Four New Phenones from the Cortexes of *Polygala tenuifolia*

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From the 95% EtOH extract of the cortexes of *Polygala tenuifolia*, four new phenones and three known xanthones were isolated. The structures of the four new phenones were identified as 4-*O*-[α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl]-2-hydroxyl-6-methoxybenzophenone (tenuiphenone A, 1), 3,5-di-*C*-β-glucopyranosyl-2,4,6,3′-tetrahydroxybenzophenone (tenuiphenone B, 2), 2′,4′,6′-trihydroxyphenyl-(24*Z*)-triacontene-1-one (tenuiphenone C, 3), 2′,4′,6′-trihydroxyphenyl-(26*Z*)-dotriacontene-1-one (tenuiphenone D, 4) respectively, on the basis of spectroscopic analyses. The isolation of 1 and 2 supplied an evidence for the hypothesis that xanthone was biosynthesized from benzophenone in the plants.

Key words *Polygala tenuifolia*; phenone; tenuiphenone

Previous reports described that many saponins, saccharide esters and xanthones had been isolated from *Polygala tenuifolia*,[1—6] whose cortex is used widely in China, Korea and Japan as a tonic, sedative, expectorant and anti-inflammation agent. In the process of our studying the chemical constituents of *P. tenuifolia*, phenones were also isolated from this plant besides the above mentioned compounds. So in this paper, we describe the isolation and structural identification of four new phenones, tenuiphenones A—D. This is the second report of phenones isolated from the genus of Polygala, besides the former report of benzophenones from *P. telephioides*.[7]

Results and Discussion

The $CHCl_3$ and *n*-BuOH soluble parts of 95% EtOH extract of *P. tenuifolia* were subjected to silica gel, Sephadex LH-20 column chromatographies and HPLC purification to give compounds **1**—**6**.

Compound **1** was obtained as a yellow amorphous powder and its molecular formula was deduced as $C_{26}H_{32}O_{13}$ from HR-SI-MS spectrometry (*m/z* 553.1923 $[M+H]^+$). The IR spectrum of **1** showed the presence of hydroxyl groups (3387 cm^{-1}), a hydrogen bonded ketone (1664 cm^{-1}), and aromatic carbons (1612, 1425 cm^{-1}). On acid hydrolysis, **1** afforded glucose and rhamnose, and the GC analyses of their L-cysteine derivatives showed their retention times were identical with those of D-glucose and L-rhamnose, respectively. The ^{13}C-NMR spectrum (Table 1) displayed 24 carbon signals in total, among which twelve were assigned to the sugar moiety, one for a methoxyl and the remaining eleven were reminiscent of a benzopheonone or a xanthone skeleton. The chemical shift of carbonyl signal (δ 194.5) indicated **1** was a benzophenone compound.[7]

The ^{1}H-NMR spectrum of **1** showed a phenyl hydroxyl proton signal at δ 9.92 (1H, br s), a group of *mono*-substituted phenyl proton signals at δ 7.69 (2H, d, J=7.5 Hz), 7.59 (1H, t, J=7.5 Hz) and 7.48 (2H, dd, J=7.5, 7.5 Hz); two singlet aromatic proton signals at δ 6.23 and 6.20; two anomeric proton signals at δ 5.11 (1H, br s) and 4.99 (1H, d, J=7.5 Hz), and a methoxyl proton signal at δ 3.57 (3H, s). In the HMBC spectrum, one of the singlet aromatic proton signal at δ 6.23 (1H, s, H-5) was correlated with δ 96.2 (C-3), 110.0 (C-1), 158.2 (C-6) and 159.5 (C-4); another singlet aromatic proton signal at δ 6.20 (1H, s, H-3) was correlated with δ 91.4 (C-5), 110.0 (C-1), 156.3 (C-2) and 159.5 (C-4); the rhamnose anomeric proton signal at δ 5.11 was correlated with C-2 (δ 76.4) of the glucosyl residue, and the glucosyl anomeric proton signal at δ 4.99 was correlated with the C-4 signal of the aglycone (δ 159.5), and the methoxyl proton signal at δ 3.57 was correlated with the C-6 signal of the aglycone (δ 158.2). In the NOESY spectrum, the correlations were observed between the proton at δ 6.23 with δ 3.57; δ 6.20 and 6.23 with δ 4.99. The configuration of the glucosyl residue was deduced to be β from the J value (7.5 Hz) of the anomeric proton, and of rhamnosyl residue to be α by comparing the ^{13}C-NMR data (δ 100.5, 70.5, 70.6, 71.9, 68.3, 18.1), especially the carbon chemical shifts of C-3 (δ 70.6) and C-5 (δ 68.3), with the literature (α-rhamnose: δ 100.1, 70.4, 70.4, 72.0, 68.5, 18.0; β-rhamnose: δ 98.6, 71.7, 74.8, 73.8, 73.2, 18.4).[8,9] Thus, **1** was determined to be 4-*O*-[α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyl]-2-hydroxyl-6-methoxybenzophenone, named tenuiphenone A.

