Sesquiterpene and Aristolochic Acid Derivatives from *Thottea hainanensis*

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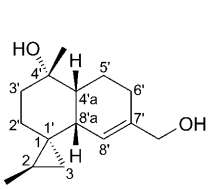
One new sesquiterpene named thotteodiol (**1**) with a novel skeleton and one new derivative of aristolochic acid named 7-hydroxyaristolochic acid III methyl ester (**2**), together with 20 known compounds, were isolated from the stems and roots of *Thottea hainanensis*. Their structures were determined by spectroscopic methods.

Introduction. – *Thottea hainanensis* (MERR. et CHUN) D. HOU (Aristolochiaceae) is a perennial shrub of the genus *Thottea* endemic to Hainan Province of China, which is the only species of *Thottea* distributed in China [1]. There are *ca.* 25 species contained in the genus *Thottea* primarily distributed in India, Vietnam, Malaysia, Philippines, and Indonesia [2]. Previous studies about plants of *Thottea* were mainly performed by entomologists on the clarification of the relationship between butterflies and their host plants [3][4]. So far, there are relatively few systemic phytochemical investigations of *Thottea* species. On the other hand, aristolochic acids are ubiquitous constituents in the plants of the genus *Aristolochia* [5] and have also been identified in some species of the genus *Asarum* [6][7], but there are very few reports on their occurrence in families other than Aristolochiaceae. The restricted distribution of aristolochic acids implicates the chemotaxonomic significance as a chemical marker in the family Aristolochiaceae. To gain more information about the chemotaxonomy of Aristolochiaceae, we carried out a phytochemical research of *T. hainanensis* in a systematic way. As the result of our investigation, we isolated two new compounds, thotteodiol (**1**) and 7-hydroxyaristolochic acid III methyl ester[1]) (**2**), together with 20 known compounds. All these compounds were isolated from this plant for the first time, and the ^{13}C-NMR data of aristololide (=10-hydroxy-8-methoxy-3,4-(methylenedioxy)phenanthrene-1-carboxylic acid γ-lactone[1]); **3**) are reported for the first time. In this article, we describe the isolation and structural elucidation of the new compounds **1** and **2**.

[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*



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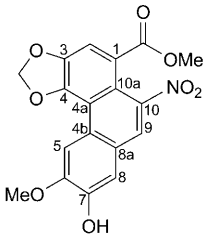
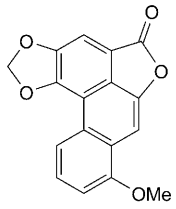


2[1])



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Results and Discussion. – *Characterization of the Isolated Compounds.* The structures of the known compounds were elucidated by comparison of their spectroscopic data (UV, IR, NMR, and MS) with published data or by comparison with authentic compounds on TLC. The known compounds isolated include two aristolochic acids, five aristololactams and three analogs, and ten other compounds, namely aristolochic acid I, aristolochic acid IIIa, aristololactam II, aristololactam FI [7], aristololactam IIIa, aristololactam AIIIa [8], aristololactam-IIIa *N*-(*β*-D-glucopyranoside) [9], cepharadione A, cepharadione B [10], aristololide (**3**) [11], (4*β*,10*β*)-aromadendrane-4,10-diol [12], kaempferol 3-[*O*-*α*-L-rhamnopyranosyl-(1 → 6)-*β*-D-galactopyranoside] [13][14], kaempferol 3-[*O*-*α*-D-xylopyranosyl-(1 → 6)-*β*-D-galactopyranoside], kaempferol 3-(*O*-*β*-D-galactopyranoside) [15], *N*-(*trans*-feruloyl)tyramine [16], (6*β*)-6-hydroxystigmast-4-en-3-one, (6*β*)-6-hydroxycampest-4-en-3-one [17], (3*β*,5*α*,8*α*,22*E*,24*R*)-5,8-epidioxyergosta-6,22-dien-3-ol [18], tetracosanoic acid, and *β*-sitosterol.

