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FOUR HEPTACYCLIC INDOLES FROM *KOPSIA TEOI*

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Key Word Index—*Kopsia teoi*; Apocynaceae; leaves; indole alkaloids.

Abstract—Two new indole alkaloids, kopsidines C and D, in addition to kopsidines A and B, were obtained from the leaf extract of *Kopsia teoi*. The structures of the new alkaloids were established by spectral methods. ©1997 Elsevier Science Ltd. All rights reserved

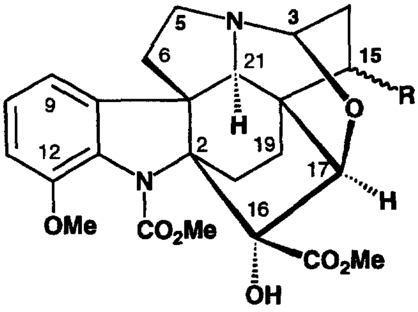
INTRODUCTION

The genus *Kopsia* comprises some 30 species, distributed mainly over south-east Asia, China and India [1, 2]. There are *ca* 18 species distributed over the lowland forest of Peninsular Malaysia. As part of our systematic studies of Malaysian members of this genus [3–11], we investigated the alkaloidal composition of *Kopsia teoi* L. Allorge and have reported in preliminary form the presence of two new heptacyclic alkaloids, kopsidines A and B [4]. We now wish to report the further isolation of two members of this novel class of indoles.

RESULTS AND DISCUSSION

In addition to kopsidine A(**1**) and kopsidine B(**2**), whose structures have been discussed previously [4], we isolated two additional compounds belonging to this structural class.

Compound **3**, was isolated in small amounts as a light yellow oil. The UV spectrum showed absorptions typical of a dihydroindole chromophore. The mass spectrum of **3** showed a $[M]^+$ at m/z 472 corresponding with the formula $C_{24}H_{28}N_2O_8$, with other major peaks at m/z 444 $[M - CH_2{=}CH_2]^+$, 427 $[M - CH_2{=}CH_2 - OH]^+$, 413 $[M - CO_2Me]^+$ and 337 $[M - 2CO_2Me\text{-}OH]^+$. The molecular formula of kopsidine C **3** (and kopsidine D **4**) indicated that it differs from kopsidine A **1** by replacement of OMe with OH; this is also indicated by the peak at m/z 427 and 337, which are also both common in the mass spectra of kopsidines A and B. Examination of the NMR data (Tables 1 and 2) revealed the structural affinity of kopsidines C and D with the previously reported kopsidines A and B [4]. Thus, in both kopsidines C and D, the signals due to the 15-alkoxy substituent are



1 R = α-OMe

2 R = α-OEt

3 R = α-OH

4 R = β-OH

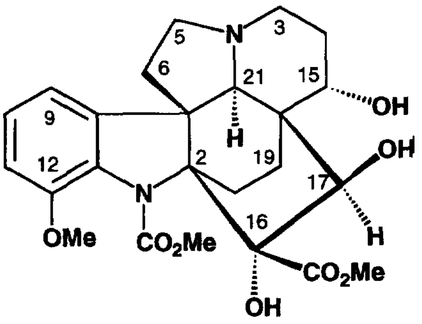


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Table 1. ^{1}H NMR spectral data for compounds **1**–**4** (270 MHz, CDCl$_3$)*

