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ANTHRAQUINONES AND PHENANTHROPERYLENEQUINONES FROM *NEPHROMA LAEVIGATUM*

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ABSTRACT.—Four anthraquinones and two phenanthroperylenequinones were isolated from the lichen *Nephroma laevigatum*. The structures were established from their spectral data as emodin [**1**], 7-chloroemodin [**2**], 7-chloro-1-*O*-methylemodin [**3**], 7-chloro-1-*O*-methyl-ω-hydroxyemodin [**4**], 7,7′-dichlorohypericin [**5**], and 2,2′,7,7′-tetrachlorohypericin [**6**]. Compounds **4**–**6** have not been reported previously. 7,7′-Dichlorohypericin [**5**] and 2,2′,7,7′-tetrachlorohypericin [**6**] were also synthesized and characterized spectroscopically.

Anthraquinones are widely distributed among microorganisms (1), plants (2), echinoderms (3), and insects (4). Within lower plants, lichens are known to produce a variety of anthraquinones, including several chlorinated metabolites (5). Currently, all known natural halogenated anthraquinones, anthrones, and their dimeric products have been isolated from lichens or fungi, with the exception of a series of bromophenanthroperylenequinones obtained from the stalked crinoid, *Gymnocrinus richeri* (6).

The foliose lichen, *Nephroma laevigatum* Ach. (Nephromataceae), may often be found growing on coastal rocks and trees in temperate regions of Canada, the United States, and Europe (7). The lichen has a characteristic yellow-orange medulla, indicative of the presence of quinonoid-like pigments. The constitution of these pigments was first studied in 1898 by Hesse (8), who identified "an hydroxyanthraquinone."

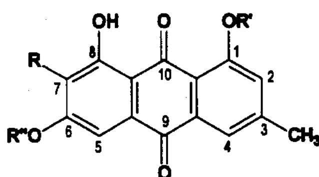
Seventy years later, Bohman and colleagues isolated five anthraquinones from the same species growing in Sweden (9). The compounds were characterized by their ir, uv, ms, and ^{1}H-nmr spectra, but their concentrations were not reported (10).

We have examined a lichen, identified as *N. laevigatum*, growing in the coastal regions of British Columbia. The extract from 0.4 kg of dried lichen gave, as the result of cc and prep. tlc, four anthraquinones and two chlorinated phenanthroperylenequinones: emodin [**1**], 7-chloroemodin [**2**], 7-chloro-1-*O*-methylemodin [**3**], 7-chloro-1-*O*-methyl-ω-hydroxyemodin [**4**], 7,7′-dichlorohypericin [**5**], and 2,2′,7,7′-tetrachlorohypericin [**6**]. Compounds **4**–**6** were not reported by Bohman and colleagues (9) as being present in the Swedish lichen, nor have they been found elsewhere in nature. On the other hand, we did not identify 7-chloro-6-*O*-methylemodin [**7**] or 7-chloro-1,6-di-*O*-methylemodin [**8**], previously found in the Swedish lichen (9).

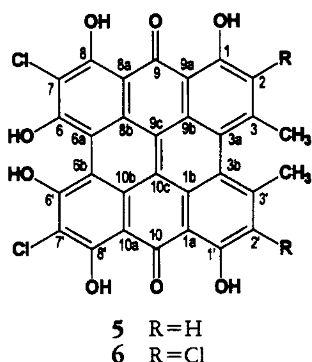
RESULTS AND DISCUSSION

The freeze-dried lichen was extracted successively with cold Et_2O, Me_2CO,and MeOH. All extracts were concentrated to small volumes and examined by tlc. The tlc of the Et_2O extract showed 12 colored spots, the primary constituent being 7-chloroemodin [**2**] (R_f 0.6; $CHCl_3$-MeOH, 9:1). The other prominent compounds were: emodin [**1**] (R_f 0.8); 7-chloro-1-*O*-methylemodin [**3**] (R_f 0.7); 7-chloro-1-*O*-methyl-ω-hydroxyemodin [**4**] (R_f 0.3); 7,7-dichlorohypericin [**5**] (R_f 0.2), and 2,2′,7,7′-tetrachlorohypericin [**6**] (R_f 0.2). Minor constituents, possibly anthraquinones and anthrones, were not present in sufficient amounts to permit identification. Examination of the Me_2CO and MeOH extracts revealed ten spots, corresponding (in each case) to the six presently identified compounds [**1**–**6**] and four unknowns; 7-chloroemodin [**2**] appeared to be the most abundant pigment in the extracts.

