then EtOH. The Me_2CO extract was chromatographed on silica gel column, eluted with a gradient of Me_2CO and petrol (bp 60–90°); three parts were obtained, each part was purified by CC on a silica gel column to give compounds **1**–**6**. From the ethanol extract, **7** was obtained.

Compound **1**. Pale yellow needles, mp 232–233°, $C_{19}H_{20}O_8$, EIMS *m/z* (rel. int.): 376 $[M]^+$ (60%), 195 $[M-C_9H_9O_4]^+$ (100%), 181 $[M-C_{10}H_{11}O_4]^+$ (40%), 167 $[M-C_{11}H_{13}O_4]^+$ (96%); ^{1}H NMR (DMSO-d_6): δ14.2 (2H, *br s*), 10.3 (2H, *br s*), 5.94 (2H, *s*), 3.82 (6H, *s*), 2.54 (6H, *s*), 3.2 (2H, *s*); ^{13}C NMR (DMSO-d_6): δ201.92 (C), 164.38 (C), 163.10 (C), 160.68 (C), 106.4 (C), 103.99 (C), 90.44 (CH), 55.31 (Me), 32.49 (Me), 15.34 (CH_2).

Compound **2**. Plates, mp 137–138°, $C_{10}H_{10}O_5$, EIMS *m/z* (rel. int.) 210 $[M]^+$ (50%), 195 $[M-Me]^+$ (40%), 193 $[M-OH]^+$ (45%), 182 $[M-28]^+$ (43%), 167 (100%); ^{1}H NMR ($CDCl_3$): δ16.73 (1H, *s*), 14.37 (1H, *s*), 11.58 (1H, *s*), 8.63 (1H, *s*), 3.96 (3H, *s*), 2.82 (3H, *s*); ^{13}C NMR ($CDCl_3$): δ203.27 (C), 192.39 (C), 171.20 (C), 170.08 (C), 166.36 (C), 104.92 (C), 90.85 (CH), 55.46 (Me), 33.12 (Me).

2,4-*Dihydroxy*-6-*methoxy*-3-*methylacetophenone*. ^{1}H NMR (DMSO-d_6): δ1.88 (3H, *s*), 3.82 (3H, *s*), 2.54 (3H, *s*), 6.08 (1H, *s*), 10.55 (1H, *s*), 14.25 (1H, *s*); ^{13}C NMR (DMSO-d_6): δ7.31 (Me), 32.65 (Me), 55.49 (Me), 90.32 (CH), 104.14 (C), 102.65 (C), 160.86 (C), 162.78 (C), 164.10 (C), 202.25 (C).

24-Methylenecycloartenol (**3**), β-amyrin acetate (**4**), sitosterol (**5**), sitosterol β-D-glucopyranoside (**6**) and sucrose (**7**) were identified by comparing their spectral data and physical constants with literature and authentic samples.

Acknowledgement—This work was supported by The National Natural Science Foundation of China.

REFERENCES

1. Jiangsu New Medical College (1978) *A Dictionary of the Traditional Chinese Medicine*, Vol. 1, p. 573. Shanghai Science Technology Press, Shanghai.
2. Uemura, D., Hirata, Y., Chen, Y.-P. and Hsu, H.-Y. (1975) *Tetrahedron Letters* 1697.
3. Uemura, D. and Hirata, Y. (1975) *Tetrahedron Letters* 1701.
4. Uemura, D., Katayama, L., Uno, E., Sasaki, K., Hirata, Y., Chen, Y.-P. and Hsu, H.-Y. (1975) *Tetrahedron Letters* 1703.
5. Uemura, D., Hirata, Y., Chen, Y.-P. and Hsu, H.-Y. (1974) *Tetrahedron Letters* 2529.
6. Uemura, D., Ohwaki, H., Hirata, Y., Chen, Y.-P. and Hsu, H.-Y. (1974) *Tetrahedron Letters* 2527.
7. Bolognese, A., Chioccara, F. and Scherillo, G. (1974) *Phytochemistry* **13**, 1989.

