HETEROCYCLES, Vol. 81, No. 10, 2010, pp. 2335 - 2341. © The Japan Institute of Heterocyclic Chemistry
Received, 15th June, 2010, Accepted, 10th August, 2010, Published online, 11th August, 2010
DOI: 10.3987/COM-10-11994

NEW XANTHONES FROM THE BARKS OF *CRATOXYLUM SUMATRANUM* SSP. *NERIIFOLIUM*

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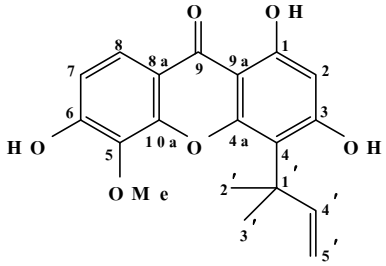
Abstract – Three new prenylated xanthones, neriifolone A-C (**1**-**3**), and eight known xanthones (**4**-**11**) were isolated from the barks of *Cratoxylum sumatranum* ssp. *neriifolium*. All the new compounds were characterized by intensive spectroscopic methods (1D and 2D NMR, UV and IR spectroscopy and mass spectrometry).

Cratoxylum is a small genus belonging to the Clusiaceae, which is distributed in several Asian countries. Some species of this genus have been used in folk medicine as a treatment for diarrhea, flatulence[1] as well as diuretic, stomachic and tonic complaints.[2] Xanthone is the major chemical substance present in this genus[3-11] and some of these chemical substances showed interesting biological activities.[4,6-8,10,11] In this paper, we describe the isolation and structural elucidation of three new xanthones (**1**-**3**) together with eight known xanthones (**4**-**11**) from the barks of *C. sumatranum* ssp. *neriifolium*.

The dichloromethane extract from the barks of *C. sumatranum* spp. *neriifolium* was separated by chromatographic techniques to afford eleven compounds: three new xanthones, neriifolone A (**1**), neriifolone B (**2**) and neriifolone C (**3**), and eight known xanthones (**4**-**11**). The structures of all of the new compounds were then elucidated using extensive 1D and 2D NMR spectroscopic techniques.



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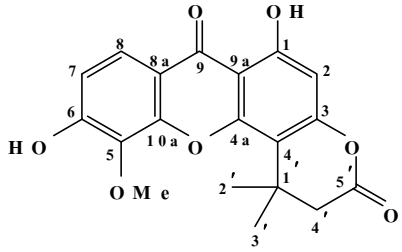

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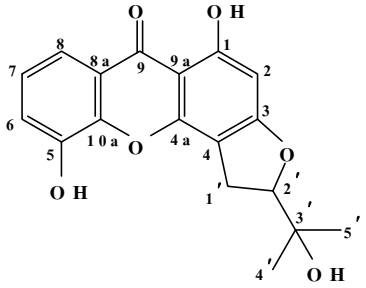

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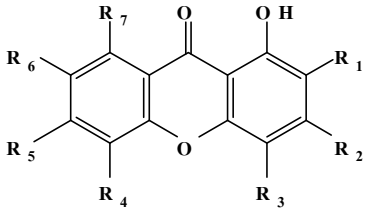
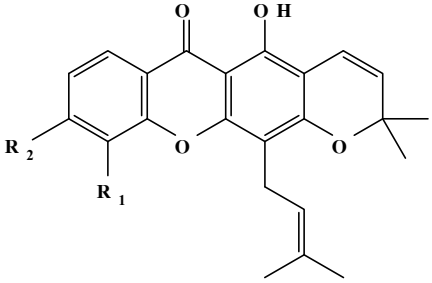
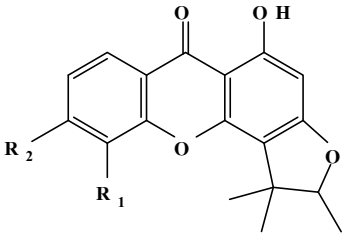


	R_1	R_2	R_3	R_4	R_5	R_6	R_7
4	Prenyl	OMe	H	H	OH	OMe	Prenyl
5	H	OH	1,1-dimethylallyl	OH	H	H	H
6	H	OH	1,1-dimethylallyl	OH	OH	H	H



