ARISTOLIDE-A AND -B, TWO NOVEL DIHYDROPHENANTHRENE-LACTONES FROM *ARISTOLOCHIA HETEROPHYLLA* HEMSL

Tian-Shung WU,* Yu-Yi CHAN and Yann-Lii LEU

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan 701, R.O.C.

Two novel compounds, aristolide-A(**1**) and -B(**2**) were isolated from the root and stem of *Aristolochia heterophylla* HEMSL. Their structures were determined by spectral analysis. This is the first instance of the isolation of dihydrophenanthrenelactones from a natural source.

Key words dihydrophenanthrenelactone; aristolide-A and -B; *Aristolochia heterophylla*

Aristolochia heterophylla HEMSL (*A. shimada*) is a well-known folk medicine. The roots and fruits of this plant are used as an expectorant, antitussive, analgesic, antiasthmatic, and for the treatment of snakebite and lung inflammation. [1] Aristolochic acids, aristolactams, terpenes, and other constituents were isolated from this species. [2-6] We report here the isolation and identification of two new compounds, aristolide-A(**1**) and -B(**2**), from methanol extracts of the root and stem of *Aristolochia heterophylla* HEMSL.

Aristolide-A(**1**) was obtained as optically active colorless needles, $[\alpha]_D$ -10.7° ($CHCl_3$; *c* 0.02), mp 226-228 ℃. Its molecular formula was determined to be $C_{17}H_{12}O_5$ ($[M]^+$, *m/z* 296.0686) by high-resolution mass spectrometry. The UV spectrum of **1** with absorption maxima at 217 (logε 3.40), 263 (3.35), 286 (3.11, sh), 313 (2.69, sh), and 328 (2.48, sh) nm was considered to be characteristic of benzenoid absorption. The IR spectrum showed the presence of a lactonic carbonyl group at 1760 cm^{-1}. In the aromatic region of the ^{1}H-NMR spectrum, an ABC-type system at δ7.48 (1H,d, *J*=7.6Hz), 7.28 (1H, t, *J*=7.6Hz), and 6.86 (1H, d, *J*=7.6Hz) was attributed to H-5, H-6, and H-7, respectively. One singlet signal at δ 7.06 (1H) was assigned to the C-2 proton. A methoxy and a methylenedioxy signal appeared at δ 3.82 (3H, s) and 6.10, 6.18 (each 1H, d, *J*=1.2Hz), respectively. In addition, three one-proton signals clearly coupled in the COSY spectrum at δ5.26 (dd, *J*=6.8, 13.6Hz), 3.91 (dd, *J*=6.8, 13.6Hz), and 2.32 (t, *J*=13.6Hz) and were assigned to H-10_{ax},

* To whom correspondence should be addressed.

$H\text{-}9_{eq}$, and $H\text{-}9_{ax}$, respectively. All unambiguous ^{13}C-NMR assigments of **1** were resolved by a combination of 1D- and 2D-NMR techniques comprising HMBC and HMQC. Thus the H-2 (7.06) signal showed HMBC (Fig. 1) correlations with signals for C-3, C-4, C-10a, and C-11. In addition, the resonance at δ 121.6 (C-8a) showed correlations with signals for H-5, H-7, $H\text{-}9_{ax}$, and $H\text{-}9_{eq}$. The location of the methoxy group at C-8 was confirmed by NOE correlations between H-7 and the methoxy signal in NOESY experiments (Fig. 1). Finally, the CD spectrum of **1** displayed a negative Cotton effect at 245 nm due to a twisted biphenyl chromophore. Therefore the absolute configuration of **1** at C-10 was suggested to be *R*. [7] On the basis of the above results, the structure of aristolide-A was assigned as **1**. [8]

Aristolide-B(**2**) was isolated as an optically active colorless powder, $[\alpha]_D$ +7.4° ($CHCl_3$; *c* 0.04). The HREIMS of **2** showed a $[M]^+$ at *m/z* 266.0577, corresponding to the molecular formula $C_{16}H_{10}O_4$. The UV and IR spectra of **2** showed the presence of a dihydrophenanthrenelactone nucleus. The ^1H-NMR spectra of **1** and **2** were very similar; the principal difference was the presence of four mutually coupled protons at δ 7.92 (1H, d, *J*=7.3Hz), and 7.37 (3H, m) instead of an ABC-coupled pattern in **1** and the absence of the methoxy signal. This indicated that there was no substituent on ring C. Analysis of the CD spectrum of **2** showed a positive Cotton effect at 244 nm, which indicated the *S* configuration at C-10. Based on these results, the structure of aristolide-B was assigned as **2**. [9] To the authors' knowledge, this is the first report of the isolation of dihydrophenanthrenelactone from a natural source.