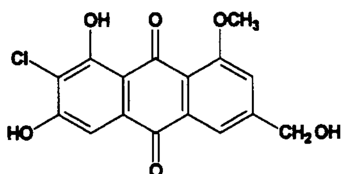
Spectral analysis of **2** supported the structure as 7-chloroemodin. The eims of **2**



1 R=R'=R''=H
2 R=Cl, R'=R''=H
3 R=Cl, R'=CH_3, R''=H
7 R=Cl, R'=H, R''=CH_3
8 R=Cl, R'=CH_3, R''=CH_3
9 R=H, R'=CH_3, R''=H



5 R=H
6 R=Cl



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showed fragment peaks at *m/z* 306 and 304, and the cims revealed fragment peaks at *m/z* 307 and 305. The 2D COSY ^{1}H-nmr spectral data of **2** are shown in Table 1. The placement of the chlorine atom at position 7 was based on the observed chemical shifts of H-5, H-4, and H-2, which were consistent with those previously reported (10–12). Several nOe nmr experiments resulted in the enhancement of the signals of H-2 and H-4 upon irradiation of the methyl protons, as well as an enhancement of the signal of H-5 upon irradiation of the hydroxyl proton at C-6. These results are consistent with structure **2**. ^{13}C-Nmr assignments listed in Table 2 are based on APT and HETCOR experiments, and calculations of ^{13}C-nmr chemical shifts used the methods described by Silverstein *et al.* (25).

Compound **3** proved to be the 1-*O*-methyl derivative of **2** by analysis of the 2D COSY ^{1}H-nmr (Table 1) and eims spectra. The eims of **3** showed fragment peaks at *m/z*

TABLE 1. ^{1}H-Nmr Data for Emodin [**1**], 7-Chloroemodin [**2**], 7-Chloro-1-*O*-methylemodin [**3**], and 1-*O*-Methylemodin [**9**].[a]

Proton(s)	Compound			
	1[b]	**2**[c]	**3**[c]	**9**[b]
2	7.15, s	7.14, s	7.45, s	7.45, s
4	7.58, s	7.50, s	7.62, s	7.67, s
5	7.25, d (2.5)	7.26, s	7.22, s	7.20, d (2.5)
7	6.65, d (2.5)			6.67, d (2.5)
OH-1	12.05, s	11.92, s		
OH-6				
OH-8	12.15, s	12.78, s		
Me	2.47, s	2.48, s	2.52, s	2.50, s
OMe			3.98, s	4.05, s

[a]Chemical shifts (δ) are reported in ppm from TMS as internal standard. The coupling constants in parentheses are given in Hz.

[b]The spectra were recorded in Me_2CO-d_6 at 300 MHz.

[c]The spectra were recorded in DMSO-d_6 at 500 MHz.

TABLE 2. ^{13}C-Nmr Data for Emodin [**1**], 7-Chloroemodin [**2**], and 7-Chloro-1-*O*-methylemodin [**3**].[a]

Carbon	Compound					
	1	**1**[b]	**2**	**2**[b]	**3**	**3**[b]
1	161.3	158.7	161.4	158.7	160.9	163.2
2	124.0	120.1	124.0	120.1	120.8	118.4
3	148.1	142.4	148.5	142.4	148.3	142.0
4	120.3	125.3	120.4	125.3	120.5	124.9
5	108.7	111.9	108.6	113.2	106.9	113.2
6	165.5	160.4	163.1	160.8	162.1	160.8
7	107.8	106.7	121.3	112.9	118.5	112.9
8	164.4	160.2	162.8	160.6	161.1	160.6
9	189.5	189.3	191.0	187.4	187.5	187.4
10	181.1	161.7	181.7	161.7	182.6	161.7
8a[c]	108.8	110.0	110.1	111.3	111.4	109.6
10a[d]	134.9	132.8	133.0	130.9	132.3	130.9
9a[c]	113.1	107.1	114.2	107.1	114.2	105.4
4a[d]	132.6	131.5	133.2	131.5	134.5	131.1
Me	21.5		21.6		21.7	
OMe					56.4	

[a]Chemical shifts (δ) are reported in ppm from TMS as internal standard. The spectra were recorded in DMSO-d_6 at 125 MHz.
[b]Values calculated according to the methods described by Silverstein *et al.* (25). The additivity values given for PhCO were used for C-9 and C-10 in the calculations.
[c]Values for C-8a and C-9a can be interchanged.
[d]Values for C-10a and C-4a can be interchanged.

