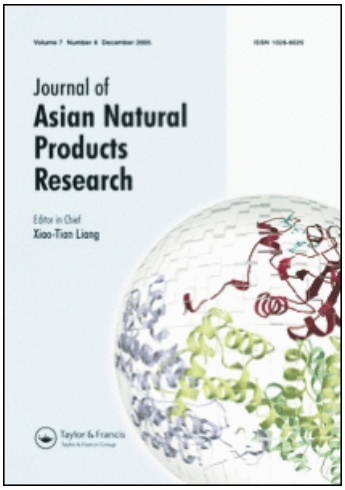

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B. Liang[a]; H.-R. Li[a]; L.-Z. Xu[a]; S.-L. Yang[a]
[a] Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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Xanthones from the roots of *Cudrania fruticosa* Wight

B. LIANG, H.-R. LI, L.-Z. XU* and S.-L. YANG*

Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100094, China

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Chemical investigation on the roots of *Cudrania fruticosa* resulted in the isolation of two new xanthones, 1,6,7-trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone (**1**) and 3,6,7-trihydroxy-1-methoxyxanthone (**2**), together with three known ones, 1,3,5-trihydroxy-4-(3-hydroxy-3-methylbutyl)xanthone (**3**), 1,3-dihydroxy-6,7-dimethoxyxanthone (**4**) and 3,5,6-trihydroxy-1-methoxyxanthone (**5**), respectively. Their structures were elucidated on the basis of spectral and chemical techniques.

Keywords: Xanthones; *Cudrania fruticosa*; Moraceae; 1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone; 3,6,7-Trihydroxy-1-methoxyxanthone

1. Introduction

Cudrania fruticosa Wight belongs to the Moraceae family, mainly distributed in Yunnan province of China. Certain plants of this genus have been reported to display anti-inflammatory and hepatoprotective effects [1], anti-lipid peroxidation [2], antifungal [3] and antimicrobial [4] activities, and cytotoxicity to human tumour cell lines [5]. However, little has been documented on the chemical constituents or biological activity of this plant to date. As a result, we have undertaken a systematic investigation on the chemical constituents of *C. fruticosa*. The present paper reports the isolation and structural elucidation of two new xanthones, 1,6,7-trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone (**1**) and 3,6,7-trihydroxy-1-methoxyxanthone (**2**) (figure 1) from the ethanolic extract of the roots of this plant, together with three known ones (**3–5**).

2. Results and discussion

Compound **1** was isolated as yellow needles. Its molecular formula was determined as $C_{19}H_{18}O_6$ by HREI-MS, which showed a $[M]^+$ ion peak at *m/z* 342.1113, corresponding to eleven degrees of unsaturation. The UV spectrum of **1** exhibited characteristic absorption

*Corresponding authors. Email: xulizhen2002@hotmail.com; Email: beibeiliang@263.net (S. Yang).

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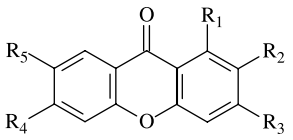

1.R_1=R_4=R_5=OH R_2=$C(CH_3)_2CH{=}CH_2$ R_3=OCH_3
2.R_1=OCH_3 R_2=H R_3=R_4=R_5=OH

Figure 1. Structures of compounds **1** and **2**.