Thotteodiol[1]) (**1**) was isolated as colorless crystals. The molecular formula $C_{15}H_{24}O_2$ (deduced from HR-EI-MS; *m*/*z* 237.1849 ($[M+H]^+$)) indicated four degrees of unsaturation. Occurrence of only two olefinic C-atoms in the ^{13}C-NMR spectrum (*Table*; *δ*(C) 122.2 and 141.8), indicated the presence of three rings in its structure. From the ^{1}H- and ^{13}C-NMR, DEPT, ^{1}H,^{1}H-COSY, and HMQC data, some parts of the structure could be deduced. H-Atoms at *δ*(H) −0.46 and 0.46 together with a C-atom at *δ*(C) 13.0 are obviously due to a cyclopropane CH_2 group and both H-atom signals were correlated with the H-atom at *δ*(H) 0.74–0.76 (H−C(2)) in the ^{1}H,^{1}H-COSY plot. There was also an obvious correlation between H−C(2) and a Me group at *δ*(H) 1.03 (Me−C(2)) in the ^{1}H,^{1}H-COSY plot. Signals in the HMBC spectrum indicated that all above mentioned H-atoms had a long-range correlation with a quaternary C-atom at *δ*(C) 22.9 and thus revealed the presence of a spirocyclopropane unit in the structure. The COSY and HMQC data indicated the presence of a partial structure with two CH_2 and three CH groups as shown in bold in *Fig. 1.* The HMBC spectrum revealed a CH_2OH group attached at an olefinic C-atom (*δ*(C) 141.8). In summary, this partial structure contained a six-membered ring. There was another coupling system revealed by the ^{1}H,^{1}H-COSY data consisting of two CH_2 groups at *δ*(H) 1.40 and 1.43 (CH_2(3′)) and 0.96–0.98 and 2.11 (CH_2(2′)).

The fragments highlighted above could be assembled as shown in *Fig. 1* by HMBCs. Briefly, the Me group at *δ*(H) 1.17 (Me−C(4′)) had long-range correlations with three C-atoms, *i.e.*, a quaternary C-atom at *δ*(C) 71.7 (C(4′)), a CH_2 group at *δ*(C) 35.3 (C(3′)), and a CH group at *δ*(C) 47.6 (C(4′a)). A CH_2 group at *δ*(H) 2.11 (1 H−C(2′))

Table. *^{1}H- and ^{13}C-NMR Data of Compounds* **1**–**3**. δ in ppm, J in Hz.

	1[a])		**2**[b])		**3**[c])	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
C(1)				126.5		112.0
H–C(2)	0.74–0.76 (*m*)	14.9	7.75 (*s*)	106.4	7.94 (*s*)	107.1
CH_2(3) or C(3)	−0.46 (*t*, *J* = 4.5), 0.46 (*dd*, *J* = 4.5, 8.5)	13.0		146.1		150.2
C(4)				147.4		149.3
C(4a)				127.6		110.8
C(4b)				128.0		125.0
H–C(5)			9.02 (*s*)	121.5	8.17 (*d*, *J* = 8)	118.6
C(6) or H–C(6)				152.0	7.65 (*t*, *J* = 8)	127.2
C(7)				150.0	7.30 (*d*, *J* = 8)	108.9
H–C(8) or C(8)			7.57 (*s*)	107.9		156.0
C(8a)				127.7		123.2
H–C(9)			8.35 (*s*)	125.5	7.63 (*s*)	98.2
C(10)				149.6		146.6
C(10a)				116.0		129.0
Me–C(2)	1.03 (*d*, *J* = 6.6)	13.2				
*Me*O–C(6)			3.91 (*s*)	60.6		
*Me*O–C(8)					4.02 (*s*)	56.0
COO*Me*			3.78 (*s*)	52.0		
OCH_2O–C(4)			6.28 (*s*)	103.5	6.59 (*s*)	104.2
*C*OOMe				167.9		165.9
HO–C(7)			9.24 (*s*)			
C(1′)		22.9				
CH_2(2′)	0.96–0.98 (*m*), 2.11 (br.)	27.4				
CH_2(3′)	1.40 (*t*, *J* = 3.3), 1.43 (*d*, *J* = 3.3)	35.3				
C(4′)		71.7				
C(4′a)	1.57 (*d*, *J* = 2.1)	47.6				
CH_2(5′)	1.57–1.60 (*m*)	21.1				
CH_2(6′)	1.98–2.00 (*m*), 2.09 (br.)	27.6				
C(7′)		141.8				
C(8′)	5.34–5.35 (*m*)	122.2				
C(8′a)	2.86–2.87 (*m*)	36.6				
Me–C(4′)	1.17 (*s*)	29.3				
CH_2–C(7′)	3.87 (*d*, *J* = 5.0)	66.7				
HO–C(4′)	3.12 (*d*, *J* = 4.5)					
CH_2(O*H*)–C(7′)	3.62–3.64 (*m*)					

[a]) At 500 (^{1}H) and 500 MHz (^{13}C) in (D_6)acetone. [b]) At 300 (^{1}H) and 300 MHz (^{13}C) in (D_6)acetone. [c]) At 500 (^{1}H) and 500 MHz (^{13}C) in (D_6)DMSO.

