N-Bearing Furanone Derivatives from an Endophytic Fungus in *Huperzia serrata*

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Two new polyketide derivatives, huaspenones C and D (**1** and **2**, resp.), were isolated from the cultures of an endophytic fungus *Peyronellaea* sp. HS-12, derived from the stems of *Huperzia serrata*. They share N-bearing furan-3(2*H*)-one backbone, and **2** has an unprecedented furo[3,2-*c*]pyridine skeleton. Their structures including the absolute configuration were elucidated by extensive spectroscopic analysis combined with quantum-chemical calculations. (2*E*,4*E*)-6-hydroxy-2-methylocta-2,4-dienoic acid (**3**), a key intermediate of the biosynthesis of **1** and **2**, was also obtained from the endophyte.

Introduction. – Endophytic fungi are microorganisms which spend their life cycle, as a whole or partly, colonizing inter- and/or intra-cellularly inside the healthy tissues of their host plant, typically causing no apparent symptoms of disease [1]. The research on endophytes showed that they are potential sources of novel biologically active secondary metabolites for exploitation in medicine, agriculture, and industry [2–5]. Furthermore, results from many researches indicated that they could metabolize the same substance as their own host plants [6–8], rendering them an alternative source of plant secondary metabolites.

Huperzia serrata, a Chinese folk medicinal herb, is well-known for the discovery of hupzine A, a potent, highly specific, and reversible inhibitor of acetylcholinesterase [9][10]. In a previous study, two new furan-3(2*H*)-one derivatives, huaspenones A and B (**4** and **5**, resp.), were isolated from *Aspergillus* sp. XW-12 derived from the stems of *H. serrata* [11][1]). In this work, two novel N-containing furan-3(2*H*)-one derivatives, **1** and **2**, were isolated from the rice culture of an endophytic fungus *Peyronellaea* sp. HS-12 obtained from the stems of *H. serrata*, together with a key intermediate of the biosynthesis of **1** and **2**, *i.e.*, (2*E*,4*E*)-6-hydroxy-2-methylocta-2,4-dienoic acid (**3**). In addition, two known compounds, andrastin A (**4**) [13] and huaspenone B (**5**) [11], were also obtained from the endophytic fungus. Their structures were elucidated by NMR spectroscopy, especially 2D-NMR spectra. The absolute configurations of **1** and **2** were determined by CD analysis, combined with quantum-chemical calculation. To the best of our knowledge, huaspenones C and D (**1** and **2**, resp.) are the first examples of N-bearing furan-3(2*H*)-one derivatives in nature, and **2** has an unprecedented furo[3,2-*c*]pyridine skeleton.

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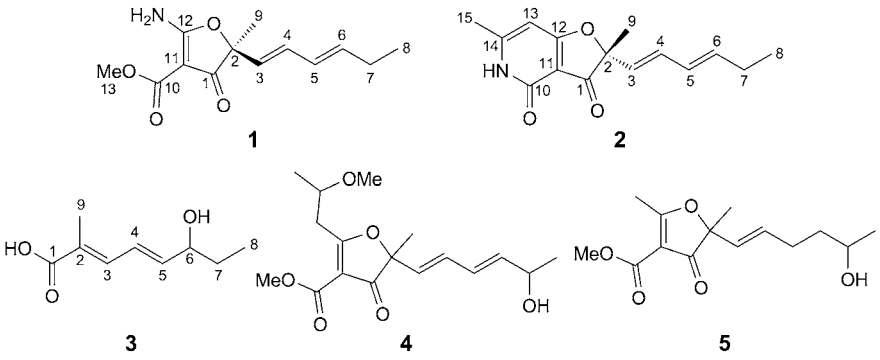
[1]) Based on [12], the structures of huaspenones A and B should be revised as **4** and **5**.



