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VEDELIANIN, A HEXAHYDROXANTHENE DERIVATIVE ISOLATED FROM *MACARANGA VEDELIANA**

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Key Word Index—*Macaranga vedeliana*; Euphorbiaceae; leaves; vedelianin; hexahydroxanthene derivative; 2α,3α-dihydroxy-7(6′-isoprenyl-5′,7′-dihydroxystyryl)-1,1-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene, geranylstilbene.

Abstract—A methanolic extract of the leaves of *Macaranga vedeliana* furnished a new hexahydroxanthene derivative, vedelianin, which can be considered as a substituted cyclized geranylstilbene.

INTRODUCTION

As part of an ethnopharmacological study of plants used by Melanesians in New Caledonia [1, 2], we have previously reported the presence in the leaves of *Macaranga vedeliana* Muell.-Arg. of macarangin, a new geranyl substituted flavonol [3]. This plant, called 'apiwa' in Lifou (Loyalty Islands, New Caledonia) is used by natives to relieve pains and to cure tonsillitis and its methanolic extract was shown to have a significant hypotensive activity. We now describe the isolation and the structure elucidation of a new hexahydroxanthene derivative, 2α,3α-dihydroxy-7(6′-isoprenyl-5′,7′-dihydroxystyryl)-1,1-dimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene, named vedelianin (**1**).

RESULTS AND DISCUSSION

Preparative HPLC and silica gel CC of the methanolic extract of the dried leaves afforded vedelianin (**1**), in 1.33% yield.

Vedelianin (**1**) was assigned the molecular formula $C_{29}H_{36}O_6$ (MS, *m/z* 480 $[M]^+$, and ^{13}C NMR). The IR spectrum ($CHCl_3$) indicated the presence of a hydroxyl group (3300 cm^{-1}). The UV spectrum (MeOH) suggested the presence of a highly conjugated system [λ_{max} 225 (ε26 500) and 330 (ε32 000)]. Examination of the ^1H NMR spectrum (CD_3OD or pyridine-d_5), and a 2D COSY experiment indicated the presence of a substituted stilbene group with an AA′ (δ6.5, *s*, 2H) system for one benzene ring and an AB (δ6.78, *d*, $J=2$ Hz, 1H, and δ6.70, *d*, $J=2$ Hz, 1H) system for the other benzene ring. The presence of an isoprenyl group was shown by signals (pyridine-d_5) at δ3.3 (2H, *d*, $J=7$ Hz), 5.14 (1H, *t*, $J=7$ Hz), 1.78 (3H, *s*) and 1.69 (3H, *s*). The remaining part of the molecule (C_{10}) was deduced from the ^1H NMR spectrum, as a cyclized geranyl group, forming a hexahydroxanthene part with one benzene ring of the stilbene. The study of the chemical shifts and correlations in ^1H–^{13}C NMR, and ^1H–^{13}C long range spectra confirmed the structure of vedelianin as **1** (Table 1).

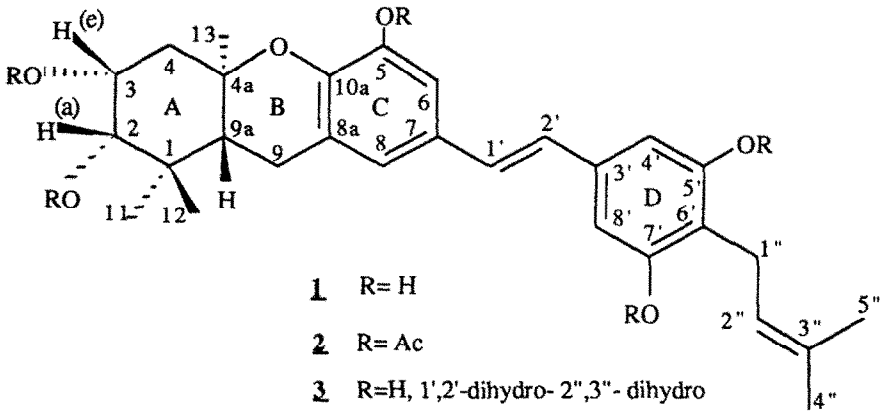
Acetylation of vedelianin gave **2**. The mass spectrum (*m/z* 690 $[M]^+$) showed an increase in M_r of 210, suggesting the presence of five hydroxyl groups in **1**. The ^1H NMR spectrum of **2** showed at δ2.10–2.30 five acetyl groups, two on vicinal aliphatic hydroxyl groups and

*Part 140 in the series 'Plants of New Caledonia'. For Part 139, see Adesanya, S. A., Païs, M., Sévenet, T. and Cosson, J. P. (1991) *J. Nat. Prod.* **54**, 1588.