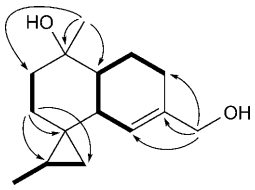

Fig. 1. *Partial structures generated from ^{1}H,^{1}H-COSY* (—) *and HMBCs* (H → C) *of* **1**

had long-range correlations with a quaternary C-atom at δ(C) 22.9 (C(1′)) and a methine C-atom at δ(C) 36.6 (C(8′a)). Based on this evidence, it is possible to assemble a partially hydrogenated naphthalene ring. Other long-range correlations observed between H−C(2′) and C(3), H−C(2′) and Me−C(2) confirmed the presence of a cyclopropane at C(1′). Therefore, the constitutional formula of compound **1** was established as shown in *Fig. 1*. The relative configuration of **1** was determined by a NOESY experiment (*Fig. 2*). The significant NOE between H−C(4′a) and H−C(8′a) suggested that they are on the same face of the module (assumed as β). In addition, a small coupling constant (J(4′a,8′a) = 2.1 Hz) between these two H-atoms confirmed their *cis* relation. The NOEs H−C(8′a)/Me−C(4′), Me−C(4′)/Me−C(2) and H−C(4′a)/Me−C(2) revealed that they are all oriented toward the β face. Thus, the relative configuration of **1** was determined as shown in *Fig. 2*. Based on the above analysis, compound **1** was determined as (2β,4α,4′aβ,8′aβ)-3′,4′,4′a,5′,6′,8′a-hexahydro-4′-hydroxy-2,4′-dimethylspiro[cyclopropane-1,1′(2′*H*)-naphthalene]-7′-methanol and named thotteodiol. This compound is a new regular sesquiterpene with a novel skeleton.

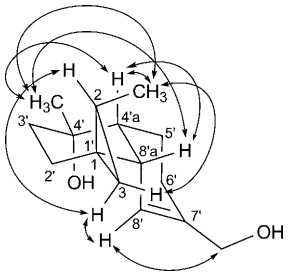

Fig. 2. *NOE Interactions* (H ↔ H) *defining the relative configuration at stereogenic centers in* **1**

Compound **2**, 7-hydroxyaristolochic acid III methyl ester[1]), was isolated as yellow crystals. Its HR-EI-MS showed the M^+ at m/z 371.0649, which corresponds to the molecular formula $C_{18}H_{13}NO_8$. The UV absorption maxima at 250 and 267 nm suggested the presence of a phenanthrene derivative. The IR spectrum showed absorption of an ester group at 1722 cm^{-1} and of an NO_2 group at 1522 and 1346 cm^{-1} (the EI-MS fragments also showing the presence of an NO_2 group: base peak at $[M-46]^+$) [19]. The absorption at 1593, 1505, and 1468 cm^{-1} indicated the presence of a phenanthrene structure [20]. All the signals in the ^{1}H-NMR spectrum of **2** (*Table*) were *s*, suggesting that there were no adjacent H-atoms. Known biosynthetic pathways of phenanthrene derivatives [21] suggested the presence of substituents at C(6) and C(7), which was established by additional spectral examinations. The ^{1}H-NMR of **2** showed two MeO and one OCH_2O signals at δ(H) 3.91 (*s*, 3 H), 3.78 (*s*, 3 H), and 6.28 (*s*, 2 H), respectively. The signal at the lowest field, δ(H) 9.24 (*s*, 1 H), is due to a phenolic OH group. Because the COOH H-atom signal was absent, we deduced that a methyl ester function was present and the groups at C(6) and C(7) should be OH and MeO. With the aid of NOESY, we determined the exact structure of this compound. The signal of H−C(5) of **2** appeared at low field, δ(H) 9.02 (*s*, 1 H), due to the deshielding effect of the A ring [22] (*Fig. 3*). The NOESY plot showed a correlation between the aromatic H-atoms at δ(H) 7.57 (*s*, 1 H) and 8.35 (*s*, 1 H) and thus, these

