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Alkaloids Isolated from *Dehaasia candolleana* (Meisn.) Kosterm

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ABSTRACT Three alkaloids were isolated from the bark of *Dehaasia candolleana* (Meisn.) Kosterm; one morphinandienone, (-)-sebiferine **1** and two bisbenzylisoquinoline alkaloids namely (-)-*O,O*-dimethylgrisabine **2** and grisabine **3**. Structural elucidations of these alkaloids were performed using spectroscopic methods notably ^{1}H, ^{13}C-NMR (1D and 2D) and compared with reported data. Alkaloids **1** and **2** exhibited potent *in vitro* antiplasmodial activities to two strains of *P. falciparum*; D10 strain (sensitive strain) and Gombak A isolate (resistant strain).

ABSTRAK Tiga alkaloid telah diasingkan daripada bahagian batang *Dehaasia candolleana* (Meisn.) Kosterm; satu morfinadienon, (-)-sebiferina **1** dan dua alkaloid bisbenzilisokuinolina; (-)-*O,O*-dimetilgrisabina **2** dan grisabina **3**. Elusidasi struktur telah dijalankan terutamanya melalui kaedah spektroskopi ^{1}H, ^{13}C NMR (1D dan 2D) dan perbandingan dengan data yang telah dilaporkan. Alkaloid **1** dan **2** telah menunjukkan aktiviti *in vitro* antiplasmodium terhadap dua strain, *P. falciparum*, D10 strain (*sensitive strain*) dan Gombak A isolate (*resistant strain*).

(*Dehaasia candolleana*, Lauraceae, morphinandienone, bisbenzylisoquinoline)

INTRODUCTION

Dehaasia, (family: Lauraceae, sub-family: Lauroideae, tribe: Perseeae, sub-tribe: Beilschmeidinea) which comprises about 35 species, is an evergreen tree of moderate size with large leaves. It was found growing in the western parts of Malaysia, Burma, Thailand, China and in the Philipines [1 - 3].

Past studies on the chemical constituents of *Dehaasia* species were reported to contain bisbenzylisoquinolines, aporphines and bisaporphines [4 - 6]. Our investigation of the alkaloidal contents of the bark of *D. candolleana* has resulted in the isolation of (-)-sebiferine **1** and two single diphenyl ether (C_{11}-O-$C_{12'}$) linkage bisbenzylisoquinoline alkaloids, namely *O,O*-dimethylgrisabine **2** and grisabine **3.**

The crude alkaloid together with alkaloids **1** and **2** from the bark of this plant have shown *in vitro* antiplasmodial activity to resistant strain *P. falciparum*, Gombak A and to sensitive strain *P. falciparum*, D10 with IC_{50} < 8μg/mL. Our previous investigation of the leaves of *Dehaasia candolleana* has resulted in the isolation of three morphinandienone alkaloids [7].

MATERIALS AND METHODS

General Experimental Procedure

Ultraviolet (UV) Absorption Spectra were recorded on Shimadzu UV-160A ultraviolet-visible spectrometer with methanol as a solvent. The IR spectra were obtained with $CHCl_3$ on a Perkin Elmer 1600 Double-Beam recording spectrometer. The optical rotations were recorded on Jasco (Japan) P1010 with tungsten lamp. HRMS was obtained on Automass Multi Thermofinnigan. 1D and 2D NMR analysis were carried out using FT-NMR lambda 400 MHz and determined in $CDCl_3$. Silica gel 60, 70-230 mesh ASTM (Merck 7734 and Merck 9385) was used for column chromatography. Silica gel 604 F_{254} was used for preparative TLC. Aluminium

supported silica gel 60 F_{254} plates were used for TLC. TLC spots were visualized under ultra-violet light (254 nm and 365 nm) followed by spraying with the Dragendorff's reagent for alkaloid detection. Meyer's test was used for alkaloid screening.