	R_1	R_2
7	OH	H
8	OMe	OH



	R_1	R_2
9	OH	H
10	OMe	OH

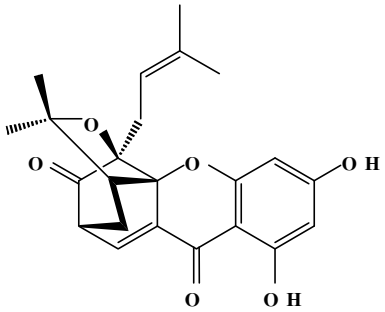


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Figure 1. Compounds isolated from *C. sumatranum* spp. *neriifolium*

Neriifolone A (**1**) was obtained as a yellow solid. The molecular formula, $C_{19}H_{19}O_6$, was determined by HRMS (ESI-TOF) ($[M+H]^+$ *m/z* 343.1194). The UV spectrum showed absorption bands of the xanthone skeleton[8-11] at 246, 256, 320 and 354 nm whereas the IR spectrum showed the stretches for the conjugated carbonyl and hydroxyl functionalities at 1647 and 3392 cm^{-1}, respectively. The ^1H NMR spectrum of **1**

(Table 1) exhibited a signal for a hydrogen bonded hydroxyl group (1-OH) at δ 13.44 and three aromatic protons at δ 7.81 (1H, *d*, *J* = 8.7 Hz), 7.03 (1H, *d*, *J* = 8.7 Hz) and 6.32 (1H, *s*) which were assigned to H-8, H-7 and H-2, respectively. Moreover, a methoxy group at δ 3.95 (3H, *s*) and a 1,1-dimethylallyl unit at δ 6.45 (1H, *dd*, *J* = 17.4, 10.5 Hz, H-4′), 4.96 (1H, *dd*, *J* = 17.4, 0.9 Hz, Ha-5′) 4.89 (1H, *dd*, *J* = 10.5, 0.9 Hz, Hb-5′) and 1.77 (6H, *s*, Me-2′ and Me-3′) were also observed in the ^{1}H NMR spectrum. The presence of a 1,1-dimethylallyl unit on C-4 was confirmed by the HMBC correlations (Figure 2) between Me-2′ (δ 1.77), Me-3′ (δ 1.77) and H-4′ (δ 6.45) to C-4 (δ 112.8). The assignment of the methoxy group on C-5 was based on the cross peak of the methoxy protons (δ 3.95) and H-7 (δ 7.03) with C-5 (δ 136.0) in the HMBC experiment.