signals were assigned to H–C(8) and H–C(9). Because of the deshielding effect of the NO_2 group, H–C(9) appeared at lower field (δ(H) 8.35). A NOE correlation between the MeO group at δ(H) 3.91 and the aromatic H-atom signal at δ(H) 9.02 was also observed, which indicated that a MeO group was present at C(6). Another NOE correlation between δ(H) 3.91 (MeO–C(6)) and δ(H) 9.24 (HO–C(7)) also suggested a MeO group being connected with C(6) and an OH group at C(7) (*Fig. 3*). From the above evidence, the structure of compound **2** was determined as 7-hydroxyaristolochic acid III methyl ester (6,7-disubstituted aristolochic acid derivatives are not so ubiquitous, and a 7-hydroxy-substituted aristolochic acid III has not been reported yet). The ^{13}C-NMR data of **2** (*Table*) also supported the above structure. We assigned the C-atom chemical shifts in analogy to published data [7].

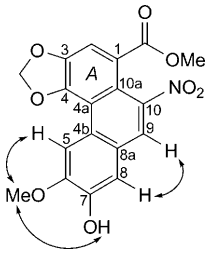

Fig. 3. *NOE Interactions* (H ↔ H) *of* **2**[1])

Active Constituents of the Herb. Among the compounds isolated, compound (3β,5α,8α,22*E*,24*R*)-5,8-epidioxyergosta-6,22-dien-3-ol showed potent inhibition to nasopharyngeal cancer cells *in vitro* (IC_{90} = 0.1 μM) in our activity-screening test. Compound (3β,5α,8α,22*E*,24*R*)-5,8-epidioxyergosta-6,22-dien-3-ol was also reported to have strong antitumor activity toward the L-1210 cell line (LD_{50} = 3.5 μg/cm^3) *in vitro* [23], inhibitory effects on proliferation of human-breast carcinoma-MCF-7 and sarcoma-*Walker-256* cell line [24], and inhibitory activity against human-liver cancer PLC/PRF/5 and KB cells [25]. It selectively enhances the inhibitory effect of linoleic acid on DNA polymerase β [26] and has anti-inflammation [27], anticomplement [28], immunosuppression [29], antiinfluenza virus [28], and promoting platelet aggregation [30] effects, *etc*. Compound *N*-(*trans*-feruloyl)tyramine was reported to have moderate inhibitory activity on LPS-activated nitric oxide production in a dose-dependent manner in RAW 264.7 cells [31] and to show strong inhibitory effects against human platelet aggregation [32].

Chemotaxonomical Significance. Aristolochic acids, which were mainly found in the family Aristolochiaceae, should be the taxonomically informative type of constituents in this family. There are eight genera contained in the family Aristolochiaceae [2][33], four genera (*Aristolochia*, *Asarum*, *Saruma,* and *Thottea*) occurring in China. Aristolochic acids are ubiquitous constituents in the plants of the genus *Aristolochia* [5] and were found in some species of the genus *Asarum* [6][7] and the genus *Saruma* (*Saruma henryi* OLIV.) [34]. Our present work is the first systematic study on the chemical constituents of the genus *Thottea*, from which aristolochic acids were identified. The present results provide evidence that aristolochic acids (especially aristolochic acid I (= 8-methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic

acid)) should be of chemotaxonomical significance. Up to now, aristolochic acids have been found in all of the four genera *Aristolochia*, *Asarum*, *Thottea*, and *Saruma* of Aristolochiaceae distributed in China. Since aristolochic acids were found in these four genera of China but seldom in other families, we may consider aristolochic acids as the characteristic constituents of the family Aristolochiaceae in China. From a chemical viewpoint, our results have also confirmed that the four genera of Aristolochiaceae in China have close affinities to each other, and that it is suitable to consider the genera *Aristolochia*, *Asarum*, *Thottea*, and *Saruma* within the family Aristolochiaceae as a natural family.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh; *Qingdao Marine Chemistry Co., Ltd.*), *Sephadex LH-20* (18–110 μm; *Pharmacia Co.*). M.p.: *XT-4A* micromelting point apparatus; uncorrected. Optical rotations: *AA-10R* polarimeter. UV Spectra: *PGENERAL-TU-1901* UV/VIS spectrometer in EtOH; λ_{max} (log ε) in nm. IR Spectra: *Thermo-Nicolet-Nexus-470* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-DRX-500* and *-300* NMR spectrometer; δ in ppm rel. to solvents as internal standards, *J* in Hz. MS: *Bruker-APEX-II* mass spectrometer; *m/z* (rel. %).

