Alkaloids from *Aristolochia manshuriensis* (Aristolochiaceae)

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From the ethanol extract of the stems of *Aristolochia manshuriensis*, two new alkaloids, namely manshurienine A (**1**) and manshurienine B (**2**), were isolated together with six known compounds, *i.e.*, aristoloside (**3**), aristolochic acid I (**4**), aristolochic acid II (**5**), aristolic acid II (**6**), aristolochic acid IVa (**7**), and aristolochic acid IIIa (**8**). The structures of **1** and **2** were elucidated on the basis of spectroscopic methods, mainly by using ^{1}H-and ^{13}C-NMR spectroscopy, and the known compounds **3**–**8** were identified by comparing their physical and spectroscopic data with those of authentic data reported in the literature.

Introduction. – The genus *Aristolochia* (Aristolochiaceae) contains more than 800 herbaceous or shrubby species growing in both temperate and tropical regions, and a number of *Aristolochia* species have been used in herbal medicines throughout the world [1]. Plants belonging to the genus *Aristolochia*, were reported to contain aristolochic acids, which were shown to possess immunostimulatory and anti-inflammatory [2] as well as nephrotoxic [3], carcinogenic [4], and mutagenic [5] activities, together with related aristololactams, which are cyclic phenanthrenecarboxamides [6]. Aristolochic acids (AA) are not only responsible for the tumor development but also for the destructive fibrotic process in the kidney because they form AA–DNA adducts, leading to permanent kidney damage in a short period [7]. Recently, *Aristolochia manshuriensis* has been reported to be nephrotoxic and oncogenic due to the aristolochic acids it contained [8]. The stems of *Aristolochia manshuriensis* KOM., a traditional Chinese medicinal herb mainly harvested from the Northeast of China, has been widely used as diuretic and anti-inflammatory, or for edema and rheumatic pain in China and in many other countries [9]. We are interested in the constituents of this plant due to the pharmacological action. The stems of *Aristolochia manshuriensis* KOM. were investigated in the present study resulting in the isolation of two new compounds, namely manshurienine A (=aristololactam IIIa 6-(β-D-glucopyranoside; **1**) and manshurienine B (aristololactam Ia 6-(β-D-glucopyranoside; **2**), besides six known compounds, *i.e.*, aristoloside (**3**), aristolochic acid I (**4**), aristolochic acid II (**5**), aristolic acid II (**6**), aristolochic acid IVa (**7**) and aristolochic acid IIIa (**8**) which were identified by comparison with literature data (*Fig. 1*). The present paper focuses on the isolation and structure elucidation of **1** and **2**.

Results and Discussion. – Manshurienine A (**1**) was obtained as an optically active yellow powder. The molecular formula was deduced as $C_{22}H_{19}NO_9$ by HR-ESI-MS (*m*/*z* 443.1213 ([*M*+2H]$^{+}$). The UV, IR, as well as the ^{1}H-NMR (*Table*) data implied that **1** was likely a derivative of aristololactam IIIa (=10-hydroxybenzo[*f*]-1,3-benzo-

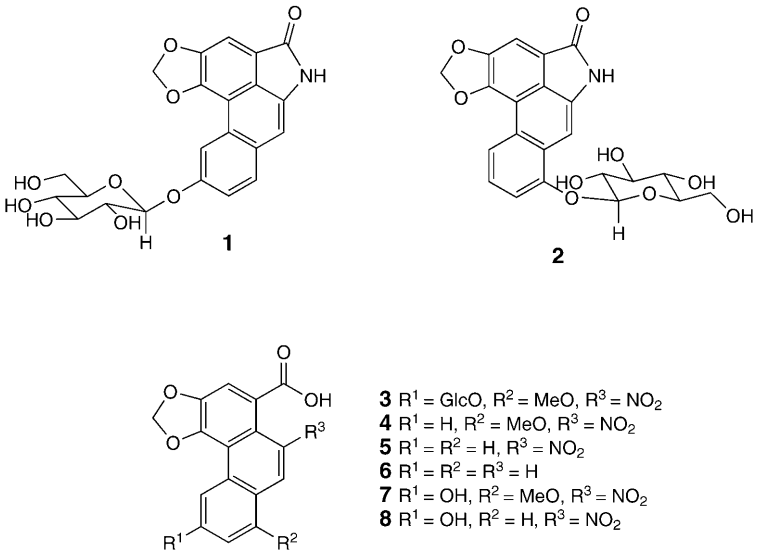

Fig. 1. *Structures of compounds* **1**–**8**

dioxolo[6,5,4-*cd*]indol-5(6*H*)-one) [10], and its structure was identified as aristololactam IIIa 6-(*β*-D-glucopyranoside) (named manshurienine A). The full assignment of the ^{1}H-and ^{13}C-NMR data (*Table*) of **1** was achieved by comparing them with those of aristololactam II, aristololactam IIIa [10], and aristololactam IIIa *N*-(*β*-glucoside) [11] and was assisted by using a HMBC experiment (*Fig. 2*).