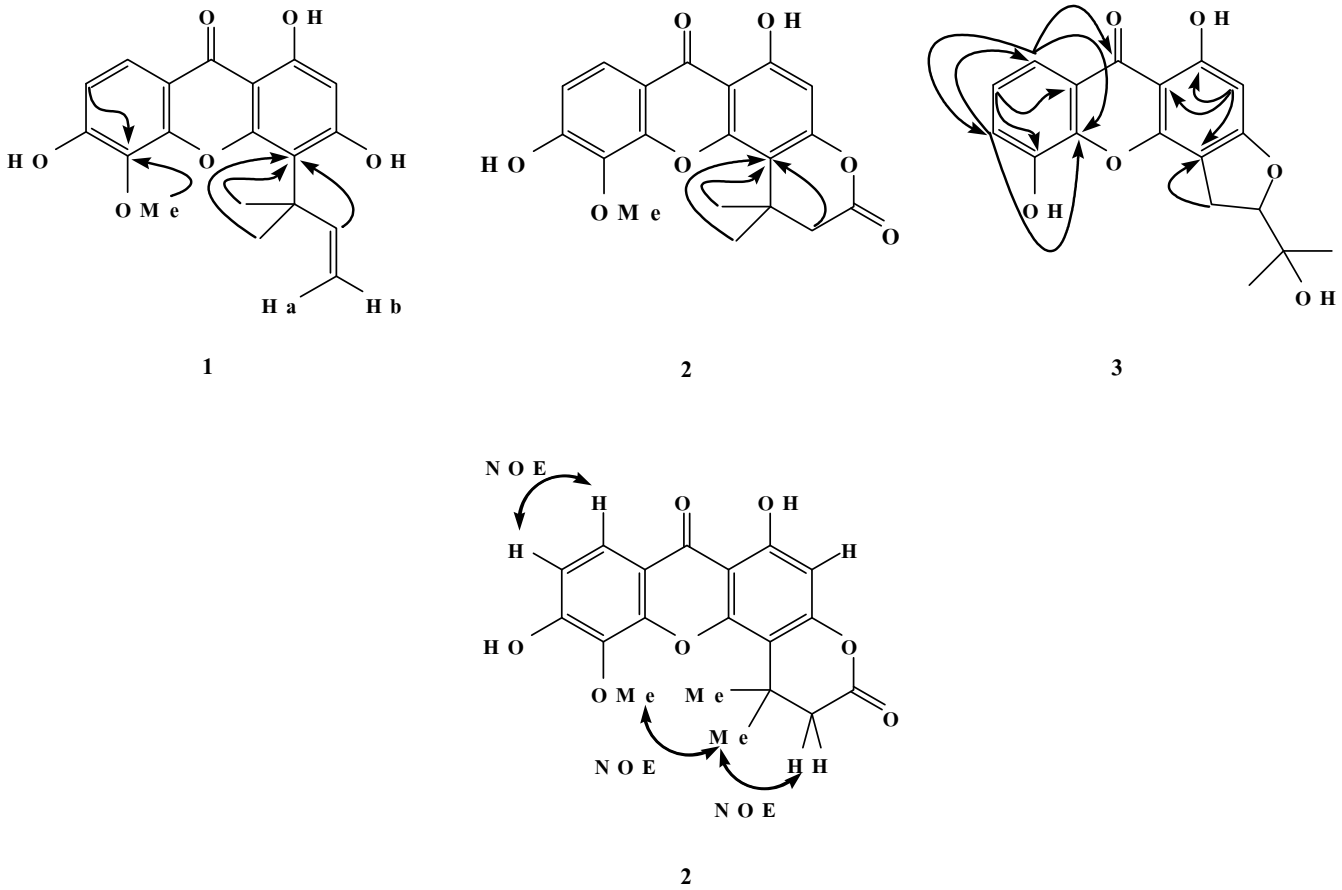

Figure 2. NOE cross peaks of **2** and HMBC correlations of **1**, **2** and **3**

Neriifolone B (**2**) was isolated as a yellow solid. The HRMS (ESI-TOF) gave a molecular ion peak at *m*/*z* 379.0789 ([M+Na]$^+$) which was consistent with the molecular formula $C_{19}H_{16}O_7$. The UV and IR spectra of **2** exhibited the same pattern as that of **1**. However, the IR spectrum of **2** also showed an additional carbonyl absorption peak at 1780 cm^{-1}. The ^{1}H and ^{13}C NMR spectral data of **2** (Table 1) were similar to those of **1** except for the disappearance of the 1,1-dimethylallyl unit. Compound **2** exhibited signals for the

3,3-dimethyl-δ-lactone ring which showed ^{1}H and ^{13}C NMR signals at δ 1.69/28.0 (Me-2′ and Me-3′), 2.85/45.1 (H/C-4′), 34.8 (C-1′) and 158.1 (C-3), 110.9 (C-4) and 167.0 (C-5′). Based on the HMBC correlations between Me-2′ and Me-3′ (δ 1.69) and H-4′ (δ 2.85) to C-4 (δ 110.9), this unit was placed at C-3 and C-4 of the xanthone skeleton. The cross peak between Me-2′ and Me-3′ (δ 1.69) with 5-OMe (δ 4.01) in the NOE experiment also supported this placement.

Table 1. ^{1}H- and ^{13}C-NMR spectral data of **1**, **2** and **3** in acetone-d_6

Position	**1**		**2**		**3**	
	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)	δ_C	δ_H (mult, *J* in Hz)	δ_C
1	-	162.6	-	162.8	-	162.1
2	6.32 (*s*)	100.1	6.41 (*s*)	100.2	6.19 (*s*)	100.0
3	-	164.8	-	158.1	-	161.6
4	-	112.8	-	110.9	-	110.6
4a	-	157.0	-	155.5	-	156.7
5	-	136.0	-	135.9	-	147.4
6	-	157.6	-	158.0	7.41 (*dd*, 8.1, 0.6)	120.9
7	7.03 (*d*, 8.7)	114.7	7.09 (*d*, 9.0)	115.4	7.28 (*t*, 8.1)	124.8
8	7.81 (*d*, 8.7)	121.9	7.85 (*d*, 9.0)	122.3	7.68 (*dd*, 8.1, 0.6)	116.1
8a	-	114.7	-	114.7	-	122.3
9	-	181.4	-	181.7	-	182.1
9a	-	103.8	-	106.3	-	105.1
10a	-	151.5	-	151.9	-	146.3
1′	-	42.0	-	34.8	2.03 (*dd*, 13.5, 2.4, *trans*-H)	46.8
					1.94 (*dd*, 13.5, 7.8, *cis*-H)	
2′	1.77 (*s*)	30.3	1.69 (*s*)	28.0	5.56 (*dd*, 7.8, 2.4)	94.0
3′	1.77 (*s*)	30.3	1.69 (*s*)	28.0	-	109.2
4′	6.45 (*dd*, 17.4, 10.5)	151.2	2.85 (*s*)	45.1	[i]1.75 (*s*)	32.8
5′	4.96 (*dd*, 17.4, 0.9, Ha)	109.2	-	167.0	[i]1.64 (*s*)	32.8
	4.89 (*dd*, 10.5, 0.9, Hb)					
1-OH	13.44 (*s*)	-	13.28 (*s*)	-	12.98 (*s*)	-
5-OMe	3.95 (*s*)	61.9	4.01 (*s*)	61.9	-	-