320 and 318, and the cims exhibited fragment peaks at *m/z* 321 and 319. The uv-vis and 2D COSY ^{1}H-nmr assignments (Table 1) are consistent with those previously reported (10,14). A series of nOe nmr experiments confirmed the structural identity of **3**, in a similar manner as the studies performed on compound **2**. The ^{13}C-nmr data of **3** are shown in Table 2. Assignments were made on the basis of APT and HETCOR experiments, as well as ^{13}C-nmr chemical shifts calculated according to the literature (25). Additional structural proof was afforded by reduction of **3** with Raney nickel to give the dechlorinated product. The 2D COSY ^{1}H-nmr shifts (Table 1) of this product were consistent with those previously reported for 1-*O*-methylemodin [**9**] (14). A comparison of R_f values between the reduction product and several published reports on 1-*O*-methylemodin also helped confirm the identity of **3** (14,15).

Emodin [**1**] was characterized by uv-vis, eims, cims, and 2D COSY ^{1}H-nmr spectra (Table 1). A series of nOe experiments confirmed that **1** was emodin. Table 2 gives the ^{13}C-nmr data of **1**. The data are consistent with those previously reported (10,19).

Compound **4** was somewhat different from the other anthraquinones. It was apparent from the 2D COSY ^{1}H-nmr spectral data that the signal corresponding to the CH_3 group of emodin had been replaced by a resonance at 4.73 ppm. This suggested the presence of a hydroxymethyl group at C-3 (Table 3). Further confirmation was obtained from the cims and uv-vis spectra, which demonstrated the compound to be 7-chloro-1-*O*-methyl-ω-hydroxyemodin (7-chloro-1-*O*-methylcitreorosein) [**4**]. An nOe nmr experiment was performed in which irradiation of the CH_2OH protons resulted in increases in the signal intensities of H-2 and H-4. 7-Chlorocitreorosein has been isolated from *Aspergillus fumigatus* (11), and carviolin (1-*O*-methylcitreorosein) has been obtained from a culture of *Penicillium roseo-purpureum* (16). Compound **4** thus represents a new natural anthraquinone.

Compounds **5** and **6** are related to the well-known natural product hypericin, found

TABLE 3. ^{1}H-Nmr Data for 7-Chloro-1-*O*-methyl-ω-hydroxyemodin [**4**], 7,7′-Dichlorohypericin [**5**], and 2,2′,7,7′-Tetrachlorohypericin [**6**].[a]

Proton(s)	Compound			
	4[b]	**5**[c]	**5**[d]	**6**[c]
2,2′	6.78, s	7.42, s	7.20, s	
4,4′	7.78, s			
5,5′	7.43, s			
7,7′				
OH-1,1′		13.79, s		13.95, s
OH-6,6′		18.28, s		
OH-8,8′		15.55, s		15.65, s
Me,Me′		2.65, s	2.70, s	2.80, s
OMe	3.95, s			
CH_2OH	4.63, d (5.0)[e]			

[a]Chemical shifts (δ) are reported in ppm from TMS as internal standard. The coupling constants in parentheses are given in Hz.

[b]The spectrum was recorded in DMF-d_6 at 300 MHz.

[c]The spectra were recorded in DMSO-d_6 at 400 MHz.

[d]The spectrum was recorded in MeOH-d_4 at 400 MHz.