Results and Discussion. – Huaspenone C (**1**) was obtained as a yellow oil. The molecular formula $C_{13}H_{17}NO_4$ was deduced from the HR-ESI-MS molecular-ion peak at *m*/*z* 252.1229 ($[M+H]^+$), implying six degrees of unsaturation. The IR absorption bands at 3405 and 1632 cm^{-1} indicated the presence of NH_2 in **1**. The ^{1}H-NMR spectrum (*Table*) of **1** showed signals of two Me groups at δ(H) 1.00 (*t*, *J* = 7.5, Me(8)), 1.50 (*s*, Me(9)), and one MeO group at δ(H) 3.75 (*s*, Me(13)). The presence of a pair of conjugated C=C bonds with (*E*)-configuration was easily established by the corresponding chemical shifts and coupling constants (δ(H) 5.83 (*dt*, *J* = 15.5, 7.0, H–C(6)); 6.04 (*dd*, *J* = 15.5, 10.5, H–C(5)); 6.30 (*dd*, *J* = 15.5, 10.5, H–C(4)); 5.58 (*d*, *J* = 15.5, H–C(3)). Thirteen C-atom signals corresponding to five quaternary C-atoms, and to four CH, one CH_2, and three Me groups were observed in the ^{13}C-NMR and DEPT

Table. *^{1}H- and ^{13}C-NMR Data of* **1**–**3** *at 500 and 125 MHz.* δ in ppm, *J* in Hz. Arbitrary atom numbering as indicated in *Formulae.*

Position	**1**[a])		**2**[b])		**3**[a])	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	–	195.5	–	196.0	–	172.2
2	–	92.3	–	92.0	–	128.4
3	5.58 (*d*, *J* = 15.5)	128.3	5.60 (*d*, *J* = 15.5)	125.9	7.18 (*d*, *J* = 11.5)	145.4
4	6.30 (*dd*, *J* = 15.5, 10.5)	133.3	6.32 (*dd*, *J* = 15.5, 10.0)	131.2	6.59 (*ddd*, *J* = 15.0, 11.5, 1.5)	126.2
5	6.04 (*dd*, *J* = 15.5, 10.5)	129.6	5.98 (*dd*, *J* = 15.5, 10.0)	127.8	6.06 (*dd*, *J* = 15.0, 6.0)	139.4
6	5.83 (*dt*, *J* = 15.5, 7.0)	140.3	5.08 (*dt*, *J* = 15.5, 6.5)	139.4	4.11 (*q*, *J* = 6.0)	74.3
7	2.09–2.11 (*m*)	26.9	2.08–2.11 (*m*)	25.7	1.55–1.57 (*m*)	31.1
8	1.00 (*t*, *J* = 7.5)	14.0	0.98 (*t*, *J* = 7.5)	13.3	0.94 (*t*, *J* = 7.5)	10.2
9	1.50 (*s*)	22.8	1.57 (*s*)	22.3	1.91 (*s*)	12.9
10	–	166.4	–	160.9		
11	–	85.6	–	103.3		
12	–	179.9	–	182.8		
13	3.75 (*s*)	51.5	5.98 (*s*)	95.5		
14			–	157.0		
15			2.46 (*s*)	20.4		
NH			12.00 (*s*)	–		

[a]) Recorded in CD_3OD. [b]) Recorded in $CDCl_3$.

spectra. The characteristic C-atom signals observed at δ(C) 195.5 and 92.3 suggested that **1** was a furan-3(2*H*)-one derivative [11][14–19].

Analysis of the ^{1}H- and ^{13}C-NMR, and HSQC spectra of **1** enabled us to assign all the H-atoms to the corresponding C-atoms. The assemblage of all C-atoms, including quaternary C-atoms and hetero atoms was mainly achieved by an HMBC experiment. A partial structure (C(3) to C(8); **a**) can be easily established by analysis of the ^{1}H,^{1}H-COSY spectrum. The attachment of the moiety **a** to C(2) was deduced from the correlations H–C(4)/C(2) and H–C(3)/C(2). The correlations Me(9)/C(1) and Me(9)/C(2) indicated that the Me(9) was located at C(2). The HMBC Me(13)/C(10) was indicative of the presence of a MeO group at C(10) to form a methyl ester. The location of the COOMe group at C(11) was deduced by comparison of the chemical shift of Me(13) with literature data [12]. Based on the molecular composition, the remaining NH_2 was located at C(5). Due to *p*-π conjugation between C(11)=C(12) and NH_2, the ^{13}C signal of C(11) was shifted upfield compared with that of other furan-3(2*H*)-one derivatives [11][14–19]. This also supported the position of NH_2 at C(12). Thus, the structure of huaspenone C (**1**) was determined with unknown configuration at C(2).