Table 1. NMR spectral data for compounds **1** and **4**

		1	**4**			**1**	**4**
C	^{13}C (CD_3OD)	^1H (CD_3OD)	^1H (C_5D_5N)	C	^{13}C (CD_3OD)	^1H (CD_3OD)	^1H (C_5D_5N)
1	39.0			1′	128.8	6.76 *d* (16)	7.51 *d* (16)
2	78.7	3.3 *d* (3) (a)	3.5 *br s*	2′	127.3	6.73 *d* (16)	7.45 *d* (16)
3	71.7	4.16 *br d* (3) (e)	4.5 *br s*	3′	141.8		
4	44.5	2.37 *dd* (14, 3) (e)	2.36 *br d* (14) (e)	4′	105.9	6.5 *br s*	7.13 *d* (2)[a]
		2.00 *dd* (14, 2) (a)	2.00 *br d* (14) (a)				
4a	78.0			5′	157.1		
5	146.8			6′	115.9		
6	111.0	6.78 *d* (2)	7.47 *d* (2)	7′	157.1		
7	130.7			8′	105.9	6.5 *br s*	7.03 *d* (2)[a]
8	120.5	6.70 *d* (2)	6.97 *d* (2)	1″	23.3	3.30 2H, *d* (7)	3.00 2H, *br s*
8a	124.1			2″	124.5	5.24 *t* (7)	1.73 2H, *br s*
9	23.8	2.72 2H, *m*	2.73 *br d* (14) (c)	3″	131.3		
			2.83 *dd* (14, 14) (a)				
9a	48.6	1.75 *dd* (12, 5)	2.8 *br d* (14)	4″	25.9	1.69 3H, *s*	1.30 3H, *s*
10a	137.6			5″	17.9	1.78 3H, *s*	1.36 3H, *s*
11	16.2	1.15 3H, *s*	1.25 3H, *s*				
12	29.3	1.15 3H, *s*	1.30 3H, *s*				
13	22.0	1.45 3H, *s*	1.66 3H, *s*				

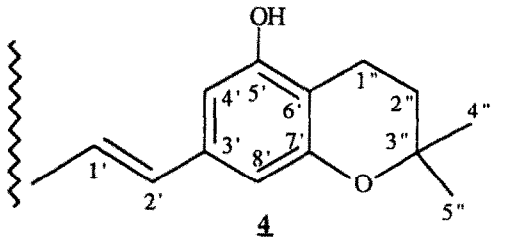
[a]May be interchangeable.



1 R= H

2 R= Ac

3 R=H, 1′,2′-dihydro- 2″,3″- dihydro



4

three on aromatic hydroxyl groups. The chemical shifts of H-2 and H-3 and the small coupling constants observed between H-3 and H-4 ($J = 3$, 2 Hz) led us to attribute an equatorial position for H-3, an axial position for H-2, and consequently *cis* stereochemistry for the vicinal hydroxy groups. These data are in agreement with the values observed for platycogenic acid, a triterpene from *Platycodon grandiflorum*, having the same ring A substitution pattern [4].

Catalytic hydrogenation of vedelianin led to **3**. Its mass spectrum (EI) showed ions at *m/z* 484 $[M]^+$, 328, 291, 273, 271, 255 and 135. The fragmentation pattern was consistent with the two parts of the molecule as shown in the Fig. 1. The ^1H NMR data showed the absence of olefinic protons.

In acidic condition, vedelianin gave compound **4**, of the same M_r as **1**. Its ^1H NMR spectrum showed: the absence of the olefinic proton of the isoprenyl substituent; a new