[e]ω-Hydroxymethyl protons were coupled to a broad hydroxyl proton. When the hydroxyl proton was exchanged by addition of a small amount of MeOH-d_4, this signal became a singlet.

in *Hypericum* spp. (17,18) and in a basidiomycete, *Dermocybe austroveneta* (19). Hypericin is the subject of current medical scrutiny because of its antiviral activity (21). Meruelo and co-workers showed that hypericin inhibited the spread of the Friend and radiation leukemia viruses in vitro and in vivo (22). The same group also reported that hypericin can inactivate human immunodeficiency virus (HIV), when measured by reverse transcriptase (RT) activity; it would appear, however, that the purified RT enzyme is not the main target of hypericin activity (23). Thus, the mode of action of hypericin still remains a topic of debate (24). The only known natural halogenated hypericin-like compounds are the gymnochromes, brominated phenanthroperylenequinones in the crinoid, *Gymnocrinus richeri* (6). The identities of compounds **5** and **6** became apparent on an examination of their uv-vis spectra, which were similar to that of hypericin; they were also in very close agreement with the uv-vis spectra of the gymnochromes (6) and synthetic brominated derivatives of hypericin (Table 4) (18). The negative-ion lsims spectrum of **5** showed three fragment peaks at *m/z* 575, 573, and 571 (relative intensities 1:4.2:6), indicative of two chlorine atoms in the molecule. A combination of 2D COSY ^{1}H-nmr (Table 3) and lsims data indicated that **5** was a symmetrical dimer. Several nOe experiments confirmed the structure of **5**. Irradiation of the methyl protons produced enhancements of the signal of H-2 and H-2′, although irradiation of the HO-8 and HO-8′ hydroxyl protons did not produce corresponding nOes at positions C-7 and C-7′.

The uv-vis spectrum of **6** was very similar to that of **5**. The lsims (negative-ion) spectrum showed four peaks at *m/z* 645, 643, 641, and 639 (relative intensities 1:3:5:3.5), indicative of four chlorine atoms in the molecule. The 2D COSY ^{1}H-nmr spectral data are shown in Table 3. Compound **6**, like **5**, must also be a symmetrical dimer.

The number of free hydroxyl groups in each assigned structure was confirmed by peracetylation with Ac_2O in pyridine. Mass spectra were determined by direct injection of the acetylation mixtures. Observation of the progressive loss of ketene was especially helpful in confirming the dimeric nature of **5** and **6**.

TABLE 4. Uv-vis Absorption Maxima of 7,7'-Dichlorohypericin [**5**], 2,2',7,7'-Tetrachlorohypericin [**6**], and Two Bromohypericins.

Compound			
5[a]	7,7'-DBH[b,c]	**6**[a]	2,2',7,7'-TBH[b,d]
251		251	
294	290	295	290
332	332	332	332
388	391	390	390
485	485	484	484
553	549	554	550
597	593	598	595

[a]The uv-vis spectrum was recorded in DMSO.
[b]The uv-vis spectrum was recorded in EtOH.
[c]7,7'-DBH=2,5-dibromohypericin.
[d]2,2',7,7'-TBH=2,5,9,12-tetrabromohypericin.

The biogenesis of the anthraquinones and the perylenequinones in *N. laevigatum* presumably takes place through the polyketide pathway. Detailed studies on the biosynthesis of emodin [**1**] in fungi and higher plants have been carried out (26–28). Hypericin is believed to be formed by the linkage of two emodin anthrone units, with subsequent oxidation leading to the perylenequinone structure (29). The mechanism and stage of formation of the chlorinated anthraquinones and hypericins are unknown at present.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were taken by means of a Kofler hot-stage microscope. ^{1}H-Nmr (2D COSY and nOe experiments) spectra were recorded on Varian Gemini 300 and 500 MHz spectrometers, and on a Bruker WH-400 MHz spectrometer. APT and HETCOR ^{13}C-nmr spectra were recorded on a Varian Gemini 500 MHz spectrometer at 125 MHz. The lsims, cims, and eims spectra were recorded on a Kratos Concept II HQ mass spectrometer, a Delsi Nermag R 10-10 C mass spectrometer, and a Finnegan 4500 CI mass spectrometer, respectively. The uv-vis spectra were recorded on Beckman DU 7 and Philips PU 8720 uv-vis scanning spectrophotometers. DMSO-d_6 (99.9% D; Isotec), DMF-d_6 (99.9% D; Aldrich), Me_2CO-d_6 (99.9% D; Isotec), and MeOH-d_4 (99.9% D; Isotec) were used in the 2D COSY and nOe ^{1}H-nmr experiments, and the APT and HETCOR ^{13}C-nmr experiments. The uv-vis spectra were recorded in solvents (DMSO, EtOH, MeOH) of uv quality.

