurense*. Phytochemistry 31, 1335–1338.

Kraus, W., Cramer, R., 1978. 17-Epi-azadiradione and 17β-hydroxyazadiradione, two new constituents from *Azadirachta indica* A. Juss. Tetrahedron Lett. 19, 2395–2398.

Kraus, W., Cramer, R., Sawitzka, G., 1981. Tetranortriterpenoids from the seeds of *Azadirachta indica*. Phytochemistry 20, 117–120.

Lavie, O., Levy, E.C., Jam, M.K., 1971. Limonoids of biogenetic Interest from *Melia azadirachta* L. Tetrahedron 27, 3927–3939.

Mulholland, D.A., Taylor, D.A.H., 1988. Limonoid extractives from the Genera *Capuronianthus*, *Neobeguea* and *Quivisianthe*. Phytochemistry 27, 1741–1743.

Musza, L.L., Killar, L.M., Speight, P., Barrow, C.J., Gillum, A.M., Cooper, R., 1995. Minor Limonoids from Trichiia rubra. Phytochemistry 39, 621–624.

Pennington, T.D., Styles, B.T., 1975. A generic monograph of the Meliaceae. Blumea 22, 419–540.

Siddiqui, S., Faizi, S., Siddiqul, B.S., 1986. Studies on the chemical constituents of *Azadirachta indica* A.Juss. (Meliaceae), Part VII. Z. Naturforsch 41b, 922–924.

Sondengam, B.L., Kamga, C.S., Connolly, J.D., 1979. Evodulone, a new tetranortriterpenoid from *Carapa procera*. Tetrahedron Lett. 20, 1357–1358.

Sondengam, B.L., Kamga, C.S., Kimbu, S.F., Connolly, J.D., 1981. Proceanone, a new tetranortriterpenoid from *Carapa procera*. Phytochemistry 20, 173–174.

Taylor, A.R.H., Taylor, D.A.H., 1984. Limonoids from *Ekebergia pterophylla*. Phytochemistry 23, 2676–2677.