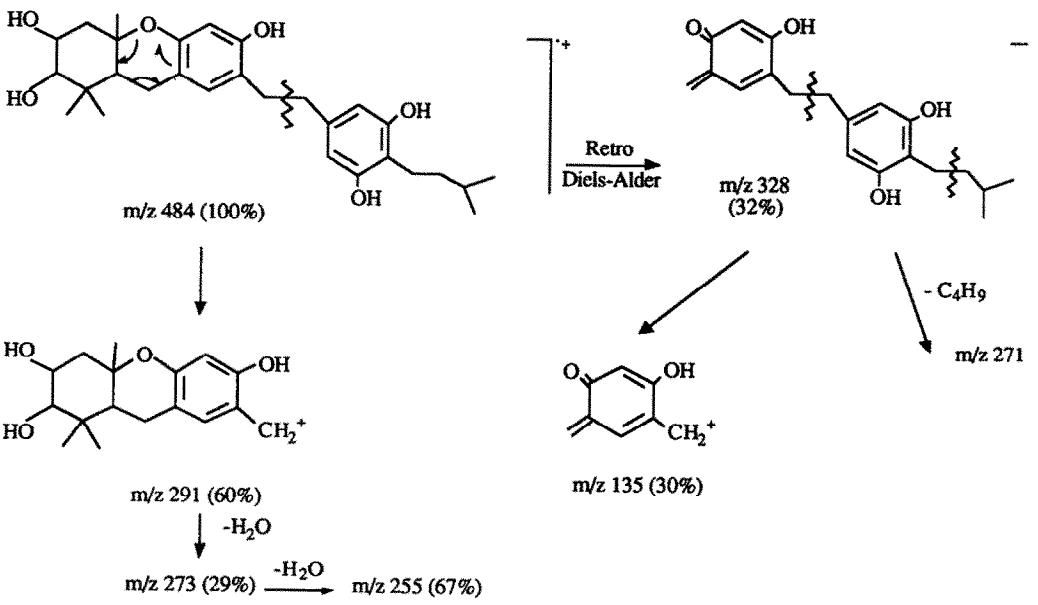


Fig. 1. Mass fragmentation pattern of compound 3.

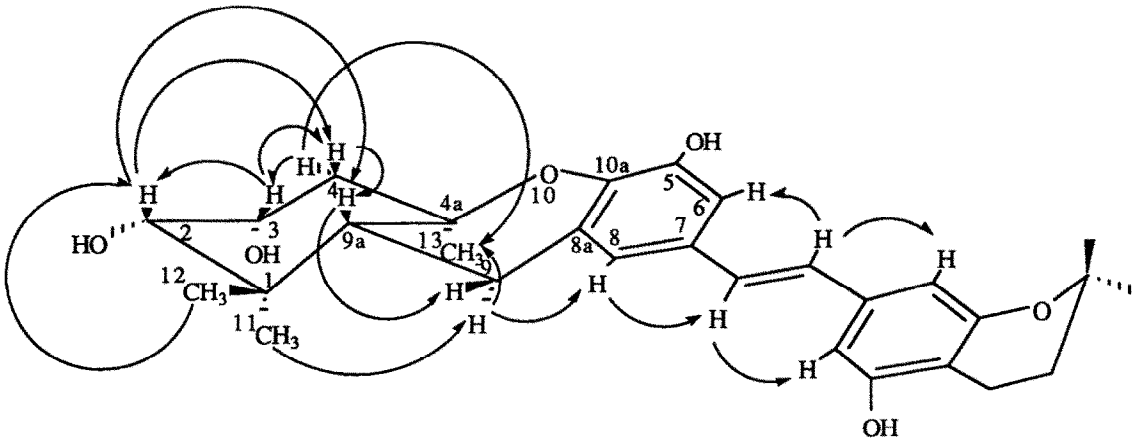


Fig. 2. ROESY interactions for compound 4.

signal (δ3, *m*, 2H) coupling with another multiplet (δ1.73, 2H) and distinct aromatic and olefinic protons.

From the ROESY NMR spectrum, we could deduce (Fig. 2): the α *cis* position of the vicinal hydroxyl groups; the *trans* diaxial junction between rings A and B, and the unambiguous position of the substituted styryl group at C-7. This position is indeed only consistent with the observed long range interaction between the olefinic and all the aromatic protons and the correlation between signals corresponding to H-9 and H-8.

Vedelianin constitutes a new example of an acid-induced cyclization product coming probably from a double cyclization of a geranyl stilbene, closely related to the metabolites isolated from *Chlorophora excelsa* [5], as has been shown with ostruthin [6] and in the condensation of geraniol and olivetol [7]. From a pharmacological point of view, vedelianin does not exhibit any hypotensive activity on the anesthesized rat.

EXPERIMENTAL

Plant material. Collected near Traput, Lifou, Loyalty Islands, New Caledonia, during January 1987. A voucher specimen (Hnawia 27) is deposited in the Herbarium of Centre ORSTOM, Noumea, New Caledonia. The identification has been carried out by one of us (E.H.) and Dr J. M. Veillon. The plant was dried under hot air (55°) and ground.

Isolation of vedelianin (1). The dried leaves (400 g) were extracted successively with hexane, EtOAc and MeOH. The methanolic extract was purified as previously described [1, 3] to provide vedelianin as a brownish powder (200 mg), together with macarangin (ref. [3]).

Vedelianin (1). $[\alpha]_D^{22}$ +37° 2 (MeOH; *c* 2.88); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 2860, 1620, 1600; UV and MS: see Results; ^1H and ^{13}C NMR: see Table 1.

Acetylation of vedelianin (1). A soln of 1 (10 mg) in pyridine (1 ml) was treated with Ac_2O (1 ml) overnight at room temp.