Plant Material. Thottea hainanensis (MERR. et CHUN) D. HOU was collected from Hainan Province of China in December 1999. Plant identification was confirmed by *S.-Q. C.* The voucher specimen (SW Dong 20000101) is deposited with the Herbarium of Pharmacognosy, School of Pharmaceutical Sciences, Peking University.

Extraction and Isolation. The stems and roots of *Thottea hainanensis* (18 kg) were extracted with EtOH (4 × 40 l) at r.t. and the extracts concentrated into a black syrup. The extract was suspended in H_2O and then partitioned successively with petroleum ether, AcOEt, and BuOH. The petroleum ether soluble part (65 g) was applied directly to CC (SiO_2, petroleum ether/acetone gradient): (4*β*,10*β*)-aromadendrane-4,10-diol (15 mg), aristololactam II (10 mg), (6*β*)-6-hydroxystigmast-4-en-3-one (15 mg), (6*β*)-6-hydroxycampest-4-en-3-one (20 mg), (3*β*,5*α*,8*α*,22*E*,24*R*)-5,8-epidioxyergosta-6,22-dien-3-ol (10 mg), *β*-sitosterol (100 mg), and tetracosanoic acid (20 mg). The AcOEt extract (90 g) was subjected to CC (SiO_2, then polyamide and *Sephadex LH-20*): **1** (15 mg), **2** (20 mg), kaempferol 3-[*O*-*α*-L-rhamnopyranosyl-(1 → 6)-*β*-D-galactopyranoside] (15 mg), kaempferol 3-[*O*-*α*-D-xylopyranosyl-(1 → 6)-*β*-D-galactopyranoside] (30 mg), kaempferol 3-(*β*-D-galactopyranoside) (15 mg), cepharadione A (15 mg), cepharadione B (5 mg), aristolochic acid I (100 mg), aristolochic acid IIIa (10 mg), aristololactam FI (20 mg), aristololactam IIIa (8 mg), aristololactam AIIIa (8 mg), aristololactam-IIIa *N*-(*β*-D-glucopyanoside) (15 mg), **3** (8 mg), and *N*-(*trans*-feruloyl)tyramine (20 mg).

Thotteodiol (= rel-*(1*R*,2*S*,4′*R*,4′a*S*,8′a*R*)-3′,4′,4′a,5′,6′,8′a-Hexahydro-4′-hydroxy-2,4′-dimethylspiro-[cyclopropane-1,1′(2′*H*)-naphthalene]-7′-methanol*; **1**): Colorless crystals. M.p. 143–145°. $[\alpha]_D^{25} = +50$ ($c = 0.05$, MeOH). ^1H- and ^{13}C-NMR: *Table.* EI-MS: 218 ($[M - H_2O]^+$), 176 ($[M - H_2O - C_3H_7]^+$). HR-EI-MS: 237.1849 ($[M + H]^+$, $C_{15}H_{25}O_2^+$; calc. 237.1855).

7-Hydroxyaristolochic Acid III Methyl Ester (= *9-Hydroxy-10-methoxy-6-nitrophenanthro[3,4-*d*]-1,3-dioxole-5-carboxylic Acid Methyl Ester*; **2**): Yellow needles. M.p. 245–246°. UV: 250.0 (3.83), 267.0 (4.01). IR (KBr): 3416–3365, 1722, 1593, 1522, 1505, 1468, 1346, 1320, 1303, 1248, 1202. ^1H- and ^{13}C-NMR: *Table.* HR-EI-MS: 371.0649 (M^+, $C_{18}H_{13}NO_8^+$; calc. 371.0641), 325.07174 ($[M - NO_2]^+$, $C_{18}H_{13}O_6^+$; calc. 325.07121).

Aristololide (= *8-Methoxy-5*H*-furo[2′,3′,4′:10,1]phenanthro[3,4-*d*]-1,3-dioxol-5-one*; **3**): Yellowish power. M.p. 220–222°. ^1H- and ^{13}C-NMR: *Table.*

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