Extraction and Isolation of the Alkaloids

D. candolleana (Meisn.) Kosterm was collected at Taman Negara Endau, Sungai Selai, Johore. Voucher specimens (KL 5013) were deposited at the Herbarium of the Department of Chemistry, University of Malaya, Kuala Lumpur, Malaysia. The dried and milled barks of *D. candolleana* (2.0 kg) were moistened with 15% NH_4OH and soaked in CH_2Cl_2 for 3 days (cold extraction). The CH_2Cl_2 extracts were reduced to 500 ml followed by acid extraction using 5% HCl until Mayer's test was negative. The extract obtained was basified with an aqueous ammonium hydroxide solution to pH ≈ 10 and reextracted with CH_2Cl_2, followed by washing with distilled H_2O and dried over anhydrous sodium sulphate. Finally, the extract was concentrated to dryness to give crude alkaloids (19 g). Further purification by a small column and preparative TLC (Silica gel $60F_{254}$) yielded the following alkaloids:

(-)-Sebiferine **1** (514 mg): $C_{20}H_{23}O_4N$ was isolated as a yellowish brown oil; $[\alpha]_D^{25}$ –8.47 (c = 0.3 $CHCl_3$); R_f= 0.46 ($CHCl_3$:CH_3OH/saturated with NH_4OH, 99:1); UV λ_{max} (CH_3OH) nm: 243, 293; IR υ_{max} (liquid film) cm^{-1}: 3003, 1620, 1463, 753 (aromatic system), 1620, 1641, 1666 (cross conjugated cylohexadienone); EIMS *m/z*: 341, 326, 313, 298, 282; ^1H NMR ($CDCl_3$) ppm: 6.29 (*s*,1H, H-8), 6.33 (*s*, 1H, H-5), 6.60 (*s*, 1H, H-1), 6.77(*s*, 1H, H-4), 3.85(*s*, 3H, C3-OCH_3), 3.82 (*s*, 3H,C2-OCH_3), 3.77(*s*, 3H, C6-OCH_3), 2.43 (*s*, 3H, *N*CH_3), 3.66 (*d*, *J* = 6 Hz, 1H, H-9), 3.01(*dd*, *J* = 6.1 and 17.8 Hz, 1H, H-10*eq*), 3.31(*d*, *J* = 17.8 Hz, 1H, H-10*ax*),. 2.53-2.60 (*m*, 2H, CH_2-16), 1.87-1.95 (*m*, 2H, CH_2-15); ^{13}C NMR ($CDCl_3$) δ: 110.4 (C-1), 148.3 (C-2), 148 (C-3), 108.6 (C-4), 118.7 (C-5), 151.3 (C-6), 180.7 (C-7), 122.4 (C-8), 60.8 (C-9), 32.6 (C-10), 128.5 (C-11), 129.8 (C-12), 42.1 (C-13), 161.1 (C-14), 40.8 (C-15), 45.6 (C-16), 55.8 (C-2-OCH_3), 56.2 (C-3-OCH_3), 55.0 (C-6-OCH_3), 41.5 (*N*CH_3).

(-)-*O*,*O*-Dimethylgrisabine **2** (30 mg): Amorphous ; $[\alpha]_D^{25}$ -33° (*c*= 0.2, $CHCl_3$); R_f = 0.73 ($CHCl_3$:CH_3OH/ saturated with NH_4OH, 99:1); UV λ_{max} (CH_3OH) nm: 235, 257, 292; IR υ_{max} cm^{-1}: 1464, 1511, 1609 (aromatic system); GC-EIMS *m/z*: 206 (100%) $[C_{12}H_{16}NO_2]^+$; ^1H and ^{13}C NMR ($CDCl_3$): see Table 1.

Grisabine **3** (5 mg): Amorphous ; $[\alpha]_D^{25}$ -23.1° (*c*= 0.2, $CHCl_3$); R_f= 0.36 ($CHCl_3$:CH_3OH/ saturated with NH_4OH, 99:1); HRFABMS (+ve mode): *m/z* 611.4120 (calc. 611.4142; $C_{37}H_{43}N_2O_6$); ^1H and ^{13}C NMR ($CDCl_3$) see Table 1.

Anti-Plasmodial Activity

The *in vitro* antimalaria assay procedure is an adaptation of the parasite lactate dehydrogenase (pLDH) assay developed by Makler *et al.* [8].