[i] Interchangeable

Neriifolone C (**3**) was isolated as a yellow solid. The molecular formula was determined as $C_{18}H_{17}O_6$ by HRMS (ESI-TOF) ($[M+H]^+$ *m*/*z* 329.1018). The UV and IR spectra confirmed that **3** has a xanthone skeleton. Compound **3** exhibited the following ^{1}H NMR (Table 1) signals for the xanthone nucleus. A chelated hydroxyl proton was located at 12.98 ppm. A singlet aromatic proton signal at δ 6.19 which showed ^{2}J and ^{3}J HMBC correlations (Figure 2) with C-1 (δ 162.1), C-4 (δ 110.6) and C-9a (δ 105.1) was assigned as the isolated proton H-2. The ABM system of spectrum at δ 7.68 (*dd*, *J* = 8.1, 0.6 Hz), 7.41 (*dd*, *J* = 8.1, 0.6 Hz) and 7.28 (*t*, *J* = 8.1 Hz) and the ^{2}J or ^{3}J HMBC correlations of H-6 (δ 7.41) with C-8 (δ 116.1) and C-10a (δ 146.3); H-7 (δ 7.28) with C-5 (δ 147.4) and C-8a (δ 122.3) and H-8 (δ 7.68) with C-6

(δ 120.9), C-9 (δ 182.1) and C-10a (δ 146.3) were assigned as aromatic protons H-8, H-6 and H-7, respectively. Also, a characteristic signal of a 2-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran moiety at δ 1.75 (*s*, H-4′), 1.64 (*s*, H-5′), 5.56 (J = 7.8, 2.4 Hz, H-2′), 2.03 (J = 13.5, 2.4 Hz, *trans*-H) and δ 1.94 (J = 13.5, 7.8 Hz, *cis*-H) and the HMBC correlations of H-1′ (δ 2.03 and 1.94) with C-4 (δ 110.6), confirmed that a 2-(1-hydroxy-1-methylethyl)-2,3-dihydrofuran moiety was fused to the xanthone nucleus at the C-3 and C-4 positions.

The remaining compounds were identified as β-mangostin (**4**),[12] pancixanthone-A (**5**),[13] assiguxanthone-A (**6**),[14] trapezifolixanthone (**7**),[15] 5-*O*-methylxanthone V_1 (**8**),[16] pancixanthone-B (**9**),[13] 5-*O*-methyl-2-deprenylrheediaxanthone B (**10**),[17] and (+)-4-oxa-tricyclo[4.3.1.0]decan-2-one scaffold (**11**),[18,19] by 1D and 2D NMR techniques and compared with previous reports of these known compounds.

EXPERIMENTAL

GENERAL

Melting points were measured with using a Bibby Stuart Scientific melting point apparatus SMP3. UV spectra were measured on a UNICAM UV-310 spectrophotometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1750 FT-IR spectrophotometer. ESI-TOF mass spectra were recorded on a Micromass LCT spectrometer. NMR spectra (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H COSY, NOESY, HMQC and HMBC) were recorded on Bruker AV300 or AV500 spectrometers. Chromatography was performed with the use of Merck prep-PLC and TLC, Merck silica gel 100 column and Sephadex LH-20 column. Optical rotation was measured in acetone solution with a sodium D line (589 nm) on an AUTOPOL® P-1020 (A068860638) automatic polarimeter.

