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

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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, $[\alpha]_D -10.7^\circ$ (CHCl₃; *c* 0.02), mp 226–228 °C. Its molecular formula was determined to be C₁₇H₁₂O₅ ($[M]^+$, *m/z* 296.0686) by high-resolution mass spectrometry. The UV spectrum of **1** with absorption maxima at 217 (log ϵ 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 ¹H-NMR spectrum, an ABC-type system at δ 7.48 (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 δ 5.26 (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},

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H-9_{eq}, and H-9_{ax}, respectively. All unambiguous ¹³C-NMR assignments 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-9_{ax}, and H-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, $[\alpha]_D +7.4^\circ$ (CHCl₃; *c* 0.04). The HREIMS of **2** showed a $[M]^+$ at *m/z* 266.0577, corresponding to the molecular formula C₁₆H₁₀O₄. 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2918, 1760 (C=O), 1573, 1469, 1425, 1353, 1338, 1045, 975 (OCH₂O); EI-MS m/z (rel. int %): 296 (M⁺, 100), 268 (34), 240 (16), 210 (52), 182 (23), 151 (13), 139 (27); ¹³C-NMR (CDCl₃, 100MHz) δ : 27.0 (C-9), 55.7 (OCH₃), 75.4 (C-10), 102.9 (OCH₂O), 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 (CHCl₃, c 7.29×10^{-4}): $[\theta]_{207}^{\text{max}}$ -366, $[\theta]_{214}^{\text{max}}$ -565, $[\theta]_{223}^{\text{max}}$ 0, $[\theta]_{226}^{\text{max}}$ +112, $[\theta]_{230}^{\text{max}}$ 0, $[\theta]_{245}^{\text{max}}$ -767, $[\theta]_{259}^{\text{max}}$ 0, $[\theta]_{270}^{\text{max}}$ +359, $[\theta]_{278}^{\text{max}}$ +275, $[\theta]_{283}^{\text{max}}$ +311, $[\theta]_{297}^{\text{max}}$ +165.
- 9) Aristolide-B(**2**): mp 212-214°C; UV $\lambda_{\text{max}}^{\text{MeOH}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2922, 1749 (C=O), 1541, 1460, 1434, 1350, 1301, 1263, 1047, 955 (OCH₂O); EI-MS m/z (rel. int %): 266 (M⁺, 36), 238 (13), 210 (11), 180 (42), 152 (100); ¹H-NMR (CDCl₃, 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, OCH₂O), 6.28 (1H, d, J =1.0Hz, OCH₂O), 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 (CHCl₃, c 3.83×10^{-4}): $[\theta]_{206}^{\text{max}}$ -1433, $[\theta]_{213}^{\text{max}}$ 0, $[\theta]_{222}^{\text{max}}$ +1791, $[\theta]_{227}^{\text{max}}$ +1713, $[\theta]_{244}^{\text{max}}$ +3355, $[\theta]_{258}^{\text{max}}$ 0, $[\theta]_{268}^{\text{max}}$ -1484, $[\theta]_{291}^{\text{max}}$ -822.

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