RESULTS AND DISCUSSION

Sebiferine **1**, $[\alpha]_D^{25}$ –8.47 (c = 0.3 $CHCl_3$) was isolated as a yellowish brown oil. The mass spectrum of sebiferine which afforded a molecular ion peak at *m/z* 341 is consistent with a molecular formula of $C_{20}H_{23}NO_4$. The other prominent fragmentation peaks were found at *m/z* 326, 313 and 298. Significant peaks of α-methoxy cross-conjugated cyclohexadienone system were observed at 1666, 1641 and 1620 cm^{-1} in the IR spectrum and the absorptions at 243 and 293 nm were observed in UV spectrum [9].

The ^1H-NMR spectrum revealed three methoxyl peaks at δ 3.77, 3.82 and 3.85. The presence of three downfield singlet protons at δ 6.60 (H-1), 6.77 (H-4) and 6.33 (H-5) were related to the aromatic ring and one proton singlet at δ 6.29 (H-8) was an α-conjugated cyclohexadienone proton [10]. The H-9 proton appeared as a doublet at δ 3.66 (*J* = 6.1 Hz) which showed the ABX system signals with H_{ax}-10 and H_{eq}-10 resonated at δ 3.31 (*d*, *J* = 17.8 Hz) and δ 3.01 (*dd*, *J* = 6.1, 17.8 Hz). These signals were observed as prominent peaks for morphinandienone alkaloids [10]. A signal resonating as multiplets at δ 2.48 was assigned to the C-16 protons. The complete assignment of protons and carbons was aided by 2D NMR (COSY and HMQC).

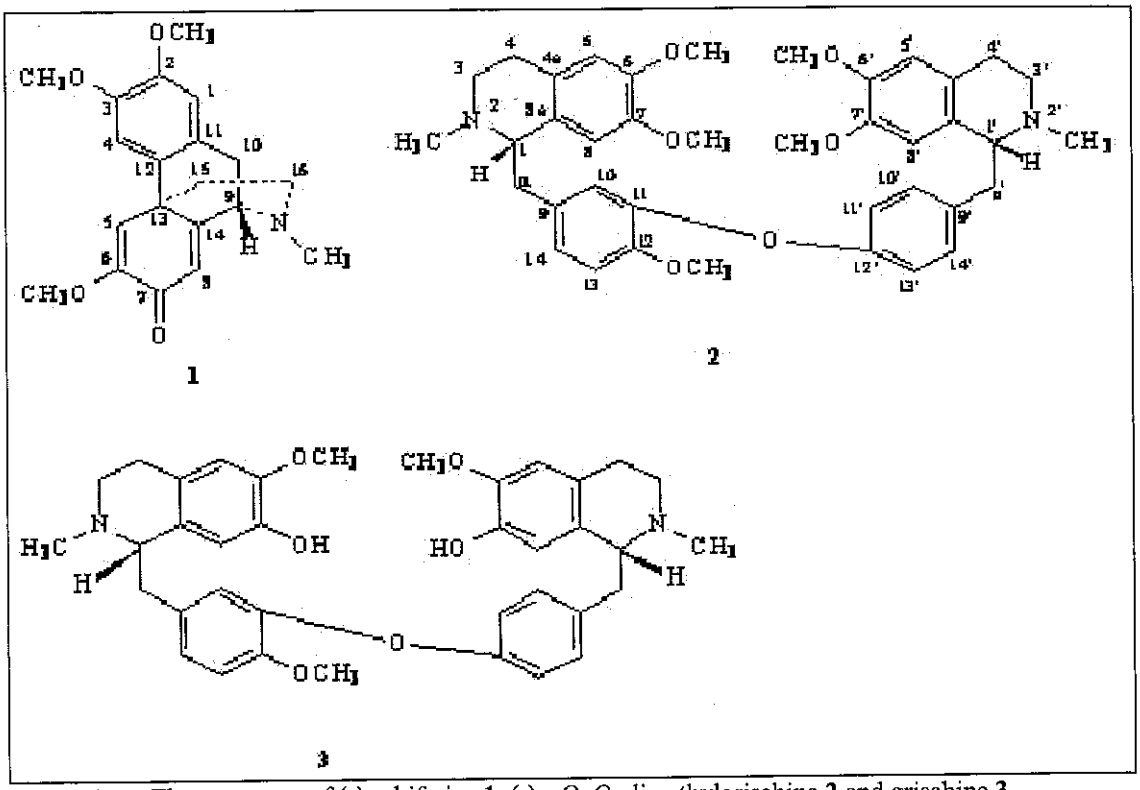

Figure 1. The structures of (-) sebiferine **1**, (-) - *O, O*- dimethylgrisabine **2** and grisabine **3**

