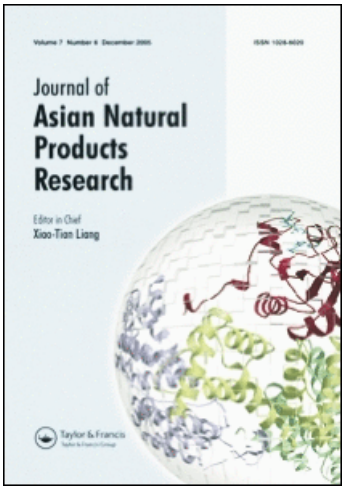

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ORIGINAL ARTICLE

Alkaloids and sesquiterpenoids from *Acorus tatarinowii*

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The rhizome of *Acorus tatarinowii* is a well-known traditional Chinese medicine. Our extensive investigation on this plant material afforded two new compounds, including a cadinane-type sesquiterpenoid and a pyrazine derivative, along with seven known compounds. The structures of the new compounds, tatarinowin B and tatarinine A, were elucidated as 2-oxocadinan-1(10),3-dien-5-ol (**1**) and 2-(3′,4′-dihydroxy-1′-butylenyl)-5-(2″,3″,4″-trihydroxybutyl)-pyrazine (**2**), respectively, by means of spectral methods.

Keywords: *Acorus tatarinowii*; alkaloids; sesquiterpenoids; tatarinowin B; tatarinine A

1. Introduction

The rhizome of *Acorus tatarinowii* Schott (Araceae) is a well-known traditional Chinese medicine for treating central nervous system-related disorders [1]. A variety of sesquiterpenoids were previously reported from plants of the genus *Acorus* [2–4]. Previous investigations on the title plant led to the characterization of mono-, sesqui-, and diterpenoids, phenylpropanoids, flavonoids, amides, and alkaloids [5–8]. Among these, phenylpropanoids were found to have anticonvulsive and spasmolytic activities [9,10]. Recently, we have discovered two novel alkaloids with a naturally unusual morpholine motif with significant antioxidant capacity in high glucose-stimulated mesangial cells [11]. In the continuous course of our investigation on this plant, two new compounds, 2-oxocadinan-1(10),3-dien-5-ol (**1**) and 2-(3′,4′-dihydroxy-1′-butylenyl)-5-(2″,3″,4″-trihydroxybutyl)-pyrazine (**2**), along with seven known compounds, isocalamediol (**3**) [4], 2-hydroxyacorenone (**4**) [4], 2-acetoxyacorenone (**5**) [4], 4α,10α-aromadendranediol (**6**) [12], calamensesquiterpinenol (**7**) [13], tatarine A (**8**) [14], and 4-(2-formyl-5-methoxymethyl pyrrol-1-yl)butyric acid methyl ester (**9**) [15] (Figure 1), were isolated and spectrally identified. All these compounds were isolated from this genus for the first time.

2. Results and discussion

Compound **1** was isolated as a colorless gum. The molecular formula of **1** was determined as $C_{15}H_{22}O_2$ from its HR-ESI-MS at *m/z* 235.1701 $[M + H]^+$. The IR spectrum showed absorptions for hydroxy (3424 cm^{-1}) and α,β-unsaturated carbonyl (1657 cm^{-1}) groups [16]. The ^1H NMR spectrum exhibited an olefinic proton