Usual work-up and purification on TLC (CH_2Cl_2–MeOH, 49:1) provided the pentaacetate **2** (8 mg) as an amorphous powder. MS 70 eV: *m/z* (rel. int.): 690 $[M]^+$ (52), 648 (10), 528 (8), 408 (8), 365 (10), 323 (12), 310 (12), 268 (10), 149 (20), 137 (20), 120 (22), 69 (23), 43 (100); ^{1}H NMR (CD_3OD, 200 MHz): δ7.03 (1H, *br s*), 7.00 (2H, *s*), 6.97 (1H, *br s*), 6.90 (1H, *d*, J = 16 Hz), 6.86 (1H, *d*, J = 16 Hz), 5.50 (1H, *br d*, J = 3 Hz), 5.00 (1H, *t*, J = 7 Hz), 4.73 (1H, *d*, J = 4 Hz), 3.15 (2H, *d*, J = 7 Hz), 2.08 (2H, *d*, J = 9 Hz), 2.30 (9H, 3*s*, 3 × Ac), 2.10 (6H, 2*s*, 2 × Ac), 1.90 (1H, *t*, J = 9 Hz), 1.73 (3H, *s*), 1.66 (3H, *s*), 1.36 (3H, *s*), 1.13 (3H, *s*), 1.00 (3H, *s*).

Hydrogenation of compound **1**. A soln of vedelianin (**1**) (25 mg) in MeOH (2 ml) was treated overnight with H_2 using Pd-C as catalyst. The reaction mixture was filtered, taken to dryness and purified by TLC (CH_2Cl_2–MeOH, 9:1) to give 22 mg of compound **3**. EI-MS 70 eV *m/z* (rel. int.): 484 $[M]^+$ (100), 328 (32), 291 (60), 273 (29), 255 (67), 137 (53), 135 (30); ^{1}H NMR (CD_3OD, 200 MHz): δ6.46 (1H, *d*, J = 1.5 Hz), 6.36 (1H, *d*, J = 1.5 Hz), 6.13 (2H, *s*), 4.13 (1H, *br d*, J = 3 Hz), 3.66 (1H, *m*), 3.56 (1H, *m*), 2.63 (*m*), 2.30 (1H, *dd*, J = 14 and 3 Hz), 1.90 (1H, *dd*, J = 14 and 2 Hz), 1.70 (2H, *m*), 1.53 (2H, *m*), 1.36 (3H, *s*) 1.10 (6H, *s*), 0.90 (6H, *d*, J = 7 Hz).

Cyclization of compound **1**. Vedelianin (**1**) (10 mg) in MeOH (0.1 ml) and 1 M HCl (1.5 ml) was heated at 100° for 3 hr. The reaction mixture was evapd to dryness and subjected to TLC (CH_2Cl_2–MeOH, 9:1) to yield **4** (5 mg). MS 70 eV *m/z* (rel. int.): 480 $[M]^+$ (100), 306 (18), 268 (20), 250 (10), 222 (10), 137 (10), 91 (10); ^{1}H and ^{13}C NMR: see Table 1.

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VERMILUTIN, A XANTHONE FROM *PENICILLIUM VERMICULATUM*

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Key Word Index—*Penicillium vermiculatum*; Hyphomycetes; vermilutin; xanthone; structural elucidation; cytotoxic effect; leukemia P388.

Abstract—Vermilutin, 8-formyl-1-hydroxy-6-methyl-4-(3-methylbut-1-enyl)xanthone, was isolated from the mycelium of *Penicillium vermiculatum* and its structure deduced from spectral data. Vermilutin and its acetate inhibited the biochemical function of *in vitro* grown P388 lympholeukemic cells.

INTRODUCTION

Penicillium vermiculatum Dang. (=*P. dangeardi* Pitt., anamorph name of *Talaromyces flavus* (Klöcker) Stolk and Samson [1]) biosynthesizes several antibiotic and cytotoxic compounds [2–5]. In the mycelium of this strain we found a new yellow crystalline compound denoted vermilutin (**1**). We present details of the isolation, structural elucidation and cytotoxic activity of **1**.

RESULTS AND DISCUSSION

TLC of the heptane extract of *P. vermiculatum* mycelium revealed **1** as a yellow spot, which turned dark green after spraying with vanillin–sulphuric acid. The UV spectrum of **1** with bands at 237, 270 and 399 nm was characteristic of a xanthone chromophore, e.g. as in anhydroarugosin [6] or shamixanthone [7]. The bathochromic shift of the long wave band to 414 nm in alkaline solution suggested the presence of a phenolic hydroxyl in **1**. Significant peaks in the mass spectrum of **1** appeared at *m/z* 322 $[M]^+$, 294 $[M-CO]$ and the base peak at *m/z* 279 $[M-C_3H_7]$. Acetylation of **1** gave the monoacetate **2** with $[M]^+$ at *m/z* 364, and further fragments at *m/z* 322 $[M-C_2H_2O]$, 321 $[M-C_2H_3O]$, 307 [322–Me], 305 $[M-C_2H_3O_2]$, 294 [322–CO] and 279 (base peak). The ^{1}H NMR of **1** (Table 1) showed signals for two aromatic protons in the *ortho*-position, two *meta*-orien-