(-) - *O, O*- Dimethylgrisabine **2** was isolated as brownish amorphous solid with $[\alpha]_D^{25}$ -33° (*c*= 0.2, $CHCl_3$); ($[\alpha]_D$ -26° from lit. [11, 13]). The absorptions at 1464, 1511 and 1609 cm^{-1} in the IR spectrum indicated the existence of conjugated aromatic system. The absence of the absorption peak at 3400 cm^{-1} showed that the hydroxyl group was absent in alkaloid **2.**

The EIMS of **2** is typical of a bisbenzylisoquinoline alkaloid containing only single tail-to-tail ether bridge [12]. Since alkaloid 2 had the same A, B and A', B' rings, only the base peak (100%) at *m/z* 206 ($C_{12}H_{16}NO_2$) was observed.

The ^{1}H and ^{13}C-NMR spectra showed a reminiscence data with that of (-) - *O, O*-dimethylgrisabine as reported by Sedmera *et al.* [11, 13]. The ^{1}H-NMR spectrum showed two *N*-methyl singlets at δ 2.47 and 2.51, with adjacent H-1 and H-1' signals at δ 3.65 and 3.72 respectively. In addition, five methoxyl groups and eleven aromatic proton signals appeared in the spectrum (Table 1). The resonance at δ 6.86 (H-14, *dd*, *J*= 1.9 and 8.3 *Hz*) was coupled with the resonances at δ 6.87 (H-13, *d*, *J*= 8.3 *Hz*) and 6.69 (H-10, *dd*, J=1.9 and 6.3 *Hz*) which were part of an *ortho-para* trisubstituted benzene ring.

The ^{13}C-NMR spectrum showed the resonances of 39 carbons and the DEPT spectrum revealed seven methyl, thirteen methine and six methylene groups. Many carbon signals were grouped in pairs, reflecting the nearly symmetrical nature of the molecule.

The gross structure of **2** was deduced from extensive analyses of the two-dimensional NMR data, including the ^{1}H-^{1}H COSY, HMQC and HMBC spectra in $CDCl_3$. The ^{1}H-^{1}H COSY spectrum revealed connectivities of two A_2B_2 systems (H-13'/H-14' and H-10'/H-11' respectively) and vicinal couplings of H-14/H-13, H-3/H-4, H-3'/H-4', H-1/H_2-α, and H-1'/H_2-α'.

In the HMBC spectrum, the ^2J and ^3J cross peak correlations of alkaloid **2** (Table 1) were found between H-10/C-11 and H-13/ C-11, H-10'/ C-12', H-11'/C-12', H-13'/C-12' and H-14'/C-12'. The correlations of ^4J between H-11'/C-11 and H-13'/C-11 were also observed and reinforced the C_{11}-O-C_{12}' ether linkage.

Grisabine **3** was isolated as yellowish amorphous solid. The HRFAB$^+$ mass spectrum showed $[M+H]^+$ peak at *m/z* 611.4120 corresponding to the molecular formula of $C_{37}H_{43}N_2O_6$ (calcd. 611.4142).

The ^{1}H-NMR spectrum of alkaloid **3** showed two *N*- methyl singlets, three superimposed methoxyls and four singlets of isolated aromatic protons (Table 1). The three superimposed methoxyl singlets at δ 3.81 and 3.82 were due to the substituents at C-6/6' and C-12, and the absence of upfield methoxyl signals around δ 3.5 [13-17], argued conclusively in favor of placing the phenol function at C-7/7'. The shifted of H-8 and H-8' chemical shifts in alkaloid **3** from ~ δ 6.00 to δ 6.21 and 6.29 respectively were due to the phenolic substituents at C-7 and C-7'. The chemical shifts of H-5/5' were almost the same as in alkaloid **2** indicating that the C-6/6' were methoxyls-substituted. The constant presence of an A_2B_2 system assigned to the protons in the 10', 11', 13', 14' positions, indicated a characteristic feature of the 11-12' single diphenyl ether linkage [13,17]. This was also proved by COSY experiment which showed the same patterns as those of alkaloid **2**.