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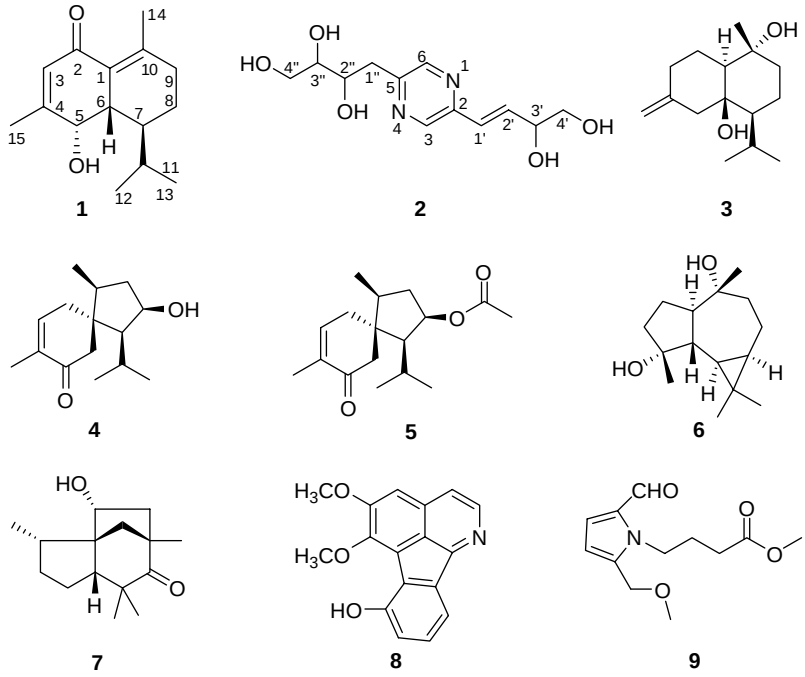

Figure 1. Structures of compounds **1**–**9**.

(δ 5.78, s, H-3), an oxymethine (δ 4.07, d, $J = 3.3$ Hz, H-5), and four methyls (δ 0.80, d, $J = 6.8$ Hz, H_3-12; 0.99, d, $J = 6.8$ Hz, H_3-13; 1.97, s, H_3-14; and 2.03, s, H_3-15). The ^{13}C NMR and DEPT spectra indicated 15 carbons attributive to four methyls, two methylenes, five methines (including one olefinic carbon), and four quaternary carbons (one carbonyl and three olefinic carbons). These spectroscopic data suggested that **1** is a cadinane-type sesquiterpenoid bearing an α,β-unsaturated carbonyl group in the molecule. The structure assembly of **1** was mainly achieved using 2D NMR experiments. The ^{1}H–^{1}H COSY spectrum showed correlations of H-11 with H_3-12 and H_3-13, suggesting the presence of an isopropyl group, of H-5 with H-6, indicating the position of the hydroxy group, and those of H-8 with H-7 and H-9. The chemical shift of C-2 at δ 190.6 suggested the presence of an α,β-unsaturated carbonyl moiety. HMBC correlations of both H-3 and H_3-15 with C-5 (δ 68.1) confirmed the location of the hydroxyl group at C-5 (Figure 2). The relative configuration of **1** was assigned via ROESY correlations, which showed interactions of H-5 with H-11, and H-6 with H_3-12, suggesting these protons are spatially vicinal. H-5 behaving as a doublet with a J value of 3.3 Hz in the ^{1}H NMR spectrum further implied that H-5 and H-6 have a *cis*-relationship. Collectively, compound **1** was determined to be 2-oxocadinan-1(10),3-dien-5-ol, with a trivial name tatarinowin B.

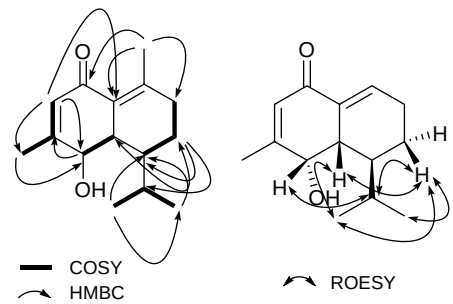

Figure 2. Important COSY, HMBC, and ROESY correlations of **1**.