Phytochemistry, Vol. 31, No 4, pp 1436–1439, 1992
Printed in Great Britain.

0031–9422/92 $5.00+0.00
Pergamon Press plc

SYNTHESIS OF HIERRIDIN, A PHENOL FROM THE LICHEN, *RAMALINA HIERRENSIS*

ANTONIO G. GONZÁLEZ, JAIME BERMEJO BARRERA* and ELSA Mª RODRIGUEZ PEREZ

Centro de Productos Naturales Orgánicos Antonio González, I.P.N.A. Consejo Superior de Investigaciones Cientificas, Carretera La Esperanza 2, La Laguna, 38206 Tenerife, Canary Islands, Spain

(*Received* 6 *August* 1991)

Key Word Index—*Ramalina hierrensis*; lichen; hierridin; 2,4-dimethoxy-6-heneicosanylphenol.

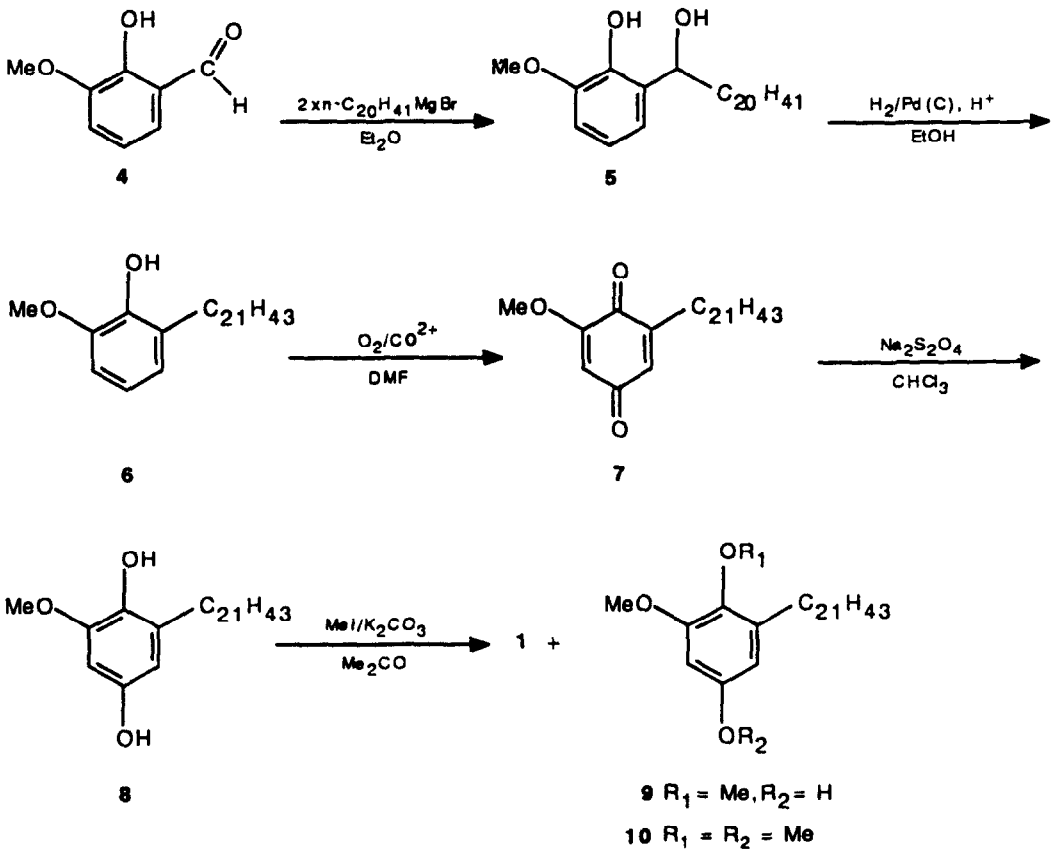
Abstract—A five-step reaction sequence was used to synthesize hierridin (2,4-dimethoxy-6-heneicosanylphenol), a new compound isolated from the lichen *Ramalina hierrensis*.