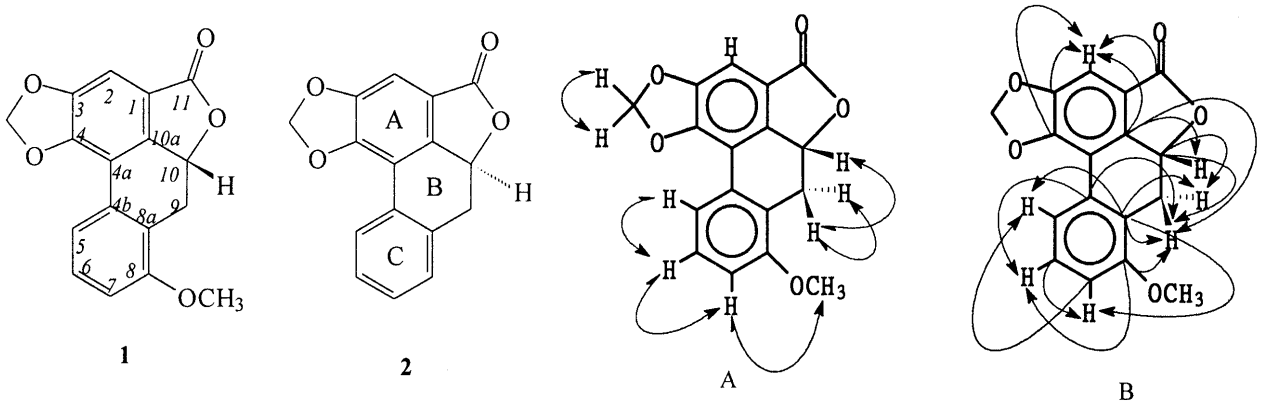

Fig.1. NOESY (A) and HMBC (B) Correlation of Aristolide-A(**1**)

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8) Aristolide-A(**1**): IR ν_{max}^{KBr} cm^{-1}: 2918, 1760 (C=O), 1573, 1469, 1425, 1353, 1338, 1045, 975 (OCH_2O); EI-MS*m/z* (rel. int %): 296 (M^+, 100), 268 (34), 240 (16), 210 (52), 182 (23), 151 (13), 139 (27); ^{13}C-NMR ($CDCl_3$, 100MHz) δ : 27.0 (C-9), 55.7 (OCH_3), 75.4 (C-10), 102.9 (OCH_2O), 103.1 (C-2), 111.3 (C-7), 117.1 (C-4a), 119.4 (C-5), 121.6 (C-8a), , 128.5 (C-6), 132.2 (C-4b), 134.3 (C-1), 145.7 (C-10a), 148.3 (C-4), 151.0 (C-3), 157.7 (C-8), 170.4 (C-11); CD ($CHCl_3$, *c* 7.29 $\times$ 10^{-4}): $[\theta]_{207}^{max}$ -366, $[\theta]_{214}^{max}$ -565, $[\theta]_{223}^{max}$ 0, $[\theta]_{226}^{max}$ +112, $[\theta]_{230}^{max}$ 0, $[\theta]_{245}^{max}$ -767, $[\theta]_{259}^{max}$ 0, $[\theta]_{270.}^{max}$ +359, $[\theta]_{278}^{max}$ +275, $[\theta]_{283}^{max}$ +311, $[\theta]_{297}^{max}$ +165.

9) Aristolide-B(**2**): mp 212-214°C; UV λ_{max}^{MeOH} nm(log ε): 211 (3.36), 262 (3.25), 283 (sh, 3.00), 293 (sh, 2.90), 316 (2.51), 328 (sh, 2.46); IR ν_{max}^{KBr} cm^{-1}: 2922, 1749 (C=O), 1541, 1460, 1434, 1350, 1301, 1263, 1047, 955 (OCH_2O); EI-MS*m/z* (rel. int %): 266 (M^+, 36), 238 (13), 210 (11), 180 (42), 152 (100); ^{1}H-NMR ($CDCl_3$, 200MHz) δ : 2.90 (1H, t, *J*=13.7Hz, H-9_{ax}), 3.43 (1H, dd, *J*=13.7, 6.4Hz, H-9_{eq}), 5.43 (1H, dd, *J*=13.7, 6.4Hz, H-10_{ax}), 6.19 (1H, d, *J*=1.0Hz, OCH_2O), 6.28 (1H, d, *J*=1.0Hz, OCH_2O), 7.36 (1H, s, H-2), 7.37 (3H, m, H-6, H-7, H-8), 7.92 (1H, d, *J*=7.3Hz, H-5); CD ($CHCl_3$, *c* 3.83 $\times$ 10^{-4}): $[\theta]_{206}^{max}$ -1433, $[\theta]_{213}^{max}$ 0, $[\theta]_{222}^{max}$ +1791, $[\theta]_{227}^{max}$ +1713, $[\theta]_{244}^{max}$ +3355, $[\theta]_{258}^{max}$ 0, $[\theta]_{268}^{max}$ -1484, $[\theta]_{291}^{max}$ -822.

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