bands of xanthone (λ_{max}^{MeOH}, 235, 261, 316, 376 nm). In addition, the presence of a free hydroxyl group at either C-6 or C-3 was indicated based on a bathochromic shift in its UV spectrum upon the addition of NaOAc. The ^{1}H NMR spectrum displayed resonances for an ABX system at δ 6.25 (1H, dd, J = 17.4,10.2 Hz, H-2′), δ 4.90 (1H, dd, J = 17.4,1.2 Hz, H-3′) and δ 4.85 (1H, dd, J = 10.2,1.2 Hz, H-3′), corresponding to an ethenyl group, three downfield proton signals at δ 10.95-9.60 (2H, brs, 6,7-OH) and δ 13.60 (1H, s, 1-OH) to two hydroxyl groups and a conjugated hydroxyl group, respectively, and signals to two methyl groups (δ 1.59, 6H, s, $2CH_3$), an aromatic methoxyl (δ 3.83, 3H, s, 3-OCH_3) and three uncoupled aromatic protons (δ 7.35, 1H, s, H-8; δ 6.80, 1H, s, H-5; δ 6.46, 1H, s, H-4). Amongst the latter three proton signals, H-8 appeared to be shifted downfield relative to the other two as a result of deshielding effect of the carboxyl group. Based upon the above findings, it was deduced that one aromatic ring of the xanthone was tri-substituted whilst the other was 6,7-di-substituted. The positions of the substituents were confirmed by the HMBC spectrum (figure 2), in which the correlations between 1-OH (δ 13.60) and C-2 (δ 112.0), C-8b (δ 102.4) suggested the location of this hydroxyl group at C-1. In addition, the correlations between 1′-CH_3 (δ 1.59) and C-2′ (δ 150.4), C-2 (δ 112.0), H-2′ (δ 6.25) and C-2 (δ 112.0) in the HMBC spectrum of **1** were also indicative of the existence of a 1,1-dimethyl-2-propenyl moiety at C-2. The presence of such a group was further supported by the presence of an ion peak at *m*/*z* 69 in the EI-MS spectrum. Moreover, the HMBC spectrum also displayed the correlations between the other two hydroxyl signals 6,7-OH (δ 10.95 $\sim$ 9.60) and C-7 (δ 143.9), C-6 (δ 154.5), respectively. As a result, it could be confirmed that these two hydroxyl groups were *ortho*-substituted at the C-6,7 of **1** whilst the correlations between the aromatic proton H-4 (δ 6.46) and C-2(δ 112.0), C-8b (δ 102.4) and between 3-OCH_3 (δ 3.83) and C-3 (δ 164.4) indicated the aromatic proton and 3-OCH_3 was located at positions C-4 and C-3, respectively. Thus, the structure of **1** was determined as 1,6,7-trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone.

Compound **2** was obtained as white powder. The $[M + H]^+$ ion peak at *m*/*z* 275.0566 in its HRESI-MS suggested a molecular formula of $C_{14}H_{10}O_6$, indicating 10 degrees of unsaturation. The UV spectrum of **2** showed absorptions at 250, 302 and 355 nm. A bathochromic shift in its UV spectrum upon the addition of NaOAc indicated the presence of a free hydroxyl group at either C-6 or C-3. The ^{1}H NMR spectrum displayed resonances for

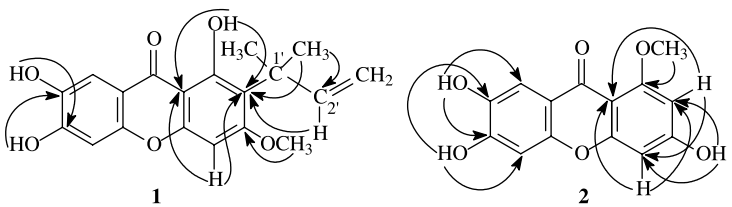

Figure 2. Key HMBC correlations of compounds **1** and **2**.