Compound **2** was obtained as a yellow amorphous powder, and its molecular formula was deduced as $C_{25}H_{30}O_{15}$ from its HR-SI-MS spectrometry (*m/z* 569.1517 $[M-H]^-$). The ^{13}C-NMR spectrum data of **2** were comprised of six sugar moiety carbon signals (δ 75.2, 72.7, 77.8, 69.0, 81.0, 59.9) assigned to be those of the *C*-glucosyl by comparing with the reported values (δ 74.7, 72.1, 77.8, 69.2, 81.1, 60.0),[7,10] and the configuration of the glucosyl residue was deduced to be β from the J value (10.0 Hz) of the anomeric proton. Besides the sugar carbon signals, there were eleven benzophenone skeleton carbon signals in the ^{13}C-NMR.[7] The ^{1}H-NMR spectrum of **2** showed a ABCX-system aromatic protons at δ 7.24 (1H, dd, J=8.0, 8.0 Hz), 7.13 (1H, d, J=8.0 Hz), 7.11 (1H, br s), and 6.94 (1H, dd, J=2.5, 8.0 Hz); four phenyl hydroxyl proton signals at δ 9.92 (1H, br s), 8.81 (2H, s) and 8.65 (1H, s). The duplicate signals of the glucosyl moiety at δ 75.2, 72.7, 77.8, 69.0, 81.0, 59.9 and of the other two signals at δ 154.8 and 104.8 indicated a symmetrical structure existed in **2**, which could also been proved by the MS data. In the HMBC spectrum of **2**, the proton signal at δ 8.81 (2H, s, –OH×2) was correlated with the carbon signals at δ 109.0 (C-1), 154.8 (C-2, 6) and 104.8 (C-3, 5); the anomeric proton of the glucosyl at δ 4.69 (2H, d, J=10.0 Hz) was correlated with the carbon signals at δ 104.8 (C-3, 5), 154.8 (C-2, 6) and

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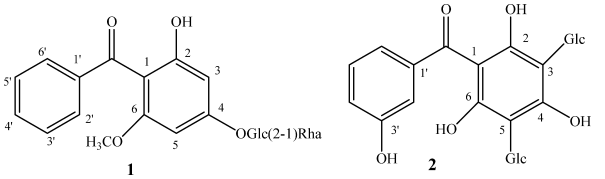
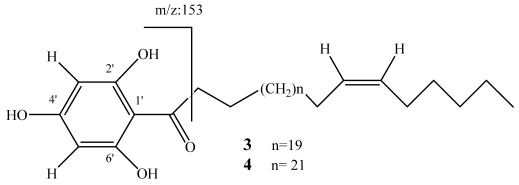


1 **2**



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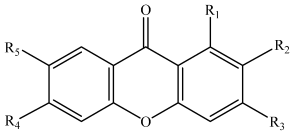
4 n=21



5 R_1=R_2=R_3=R_5=OCH_3, R_4=OH
6 R_1=R_5=OCH_3, R_2=R_3=R_4=H
7 R_1=R_2=R_3=OCH_3, R_5=OH, R_4=H

Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **1** and **2** (in DMSO-d_6)[a)]