Compound **2** was isolated as a yellow powder. The molecular formula of compound **2** was determined as $C_{12}H_{18}N_2O_5$ by HR-ESI-MS at *m/z* 271.1297 $[M+H]^+$. The IR spectrum revealed the presence of hydroxy groups (3417 cm^{-1}) [17]. The UV absorption maxima at 301 and 237 nm suggested the presence of the pyrazine moiety [18]. The ^1H NMR signals at δ 8.43 (1H, s, H-3) and 8.34 (1H, s, H-6) were ascribable to a pyrazine moiety with a *para*-substituted pattern [19]. In addition, two olefinic protons at δ 6.80 (1H, d, $J = 15.9$ Hz) and 6.96 (1H, dd, $J = 15.9$, 5.2 Hz) were observed. The ^{13}C NMR and DEPT spectra showed 12 carbons attributed to four aromatic carbons, two olefinic carbons, and six aliphatic carbons. $^1H-^1H$ COSY cross-peaks disclosed two spin systems which were H-1″/H-2″/H-3″/H-4″ and H-1′/H-2′/H-3′/H-4′, corresponding to 2,3,4-trihydroxybutyl and 3,4-dihydroxy-1-butylenyl groups, respectively. In the HMBC spectrum, the following correlations (Figure 3) were observed: H-1″/C-5, C-6, and C-3″; H-1′/C-2, C-3, and C-3′; H-2′/C-2; H-3/C-2 and C-5; H-6/C-2, which established the linkage of two side chains with the pyrazine motif. The *E*-double bond was indicated by the large coupling constant of H-1′ and H-2′. The absolute configurations at three chiral centers of side chains were not determined yet. Accordingly, the structure of compound **2** was elucidated as 2-(3′,4′-dihydroxy-1′-butylenyl)-5-(2″,3″,4″-trihydroxybutyl)-pyrazine, with a trivial name tatarinine A.

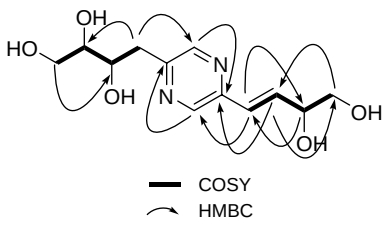

Figure 3. Important COSY and HMBC correlations of **2**.

3. Experimental

3.1 General experimental procedures

Optical rotations were recorded on a Horiba SEPA-300 polarimeter. UV spectra were measured on a Shimadzu UV-2401PC spectrophotometer. IR spectra were obtained on a Tensor 27 with KBr pellets. NMR spectra were recorded on a Bruker AV-400 or a DRX 500 MHz spectrometer. EI-MS was obtained on a Finnigan-4510 spectrometer. ESI-MS and HR-ESI-MS were determined with an API QSTAR Pulsar 1 spectrometer. Silica gel (200–300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), RP-18 gel (40–63 μm; Daiso Co., Osaka, Japan), and Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden) were used for column chromatography.

3.2 Plant material

The rhizome of *A. tatarinowii* was purchased from the Yunnan Corporation of Materia Medica (YCMM), Yunnan Province, China, and authenticated by Mr H.Y. Sun at YCMM. A voucher specimen (CHYX0001) is deposited at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, China.

3.3 Extraction and isolation

The dried rhizome powder (50 kg) of *A. tatarinowii* was extracted with boiling water (2 × 100 liters) and then with ethanol (1 × 100 liters) to give a dark brown extract (4.7 kg), which was suspended in water followed by successive partition with EtOAc and *n*-BuOH (each 3 × 6 liters). The EtOAc extract (278 g) was fractionated by a silica gel column eluted with $CHCl_3$ with increasing amounts of MeOH to afford seven fractions (1–7). Fraction 3 (19 g) was separated on a silica gel column eluted with petroleum ether–Me_2CO (25:1 to 10:1) and then subjected to Sephadex