two *meta*-protons at δ 6.34 (1H, s-like, H-4) and δ 6.30 (1H, s-like, H-2), an aromatic methoxyl at δ 3.79 (3H, s, 1-OCH_3) and three free hydroxyl groups at δ 10.71, 10.29, and 9.51 (each 1H, s, 3,6,7-OH), respectively, and signals corresponding to two uncoupled aromatic protons (δ 6.74, 7.32, each 1H, s, H-5,8). These results indicated that one of the aromatic rings of this xanthone was *meta*-oxygenated whilst the other was 6,7-dioxygenated. In addition, the signal at δ 172.9 (C-9) in the ^{13}C NMR spectrum indicated the absence of a conjugated hydroxyl group. Such a result was in agreement with the absence of a signal for conjugated hydroxyl group in the ^{1}H NMR spectrum. The positions of the substituents were deduced based on the HMBC spectrum (figure 2). For example, the correlations between 6-OH (δ 10.29) and C-7 (δ 143.2) and C-5(δ 102.1), and between 7-OH (δ 9.51) and C-6 (δ 152.2) and C-8 (δ 109.3) in the HMBC spectrum suggested that these two hydroxyl groups were *ortho*-substituted at the C-6,7 positions of the xanthone. In addition, the aromatic proton signal H-2 (δ 6.30) was correlated with both C-4 (δ 94.8) and C-8b (δ 104.9), and the aromatic proton signal H-4 (δ 6.34) was correlated with both C-2 (δ 95.3) and C-8b (δ 104.9); therefore, these two aromatic protons were located at C-2 and C-4, respectively. Moreover, the correlations between 3-OH (δ 10.71) and C-4 (δ 94.8) and C-2 (δ 95.3), and between the methoxyl signal 1-OCH_3 (δ 3.79) and C-1 (δ 161.7) confirmed the C-1 location of the methoxyl group and the C-3 location of the hydroxyl group, respectively. On the basis of the above findings, the structure of **2** was concluded to be 3,6,7-trihydroxy-1-methoxyxanthone.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. UV spectra were measured on a Philips PYE Unican Pu8800 spectrophotometer. IR spectra were recorded on a Perkin–Elmer 983G spectrometer. NMR spectra were measured in DMSO-d_6 on a Bruker AM-500 spectrometer, using TMS as internal standard. Coupling constants (J values) are given in Hz. A Zabspec E spectrometer was used to record the EI-MS and HREI-MS. The TLC and HPTLC employed precoated silica gel plates (Qingdao Haiyang Chem. Co. Ltd.). For the column chromatography, silica gel (Qingdao Haiyang) and Sephadex LH 20 (Pharmacia) were used. MPLC were performed on a system equipped with a Büchi pump B-688, Büchi B-684 Fraction collector, UVOLOG-5IIIA UV-Detector, and Büchi columns and precolumns, with the stationary phase silica gel 60 (15–40 μm, Qingdao Haiyang) and polyamide (100–200 mesh, Taizhou Zhejiang).

3.2 Plant material

The roots of *Cudrania fruticosa* were collected in Yunnan province of China and identified by Professor Hong Wang (Menglun Botanical Garden).

3.3 Extraction and isolation

The dried roots (11 kg) of the plant material were ground and extracted with 95% EtOH (110 L × 3, 4 h each) under reflux. The EtOH extract (590 g) was subjected to vacuum liquid chromatography column (VLC, silica gel H) and eluted with CH_2Cl_2, petroleum

ether/acetone (9:1–0:1, gradient) and CH_3OH to give 8 fractions. Fraction 3 (25 g) was isolated by VLC (silica gel 200–300 mesh) using petroleum ether/acetone (99:1–90:10, gradient) to give 140 parts. Parts 10–44 were purified on a polyamide chromatography column, which was eluted with a gradient of $CHCl_3/CH_3OH$ (100:0–90:10) and Sephadex LH 20 to give **1** (5 mg) and **3** (6 mg). Fraction 2 (10 g) was further separated by MPLC (Silica gel 100–200 mesh), eluted with petroleum ether/acetone (99:1–50:50, gradient) to afford 98 parts. Parts 75–98 were purified by repeated Silica gel chromatography column (petroleum ether/acetone 9:1–3:1, gradient) and Sephadex LH 20 to give **4** (4 mg). Fraction 6 (87 g) was column chromatographed (polyamide 100–200 mesh) using $CHCl_3/CH_3OH$ (98:2–0:1, gradient) to give 13 parts. Part 7 was further separated with polyamide chromatography column ($CHCl_3$:/CH_3OH 98:2–0:1, gradient) and Sephadex LH 20 to provide **2** (7 mg) and **5** (11 mg).