PLANT MATERIAL

Barks of *C. sumatranum* ssp. *neriifolium* (Clusiaceae) were collected at Amphur Bannasan, Suratthani Province, Thailand, in February 2009. The plant was identified by Assistant Professor Dr. Maruay Mekanawakul, a specialist in the botanics, and the voucher specimen (WU 1453) is deposited at the botanic garden, Walailak University, Nakhon Si Thammarat, Thailand.

EXTRACTION AND ISOLATION

Chopped dried barks of *C. sumatranum* ssp. *neriifolium* (18.5 kg) were extracted with CH_2Cl_2 at room temperature for 3 days. After a removal of solvents, a yellow-brown viscous CH_2Cl_2 extract (366.28 g) was obtained. This extract (366.28 g) was dissolved in acetone. The acetone-soluble portion (255.28 g) was fractionated by quick column chromatography over silica gel 60H with the use of hexane, hexane- CH_2Cl_2, CH_2Cl_2, CH_2Cl_2-acetone, acetone and acetone-MeOH as eluents to afford 10 fractions (FCN1-FCN10).

Fraction FCN5 (8.01 g) was subjected to Sephadex LH-20 column chromatography with MeOH as an eluent, yielding 5 subfractions (FCN5a- FCN5e). **7** (6.4 mg) was obtained from repeated Sephadex LH-20 column chromatography with MeOH as an eluent and then by prep-TLC (CH_2Cl_2: hexane, 3:2 v/v) of subfraction FCN5e (218.7 mg). Repeated Sephadex LH20 gel filtration of fraction FCN6 (20.14 g) gave **4** (32.9 mg), **8** (1.4 mg) and **9** (110.6 mg). Fraction FCN7 (15.52 g) was separated by Sephadex LH-20 column chromatography with MeOH as an eluent, yielding **10** (40.0 mg). Fraction FCN8 (9.16 g) was purified by Sephadex LH-20 column chromatography with MeOH as an eluent and then by prep-TLC (CH_2Cl_2), affording **2** (17.5 mg). Fraction FCN8e (464.5 mg) was separated by Sephadex LH-20 column chromatography with MeOH as an eluent, yielding 6 subfractions (FCN8e1- FCN8e6). Subfraction FCN8e3 (40.4 mg) was purified by prep-PLC (100% CH_2Cl_2) to afford **1** (19.3 mg) while **5** (32.7 mg) and **3** (6.6 mg) were derived from subfraction FCN8e4 (160.0 mg) by prep-PLC (100% CH_2Cl_2). Subfraction FCN8e5 (27.0 mg) and subfraction FCN8-f (50.0 mg) were purified by prep-PLC (100% CH_2Cl_2) to afford **11** (15.0 mg) and **6** (18.9 mg), respectively.

Neriifolone A **1**: Yellow solid. mp 146–147 °C. UV λ_{max} (MeOH) (log ε): 246 (4.08), 256 (3.92), 320 (3.86), 354 (3.38) nm. IR (neat) ν_{max}: 3392 (OH), 1647 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+H]^+$ *m/z*: 343.1194 for $C_{19}H_{19}O_6$ (calcd. 343.1176).

Neriifolone B **2**: Yellow solid. mp 231–232 °C. UV λ_{max} (MeOH) (log ε): 244 (4.42), 314 (4.00), 348 (3.77) nm. IR (neat) ν_{max}: 3368 (OH), 1780 (C=O), 1651 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+Na]^+$ *m/z*: 379.0789 for $C_{19}H_{16}O_7Na$ (calcd. 379.0788).

Neriifolone C **3**: Yellow solid. mp 297–298 °C. Optical rotation: $[\alpha]_D^{23.6}$-27.42° (*c* 0.2600 %w/v in acetone). UV λ_{max} (MeOH) (log ε): 248 (4.28), 256 (4.27), 318 (4.02), 366 (3.07) nm. IR (neat) ν_{max}: 3392 (OH), 1651 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, acetone-d_6) and ^{13}C-NMR (75 MHz, acetone-d_6) see Table 1. TOF-MS $[M+H]^+$ *m/z*: 329.1018 for $C_{18}H_{17}O_6$ (calcd. 329.1020).

ACKNOWLEDGEMENTS

W.N. is grateful to the Thailand Graduate Institute of Science and Technology (TGIST) for a doctoral scholarship. Technical support from the Utilization of Natural Products Research Unit, Walailak University, is gratefully acknowledged and we also thank Assistant Professor Dr. Surat Laphookhieo, School of

Science, Mae Fah Luang University, for his valuable suggestions.

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