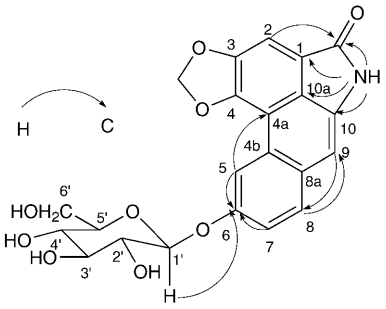

Fig. 2. *Key HMBC correlations of compound* **1**[1])

The ^{13}C-NMR spectrum of **1** showed 16 C-atoms for the phenanthrene moiety and 6 C-atoms for the hexose moiety (*Table*). An anomeric proton resonating as a *d* at *δ*(H) 4.97 (*J*=7.3 Hz) indicated the *β*-configuration for **1**, and the negative value of the optical rotation suggested that the glucose likely is present in the D-form. The HMBC experiment showed the correlation of a C-atom at *δ*(C) 155.3 (C(6)) with H–C(1′) (at *δ*(H) 4.97), so the sugar moiety should be located at O–C(6)[1]).

The characteristic UV absorption maxima observed at 238, 253, 280, and 324 nm and IR absorptions at 3075 (CONH), 1693 (CO), 1614, 1535, 792, and 740 cm^{-1} (phenanthrene) furthermore suggested the presence of an aristololactam moiety in **1**. The ^{1}H-NMR spectrum showed the presence of an NH at

[1]) The atom numbering of **1** and **2** (and of **3**–**8**) is arbitrary; for systematic names, see *Exper. Part.*

Table 1. *^{1}H- and ^{13}C-NMR Data of Compounds* **1** *and* **2**. δ in ppm, J in Hz. Trivial numbering.

	1		**2**	
	δ(H)[a])	δ(C)[b])	δ(H)[a])	δ(C)[b])
C=O	–	168.2	–	168.5
C(1)	–	119.5	–	119.5
H–C(2)	7.64 (*s*)	105.6	7.66 (*s*)	105.8
C(3)	–	148.8	–	149.2
C(4)	–	147.1	–	147.4
C(4a)	–	110.9	–	111.2
C(4b)	–	125.2	–	125.2
H–C(5)	8.20 (*d*, J=2.4)	113.2	8.23 (*d*, J=8.0)	120.4
C(6) or H–C(6)	–	155.3	7.51 (*t*, J=8.0)	125.9
H–C(7)	7.37 (*dd*, J=8.9, 2.4)	117.6	7.39 (*d*, J=8.0)	113.1
H–C(8) or C(8)	7.92 (*d*, J=8.9)	130.1	–	153.8
C(8a)	–	129.1	–	125.1
H–C(9)	7.10 (*s*)	104.4	7.56 (*s*)	99.1
C(10)	–	133.8	–	135.0
C(10a)	–	125.5	–	125.3
H–N	10.71(*s*)	–	10.79 (*s*)	–
OCH_2O	6.49 (*s*), 6.45 (*s*)	103.5	6.49 (*s*)	103.5
H–C(1′)	4.97 (*d*, J=7.3)	101.3	5.08 (*d*, J=7.6)	101.3
H–C(2′)	3.75 (*dd*, J=9.6, 7.3)	73.4	3.73 (*dd*, J=7.6, 8.5)	73.8
H–C(3′)	3.34 (*t*, J=9.6)	77.4	3.36 (*t*, J=8.5)	77.4
H–C(4′)	3.25 (*t*, J=9.6)	69.8	3.26 (*t*, J=8.5)	70.0
H–C(5′)	3.29–3.37 (*m*)	76.8	3.31–3.43 (*m*)	76.9
CH_2(6′)	3.55 (*dd*, J=11.7, 6.2), 3.38 (*dd*, J=11.7, 2.0)	60.7	3.50 (*dd*, J=6.0, 11.7), 3.38 (*dd*, J=11.7, 1.8)	60.9

[a]) Measured at 500 MHz in (D_6)DMSO. [b]) Measured at 125 MHz in (D_6)DMSO.

