PERGAMON

Phytochemistry 52 (1999) 1371–1373

PHYTOCHEMISTRY

Xanthones from *Hypericum ascyron*

Li-Hong Hu, See-Chung Yip, Keng-Yeow Sim*

Department of Chemistry, National University of Singapore, Kent Ridge 119260, Singapore

Received 26 April 1999; accepted 14 July 1999

Abstract

The isolation and identification of eight xanthones, together with friedelin, from the aerial parts of *Hypericum ascyron* are reported. One of these xanthones, 3,6-dihydroxy-1,7-dimethoxyxanthone is a new compound and the other 5-chloro-1,6-dihydroxy-3-methoxy-8-methylxanthone is the first chloroxanthone isolated from higher plants.

Keywords: *Hypericum ascyron*; Guttiferae; Xanthone; 5-Chloro-1,6-dihydroxy-3-methoxy-8-methylxanthone; 3,6-Dihydroxy-1,7-dimethoxyxanthone

1. Introduction

Hypericum ascyron L. is a Chinese herbal medicine used in the treatment of numerous disorders such as abscesses, boils, headache, nausea and stomach ache (Jiang Su New Medical College, 1977). *H. ascyron* was previously reported to contain flavonoids (Wang & Wang, 1980). In continuation with our phytochemical work on the plants of *Hypericum* genus (Hu & Sim, 1998, 1999) we wish to report the isolation and structure elucidation of eight xanthones (**1**–**8**), including a new product 1,7-dimethoxy-3,6-dihydroxyxanthone (**5**), together with friedelin (**9**), from aerial parts of *H. ascyron*.

An ethanol extract of the aerial parts of *H. ascyron* was partitioned between H_2O and $CHCl_3$. The $CHCl_3$-soluble part was fractionated on a silica gel column, affording eight groups of eluates, which yielded eight xanthones (**1**–**8**) and friedelin (**9**) after further chromatographic purification.

2. Results and discussion

The compounds **1**–**3** and **6**–**9** were characterized by detailed NMR–MS analyses to be as 2-methoxyxanthone (**1**), euxanthone (**2**), 1-hydroxy-7-methoxyxanthone (**3**) (Della Monache, Marquina, Delle Monache, Marini Bettdo & Alves De lima, 1983), 7-methoxy-1,5,6-trihydroxyxanthone (**6**) (Iinuma, Tosa, Ito, Tahaka & Aqil, 1995), toxyloxanthone B (**7**) (Chen & Chen, 1985), 1,3,6,7-tetrahydroxy-8-(3-methylbut-2-enyl)xanthone (**8**) (Nielsen & Arends, 1979), and friedelin (**9**) (Iveland & Walha, 1976).

The mass spectrum of compound **4**, with a characteristic isotopic pattern, indicated the presence of chlorine and the HREIMS established its molecular formula as $C_{15}H_{11}O_5Cl$. The UV, IR and NMR spectral data indicated that it is a pentasubstituted chloroxanthone, probably identical to vinetorin isolated from the lichen *Lecanora vinetorum* (Poelt & Huneck, 1968). The original proposed incorrect structure for vinetorin was revised to 5-chloro-1,6-dihydroxy-3-methoxy-8-methylxanthone (**4**) on the grounds of its ^{1}H-NMR spectrum (Sundholm, 1978; Huneck & Hofle, 1978) and this had been confirmed by synthesis (Sundholm, 1979; Fitzpatrick, Sala & Sargent, 1980).

* Corresponding author. Tel.: +65-874-2667; fax: +65-7791691.
E-mail address: chmsimky@nus.edu.sg (K.Y. Sim).

0031-9422/99/$ - see front matter
PII: S0031-9422(99)00412-4

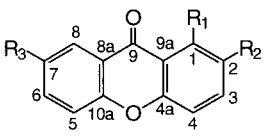
Table 1
NMR data for compounds **4** and **5**

	4				**5**			
Position	H[a]	^{13}C[b]	DEPT	HMBC[c]	^{1}H[a]	^{13}C[b]	DEPT	HMBC[c]
1		162.6	C			162.6	C	
2	6.33 *d* (2.1)	97.3	CH	1, 3, 4, 9a	6.33 *d* (1.9)	95.4	CH	1, 3, 4, 9a
3		165.8	C			162.8	C	
4	6.53 *d* (1.9)	92.0	CH	2, 3, 4a, 9a	6.37 *d* (1.8)	94.8	CH	2, 3, 4a, 9a
4a		156.1	C			158.5	C	
5		104.6	C		6.80 *s*	102.2	CH	6, 7, 8a, 10a
6		158.6	C			150.1	C	
7	6.81 *s*	115.5	CH	5, 8a, 8-Me		145.5	C	
8		140.3	C		7.38 *s*	105.8	CH	6, 7, 9, 10a
8a		111.6	C			114.3	C	
9		181.3	C			172.5	C	
9a		102.7	C			104.3	C	
10a		153.9	C			152.7	C	
1-OH or OMe	13.17 *s*			1, 2, 9a	3.81 *s*	55.8	CH_3	1
3-OH or OMe	3.88 *s*	56.0	CH_3	3	10.46 *s*			
6-OH	11.65 *s*				10.42 *s*			
7-OMe					3.84 *s*	55.7	CH_3	7
8-Me	2.71 *s*	22.8	CH_3	7, 8, 8a				

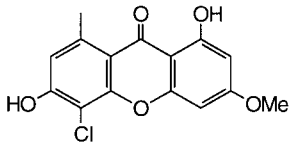
[a] Recorded in DMSO-d_6 at 300 MHz.
[b] Recorded in DMSO-d_6 at 75 MHz.
[c] Carbons that correlate with the proton resonance.