LH-20 ($CHCl_3$–MeOH, 6:4) to yield **1** (5 mg) and **4** (10 mg). Fraction 4 (23 g) was chromatographed on a silica gel column eluted with petroleum ether–EtOAc (20:1 to 5:1), and then purified by preparative TLC (petroleum ether–Me_2CO, 5:1) to afford **3** (8 mg) and **5** (7 mg). Fraction 6 (20 g) was loaded onto a silica gel column eluted with petroleum ether–Me_2CO (15:1 to 5:1) and then purified by Sephadex LH-20 ($CHCl_3$–MeOH, 6:4) to afford **6** (150 mg) and **7** (93 mg). The *n*-BuOH extract (315 g) was divided into six fractions (1–6) on a silica gel column eluted with gradient $CHCl_3$–MeOH–H_2O (95:5:0 to 70:30:5). Fraction 2 (20 g) was separated on a silica gel column using $CHCl_3$–MeOH (25:1 to 10:1) as solvents followed by RP-18 column chromatography (MeOH–H_2O, 30:70 to 80:20) to yield **8** (7 mg) and **9** (11 mg). The combination of silica gel ($CHCl_3$–MeOH, 15:1 to 5:1), RP-18 (MeOH–H_2O, 40:60 to 100% MeOH), and Sephadex LH-20 (MeOH) chromatography of fraction 4 (53 g) gave compound **2** (5 mg).

*3.3.1 2-Oxocadinan-1(10),3-dien-5-ol (**1**)*

Colorless gum; $[\alpha]_D^{27}$ −55.3 ($c = 0.08$, MeOH). UV (MeOH) λ_{max} (log ε): 279 (3.26), 243 (3.47) nm. IR (KBr) ν_{max}: 3424, 2926, 1657, 1376, 1280, 1032 cm^{-1}. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectral data, see Table 1. EI-MS: *m/z* 234 $[M]^+$ (86), 219 (26), 205 (100), 191 (47), 163 (61), 149 (49), 145 (46), 117 (50), 91 (61), 85 (72), 83 (92), 69 (48). HR-ESI-MS: *m/z* 235.1701 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698).

*3.3.2 2-(3′,4′-Dihydroxy-1′-butylenyl)-5-(2″,3″,4″-trihydroxybutyl)-pyrazine (**2**)*

Yellow powder; $[\alpha]_D^{27}$ −32.9 ($c = 0.2$, MeOH). UV (MeOH) λ_{max} (log ε): 301 (3.44), 237 (3.61), 202 (3.56) nm. IR (KBr) ν_{max}: 3417, 2956, 2918, 2849, 1630, 1472, 1462, 1261, 1072, 1037, 872, 802, 730, 719 cm^{-1}. ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectral data, see Table 2. ESI-MS: *m/z* 293 $[M + Na]^+$, 271 $[M + H]^+$. HR-ESI-MS: *m/z* 271.1297 $[M + H]^+$ (calcd for $C_{12}H_{19}N_2O_5$, 271.1293).

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

Position	δ_C	δ_H (*J* in Hz)
1	127.7	
2	190.6	
3	129.3	5.78 (1H, s)
4	159.3	
5	68.1	4.07 (1H, d, $J = 3.3$)
6	44.8	2.50 (1H, m)
7	40.1	1.87 (1H, m)
8	20.7	1.72 (1H, m, H-8a)
		1.17 (1H, m, H-8b)
9	34.8	2.15 (2H, m)
10	150.1	
11	27.5	2.02 (1H, m)
12	16.4	0.80 (3H, d, $J = 6.8$)
13	21.9	0.99 (3H, d, $J = 6.8$)
14	22.5	1.97 (3H, s)
15	22.0	2.03 (3H, s)

Table 2. ^1H and ^{13}C NMR spectral data of compound **2** in CD_3OD.

Position	δ_C	δ_H (*J* in Hz)
2	151.6	
3	141.2	8.43 (1H, s)
5	156.6	
6	144.4	8.34 (1H, s)
1′	127.8	6.80 (1H, d, $J = 15.9$)
2′	138.4	6.96 (1H, dd, $J = 15.9, 5.2$)
3′	73.7	4.36 (1H, m)
4′	67.0	3.60 (1H, m)
		3.58 (1H, m)
1″	39.7	3.19 (1H, $J = 14.3, 2.8$)
		2.88 (1H, $J = 14.3, 9.5$)
2″	73.0	3.98 (1H, ddd, $J = 9.5$, 6.0, 2.8)
3″	76.2	3.54 (1H, m)
4″	64.6	3.77 (1H, dd, $J = 11.1, 3.6$)
		3.62 (1H, dd, $J = 11.1, 5.6$)

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