δ(H) 10.71 (*s*). By comparison of the ^{1}H-NMR spectrum of **1** with that of aristoloside (=10-(β-D-glucopyranosyloxy)-8-methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic acid; **3**) [12], 2 *s* at δ(H) 6.49 and 6.45 (together 2 H) were assigned to the methylenedioxy group. The aromatic region of the ^{1}H-NMR spectrum contained signals at δ(H) 8.20 (*d*, J=2.4 Hz), 7.92 (*d*, J=8.9 Hz), and 7.37 (*dd*, J=8.9, 2.4 Hz) attributable to H–C(5), H–C(8), and H–C(7), respectively. The downfield appearance of the H–C(5) signal is due to the deshielding effect of the A-ring in the aristololactam derivatives. Two *s* at δ(H) 7.64 and 7.10 (each 1H) were assigned to H–C(2) and H–C(9), respectively. The signals at δ(C) 101.3, 73.4, 77.4, 69.8, 76.8, and 60.7, were assignable to a glucopyranosyl moiety [13]. Acid hydrolysis of the sample afforded an aglycone and D-glucose which was identified by direct comparison with an authentic sample on TLC, and further confirmed by ^{13}C-NMR spectrum.

Manshurienine B (**2**) was also obtained as an optically active yellow powder. The HR-ESI-MS of **2** displayed $[M+H]^+$ at m/z 442.1133, which was consistent with the molecular formula $C_{22}H_{19}NO_9$. According to its ^{1}H- and ^{13}C-NMR spectra, **2** possessed an aristololactam aglycone and a glucosyl moiety, and the only difference between **2** and **1** laid in the position of glycosylation. Based on comparison of ^{1}H-NMR spectra of compound **2** and aristololactam Ia (=8-hydroxybenzo[*f*]-1,3-benzodioxolo[6,5,4-*cd*]indol-5(6*H*)-one), the absence of OH–C(8) signal in compound **2** suggested the sugar moiety should be located at O–C(8)[1]). The full assignment of the ^{1}H- and ^{13}C-

NMR data of **2** (*Table*) was achieved by comparing them with those of aristololactam II, aristololactam Ia [10] and aristololactam Ia *N*-(β-glucoside) [14] and by using a HMBC experiment (*Fig. 3*) and established its structure as aristololactam Ia 8-(β-D-glucopyranoside) (named manshurienine B).

In the HMBC plot of **2**, a correlation of the anomeric H–C(1′) at δ(H) 5.08 (d, J = 7.6 Hz) with C(8) at δ(C) 153.8 was observed (*Fig. 3*). Hence, the glucosyl moiety was attached to O–C(8) of the aglycone. Compound **2** exhibited a UV spectrum characteristic of a phenanthrene chromophore. The appearance of bands at 3472, 3075, 1659, 1650, 810, and 742 cm^{-1} in its IR spectrum revealed the presence of an aristololactam moiety in **2**. In the ^{1}H-NMR spectrum, the signals of an NH group and a methylenedioxy group appeared at δ(H) 10.79 (*s*, 1H) and 6.49 (*s*, 2 H), respectively. The aromatic region of the ^{1}H-NMR spectrum contained signals at δ(H) 8.23 (d, J = 8.0 Hz), 7.51 (t, J = 8.0 Hz), and 7.39 (d, J = 8.0 Hz) attributable to H–C(5), H–C(6), and H–C(7), respectively. Two *s* at δ(H) 7.66 and 7.56 were assigned to H–C(2) and H–C(9), respectively. The anomeric H-atom signal at δ(H) 5.08 and the signals at δ(C) 101.3, 73.8, 77.4, 70.0, 76.9, and 60.9 were typical for a β-glucopyranosyl moiety [13]. This was further corroborated by TLC comparison of the hydrolysis product of **2** with an authentic glucose sample.

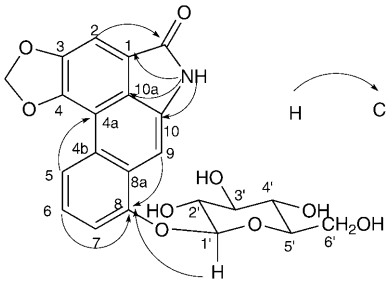

Fig. 3. *Key HMBC correlations of compound* **2**[1])

In addition to **1** and **2**, six known compounds, aristoloside (**3**) [12], aristolochic acid I (**4**) [15], aristolochic acid II (**5**) [16], aristolic acid II (**6**) [17], aristolochic acid IVa (**7**) [18], and aristolochic acid IIIa (**8**) [19] were also isolated from this plant and identified by comparison with literature data.