The HMBC and NOESY data confirmed that our compound can be assigned as 5-chloro-1,6-dihydroxy-3-methoxy-8-methylxanthone (**4**) and it is interesting to note that it is the first chloroxanthone to be isolated from a higher plant. Xanthones from higher plants are biosynthesised by the mixed shikimate-polyketide pathway whereas those from the lower plants are formed from a single polyketide chain. Chloro-substituted xanthones, which are of chemotaxonomic interest in recent systematic studies of lichens, are found frequently in many lichens (Sundholm, 1978; Elix & Crook, 1992) and we cannot exclude the possibility that the metabolite **4** might have come from a lichen growing on our plant sample.

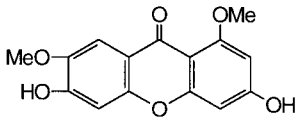
Compound **5**, obtained as a yellow powder, showed the $[M]^+$ at *m/z* 288.0614 in the HREIMS, which corresponds to $C_{15}H_{12}O_6$ (calcd. 288.06340). The UV and IR spectra were suggestive of a xanthone derivative. In the ^{1}H-NMR spectrum, the presence of two hydroxyl groups [δ 10.42 ppm (1H, *brs*) and 10.46 ppm (1H, *brs*)] and two methoxyl groups [δ 3.81 ppm (3H, *s*) and 3.84 ppm (3H, *s*)] were observed in addition to two *meta*-coupled protons [δ 6.33 ppm (1H, *d*, J = 1.9 Hz) and 6.37 ppm (1H, *d*, J = 1.8 Hz)] and two singlet aromatic protons [δ 7.38 ppm (1H, *s*) and 6.80 ppm (1H, *s*)]. All protonated carbons were assigned by the HMQC spectrum. In the HMBC spectrum, the singlet proton at δ 7.38 ppm was correlated to three aromatic carbons at δ



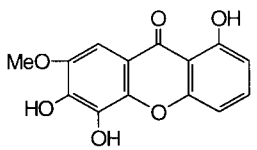
1. R_1=H, R_2=OMe, R_3=H
2. R_1=OH, R_2=H, R_3=OH
3. R_1=OH, R_2=H, R_3=OMe



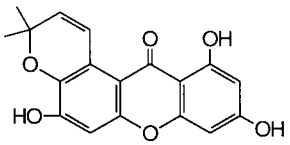
4



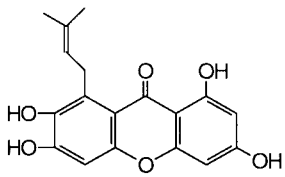
5



6



7



8

145.5, 150.1 and 152.9 ppm, and the ketone carbon at δ 172.5 ppm, the former of which (δ 145.5 ppm) was further correlated to one of the other singlet aromatic proton at δ 6.80 ppm. An NOE was observed between the proton at δ 7.38 ppm and the methoxyl protons at δ 3.84 ppm. These results indicated that **5** was a 6-hydroxy-7-methoxyxanthone derivative, which was further supported by the other correlations in the HMBC spectrum (Table 1). The substituent pattern of the other ring (1-methoxy-3-hydroxy) was determined to be similar to calophyllumin B (Iinuma et al., 1996), isolated from the roots of *Calophyllum inophyllum*, by comparison of their proton and carbon-13 spectral data. This was confirmed by a NOE cross peak between one of *meta*-coupled protons at δ 6.33 ppm and the methoxyl protons at δ 3.81 ppm and by the other correlations in the HMBC spectrum (Table 1). Thus compound **5** was characterized as 3,6-dihydroxy-1,7-dimethoxyxanthone.

3. Experimental

3.1. General

EIMS were determined on a Micromass VG 7035 mass spectrometer at 70 ev. NMR spectra were recorded on Bruker ACF 300 [300 MHz (^{1}H) and 75 MHz (^{13}C)] and AMX 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] instruments using $CDCl_3$ solutions, unless otherwise stated, with TMS as an internal standard. IR spectra were recorded on a Bio-Rad FTIR spectrophotometer and UV spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer. Chromatographic separations were carried out on silica gel 60 (40–63 μm), silica gel 60 RP-18 (40–63 μm) and Sephadex LH-20.

3.2. Plant material

The whole plant of *Hypericum ascyron* was collected from Suzhou, Jiangsu Province, P.R. China in August 1997. A voucher specimen is deposited at the herbarium of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, P.R. China.