INTRODUCTION

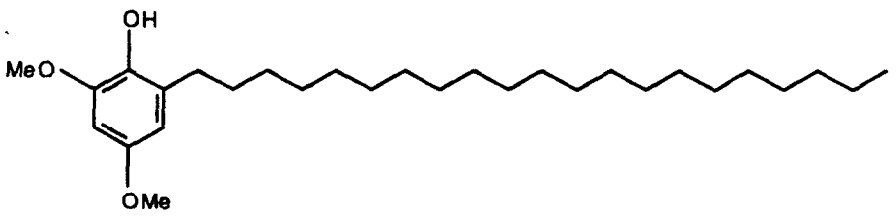
Recently we reported the isolation of several lichen substances from *Ramalina hierrensis* Krog & Osth. Among these was hierridin (**1**), a new compound identified by spectroscopy (IR, MS, ^{1}H NMR, ^{13}C NMR, NOE) and shown to possess a structure not previously seen in compounds from lichens [1]. The literature reports only one natural product with a similar structure, namely miconidin (**2**) [2] from *Miconia* spp. (Melastomataceae). This is found associated with the quinone, primin (**3**). Miconidin exhibited antimicrobial and antineoplastic activity [3] and has proved to be an antifeedant to six species of insects [4]. Hierridin (**1**) is a partly methylated hydroquinone which has compound **8** (Scheme 1) as its immediate precursor. Because of the potential for promising biological activity we embarked on its synthesis. Successful completion of this would serve to confirm its structure and provide sufficient material for more complete evaluation of its biological activity.

RESULTS AND DISCUSSION

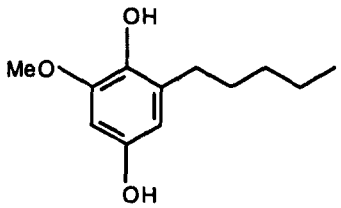
The substances *o*-vanillin (**4**) and *n*-eicosanol were used as starting materials according to the reaction sequence shown in Scheme 1. The *o*-vanillin (**4**) in diethyl ether was treated with *n*-eicosanyl magnesium bromide in diethyl ether under an argon atmosphere. The bromide, in its turn, had been prepared from commercial *n*-eicosanol by the standard method [5] using hydrobromic acid (48%) and concentrated sulphuric acid. Compound **5**, obtained



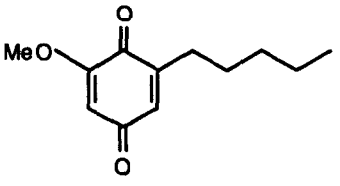
Scheme 1. Synthetic route to compound **1** from **4**.



1



2



3

in 65% yield, was hydrogenated in ethanol at room temperature under atmospheric pressure in the presence of 10% Pd(C) and traces of 1 M H_2SO_4 to give **6** in 97% yield. Phenol **6** was oxidized by streaming oxygen into a solution in DMF containing salcomine as catalyst. This procedure is known to give better results than are usually obtained with Fremy's salt [6]. Quinone **7** was obtained in 95% yield and excellent purity and was converted to **8** (90%) using $Na_2S_2O_4$ as reducing agent. The new hydroquinone was immediately crystallized to avoid being oxidized too rapidly and various gentle methods were applied in an attempt to achieve its partial methylation.

The first methylating agent tested was diazomethane in diethyl ether. Although the hydroxy group was methylated as desired, its low acidity resulted in only very poor yields. Controlled methylation with methyliodide and K_2CO_3, however, gave a good yield of **1** by the preferred reaction of the less sterically hindered hydroxy group. When **8**, dissolved in acetone, was refluxed with dry K_2CO_3 (1 equiv) and methyl iodide (1.5 equiv) for 24 hr, only half the starting material reacted, affording **1** (53%) and the minor products **9** (13%) and **10** (12.5%). If the reaction conditions were forced, either by increasing the amount of methyliodide or the reaction time, the yield of **1** was diminished and that of **10** enhanced. The controlled methylation described above clearly gave the best results and the product of this synthesis was identical (mp, TLC, IR, MS, NMR) to naturally occurring hierridin (**1**) [1].