Experimental Part

General. All solvents used were of anal. grade (*Shanghai Chemical Plants*, Shanghai, P. R. China). Column chromatography (CC): silica gel (200–300 mesh), silica gel *H60* (*Qingdao Haiyang Chemical Plant*, Qingdao, P. R. China). TLC: precoated silica gel *GF254* plates (*Qingdao Haiyang Chemical Plant*, Qingdao, P. R. China). M.p.: *XT-4* micro-melting-point apparatus; uncorrected. Optical rotation: *Perkin-Elmer-341* polarimeter. UV Spectra: *Shimadzu-UV-260* UV/VIS recording spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer-577* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-ARX-500* spectrometer, at 500 and 125 MHz, resp.; δ in ppm, J in Hz. HR-ESI-MS: *ABQ-STAR-Pulsar* mass spectrometer.

Plant Material. The stems of *Aristolochia manshuriensis* KOM. (*Guanmutong*) were bought from *Jiangsu Province Medicine Co., Ltd*., in October 2004, and authenticated by Professor *Xing Sun* (Nanjing University of Traditional Chinese Medicine). The voucher specimen (No.031012) was deposited at the Department of Phytochemistry, College of Traditional Chinese Medicine, China Pharmaceutical University.

Extraction and Isolation. Air-dried stems of *Aristolochia manshuriensis* KOM. (20 kg) were extracted with 90% ethanol under reflux at r. t. (3 × 60 l, each for 3 h) and the extract was concentrated to give a dark syrup, which was treated with an aq. Na_2CO_3 soln. under stirring to adjust the pH to *ca.* 8–9 and

then defatted with petroleum ether. The pH was then adjusted to *ca.* 3–4 with 6M HCl. The obtained mixture was extracted successively with AcOEt and BuOH, yielding, after solvent evaporation, an AcOEt-, BuOH-, and H_2O-soluble portion (*Fractions 1–3*). The BuOH residue (*Fr. 1*) was dissolved in a small amount of H_2O and absorbed on *D101* resin, and then eluted with H_2O, 20% (*v/v*) EtOH/H_2O, 50% EtOH/H_2O, and 90% EtOH/H_2O. The 50% EtOH/H_2O part (47 g) was subjected to CC (silica gel, $CHCl_3$/MeOH 10:1 → 1:1; 10–20°): *Fr. 1.1–1.8*. *Fr. 1.2* (0.2 g) was purified by crystallization ($CHCl_3$/MeOH 10:1) to afford *manshurienine A* (**1**; 12 mg) and *aristoloside* (**3**; 20 mg). The 90% EtOH/H_2O part (31 g) was separated by CC (silica gel, $CHCl_3$/MeOH 10:1 → 1:1; 10–20°): *Fr. 1.9–1.16*. *Fr. 1.11* (0.3 g) was purified by CC (silica gel, $CHCl_3$/MeOH 10:1) to afford *manshurienine B* (**2**; 10 mg). The AcOEt-soluble part (*Fr. 2*; 190 g) was subjected to CC (silica gel, $CHCl_3$/MeOH 10:0 → 10:10): *Fr. 2.1–2.10*. *Fr. 2.2* (2.5 g) was kept at r.t. in MeOH to afford crystals of *aristolochic acid I* (**4**; 900 mg). *Fr. 2.3* and *2.4* were resubjected to CC (silica gel, $CHCl_3$/MeOH 10:0 → 10:10) to afford *aristolochic acid II* (**5**; 10 mg), *aristolic acid II* (**6**; 8 mg), *aristolochic acid IVa* (**7**; 5 mg), and *aristolochic acid IIIa* (**8**; 8 mg).

Manshurienine A (=*Aristololactam IIIa 6-(β-*D*-Glucopyranoside)=10-(β-*D*-Glucopyranosyloxy)-benzo[*f*]-1,3-benzodioxolo[6,5,4-*cd*]indol-5(6*H*)-one*; **1**): Yellow powder. M.p. 236–237°. $[\alpha]_D^{25} = -8.5$ ($c = 0.20$, MeOH). UV (MeOH): 238, 253, 280, 324. IR (KBr): 3472, 3075, 2888, 1693, 1680, 1661, 1633, 1614, 1535, 1513, 1477, 1422, 1372, 1268, 1221, 1127, 1073, 1043, 940, 868, 792, 740, 655. ^{1}H- and ^{13}C-NMR: see the *Table*. ESI-MS (pos.): 443 (100, $[M+2\,H]^+$), 442 (25, $[M+H]^+$). ESI-MS (neg.): 440 (10, $[M-H]^-$). HR-ESI-MS: 443.1213 ($[M+2\,H]^+$, $C_{22}H_{21}NO_9^+$; calc. 443.1216).