3.3. Extraction and isolation

The whole air-dried ground plants (5.0 kg) were extracted at room temperature with 95% EtOH for 7 days, the extract was concentrated in vacuo and the residue partitioned between H_2O and $CHCl_3$, *n*-BuOH, respectively. The $CHCl_3$-soluble portion (50.0 g) was then separated into eight fractions by silica gel cc, eluted with different proportions of hexane-acetone (1:0, 20:1, 10:1, 5:1, 2:1, 1:1, 1:5, 0:1). Further chromatographic purification (Sephadex LH-20 and ODS) yielded the compounds as follows: **1** (5.2 mg), **2** (3.5 mg), **3** (50.2 mg), **4** (7.6 mg), **5** (13.2 mg), **6** (8.4 mg), **7** (7.3 mg), **8** (4.7 mg) and **9** (23.2 mg).

3.3.1. 5-Chloro-1,6-dihydroxy-3-methoxy-8-methylxanthone (*4*)

Yellow powder, mp 243–244°C (dec.). EI-HRMS: *m/z* 306.0246, $C_{15}H_{11}O_5^{35}Cl$ requires 306.0295. EI-MS *m/z*: 308 $[C_{15}H_{11}O_5^{37}Cl]^+$, 306 $[C_{15}H_{11}O_5^{35}Cl]^+$, 277, 262, 242, 185, 153, 115, 77, 43. IR (KBr) ν_{max} 3318, 1665, 1597, 1522, 1406, 1285, 1201 cm^{-1}. UV (MeOH) λ_{max} (log ε) 214 (3.97), 246 (3.91), 272 (3.52). ^{1}H- and ^{13}C-NMR (determined in DMSO-d_6) see Table 1. ^{1}H-NMR (acetone-d_6 for comparison with spectrum reported in literature) 500 MHz: 6.31 (1H, *d*, *J* = 2.2 Hz, H-2), 6.54 (1H, *d*, *J* = 2.0 Hz, H-4), 6.90 (1H, *s*, H-7), 13.23 (1H, *s*, HO-1), 3.94 (3H, *s*, MeO-3), 7.37 (1H, *brs*, HO-7), 2.78 (3H, *s*, Me-8).

3.3.2. 3,6-Dihydroxy-1,7-dimethoxyxanthone (*5*)

Yellow powder, mp 251–252°C (dec.). EI-HRMS: *m/z* 288.0614, $C_{15}H_{12}O_6$ requires 288.0634. EI-MS *m/z*: 288 $[M]^+$, 271, 259, 242, 215, 144, 44. IR (KBr) ν_{max} 3384, 1617, 1601, 1570, 1466, 1438, 1280 cm^{-1}. UV (MeOH) λ_{max} (log ε) 212 (4.17), 250 (4.03), 302 (3.65), 348 (3.61) nm. ^{1}H- and ^{13}C-NMR, see Table 1.

Acknowledgements

We thank the National University of Singapore for a grant (RP950603) for this research.

References

Chen, M.-T., & Chen, C.-M. (1985). *Heterocycles*, *23*, 2543.
Della Monache, F., Marquina, M., Delle Monache, G., Marini Bettdo, G. B., & Alves De lima, R. (1983). *Phytochemistry*, *22*, 227.
Elix, J. A., & Crook, C. E. (1992). *The Bryologist*, *95*, 52.
Fitzpatrick, L., Sala, T., & Sargent, M. V. (1980). *J. Chem. Soc., Perkin Transactions*, *I 1980*, 85.
Hu, L.-H., & Sim, K.-Y. (1998). *Tetrahedron Lett*, *39*, 7999.
Hu, L.-H., & Sim, K.-Y. (1999). *Tetrahedron Lett*, *40*, 759.
Huneck, S., & Hofle, G. (1978). *Tetrahedron*, *34*, 2491.
Iinuma, M., Tosa, H., Ito, T., Tahaka, T., & Aqil, M. (1995). *Phytochemistry*, *40*, 267.
Iinuma, M., Tosa, H., Tanaka, T., Ito, T., Yonemori, S., Chelladurai, V., Aquil, M., Takahashi, Y., & Naganawa, H. (1996). *Heterocycles*, *43*, 1521.
Iveland, R. E., & Walha, D. E. (1976). *Tetrahedron Lett*, *32*, 1071.
Jiang Su New Medical College (1977). Dictionary of Chinese crude drugs. Shanghai: Shanghai Scientific Technological Publishers, p. 1002.
Nielsen, H., & Arends, P. (1979). *J. Nat. Prod*, *42*, 301.
Poelt, J., & Huneck, S. (1968). *Osterreichische Botanische Zeitschrift*, *115*, 412.
Sundholm, E. G. (1978). *Tetrahedron*, *34*, 577.
Sundholm, E. G. (1979). *Acta Chemica Scandinavica*, *B 33*, 475.
Wang, Z.-Q., & Wang, X.-R. (1980). *Yao Hsueh Hsueh Pao*, *6*, 365.