Pergamon

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A SESQUITERPENE LACTAM FROM *ARTRACTYLODES MACROCEPHALA*

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Key Word Index—*Atractylodes macrocephala*, Compositae, sesquiterpene lactam, atractylenolactam, 8β-methoxy-atractylenolide I.

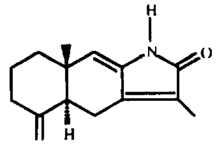
Abstract—A sesquiterpene lactam, atractylenolactam and 8β-methoxy-atractylenolide I have been isolated from the rhizome of *Atractylodes macrocephala*. Their structures were elucidated by spectroscopic methods. © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

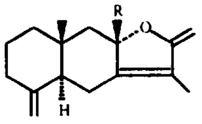
The rhizome of *Atractylodes macrocephala* Koidz is known as a tonic in China. It is reported as a nutrient for energy and stomach complaints and for treatment of dyspepsia and anorexia in the pharmacopeia of People's Republic of China [1]. In Chinese traditional medicine there are two famous *Atractylodes* medicinal plants, namely *A. lancea* (cang-zhu) and *A. macrocephala* (bai-zhu). These two medicinal plants have been used for a very long time and were reported in Shen-nong-ben-cao-jing, the first Chinese pharmacopoeia written in the Han Dynasty about 100–200 B.C. However, these two relatively crude drugs are said to possess different therapeutic effects, the former having antisudorific activity and the latter diaphoretic activity [2, 3]. The chemical constitutions of both plants also show differences in sesquiterpenes and acetylene compounds [4].

Our previous chemical investigation of *A. macrocephala* showed that the rhizome of cultivated plants contained atractylenolides I, II, III and 3β-acetoxy-atractylenolide III [5], and eight polyacetylene compounds [6, 7]. Here we report the study of another wild plant Qi-zhu which was collected from Qimen county, Anhui province, and is widely used for medicinal purposes as Bai-zhu.

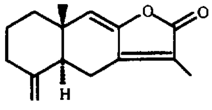
In addition to eight known compounds (sitosterol, sitosterol-3-glucoside, scopoletin, atractylenolide I, II, III, 3β-acetoxy-atractylenolide III and 3β-acetoxy-atractylone) a novel nitrogen containing sesquiterpene, atractylenolactam (**1**) and 8β-methoxy-atractylenolide I (**2**) were isolated.



1



2 R=OCH$_3$
4 R=OH
5 R=OCH$_2$CH$_3$



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RESULTS AND DISCUSSION

Atractylenolactam (**1**) had an EI-mass spectrum which showed an odd molecular ion at *m/z* 229 and its molecular formula was determined to be $C_{15}H_{19}ON$ (anal. 229.1449, calcd 229.1467) by HRMS. The IR spectrum of **1** presented an absorption at 1690 cm^{-1}, indicating an unsaturated lactam carbonyl. The ^{1}H NMR spectrum of **1** (Table 1) contained the H-5 and two H-6 signals at δ 1.54 *dd* (*J* = 4, 14 Hz), 2.46 *br dddd* (*J* = 14, 14Hz), 2.62 *dd* (*J* = 4, 14 Hz) and a H-9 vinyl-proton at δ 5.43, two methyl proton signals at δ 0.92 *s* (3H) and 1.87 *s* (3H) and two exomethylenic protons at δ 4.61 *br s* and 4.87 *br s*. These ^{1}H NMR data are very similar to atractylenolide II (**3**); the main difference between **1** and **3** is that **1** contains an extra N-H proton which resonates at δ 7.36. The fragmentation shown in the mass spectrum was similar to

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Table 1. ^{1}H NMR data compounds of **1** and **2** (400 MHz, $CDCl_3$)

Compounds	**1**	**2**
H-1	2.03 *ddd* (1H, 3, 13, 13 Hz)	14.80 *brd* (10 Hz)
	2.30 *dd* (1H, 13, 4 Hz)	1.92 *brdd* (10, 10 Hz)
H-2	1.64 *m* (2H)	1.64 *m* (2H)
H-3	1.64 *m* (1H)	1.20 *m* (1H)
	2.36 *dd* (1H, 11, 2 Hz)	1.64 *m* (1H)
H-5	1.56 *dd* (1H, 14, 4 Hz)	1.54 *dd* (1H, 13, 3 Hz)
H-6	2.46 *dd* (1H, 14, 14 Hz)	2.22 *dd* (1H, 13, 13 Hz)
	2.62 *dd* (1H, 14, 4 Hz)	2.58 *dd* (1H, 13, 3 Hz)
H-9	5.43 *s* (2H)	1.40 *d* (1H, 14 Hz)
		2.34 *d* (1H, 14 Hz)
Me-13	1.87 *s* (3H)	1.83 *s* (3H)
Me-14	0.92 *s* (3H)	0.94 *s* (3H)
H-15	4.61 *brs* (1H)	4.53 *brs* (1H)
	4.87 *brs* (1H)	4.84 *brs* (1H)
Other signals	7.36 *brs* (NH)	3.13 *s* (OMe)

that of **3**, showing the peaks at *m/z* 214 $[M^+ - CH_3]$ and 186 $[M^+ - CO - CH_3]$. Therefore, we suggest the structure of compound **1** as a new sesquiterpene lactam.