	1		**2**	
	^{1}H	^{13}C	^{1}H	^{13}C
1		110.0		109.0
2		156.3		154.8
3	6.20 (1H, s)	96.2		104.8
4		159.5		156.4
5	6.23 (1H, s)	91.4		104.8
6		158.2		154.8
1′		137.8		140.3
2′	7.69 (1H, d, J=7.5 Hz)	128.8	7.11 (1H, br s)	115.1
3′	7.48 (1H, dd, J=7.5, 7.5 Hz)	128.6		157.2
4′	7.59 (1H, t, J=7.5 Hz)	133.1	6.94 (1H, dd, J=2.5, 8.0 Hz)	119.5
5′	7.48 (1H, dd, J=7.5, 7.5 Hz)	128.6	7.24 (1H, dd, J=8.0, 8.0 Hz)	129.2
6′	7.69 (1H, d, J=7.5 Hz)	128.8	7.13 (1H, d, J=8.0 Hz)	119.9
–C=O		194.5		195.9
OMe	3.57 (3H, s)	55.4		
OH	9.92 (1H, br s)		9.92 (1H, br s), 8.81 (2H, s), 8.65 (1H, s)	
Glc-1	4.99 (1H, d, J=7.5 Hz)	98.3	4.69 (2H, d, J=10.0 Hz)	75.2
2		76.4		72.7
3		77.0		77.8
4		69.8		69.0
5		77.5		81.0
6		60.5		59.9
Rha-1	5.11 (1H, br s)	100.5		
2		70.5		
3		70.6		
4		71.9		
5		68.3		
6		18.1		

a) The assignments were based on COSY, HMQC and HMBC experiments.

156.4 (C-4). Thus, **2** was identified as 3,5-di-*C*-β-glucopyranosyl-2,4,6,3′-tetrahydroxybenzophenone, named tenuiphenone B.

It had been reported that polyhydroxybenzophenones could be intermediate precursors in the formation of xanthones.[11—13)] Except the two above reported benzophenones **1** and **2**, several xanthone and its *O*-glycosides or *C*-glycosides with the similar structural characteristics to **1** and **2** have been also isolated from *P. tenuifolia*,[1,5,8)] which supply another evidence to the hypothesis that xanthone is biosynthesized from benzophenone in the plants.