EXPERIMENTAL

General. Mp: uncorr. NMR spectra: 200 MHz using $CHCl_3$ as int. standard. Merck silica gel (0.06–0.2 mm) was used for CC and TLC was carried out with Schleicher and Schüll silica gel. Spots were revealed by spraying with oleum (H_2SO_4–H_2O–HOAc 1:4:20) and heating to 100°. All solvents were dried and dist. immediately before use.

n-Eicosanyl bromide. HBr (48%, 2.13 g, 12.79 mmol) was mixed with concd H_2SO_4 (0.72 g, 0.4 ml) and *n*-eicosanol (2 g, 6.70 mmol) was added. After reflux for 6 hr, the mixt. was diluted with H_2O and extracted with Et_2O. Evapn of the solvent *in vacuo* left a residue which was adsorbed onto a silica gel column, and flash chromatography (solvent: hexane) gave *n*-eicosanyl bromide (2.37 g, 98%) as crystals: mp 33–34° (from $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2926, 2853, 1465, 1458, 1373, 1302; MS *m/z* (rel. int.): 362 $[M]^+$ (2), 361 (1), 360 (2), 282 (3), 281 (12), 151 (14), 149 (15), 141 (8), 137 (67), 135 (66), 127 (10); ^1H NMR ($CDCl_3$): δ 0.88 (3H, *t*, J = 6.0 Hz, Me-20), 1.26 (32H, *br s*, 16 × CH_2), 1.86 (4H, *m*, 2 × CH_2), 3.41 (2H, *t*, J = 6.9 Hz, H_2-1).

6-(1-hydroxyheneicosanyl)-2-Methoxyphenol (**5**). Eicosanyl magnesium bromide (2 equiv.) was prepd from Mg turnings (96 mg, 3.94 mmol) and eicosanyl bromide (2.3 g, 6.36 mmol) in dry Et_2O (10 ml) under an Ar atmosphere. *o*-Vanillin (0.48 g, 3.15 mmol) was gradually added and the mixt. was then refluxed for 2 hr, cooled and poured into a satd soln of NH_4Cl (10 ml). The layers were sepd and the aq. phase thoroughly extracted with Et_2O. The organic extracts were washed once with H_2O, dried and evapd. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 4:1) yielding **5** (65%, 889 mg) as an amorphous solid: mp 55–57°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3589, 3530 (OH), 1619, 1590 (aromatic ring); MS *m/z* (rel. int.): 434 $[M]^+$ (2), 416.3638 $[M-H_2O]^+$ (49) (calc. for $C_{28}H_{48}O_2$: 416.3654), 163 (25), 153 (31), 151 (12), 150 (41), 138 (32), 137 (100); ^1H NMR ($CDCl_3$): δ 0.88 (3H, *t*, J = 6.0 Hz, Me-21'), 1.25 (34H, *br s*, 17 × CH_2), 1.60 (2H, *m*, H_2-3'), 1.81 (2H, *m*, H_2-2'), 3.89 (3H, *s*, OMe-2), 4.88 (1H, *t*, J = 6.5 Hz, H-1'), 6.30 (1H, *s*, OH-1), 6.81 (3H, *m*, H-3, H-4, H-5).

2-Methoxy-6-heneicosanylphenol (**6**). Compound **4** (850 mg, 1.96 mmol) was hydrogenated in EtOH (10 ml) for 3 hr at room temp. and atmos. pres. in the presence of 10% Pd(C) (40 mg) and 1 M H_2SO_4 (0.02 ml) and, after standard work-up, afforded **6** (97%, 795 mg) as an amorphous solid: mp 54–56°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH), 1619, 1590 (aromatic ring); MS *m/z* (rel. int.): 418.3822 $[M]^+$ (100) (calc. for $C_{28}H_{50}O_2$: 418.3811), 137 (21); ^1H NMR ($CDCl_3$): δ 0.89 (3H, *t*, J = 6.0 Hz, Me-21'), 1.27 (34H, *br s*, 17 × CH_2), 1.62 (2H, *m*, H_2-2'), 2.64 (2H, *t*, J = 7.5 Hz, H_2-1'), 3.88 (3H, *s*, OMe-2), 5.68 (1H, *s*, OH-1), 6.76 (3H, *m*, H-3, H-4, H-5).