Compound **2** had an EI-mass spectrum which showed the molecular ion at *m/z* 262 for the molecular formula $C_{16}H_{22}O_3$, this is 14 a.m.u. more than atractylenolide III (**4**) and like a methyl derivative of **4**. The ^{1}H NMR spectrum revealed H-5 and two H-6 proton signals at δ 1.58 *dd* (J = 3, 13 Hz), 2.22 *br dd* (J = 13, 13 Hz) and 2.58 *dd* (J = 13, 3 Hz), two H-9 proton signals at δ 1.40 *d* (J = 14 Hz) and 2.34 *d* (J = 14 Hz), further signals at 1.83 *s* (CH_3-13), 0.94 *s* (CH_3-14), exomethylenic protons at δ 4.53 *br s* and 4.84 *br s* and a methoxy group signal at 3.13 *s* (3H). This ^{1}H NMR spectrum was very similar to those of **4** and **5**, which we isolated previously from the same plant [6]. The mass spectrum of **2** was also very similar to that of **5**, so we deduced the structure of **2** to be 8β-methoxyatractylenolide I.

In general, the 8-hydroxy group of atractylenolide III (**4**), an allylic hemiacetal hydroxy group, may be rather active in its chemical behaviour; we isolated an ethyl derivative of **4** previously [6]. We suppose compound **5** was an artifact formed by ethylation during the extraction of the drug with ethanol. As we avoided using methanol we are sure that compound **2** is not an artifact.

N-containing sesquiterpenes are very rarely found in nature. However, atractylenolactam, the novel sesquiterpene compound, is very interesting with a view to its biosynthesis. We assume that the lactone oxygen atom of atractylenolide III (**4**) possesses the characters of an α,β-unsaturated ester and a vinyl hemiketal and may be rather active in replacement of a nitrogen atom in plant tissue.

EXPERIMENTAL

General. Mps were determined on a Kofler hot-stage apparatus and are uncorr. MS were obtained on Varian MAT-711 and MAT-44. IR spectra were run on a Perkin-Elmei 588B spectraphotometer and the NMR spectra were measured on Brucker AM-400.

Plant material. The rhizomes of *Atractylodes macrocephala* were collected at Qimen county, southern Anhai Province during autumn. Identification of the plant was done at Pharmacognosy Laboratory of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, where a voucher specimen is deposited.

Extraction and isolation. Air dried and powdered rhizomes (5 kg) were extracted with EtOH. After evapn of the solvent the crude extract was partitioned between EtOAc–H_2O. The organic layer was evapd to dryness to yield a residue of 200 g. This residue (40 g) was subjected to CC on silica gel with the solvent systems petrol, petrol–Et_2O (9:1, 3:1, 1:1) and Et_2O. Prep. TLC of the fr. obtained with petrol–Et_2O (3:1) afforded 80 mg atractylenolide I, 40 mg 8β-methoxyatractylenolide I (**2**) and 250 mg 3β-acetoxyatractylon. TLC sepn of the petrol–Et_2O (1:1) fr. afforded 25 mg atractylenolactam (**1**) 120 mg atractylenolide II, 150 mg atractylenolide III and additionally 100 mg scopoletin and 140 mg sitosterol-3-glucoside from the Et_2O fr. All known compounds were identified by comparison of the IR and ^{1}H NMR spectra with authentic compounds.

Atractylenolactam (**1**). Needles, mp 225–227°. HR-MS: *m/z* (rel. int.): 229.1449 (33) $C_{15}H_{19}NO$, 214.1205 (100), 186.1256 (24), 186.0886 (24), 160.0753 (38) and 158.0972. IR ν_{max}^{KBr} cm^{-1}: 3160, 1690, 1650, 1434, 1345, 890.

8β-Methoxy atactylenolide I (**2**). Prisms, mp 72–73°. MS *m/z* (rel. int): 262 (14) $C_{16}H_{22}O_3$, 234 (23), 219 (19), 203 (20), 175 (24), 159 (22), 147 (100), 119 (40), 105 (46).

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