Manshurienine B (=*Aristololactam Ia* 8-(*β-*D*-Glucopyranoside*) =8-(*β-*D*-Glucopyranosyloxy)-benzo-[f]-1,3-benzodioxolo[6,5,4-*cd*]indol-5(6*H*)-one*; **2**): Yellow powder. M.p. 292–293°. $[\alpha]_D^{25} = -10.5$ ($c = 0.20$, MeOH). UV (MeOH): 246, 264, 275, 318. IR (KBr): 3475, 3415, 3234, 3075, 2909, 1754, 1659, 1650, 1642, 1620, 1470, 1427, 1383, 1218, 1095, 1037, 990, 929, 810, 742. ^{1}H- and ^{13}C-NMR: see the *Table*. ESI-MS (pos.): 442 (100, $[M+H]^+$). ESI-MS (neg.): 440 (5, $[M-H]^-$). HR-ESI-MS: 442.1133 ($[M+H]^+$, $C_{22}H_{20}NO_9^+$; calc.442.1138).

Aristoloside (=*10-(β-*D*-Glucosyloxy)-8-methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **3**): Orange crystal. M.p. 250–251°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.25 (*s*, COOH); 8.52 (*s*, H–C(9)); 8.35 (*d*, $J = 2.0$, H–C(5)); 7.79 (*s*, H–C(2)); 7.12 (*d*, $J = 2.0$, H–C(7)); 6.49, 6.44 (2*s*, OCH_2O); 4.07 (*s*, MeO–C(8)); 5.10 (*d*, $J = 7.4$, H–C(1′)); 3.20–3.80 (4*m*, H–C(2′), H–C(3′), H–C(4′), H–C(5′), CH_2(6′)).

Aristolochic Acid I (=*8-Methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **4**): Yellow needles. M.p. 279–280°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.32 (*s*, COOH); 8.65 (*d*, $J = 8.4$, H–C(5)); 8.58 (*s*, H–C(9)); 7.86 (*t*, $J = 8.4$, H–C(6)); 7.82 (*s*, H–C(2)); 7.37 (*d*, $J = 8.4$, H–C(7)); 6.50 (*s*, OCH_2O); 4.07 (*s*, MeO–C(8)).

Aristolochic Acid II (=*6-Nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **5**): Yellow needles. M.p. 268–270°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.34 (*s*, COOH); 9.07 (*d*, $J = 8.3$, H–C(5)); 8.58 (*s*, H–C(9)); 8.25 (*m*, H–C(8)); 7.81 (*s*, H–C(2)); 7.90 (*t*, $J = 8.3$, H–C(6)); 7.82 (*t*, $J = 8.3$, H–C(7)); 6.51 (*s*, OCH_2O).

Aristolic Acid II (=*Phenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **6**): Yellowish powder. M.p. 184–185°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.34 (*s*, COOH); 9.05 (*d*, $J = 9.3$, H–C(5)); 8.79 (*d*, $J = 9.7$, H–C(9)); 7.89 (*s*, H–C(2)); 7.89 (*d*, $J = 9.3$, H–C(8)); 7.80 (*d*, $J = 9.7$, H–C(10)); 7.70 (2*m*, H–C(6), H–C(7)); 6.45(*s*, OCH_2O).

Aristolochic Acid IVa (=*10-Hydroxy-8-methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **7**): Red needles. M.p. 262–263°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.17 (*s*, COOH); 10.67 (*s*, OH–C(6)); 8.49 (*s*, H–C(9)); 8.09 (*d*, $J = 1.4$, H–C(5)); 7.75 (*s*, H–C(2)); 6.82 (*d*, $J = 1.4$, H–C(7)); 6.48 (*s*, OCH_2O); 4.01(*s*, MeO–C(8)).

Aristolochic Acid IIIa (=*10-Hydroxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid*; **8**): Red needles. M.p. 283–284°. ^{1}H-NMR (300 MHz, (D_6)DMSO)[1]): 13.18 (*s*, COOH); 10.67 (*s*, OH–C(6)); 8.49 (*s*, H–C(9)); 8.48 (*d*, $J = 2.5$, H–C(5)); 8.10 (*d*, $J = 8.5$, H–C(8)); 7.76 (*s*, H–C(2)); 7.29 (*dd*, $J = 8.5, 2.5$, H–C(7)); 6.48 (*s*, OCH_2O).

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