Compounds **3** and **4** were obtained as white solid, mp 197—200 °C. The IR spectrum of **3** and **4** showed the presence of hydroxyl groups (3281 cm^{-1}), a hydrogen bonded ketone (1657 cm^{-1}), aromatic carbons (1602, 1525, 1469 cm^{-1}), and long chain alkane absorption at 720 cm^{-1} (–$(CH_2)_n$, n≥4). At first, the solid was considered to be a pure compound, but when its HR-SI-MS spectrum were measured, two quasimolecular ion peaks were found at m/z 559.4724 $[M+H]^+$ and 587.5057 $[M+H]^+$, which indicated that it should be a two compounds mixture, and their molecular formulae were $C_{36}H_{62}O_4$ and $C_{38}H_{66}O_4$, respectively. The ^{1}H-NMR of **3** and **4** showed three hydroxyl signals at δ 11.81, 11.70 (hydrogen bonded hydroxyls) and 9.14 (a free hydroxyl), two aromatic proton signals at δ 5.90 (2H, s), two olefinic proton signals δ 5.33 (2H, t, J=4.8 Hz), and a series of long chain aliphatic alkane proton signals at δ 3.05 (2H, t, J=7.5 Hz), 2.04 (m), 1.65 (2H, m), 1.27 (br s, –CH_2–) and 0.87 (3H, t, J=6.9 Hz, CH_3). The carbon signals were assigned by HMQC and DEPT spectra to be a group of phenyl signals at δ 95.69/95.60 (2C), 105.06, 164.27/164.96 (2C) and δ 165.40/164.92; a carbonyl group at δ 206.33, two olefinic carbon signals at δ 130.44 (2C), and a series of long chain alkane carbon signals at δ 44.39/44.36 (–CH_2–X), 32.53, 30.57—29.03, 27.69/27.67, 25.44, 23.23 (–CH_2–) and 14.31 (–CH_3). Comparing with the known compound 2′-eicosanoylphloroglucinol, the phenyl carbon signals of the two compounds were similar, but the carbon signals of the long alkane chain were different.[14)] In the HMBC spectrum, the proton signal at δ 9.14 (1H, s, 4′-OH) was correlated with δ 165.27/164.92 (C-4′) and 95.69/95.66 (C-3′, 5′); δ 5.90 (2H, s, H-3′, 5′) was correlated with δ 95.69/95.66 (C-3′, 5′), 105.06 (C-1′), 165.27/164.92 (4′) and 165.40/164.92 (C-2′, 6′), 206.33 (–C=O); δ 3.05 (2H, s, H-2) and 1.65 (2H, m, H-3) were correlated with δ 206.33 (–C=O), which suggested that an acylphloroglucinol moiety existed in the **3** and **4**, and this could be proved further by the segment ion peak at 153 $[C_7H_5O_4]^+$ in the EI-MS spectrum. The difference between **3** and **4** was the length of the alkane chain: **3** was a triacontenoylphloroglucinol, while **4** was a dotriacontenoylphloroglucinol. The *Z*-configuration of the double bond was deduced from the J value (4.8 Hz) and ^{13}C-NMR data (δ 130.44, 27.67),[14)] and its position was deduced to be at the terminal C-6 position through the following segment ion peaks: 71 $[CH_3(CH_2)_4]^+$, 97 $[CH_3(CH_2)_4CH=CH–]^+$ and 111 $[CH_3(CH_2)_4CH=CH–CH_2]^+$. So, **3** and **4** were elucidated as 2′,4′,6′-trihydroxyphenyl-(24*Z*)-triacontene-1-one (**3**) and 2′,4′,6′-trihydroxyphenyl-(26*Z*)-dotriacontene-1-one (**4**), named as tenuiphenone C and D, respectively.

Compounds **5**—**7** were determined to be 6-hydroxy-1,2,3,7-tetramethoxyxanthone (**5**),[1)] 1,7-dimethoxyxanthone (**6**) and 7-hydroxy-1,2,3-trimethoxyxanthone (**7**)[15)] by comparing their spectral data with the literature values.

Experimental

General mp uncorr. were carried out using a XT4A melting point apparatus. Optical rotations were measured on a Perkin-Elmer 243B polarimeter. IR spectra were obtained on an AVATER-360 spectrophotometer. HR-SI-MS spectra were performed at an APEX II mass spectrometer. ^{1}H-, ^{13}C-NMR, HMQC and HMBC spectra were measured on a JEOL JNM-A300 or Bruker AM-500 spectrometer. D101 resin was purchased from Tianjin Chemical

Co. Column chromatography silica gel, 200—300 mesh, supplied by Qingdao Marine Chemical Factory. Sephadex LH-20 was Pharmacia Co. product. Preparative HPLC was performed on a Waters model 2487 instrument (Waters Co. Ltd., America). GC analysis was carried out on an Angilent 6890N gas chromatography using a HP-5 capillary column (28 m×0.32 mm i.d.); detection, FID; detector temperature, 260 °C; column temperature, 180 °C; carrier gas, N_2; flow rate, 40 ml/min. Hexamethyldisilazine and trimethylsilylchloride reagents were bought from Acros Co. (New Jersery, U.S.A.).

Plant Materials The cortexes of *P. tenuifolia* were collected from Shanxi Province, P. R. China, in October 2000. The plant was identified by Professor Pengfei Tu, School of Pharmaceutical Sciences, Peking University Health Science Center. A voucher specimen (No. 001020) was deposited in the herbarium of School of Pharmaceutical Sciences, Peking University, Beijing, China.

Extraction and Isolation The air-dried cortexes of *P. tenuifolia* (11 kg) were ground and refluxed with 95% EtOH (77 l) for three times. The solution was combined and evaporated in vacuum to yield 4.9 kg of residue, a portion (2 kg) of which was suspended in water and extracted successively with petroleum, $CHCl_3$ and *n*-BuOH to give the petroleum extract (462.6 g), $CHCl_3$ extract (157.9 g) and *n*-BuOH extract (914.8 g).