3.3.1 1,6,7-Trihydroxy-2-(1,1-dimethyl-2-propenyl)-3-methoxyxanthone (1). Yellow needles (CH_3OH), mp 182–185°C; UV λ_{max}^{MeOH} nm (log ε): 235 (4.05), 261 (4.14), 316 (3.77), 376 (3.78); + NaOAc: 262, 390; IR (KBr) ν_{max} cm^{-1}: 3330, 1645, 1620, 1580, 1460, 1200, 820; EI-MS *m/z*: 342 [M^+, 65], 327 [100], 316 [8], 300 [15], 257 [8], 190 [2], 69 [5]; HREI-MS *m/z* 342.1113 (calcd for $C_{19}H_{18}O_6$, 342.1103); ^1H NMR and ^{13}C NMR data, see table 1.

3.3.2 3,6,7-Trihydroxy-1-methoxyxanthone (2). White powder (CH_3OH), mp >300°C (decomp.); UV λ_{max}^{MeOH} nm (log ε): 250 (2.84), 302 (2.49), 355 (2.47); + NaOAc: 254, 371; IR (KBr) ν_{max} cm^{-1}: 3417, 2925, 1639, 1622, 1580, 1469, 1385; positive ESI-MS *m/z*: 275.3

Table 1. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data of **1** and **2** in DMSO-d_6.

Position	***1***		***2***	
	δ_H *(J in Hz)*	δ_C	δ_H *(J in Hz)*	δ_C
1	13.60 (s, HO)	161.1		161.7
2		112.0	6.30 (s-like)	95.3
3		164.4	10.71 (s, HO)	162.8
4	6.46 (s)	95.2	6.34 (s-like)	94.8
4a		154.3		159.0
4b		150.8		149.2
5	6.80 (s)	102.1	6.74 (s)	102.1
6	10.95–9.60 (brs, HO)	154.5	10.29 (s, HO)	152.2
7	10.95–9.60 (brs, HO)	143.9	9.51 (s, HO)	143.2
8	7.35 (s)	107.6	7.32 (s)	109.3
8a		111.0		114.7
8b		102.4		104.9
9		179.6		172.9
1′		40.6		
2′	6.25 (dd, 17.4, 10.2)	150.4		
3′	4.90 (dd, 17.4, 1.2)	107.0		
	4.85 (dd, 10.2, 1.2)			
1-OCH_3			3.79 (s, CH_3O)	55.9
3-OCH_3	3.83 (s, CH_3O)	55.9		
1′-CH_3	1.59 (s, $2CH_3$)	29.2		
		29.2		

$[M + H]^+$; HRESI-MS *m/z* 275.0566 (calcd for $C_{14}H_{10}O_6$, 275.0556); ^1H NMR and ^{13}C NMR data: see table 1.

3.3.3 1,3,5-Trihydroxy-4-(3-hydroxy-3-methylbutyl) xanthone (3). Yellow needles (CH_3OH), mp 286–287°C; all the spectral data were in excellent agreement with those of 1,3,5-trihydroxy-4-(3-hydroxy-3-methylbutyl) xanthone [6].

3.3.4 1,3-Dihydroxy-6,7-dimethoxyxanthone (4). Yellow needles (CH_3OH), mp 286–287°C; all the spectral data were identical to those of 1,3-dihydroxy-6,7-dimethoxyxanthone [7].

3.3.5 3,5,6-Trihydroxy-1-methoxyxanthone (5). White powder (CH_3OH), mp 294°C (decomp.); all the spectral data were in well agreement with 3,5,6-trihydroxy-1-methoxyxanthone [8].

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