2-Methoxy-6-heneicosanyl-1,4-benzoquinone (**7**). A soln of **6** (750 mg, 1.79 mmol) and salcomine (5 mg) in DMF (10 ml) was stirred in an O_2 atmosphere for 24 hr at room temp. After H_2O (100 ml) had been added, the soln was extracted with $CHCl_3$ (3 × 30 ml). The organic extract was dried over Na_2SO_4, the solvent was evapd and the residue crystallized from petrol yielding **7** (95%, 735 mg) as yellow needles, mp 84–86°; UV (EtOH) nm 267, 360 (log ε 4.70, 2.90); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678, 1649, 1627, 1602 (quinone); MS *m/z* (rel. int.): 432.3607 $[M]^+$ (96) (calc. for $C_{28}H_{48}O_3$: 432.3603), 179 (11), 167 (7), 166 (9), 154 (100), 153 (64), 139 (9), 125 (13); ^1H NMR ($CDCl_3$): δ 0.87 (3H, *t*, J = 6.2 Hz, Me-21'), 1.25 (36H, *br s*, 18 × CH_2), 1.54 (2H, *m*, H_2-2'), 2.42 (2H, *t*, J = 6.8 Hz, H_2-1'), 3.81 (3H, *s*, OMe-2), 5.67 (1H, *d*, J = 2.4 Hz, quinone CH), 6.48 (1H, *m*, quinone CH).

2-Methoxy-6-heneicosanyl-1,4-dihydroxybenzene (**8**). Compound **7** (650 mg, 1.50 mmol) was dissolved in $CHCl_3$ (5 ml) and added to a soln of $Na_2S_2O_4$ (1.3 g) in hot H_2O (10 ml). The mixt. was shaken for 10 min and after the aq. layer had been drawn off, the $CHCl_3$ was shaken with brine and dried over Na_2SO_4, the solvent was evapd and the residue crystallized from CH_2Cl_2, yielding **8** (90%, 586 mg) as needles: mp 102–103°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3601, 3551(OH), 1607 (aromatic ring); MS *m/z* (rel. int.) 434.3757 $[M]^+$ (99) (calc. for $C_{28}H_{50}O_3$: 434.3760), 154 (81), 153 (60), 139 (15), 135 (16), 125 (29), 123 (11); ^1H NMR ($CDCl_3$): δ 0.88 (3H, *t*, J = 6.7 Hz, Me-21'), 1.25 (34H, *br s*, 17 × CH_2), 1.59 (4H, *m*, 2 × CH_2), 2.56 (2H, *t*, J = 8.0 Hz, H_2-1'), 3.84 (3H, *s*, OMe-2), 4.43 (1H, *br s*, OH-4), 5.22 (1H, *s*, OH-1), 6.21 (1H, *d*, J = 2.8 Hz, H-5), 6.30 (1H, *d*, J = 2.8 Hz, H-3).

Methylation of compound **8**. The hydroquinone **8** (400 mg, 0.92 mmol) was dissolved in Me_2CO (5 ml) and dry K_2CO_3 (130 mg, 0.93 mmol) was added followed by MeI (198 mg, 1.39 mmol). The mixt. was allowed to reflux over a water bath at 60–70° for 24 hr. The Me_2CO was distilled off and the residue poured into H_2O. The oil which sepd was extracted with EtOAc in the usual way. Evapn of the solvent *in vacuo* left a residue which was adsorbed onto a column of silica gel and flash chromatography (solvent hexane–EtOAc, 19:1) gave **8** (50%), **1** (27%, mp 70–72° from EtOH) identical in all respects (TLC, IR, MS, NMR) with natural hierridin (**1**) [1], and the minor products **9** (6.5%) and **10** (6%).