The $CHCl_3$ extract (100 g) was subjected to silica gel (1.2 kg), eluting with $CHCl_3$–MeOH in a gradient manner (500 : 1→6 : 4), and got 100 fractions altogether. Fractions 18—24 were purified by preparative TLC to furnish compound **6** (36.2 mg), using cyclohexane–EtOAc (2 : 1) as spreading solvent for twice. Fractions 25—39 were isolated by reduced silica gel Column Chromatography (CC) using petroleum–acetone as eluent from 10 : 1 to 4 : 6 (40 ml as a portion). Among them, subfractions 10—15 gave compound **5** (33.1 mg). Fractions 41—43 were further chromatographed on a silica gel, eluting with petroleum–acetone (10 : 1→7 : 3) to gave 140 fractions. Among them, subfractions 42—71 were purified by Sephadex LH-20, with $CHCl_3$–MeOH (7 : 3) as eluent to give compounds **3** and **4** (29.3 mg); Subfractions 83—98 were first chromatographed on a Sephadex LH-20, eluting with $CHCl_3$–MeOH (7 : 3), then purified by preparative TLC using cyclohexane–EtOAc (1 : 1) as spreading solvent to furnish compound **7** (1.3 mg).

The *n*-BuOH extract (325 g) was subjected to a macroporous resin D101 column (11.5×85.5 cm). The adsorbed material was successively eluted with H_2O, 20, 50, 70, and 95% EtOH. The 50% EtOH eluate (78 g) was chromatographed on a silica gel (1.6 kg), eluting with $CHCl_3$–MeOH–H_2O in a gradient manner (9 : 1 : 0→12 : 8 : 1, 500 ml as one fraction). Fractions 61—69 were subjected to Sephadex LH-20 eluting with MeOH to afford 12 fractions. Subfractions 4—5 were further isolated by HPLC (Waters Prep Nova-pak®HR C_{18} column, 5 μ, 7.8×300 mm, MeOH–H_2O (23 : 77) as mobile phase, the flow rate was 3.0 ml/min and the detecting wavelength were 228 and 311 nm) to furnish compound **1** (5.2 mg).

The 20% EtOH eluate (19.8 g) was chromatographed on a silica gel (60 g), eluting with $CHCl_3$–MeOH–H_2O in a gradient manner (6 : 1 : 0→12 : 8 : 1, 100 ml as one fraction). Fractions 50—61 were further purified by Sephadex LH-20 and HPLC (Alltima C_{18} column, 5 μ, 10×250 mm, MeOH–0.05% TFA (30 : 70) as mobile phase, the flow rate was 2.0 ml/min and the detecting wavelength were 228 and 311 nm) to gave compound **2** (18.5 mg).

Acid Hydrolysis of 1 Compound **1** (3 mg) was hydrolyzed with 2 N aqueous CF_3COOH (5 ml) on a water bath for 3 h in a sealed tube.[16] After this period, the reaction mixture was diluted with H_2O (15 ml) and extracted with $CHCl_2$ (3×5 ml). Then, the aqueous layer was repeatedly evaporated to dryness with MeOH until neutral. The sugars were identified by TLC analyses with authentic samples, using *n*-BuOH–CH_3COOH–H_2O (4 : 2 : 1) as developing solvent, and the *Rf* values of glucose and rhamnose were 0.54 and 0.69, respectively. Furthermore, the sugar residue was dissolved in pyridine (60 μl), then L-cysteine methyl ester hydrochloride and hexamethyldisilazine–trimethylsilylchloride (3 : 1) were added, and the reaction mixture was stirred at 60 °C for 30 min. After centrifugation of the precipitate, the supernatant was concentrated and partitioned between *n*-hexane and H_2O, and the hexane layer was analyzed by GC. D-Glucose (12.92 min) and L-rhamnose (5.34 min) were detected from **1** by comparing with the standard monosaccharides (the retention times of the standard monosaccharide L-cysteine derervative were D-glucose 12.45 min and L-rhamnose 5.32 min, respectively).