Although most of the carbon-13 signals of alkaloid **3** (Table 1) showed similarity with the signals of alkaloid **2**, however the C-8, C-8' were shifted downfield, indicating that C-7, C-7' were both substituted with hydroxyl groups.

The crude alkaloid, sebiferine **1** and (-) - *O, O*-dimethylgrisabine **2** exhibited potency *in vitro* antiplasmodial activities to both *P. falciparum*, D10 strain (sensitive strain) and Gombak A isolate (resistant strain) with IC_{50} as shown in Table 2. Grisabine **3** was not tested for antiplasmodial activity due to the small amount isolated.

Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR Data (100 MHz, $CDCl_3$) of Alkaloids **2** and **3**

	2			**3**	
POSITION	**δ ^{13}C**	**δ ^{1}H (*J* Hz)**	**HMBC (^2J and ^3J) (H to C)**	**δ ^{13}C**	**δ^{1}H (*J* Hz)**
1	64.6 *d*	3.65 *dd* (5.3, 7.5)	3, α, 4a, 8	64.6 *d*	3.64 *t*
3	46.6 *t*	2.76 *m*, 3.071 *m*	1, 4, , *N*-CH$_3$,	47.2 *t*	2.71 *m*, 3.12 *m*
4	25.1 *t*	2.55 *m*, 2.808 *m*	5	25.1 *t*	2.55 m, 2.73 *m*
4a	125.6 *s*			125.0 *s*	
5	111.2 *d*	6.49 *s*	4, 6,7, 8a	110.6 *d*	6.46 *s*
6	147.5 *s*			145.5 *s*	
7	146.5 *s*			143.6 *s*	
8	110.9 *d*	6.01 *s*	1, 6, 7	114.2 *d*	6.21 *s*
8a	128.1 *s*			130.5 *s*	
α	40.2 *t*	2.71 *dd* (7.5, 12.9) 3.09 *dd* (5.3, 12.9)	1, 10	40.5 *t*	2.781 *m*, 3.06 *dd* (5.0,13.0)
9	132.5 *s*			132.3 *s*	
10	122.5 *d*	6.69 *dd* (1.9, 6.3)	11, 14, α	121.2 *d*	6.65 *d* (1.7)
11	144.5 *s*			145.3 *s*	
12	149.8 *s*			149.2 *s*	
13	112.6 *d*	6.87 *d* (8.3)	9, 11	112.3 *d*	6.82 *d* (8.3)
14	126.0 *d*	6.86 dd (1.9, 8.3)	10, 13, α	125.1 *d*	6.81 *dd* (1.7, 8.5)
1'	64.8 *d*	3.72 dd (4.9, 8.0)	8', α', 3', 4'a	64.7 *d*	3.74 *t* (6.0,13.0)

Table 1. ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR Data (100 MHz, $CDCl_3$) of Alkaloids **2** and **3** (continued)