PLANT MATERIAL.—*Nephroma laevigatum* Ach. (Nephromataceae) was collected from coastal areas of Gabriola Island in southwestern British Columbia. The lichen was identified by one of us (P.A.C.), and reference samples have been deposited in the University of British Columbia Botany Department Herbarium.

EXTRACTION AND ISOLATION.—A sample of cleaned and dried lichen (0.4 kg) was extracted successively with Et_2O (2 liters), Me_2CO (2 liters), and MeOH (2 liters) at 0°. Following tlc examination, the orange-red extracts were combined and concentrated to a brown-red solid. The solid (10 g) was divided into three equal portions. One portion (3.33 g) was purified by cc on 100 g of Sephadex LH-20 using a gradient of $CHCl_3$-MeOH (9:1) to MeOH. Fractions (20 ml) were collected and analyzed by tlc. Fractions 2–4 contained emodin [**1**] and 7-chloro-1-*O*-methylemodin [**3**], fractions 5–7 contained 7-chloro-1-*O*-methylemodin [**3**], fractions 6–8 contained 7-chloro-1-*O*-methylemodin [**3**] and 7-chloroemodin [**2**], fractions 9–12 contained 7-chloroemodin [**2**], and 7-chloro-1-*O*-methyl-ω-hydroxyemodin [**4**] came from fractions 13–18. Small quantities of 7,7'-dichlorohypericin [**5**] and 2,2',7,7'-tetrachlorohypericin [**6**] were found in fractions 19–22. In order to improve the yields of **5** and **6**, the immobile purple layer was extruded from the Sephadex column and then extracted overnight with 300 ml of pyridine. The purple extract was concentrated to give a mixture of **5** and **6**. The two compounds were separated by cc on Sephadex LH-20 using MeOH.

All compounds were purified by reversed-phase hplc (Waters C_{18} column, 3.9×30 cm; flow rate 1 ml/min) and recrystallization from a suitable solvent. The reported yields are based on 3.33 g of crude extract.

Emodin [**1**].—Orange crystals (EtOAc) (3 mg, 0.002%): mp 256–257°; uv (EtOH) λ max (log ε) 253 (4.31), 265 (4.29), 289 (4.36), 438 (4.18) nm; cims *m/z* $[MH]^+$ 271 (94), 197 (100); cims *m/z* $[MH]^-$ 270 (100). For nmr data, see Tables 1 and 2.

7-Chloroemodin [**2**].—Orange crystals (EtOAc) (78 mg, 0.06%): mp 281–283°; uv (EtOH) λ max (log ε) 216 (4.49), 257 (4.24), 315 (4.22), 325 (4.08), 437 (3.88), 504 (3.70) nm; cims *m/z* $[MH]^+$ 307 (26), 305 (100); eims (70 eV) *m/z* $[M]^+$ 306 (35), 304 (100). For nmr data, see Tables 1 and 2.

7-Chloro-1-O-methylemodin [**3**].—Orange crystals (82 mg, 0.06%) (EtOAc): mp 289–291°; uv (EtOH) λ max (log ε) 256 (4.24), 286 (4.23), 423 (3.78) nm; cims *m/z* $[MH]^+$ 321 (30), 319 (100); eims (70 eV) *m/z* $[M]^+$ 320 (35), 318 (100). For nmr data, see Tables 1 and 2.

7-Chloro-1-O-methyl-ω-hydroxyemodin [**4**].—Pink crystals (1 mg, 0.008%) (EtOH): mp >290°; uv (EtOH) λ max (log ε) 222 (4.50), 250 (4.20), 300 (4.23), 434 (3.95), 452 (3.90), 490 (3.78), 525 (3.60) nm; cims *m/z* $[MH]^+$ 337 (3), 335 (12); [**4**] triacetate: cims *m/z* $[MH]^+$ 480 (49), 478 (100), 463 (35), 461 (79). For nmr data, see Table 3.

7,7'-Dichlorohypericin [**5**].—Purple crystals (1.4 mg, 0.001%) (AcOH): mp >350°; uv (DMSO) λ max (log ε) 251 (4.70), 294 (4.60), 332 (4.50), 388 (3.93), 485 (4.08), 553 (4.29), 597 (4.58) nm; lsims *m/z* $[M-H]^-$ 575 (9), 573 (38), 571 (54). For nmr data, see Table 3.