Tenuiphenone A (**1**): Yellow amorphous powder, $[\alpha]_D^{20}$ +62.3° (c=0.10, MeOH). UV λ_{max} (MeOH) nm: 211, 221, 247, 297; λ_{max} (MeOH+NaOAc) nm: 211, 246, 298. IR ν_{max} (KBr) cm^{-1}: 3387 (OH), 1664 (C=O), 1612, 1425 (aromatic ring). HR-SI-MS (positive mode): *m/z* 553.1923 ($C_{26}H_{33}O_{13}$ $[M+H]^+$, Cacld for 553.1915). ^{1}H- and ^{13}C-NMR data: Table 1.

Tenuiphenone B (**2**): Yellow amorphous powder, $[\alpha]_D^{20}$ +61.3° (c=0.11, MeOH). UV λ_{max} (MeOH) nm: 218, 306; λ_{max} (MeOH+NaOAc) nm: 220, 341. IR ν_{max} (KBr) cm^{-1}: 3354 (OH), 1675 (C=O), 1621, 1453 (aromatic ring). HR-SI-MS (negative mode): *m/z* 569.1517 ($C_{25}H_{29}O_{15}$ $[M-H]^-$, Cacld for 569.1507). ESI-MS (positive mode): *m/z* 571 $[M+H]^+$, 593 $[M+Na]^+$; ESI-MS (negative mode): *m/z* 569 $[M-H]^-$. ^{1}H- and ^{13}C-NMR data: Table 1.

Tenuiphenone C (**3**) and Tenuiphenone D (**4**): White solid (acetone), mp 197—200 °C. HR-SI-MS (positive): *m/z* 559.4724 ($C_{36}H_{63}O_4$ $[M+H]^+$, Cacld for 559.4721)/587.5057 ($C_{38}H_{67}O_4$ $[M+H]^+$, Cacld for 587.5034), 581.4540 $[M+Na]^+$/609.4823 $[M+Na]^+$. IR ν_{max} (KBr) cm^{-1}: 3281 (–OH), 2918, 2850 (–CH_2, –CH_3), 1657 (–C=O), 1602, 1525, 1469 (aromatic ring), 720 (–$(CH_2)_n$, $n\geq4$). EI-MS (*m/z*): 43 $[C_3H_7]^+$, 57 $[C_4H_9]^+$, 71 $[C_5H_{11}]^+$, 97 $[C_5H_{11}$–CH=CH–$]^+$, 111 $[C_5H_{11}$–CH=CH–$CH_2]^+$, 153 $[C_7H_5O_4]^+$, 168 $[C_8H_7O_4+H]^+$, 181 $[C_9H_9O_4]^+$. ^{1}H-NMR (500 MHz, acetone-d_6): δ 11.81/11.70 (2′, 6′-OH), 9.14 (4′-OH), 5.90 (2H, s, H-3′, 5′), 5.33 (2H, t, J=4.8 Hz, H-24 or 26), 3.05 (2H, t, J=7.5 Hz, –$COCH_2$–), 2.04 (m, –$\underline{CH_2}$CH=), 1.65 (2H, m, –$COCH_2\underline{CH_2}$–), 1.27 (br s, –CH_2–), 0.87 (3H, t, J=6.9 Hz, CH_3). ^{13}C-NMR (125 MHz, acetone-d_6): δ 206.33 (–CO–, overlapped), 164.27/164.96, 165.40/164.92 (C-2′, 6′, 4′ signals could be interchangeable), 105.06(C-1′), 95.69/95.60 (C-3′, 5′), 130.44 (C-24, 25/26, 27), 44.39/44.36 (–$\underline{CH_2}$CO), 32.53, 30.57—29.03, 27.69/27.67, 25.44, 23.23 (–CH_2–), 14.31 (–CH_3).

Acknowledgements We thank the staff of the NMR measurement office of our University, for measuring the NMR spectra, and the members of MS measurement center of Chemical Institute, Chinese Academy of Science, for providing the MS data.

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