The molecular formula of huaspenone D (**2**) was determined as $C_{15}H_{17}NO_3$ by HR-ESI-MS (*m*/*z* 260.1276 ($[M+H]^+$; calc. 260.1287)), implying eight degrees of unsaturation. The IR spectrum showed absorption bands for a ketone (1703 cm^{-1}) and an amide group (1656 cm^{-1}), which were confirmed by C-atom signals in the ^{13}C-NMR at δ(C) 196.0 (C(1)) and δ(C) 160.9 (C(10)), respectively (*Table*). In the ^{1}H-NMR spectrum (*Table*), three Me signals (δ(H) 0.98, 1.57, and 2.46) and a trisubstituted-C=C-bond H-atom at δ(H) 5.98 (*s*, H–C(13)) were observed. Furthermore, the structure of **2** also contained a pair of conjugated C=C bonds on the basis of its ^{1}H-NMR spectroscopic data. The ^{13}C-NMR and DEPT spectra of **2** revealed 15 C-atom signals due to six quaternary C-atoms (including five sp^2 and one sp^3), five sp^2 CH, one CH_2, and three Me groups. All these functional groups accounted for six degrees of unsaturation, thus requiring two rings in the structure.

High similarity was observed between the NMR data of **1** and those of **2**, implying a close structural resemblance. The major differences were the disappeance of an MeO signal and the appearance of NMR signals for C(13) to C(15) in the NMR spectra of **2** compared with NMR spectra of **1**. The linkage of C(13) and C(15) *via* C(14) could be deduced from the HMBCs H–C(13)/C(14) and H–C(13)/C(15) (*Fig. 1*). In the same way, the HMBCs from H–C(13) to C(11) and C(12) indicated the connection of C(13) and C(11) *via* C(12). The downfield-shifted signal of C(14) indicated that there was an N-atom at C(14) in **2**. The HMBC between the H-atom signal at δ(H) 12.00 and 160.9 (C(10)) indicated the linkage of N-atom with C(10) to form a lactam. Thus, the structure of huaspenone D was determined as **2**, which contains an unprecedent furo[3,2-*c*]pyridine skeleton.

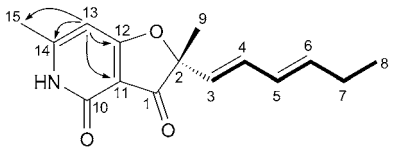


Fig. 1. *Selected ^{1}H,^{1}H-COSY correlations* (—) *and HMBCs* (→) *of* **2**.

The absolute configurations of **1** and **2** were determined by quantum-chemical calculations of their electron-capture dissociation (ECD) spectra and specific optical rotations. First, the conformational analysis was carried out *via* Monte Carlo searching at the HF/3-21G level in the SPARTAN 08 software package [20]. The results provided six lowest-energy conformers, with relative energy being within 2 kcal/mol for each of **1**. Subsequently, the conformers were reoptimized using DFT at the B3LYP/6-31 + + G (2d, 2p) level in the gas phase in the GAUSSIAN 09 program [21]. The B3LYP/6-31 + + G (2d, 2p) harmonic vibrational frequencies were further calculated to confirm their stability. The energies, oscillator strengths, and rotational strengths of the first 40 electronic excitations were calculated using the TDDFT methodology at the B3LYP/aug-cc-pVDZ level in a polarizable continuum model (PCM) of EtOH. The ECD spectra were simulated by the overlapping *Gaussian* function ($\sigma = 0.4$ eV) [22], in which the first three excitations for **1** and 25 excitations for **2** were adopted. To obtain the final spectra, for each compound, the simulated spectra of the six lowest-energy conformations were averaged according to the *Boltzmann* distribution theory and their relative *Gibbs* free energy (ΔG).

For compound **1**, in the 200–400-nm region, compared to the experimental first negative and second positive *Cotton* effects around 261 and 233 nm, the calculated ECD curve for (2*S*)-**1** showed two corresponding *Cotton* effects around 300 (+ 39) and 248 (+15) nm, respectively (*Fig. 2*,*a*). Therefore, qualitative analysis of the result allowed the assignment of the absolute configuration of **1** as (2*S*). For compound **2**, in the 200–400-nm region, compared to the experimental first negative (335 nm), second and third positive (308, 239 nm), and fourth negative (221 nm) *Cotton* effects, the simulated ECD curve for (2*R*)-**2** showed four corresponding *Cotton* effects around 370 (+ 35), 304 (− 4), 246 (+ 7) and 214 (− 7) nm, respectively (*Fig. 2*,*b*). Therefore, the absolute configuration of **2** was assigned as (2*R*).