2,2',7,7'-Tetrachlorohypericin [**6**].—Purple crystals (AcOH) (0.8 mg, 0.0006%): >350°; uv (DMSO) λ max (log ε) 251 (4.70), 295 (4.60), 332 (4.50), 390 (3.90), 484 (4.06), 554 (4.27), 598 (4.56) nm; lsims *m/z* $[M-H]^-$ 645 (2), 643 (6), 641 (10), 639 (7). For nmr data, see Table 3.

REDUCTION OF **3** WITH RANEY NICKEL.—7-Chloro-1-*O*-methylemodin [**3**] (1.5 mg, 0.005 mmol) was dissolved in 5 ml of 0.015 M NaOH. Raney nickel (3.0 mg) was added, in one portion, to the stirred solution. The reaction mixture was heated at reflux for 15 min, cooled to room temperature and filtered. The red filtrate was acidified to pH 7 with 6 N HCl. The yellow solution was extracted 3 times with 50-ml portions of Et_2O. The combined Et_2O layers were dried and concentrated to a yellow solid. Recrystallization from toluene-$CHCl_3$ (3:1) afforded 1.0 mg of 1-*O*-methylemodin [**9**] (0.004 mmol, 75% yield). The R_f values of the product were 0.30 (C_6H_6-EtOAc, 5:1), 0.15 (toluene-$CHCl_3$-EtOAc, 3:3:1), and 0.60 ($CHCl_3$-petroleum ether-EtOAc-MeOH, 70:20:8:2). The product [**9**] was characterized by cims and 2D COSY ^{1}H-nmr spectra (Table 1).

SYNTHESES OF 7,7'-DICHLOROHYPERICIN [**5**] AND 2,2',7,7'-TETRACHLOROHYPERICIN [**6**].—Hypericin (7 mg, 0.014 mmol) was dissolved, with stirring, in 10 ml of dry DMF. To the stirred, deep-purple solution

TABLE 5. ^{13}C-Nmr Data for 7,7'-Dichlorohypericin [**5**] and Hypericin.[a]

Carbon	Compound		
	5[b]	Hypericin[b]	Hypericin[c]
1,1'	162.8	161.4	161.2
2,2'	117.2	118.9	118.6
3,3'	144.3	143.4	143.5
6,6'	175.2	174.2	174.7
7,7'	107.7	105.5	105.4
8,8'	167.5	168.1	166.0
9,10	184.3	183.6	183.3
1a,9a	101.6	102.0	101.9
1b,9b[d]	120.3	120.6	119.2
3a,3b[d]	120.4	120.7	120.7
6a,6b[e]	125.2	127.0	126.6
8a,10a	109.6	108.3	108.3
8b,10b[e]	124.3	126.0	126.0
9c,10c	120.8	121.2	121.2
Me-3,Me-3'	23.8	23.6	23.6

[a]Chemical shifts (δ) are reported in ppm from TMS as internal standard.
[b]The spectra were recorded in DMSO-d_6 at 125 MHz.
[c]The spectrum was recorded in DMSO-d_6 at 90 MHz.
[d]Values for C-1b/C-9b and C-3a/C-3b can be interchanged.
[e]Values for C-6a/C-6b and C-8b/C-10b can be interchanged.

was added *N*-chlorosuccinimide (4 mg, 0.03 mmol). After 4 h at room temperature, solvent was removed under reduced pressure and the residual purple solid was dried, *in vacuo*, for 24 h. This material was chromatographed on a column of Sephadex LH-20 with MeOH-pyridine (9:1) as eluent. Compound **6** (1.8 mg from AcOH, 20% yield) was eluted first and was characterized by uv, lsims, and 2D COSY ^{1}H-nmr spectra. The compound proved to be identical with the natural product isolated from *N. laevigatum* in all respects. Compound **5** (4 mg from AcOH, 50% yield) was characterized by analysis of its uv, ms, 2D COSY ^{1}H-nmr, and ^{13}C-nmr spectra. The ^{13}C-nmr shifts for **5** (Table 5) were determined using APT and HETCOR techniques. A series of nOe experiments revealed the presence of protons at C-2 and C-2′; irradiation of the methyl protons resulted in an increase in each proton signal at C-2 and C-2′. Thus, the compound proved to be identical with the natural product isolated from *N. laevigatum* in all respects.

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