	2			**3**	
POSITION	**δ 13C**	**δ 1H (J Hz)**	**HMBC (2J and 3J) (H to C)**	**δ 13C**	**δ1H (J Hz)**
3'	46.4 *t*	2.82 *m*, 3.13 *m*	1', N'-CH$_3$, 4'	46.6 *t*	2.76 *m*, 3.24 *m*
4'	24.8 *t*	2.60 *m*, 2.83 *m*	H-5'	24.7 *t*	2.60 *m*, 2.79 *m*
4a'	125.1 *s*			124.7 *s*	
5'	111.1 *d*	6.53 *s*	4'	110.6 *d*	6.51 *s*
6'	147.5 *s*			145.5 *s*	
7'	146.4 *s*			143.6 *s*	
8'	111.2 *d*	5.96 *s*	1'	113.8 *d*	6.33 *s*
8a'	128.1 *s*			130.5 *s*	
α'	40.5 *t*	2.73 *dd* (8.0,12.2) 3.20 *dd* (4.9, 12.2)	1', 10', 14'	40.6 *t*	2.83 *dd* (6.0,13.0), 3.09 *m*
9'	133.2 *s*			133.6 *s*	
10'	130.8 *d*	6.97 A_2B_2 (8.6)	12', 14', α'	130.6 *d*	7.00 A_2B_2 (8.6)
11'	116.7 *d*	6.81 A_2B_2 (8.6)	10', 11 (^4J), 12', 13', 14'	117.8 *d*	6.80 A_2B_2 (8.6)
12'	156.4 *s*			155.8 *s*	
13'	116.7 *d*	6.81 A_2B_2 (8.6)	10', 11', 11(^4J), 12', 14'	117.8 *d*	6.80 A_2B_2 (8.6)
14'	130.9 *d*	6.97 A_2B_2 (8.6)	10', 12', α'	130.6 *d*	7.00 A_2B_2 (8.6)
N-CH$_3$	42.3 *q*	2.47 *s*	1, 3	42.3 *q*	2.44 *s*
N'-CH$_3$	42.1 *q*	2.51 *s*	1', 3'	42.3 *q*	2.49 *s*
6-OCH$_3$	55.7 *q*	3.78 *s*		55.8 *q*	3.81 *s*
6'-OCH$_3$	55.7 *q*	3.80 *s*	6'	55.8 *q*	3.81 *s*
7-OCH$_3$	55.5 *q*	3.56 *s*	7		
7'-OCH$_3$	55.6 *q*	3.52 *s*	7'		
12-OCH$_3$	56.1 *q*	3.76 *s*	12	56.1 *q*	3.82 *s*

Table 2. IC_{50} values for *P. falciparum*, D10 strain and *P. falciparum*, Gombak A of CH_2Cl_2 crude alkaloid, sebiferine **1** and (-) - *O, O*- dimethylgrisabine **2**

SAMPLES	***P. falciparum*, D10 STRAIN (pLDH IC_{50} µg/mL)**	***P. falciparum*, GOMBAK A (pLDH IC_{50} µg/mL)**
Crude alkaloid	0.6182	0.3561
Sebiferine **1**	9.1407	20.9241
(-)-*O,O*-dimethylgrisabine **2**	0.7121	2.2739

In conclusion, the barks of *D. candolleana* produced morphinandienone; (-)-sebiferine **1** and two single diphenyl ether (C_{11}-O-C_{12}') linkage bisbenzylisoquinoline alkaloids, namely (-)-*O,O*-dimethylgrisabine **2** and grisabine **3**. Previously, sebiferine was isolated by Nordin *et al.* from the leaves of *Alseodaphne perakensis* (Lauraceae) [10]. (-)-*O,O*-Dimethylgrisabine **2** was also found in *Phaenthus vietnamensis* (Annonaceae) [11], while grisabine **3** was isolated from *Abuta grisebachii* and *Gyrocarpus americanus*[17]. However the ^{13}C-NMR data of grisabine **3** have not been reported in the literature.

In Malaysia, three Malaysian *Dehaasia* species have been reported; *D. candolleana*, *D.*

longipedicellata and *D. incrassata*. The phytochemical analysis of *D. longipedicellata* [18] and *D. candolleana* [7] reveal the presence of morphinandienone as a major component. However, *D. incrassata* produced only bisbenzylisoquinoline [19]. The study by Said *et al.*, 1991 reported that *D. incrassata* consists mostly of bisbenzylisoquinolines and aporphines [20]. Another study by Lu *et al.*, 1989 [4] and Lee *et al.*, 1996 [5] showed that bisbenzylisoquinolines are also the main chemical constituents of *D. triandra* besides aporphines and the ether-linked bisaporphine [6]. The occurrence of aporphines was also reported in *D. kurzii* (Plant from Bangladesh, Atta-ur-rahman *et al*, 1991) [21]. The fact that morphinoids and bisbenzylisoquinoline alkaloids were present in all the *Dehaasia* species studied [7, 18 - 20] suggest that these type of alkaloids can be used as a chemotaxonomic marker for future studies of Malaysian *Dehaasia* species.

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