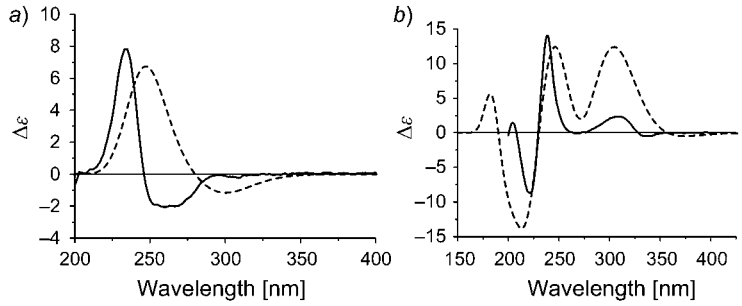


Fig. 2. *B3LYP/aug-cc-pVDZ/SCRF(PCM, ethanol)//B3LYP/6-31 + + G(2d,2p) Calculated ECD spectra* (---) *and the experimental ECD spectra* (—) *of* **1** (*a*) *and* **2** (*b*).

Compound **3** exhibited a *pseudo*-molecular-ion peak at *m*/*z* 169.0872 ($[M - H]^-$) in the HR-ESI mass spectrum, consistent with the molecular formula $C_9H_{14}O_3$. The ^{1}H-NMR spectrum showed two Me signals (δ(H) 0.94 and 1.91) and a signal for an O-bearing CH group (δ(H) 4.11). Additionally, three olefinic H-atom signals (δ(H) 7.18, 6.59, and 6.06) were observed. Nine C-atom signals corresponding to two sp^2 quaternary C-atoms, four CH, one CH_2, and two Me groups were detected in the

^{13}C-NMR and DEPT spectra. The connectivity of C(3) to C(8) can be established by ^{1}H,^{1}H-COSY spectrum, and further confirmed by HMBC spectrum. The HMBCs H–C(3)/C(1), H–C(3)/C(2), and H–C(3)/C(9) indicated the linkage of C(1), C(3), and C(9) *via* C(2). The large vicinal coupling constants of H–C(4) and H–C(5) (J = 15.5) clearly indicated an (E)-geometry of the C(4)=C(5) bond in **3**. The C(2)=C(3) bond was also assigned as (E) on the basis of the downfield shifted C-atom signal of Me(9) [23][24]. Accordingly, the structure of **3** was determined as (2*E*,4*E*)-6-hydroxy-2-methylocta-2,4-dienoic acid, which should be an important intermediate of the biosynthesis of **1** and **2**.

The furan-3(2*H*)-one derivatives constitute a group of polyketides produced by fungi [14][17][19][25], and they show a wide range of bioactivities, such as phytotoxic [25][26] and DNA polymerase [19] inhibitory activities. Though many furan-3(2*H*)-one derivatives have been characterized in nature, to the best of our knowledge, this is the first report on N-bearing furanone derivatives.

Experimental Part

General. All solvents used were of anal. grade (*Hangzhou Gaojin Fine Chemical Plan Chemical Plant*). TLC: Precoated silica-gel GF_{254} plates (*Qingdao Haiyang Chemical Plant*). Column chromatography (CC): silica gel (SiO_2; 230–400 mesh), *MCI CHP20P* gel (75–150 μm; *Mitsubishi Chemical Industries Ltd.*), and *Lichroprep RP-18* gel (40–63 μm, *YMC ODS-A*). Optical rotations: *Rudolph-Autopol-IV* polarimeter. UV Spectra: *Shimadzu UV-2450* spectrometer. CD Spectra: *JASCO J-815* spectrometer. IR Spectra: *Thermo-Nicolet-6700* spectra-photometer; in cm^{-1}. NMR Spectra: *Bruker AM-500* apparatus; δ in ppm rel. to Me_4Si, J in Hz. ESI-MS: *Agilent-6210-Lc/Tof* mass spectrometer; in m/z.

Microbial Material and Fermentation. The strain *Peyronellaea* sp. HS-12 was isolated from the healthy stems of *Huperzia serrata* collected from Xishuangbanna Tropical Plant Garden, Chinese Academy of Sciences, Yunnan Province, P. R. China, in September 2008 [27], and was identified on the morphology level and Internal Transcribed Spacer (ITS) by *Sangon Biotech Co., Ltd.* (Shanghai). The strain is deposited with the Zhejiang University of Technology (accession No. ZJUT-HS-12).