H	**1**	**2**	**3**	**4**
3	4.47 *t* (2.5)	4.47 *t* (2.5)	4.45 *t* (2.5)	4.35 *t* (2.5)
5	2.98 *m*	2.98 *m*	2.98 *m*	3.00 *m*
	3.05 *m*	3.05 *m*	3.04 *m*	3.07 *m*
6	3.12 *m*	3.12 *m*	3.12 *m*	3.14 *m*
	1.44 *m*	1.44 *m*	1.44 *m*	1.45 *m*
9	6.82 *d* (8)	6.82 *d* (8)	6.83 *d* (8)	6.83 *d* (8)
10	7.00 *dd* (8, 7)	7.01 *dd* (8, 7)	7.02 *dd* (8, 7)	7.02 *dd* (8, 7)
11	6.83 *d* (7)	6.83 *d* (7)	6.82 *d* (7)	6.79 *d* (7)
14	2.01 *dd* (14, 2.5)	2.00 *dd* (14, 2.5)	1.91 *dd* (15, 2.5)	1.82 *m*
	2.15 *ddd* (14, 7.5, 2.5)	2.19 *ddd* (14, 7.5, 2.5)	2.39 *ddd* (15, 9, 2.5)	2.55 *ddd* (13, 10, 2.5)
15	3.31 *d* (7.5)	3.41 *d* (7.5)	*ca* 3.80	4.02 *dd* (10, 5.4)
17	3.72 *s* (4.03, *d*, 2 Hz)†	3.74 *d* (2)	3.70 *d* (2)	4.20 *d* (2)
18	1.48 *m*	1.49 *m*	1.48 *m*	1.50 *m*
	2.07 *m*	2.10 *m*	2.12 *m*	2.15 *br t* (12)
19	1.51 *m*	1.51 *m*	1.60 *m*	1.12 *br t* (12)
	1.73 *br t* (12)	1.72 *br t* (12)	1.72 *m*	1.94 *m*
21	3.72 *s* (4.01, *d*, 2 Hz)†	3.70 *d* (2)	3.72 *d* (2)	3.35 *d* (2)
16-OH	6.12 *s*	6.11 *s*	6.10 *s*,	6.04 *s*
Ar–OMe	3.83 *s*	3.84 *s*	3.84 *s*	3.84 *s*
$NCO_2\underline{Me}$	3.83 *s*	3.84 *s*	3.84 *s*	3.84 *s*
$CO_2\underline{Me}$	3.79 *s*	3.80 *s*	3.80 *s*	3.80 *s*
$15\text{-}O\underline{Me}$	3.36 *s*	—	—	—
$15\text{-}O\underline{CH_2}CH_3$	—	3.37 *dq* (10, 7)	—	—
	—	3.71 *m*	—	—
$15\text{-}OCH_2\underline{CH_3}$	—	1.19 (7)	—	—

* Assignments based on COSY, LRCOSY and HMQC.

† δ in C$_6$D$_6$.

Table 2. ^{13}C NMR spectral data for compounds **1**–**4** (67.8 MHz, CDCl$_3$)*

C	**1**	**2**	**3**	**4**
2	77.7†	76.4	76.4	75.7
3	86.5	86.4	86.4	86.5
5	53.4	53.3	53.3	53.1
6	40.7	40.5	40.6	40.7
7	58.9	58.7	58.8	58.8
8	144.0	143.8	143.7	143.6
9	112.4	112.1	112.3	112.3
10	124.9	124.8	125.1	125.0
11	113.2	113.1	112.9	112.8
12	148.9	148.6	148.8	148.9
13	128.4	128.1	128.2	128.3
14	35.8	36.9	40.0	39.5
15	77.3†	74.4	67.4	68.1
16	78.5†	77.2	77.3	76.5
17	79.9	79.9	79.5	77.4
18	25.7	25.5	25.6	25.2
19	21.0	20.8	20.2	20.8
20	37.2	36.8	37.7	38.3
21	59.5	59.3	59.2	63.7
Ar–OMe	56.3	56.1	56.2	56.2
NCO$_2$Me	53.0	52.9	53.1	53.1
CO$_2$Me	52.1	52.2	52.3	52.3
$\underline{C}O_2Me$	171.3	171.2	171.2	171.3
$N\underline{C}O_2Me$	156.1	156.0	156.0	156.0
15-OMe	56.9	—	—	—
$15\text{-}O\underline{C}H_2CH_3$	—	64.8	—	—
$15\text{-}OCH_2\underline{C}H_3$	—	15.1	—	—

*Assignments based on HMQC and HMBC.