3,4-Dimethoxy-5-heneicosanylphenol (**9**). Mp 64–66° (from petrol); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3599 (OH), 1605, 1597 (aromatic ring); MS *m/z* (rel. int.): 448.3927 $[M]^+$ (100) (calc. for $C_{29}H_{52}O_3$: 448.3916), 168 (16), 167 (15), 153 (30), 152 (18); ^1H NMR ($CDCl_3$): δ 0.91 (3H, *t*, J = 6.0 Hz, Me-21'), 1.25 (34H, *br s*, 17 × CH_2), 1.58 (4H, *m*, 2 × CH_2), 2.55 (2H, *t*, J = 7.5 Hz, H_2-1'), 3.74 (3H, *s*, OMe-4), 3.82 (3H, *s*, OMe-3), 4.61 (1H, *s*, OH-1), 6.21 (1H, *d*, J = 2.9 Hz, H-6), 6.30 (1H, *d*, J = 2.9 Hz, H-2).

1,2,4-Trimethoxy-6-heneicosanylbenzene (**10**). Mp 58–60° (from EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1599 (aromatic ring); MS *m/z* (rel. int.): 462.4045 $[M]^+$ (76) (calc. for $C_{30}H_{54}O_3$: 462.4073), 181 (48), 168 (16), 167 (100), 153 (9), 151 (10), 139 (14); ^1H NMR ($CDCl_3$): δ 0.88 (3H, *t*, J = 6.5 Hz, Me-21'), 1.26 (36H, *br s*, 18 × CH_2), 1.59 (2H, *m*, H_2-2'), 2.59 (2H, *t*, J = 7.5 Hz, H_2-1'), 3.75 (3H, *s*, OMe-1), 3.77 (3H, *s*, OMe-4), 3.83 (3H, *s*, OMe-2), 6.29 (1H, *d*, J = 2.9 Hz, H-5), 6.35 (1H, *d*, J = 2.9 Hz, H-3).

Acknowledgements—This work has been partly financed by a grant from CICYT (PB88-0049). AGG is indebted to the AIETI Foundation, Madrid, and EMRP to the Ministerio de Educación y Ciencia for an FPI scholarship.

REFERENCES

1. González, A. G., Barrera, A. G. and Rodríguez, E. M. (1992) *Planta Med.* (in press).
2. Marini-Bettolo, G. B., Della Monache, F., Gonçalves da Lima, O. and de Barros Coêlho, S. (1971) *Gazzetta* **101**, 41.
3. Gonçalves da Lima, O., Marini-Bettolo, G. B., de Barros Coêlho, J. S., d'Albuquerque, I. L., da S. B. Cavalcanti, M., Martins, D. G. and Lins de Olivera, L. (1970) *Rev. Inst. Antibiot. Univ. Fed. Pernambuco, Recife* **10**, 35.
4. Bernays, E., Lupi, A., Marini-Bettolo, R., Mastrofrancesco, C. and Tagliatesta, P. (1984) *Experientia* **40**, 1010.
5. Kam, O., Marvel, C. S., Clarke, H. T. and Davis, A. W. (1941) *Organic Syntheses* Vol. I, p. 25. John Wiley, New York.
6. Bieber, L. W., de Andrade Chiappeta, A., de Moraes Esouza, M. A. and Generino, R. M. (1990) *J. Nat. Prod.* **53**, 706.

Phytochemistry, Vol. 31, No. 4, pp. 1439–1442, 1992
Printed in Great Britain.

0031-9422/92 $5.00+0.00
Pergamon Press plc

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

ODILE THOISON, EDOUARD HNAWIA,† FRANÇOISE GUÉRITTE-VOEGELEIN and THIERRY SÉVENET

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France; †Université Française du Pacifique, B.P. 64, Nouméa, New Caledonia

(*Received* 8 *July* 1991)

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.