The fungal strain was cultured on slants of potato dextrose agar (PDA) at 25° for 10 d. Three *Erlenmeyer* flasks (250 ml), each containing 50 ml of media (0.4% glucose, 1% malt extract, and 0.4% yeast extract; final pH, 6.5), were autoclaved at 121° for 30 min. After inoculation, three flasks were incubated at 28° on a rotary shaker at 180 rpm for 5 d to prepare the seed culture. Spore inoculum was prepared by suspending the seed culture in sterile, dist. H_2O to give a final spore/cell suspension of 1×10^{-6}/ml. Fermentation was carried out in 48 *Erlenmeyer* flasks (500 ml), each containing 80 g of rice. Dist. H_2O (120 ml) was added to each flask, and the contents were soaked overnight before autoclaving at 121° for 30 min. After cooling to r.t., each flask was inoculated with 5.0 ml of the spore inoculum and incubated at 28° for 40 d under static conditions.

Extraction and Isolation. The culture was extracted three times in 95% EtOH by refluxing. The combined extracts were evaporated to dryness under reduced pressure to afford the residue (156 g). The residue was dissolved in H_2O (2 l) to form a suspension, which was then extracted with AcOEt (6 × 0.5 l). The org. solvent was evaporated to dryness under vacuum to afford a crude extract (16.3 g), which were then subjected to CC (*MCI-CHP20P*; MeOH/H_2O 1:4 → 9:1) to afford three major *Fractions A–C*. *Fr. A* (928.4 mg) was subjected to CC (SiO_2; $CHCl_3$/MeOH 15:1) to yield **3** (6.5 mg). *Fr. B* (598.0 mg) was separated by CC (*RP-18* CC; MeOH/H_2O 1:1 → 3:2) to afford *huaspenone* B (**5**, 2.6 mg) and *andrastin A* (**4**, 13.8 mg). *Fr. C* (1.2 g) was also purified by CC (*RP-18*; MeOH/H_2O 3:2) to give **1** (1.5 mg) and **2** (5.0 mg).

Huaspenone C (= *Methyl (5*S*)-2-Amino-5-[(1*E*,3*E*)-hexa-1,3-dien-1-yl]-5-methyl-4-oxo-4,5-dihydrofuran-3-carboxylate*; **1**). Yellow viscous oil. $[\alpha]_D^{20} = -180.0$ (c = 0.03, EtOH). UV (EtOH): 234

(3.93). CD (c = 16.0 μg/ml): 261 (−2.06), 233 (7.81). IR (KBr): 3405, 3102, 2962, 2926, 2858, 1700, 1632, 1527, 1377, 1259, 987. ^{1}H- and ^{13}C-NMR: see the *Table*. ESI-MS (pos.): 252 ($[M+H]^+$). HR-ESI-MS: 252.1229 ($[M+H]^+$, $C_{13}H_{18}NO_4^+$; calc. 252.1236).

Huaspenone D (=*(2*R*)-2-[(1*E*,3*E*)-Hexa-1,3-dien-1-yl]-2,6-dimethylfuro[3,2-*c*]pyridine-3,4(2*H*,5*H*)-dione*; **2**). Yellow viscous oil. $[\alpha]_D^{20} = +70.6$ (c = 0.10, EtOH). UV (EtOH): 316 (3.74), 230 (4.25), 204 (4.26). CD (c = 2.0 μg/ml): 335 (−0.50), 308 (2.31), 239 (14.05), 221(−8.70). IR (KBr): 3112, 2966, 2926, 1703, 1656, 1618, 1562, 1452, 1065, 979. ^{1}H- and ^{13}C-NMR: see the *Table*. ESI-MS (pos.): 260 ($[M+H]^+$). HR-ESI-MS: 260.1287 ($[M+H]^+$, $C_{15}H_{18}NO_3^+$; calc. 260.1287).

*(2*E*,4*E*)-6-Hydroxy-2-methylocta-2,4-dienoic Acid* (**3**). Amorphous powder. $[\alpha]_D^{20} = -36.8$ (c = 0.15, EtOH). UV (EtOH): 262 (3.94), 204 (3.69). IR (KBr): 3748, 2968, 2929, 2877, 1686, 1646, 1389, 1270, 974. ^{1}H- and ^{13}C-NMR: see the *Table*. ESI-MS (neg.): 169 ($[M-H]^-$). HR-ESI-MS: 169.0872 ($[M-H]^-$, $C_9H_{13}O_3^-$; calc. 169.0865).

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