† δ in C$_6$D$_6$.

missing in ^{1}H, as well as ^{13}C NMR. Instead, the presence of a 15-OH is indicated by the oxymethine signal at δ_C 67.4 (**3**) and 68.1 (**4**). As in the case of kopsidine A, irradiation of the H-15 signal caused NOE enhancement of the H-17 signal, establishing the stereochemistry of the 15-OH as α. In addition, $NaBH_4$ reduction of kopsidine C **3** gave kopsinganol **5** [12, 13], thus confirming the stereochemical assignment of the 15-OH. Compound **4** had identical EI ms and UV spectrum compared to **3**. The ^{1}H and ^{13}C NMR spectral data were also essentially similar, except for changes at positions 15, 17 and 21. Irradiation of the H-21 signal caused NOE enhancement of the H-15 signal and *vice versa*, whereas no enhancement of H-17 was observed on irradiation of the H-15 signal. These observations indicate that kopsidine D is the C-15 epimer of kopsidine C, as shown in structure **4**.

EXPERIMENTAL

Plant material. Details of collection and deposition of voucher specimens are as reported earlier [3].

Extraction and isolation. Extraction of alkaloids was carried out in the usual manner as described in ref. [3]. Alkaloids were isolated by CC, prep. TLC and centrifugal TLC on silica gel. Solvent systems used for CC were $CHCl_3$–MeOH and Et_2O–EtOAc. Solvent system used for prep. TLC and centrifugal TLC were Et_2O, Et_2O–EtOAc (30:1) and MeOH–$CHCl_3$. The yields (g kg^{-1}) of alkaloids from the leaf extract were: **1** (0.022), **2** (0.019), **3** (0.0015) and **4** (0.0017).

Compound **1**, *kopsidine A.* $[\alpha]_D = +16°$ ($CHCl_3$, *c* 0.21). UV λ_{max}^{EtOH} nm (log ε): 217 (4.56), 254 (4.10), 281 (3.46), 291 (3.40). EIMS (probe) 70 eV, *m/z* (rel. int.): 486 [M^+, $C_{25}H_{30}N_2O_8$] (4), 458 (3), 455 (3), 441 (1), 427 (15), 425 (12), 369 (5), 337 (9), 130 (7), 107 (16). FABMS, $[MH]^+$, *m/z* 487. ^{1}H and ^{13}C NMR: Tables 1 and 2.

Compound **2**, *kopsidine B.* $[\alpha]_D = +11°$ ($CHCl_3$, *c* 0.073). UV λ_{max}^{EtOH} nm (log ε) 217 (4.59), 253 (4.14), 281 (3.49), 291 (3.42). EIMS (probe) 70 eV, *m/z* (rel. int.): 500 [M^+, $C_{26}H_{32}N_2O_8$] (6), 472 (3), 455 (2), 441 (4), 427 (12), 425 (11), 383 (7), 337 (5), 130 (4), 107 (3). FABMS, $[MH]^+$, *m/z* 501.^{1}H and ^{13}C NMR: Tables 1 and 2.

Compound **3**, *kopsidine C.* $[\alpha]_D = +12°$ ($CHCl_3$, *c* 0.208). UV λ_{max}^{EtOH} nm (log ε): 217 (4.50), 254 (3.99), 282 (3.28), 289 (3.25). EIMS (probe) 70 eV, *m/z* (rel. int.): 472 [M^+, $C_{24}H_{28}N_2O_8$] (43), 444 (35), 427 (20), 425 (50), 413 (12), 355 (11), 337 (100), 107 (18). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Compound **4**, *kopsidine D.* $[\alpha]_D = -16°$ ($CHCl_3$, *c* 0.058). UV λ_{max}^{EtOH} nm (log ε): 217 (4.36), 254 (3.90), 282 (3.33), 289 (3.30). EIMS (probe) 70 eV, *m/z* (rel. int.): 472 [M^+, $C_{24}H_{28}N_2O_8$] (100), 472 (3), 444 (80), 427 (45), 425 (140), 355 (80), 337 (83), 107 (20). ^{1}H and ^{13}C NMR: Tables 1 and 2.

Reduction of **3** *to* **5**. $NaBH_4$ (0.042 mmol) was added to a stirred soln of **3** (0.04 mmol) in MeOH (10 ml) at 0°. After *ca* 15 min., H_2O (10 ml) was added and the mixt. extracted with Et_2O (3 × 10 ml). The extract was then dried (Na_2SO_4) and the solvent evapt. Flash CC over silica gel (MeOH–$CHCl_3$, 1:99) afforded 14 mg (74%) of **5**.

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