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Kopsinitarines A, B and C, Novel Cage Alkaloids from a Malaysian *Kopsia*

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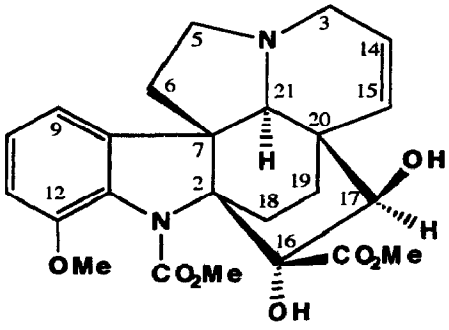
***Abstract** : Novel indole alkaloids possessing an unprecedented cage skeletal system were isolated from a Malaysian Kopsia species and the structures were elucidated by spectral methods, especially 2-D NMR.*

We have previously reported the isolation and structure of the novel heptacyclic alkaloids, kopsidine A and B from *Kopsia teoi* [1]. We now wish to report the presence of a novel class of indoles, kopsinitarines A - C (**2** - **4**) which possess an unprecedented cage skeletal system from the same plant.

The unique kopsinitarines (**2** - **4**) are extremely minor alkaloids and were isolated in minute quantities (*ca.* 10 mg) from extraction of more than 3 Kg of dried leaves. The EIMS of kopsinitarine A **2**[3] showed a molecular ion at *m/z* 422 ($C_{23}H_{22}N_2O_6$) which is also the most abundant ion. As with the other kopsinitarines, the mass spectrum is characterised by a strong molecular ion peak with other significant fragments at *m/z* 394 (31%, M - CH_2=CH_2), 393 (63%, M - CH_2=CH_2 - H), 363 (14%, M - CO_2Me), 362 (15%, M - CO_2Me - H) and 335 (22%, M - CH_2=CH_2 - CO_2Me). The UV spectrum is typical of a dihydroindole chromophore[3]. The ^1H and ^{13}C NMR spectral data showed that kopsinitarine A **2** has a basic aspidofractinine skeleton somewhat similar to that of kopsingine **1** which is the predominant alkaloid found in this plant[2], except for some significant changes. Thus the NMR spectral data confirm the presence of a dihydroindole nucleus with a methoxy substituent at C-12, a 14,15 double bond, a 16-OH function, a urethane substituent on N-1, and the C-17 oxymethine function. In addition the presence of a ketonic carbonyl function is indicated by the carbon resonance at δ 205.6 in place of the C-16 ester group in kopsingine. The most significant feature of the NMR spectrum which distinguishes it from other aspidofractinine derivatives is the significant downfield shift of the ring D, H-5 and H-6 resonances which now appear as a pair of AX doublets at δ 5.20 and 2.78 respectively with coupling constant of 4.9 Hz. The corresponding ^{13}C resonances have also undergone a similar downfield shift to δ 95.8 (C-5) and 56.2 (C-6) respectively. The molecular

formula of kopsinitarine A indicates that the number of degrees of unsaturation exceeds that of kopsingine by two. Since no additional double bonds are indicated by the NMR spectra, formation of two additional rings is indicated. This observation as well as the use of 2-D H-H COSY and HMQC allows the novel octacyclic cage structure as shown in **2** to be assembled in which C-5 and C-17 are connected *via* an oxygen bridge while C-6 and C-16 are connected *via* a carbonyl group. This conclusion is supported by the NMR chemical shifts of both the H-5 and 6 as well as C-5 and 6. The proposed structure is further confirmed by LR COSY which revealed long range coupling (^4J) between H-5 and H-17 as well as by the long range heteronuclear correlation between H-17 and C-5 (^3J), H-5 and C-17 (^3J) and between H-6 and the ketonic C-22 (^2J). Other heteronuclear correlations (^2J and ^3J) from HMBC experiments are also in accord with the proposed structure. The stereochemistry of H-17 remains similar to that in kopsingine, *i.e.* α, from the W coupling observed between H-17 and H-21. In addition to kopsinitarine A **2**, the N_1-decarbomethoxy derivative, kopsinitarine B **3**[4], and the 15-α-hydroxy-N_1-decarbomethoxy derivative, kopsinitarine C **4**[5,6], were also isolated. The kopsinitarines represent a novel class of indole alkaloids in which additional ring formation between C-5 and C-17 as well as between C-6 and C-16 has resulted in an unprecedented cage skeletal system, the cage unit being circumscribed by two 5-membered rings and three 6-membered rings as shown in the partial structure **5**.



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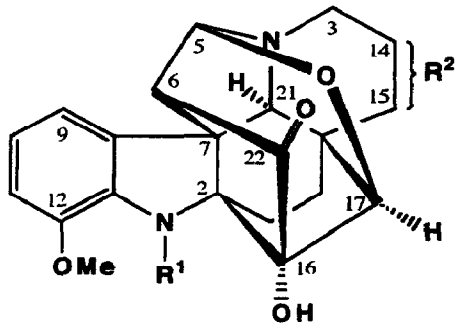

2 $R^1 = CO_2Me$, $R^2 = \Delta^{14,15}$
3 $R^1 = H$, $R^2 = \Delta^{14,15}$
4 $R^1 = H$, $R^2 = 15\text{-}\alpha\text{-}OH$

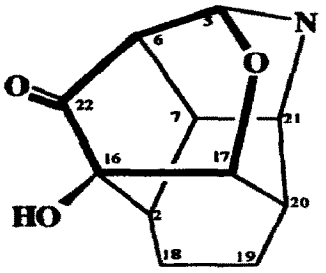

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Table 1. ^{1}H and ^{13}C NMR Spectral Data for **1**, **2** and **4**[a]

	1		2		4	
Position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	76.2	-	72.2	-	68.3	-
3a	49.8	3.12-3.26 m	47.4	3.60-3.76 m	42.2	3.25 dd (14, 6.4)
3b	-	3.47 ddd (16, 4.5, 2)	-	3.60-3.76 m	-	3.52 td (14, 4.9)
5a	48.6	2.65 ddd (12, 8.5, 4)	95.8	5.20 d (4.9)	95.2	5.20 d (4.9)
5b	-	2.92 dd (8.5, 6)	-	-	-	-
6a	40.5	1.74 dd (13, 4)	56.2	2.78 d (4.9)	58.3	2.73 d (4.9)
6b	-	3.12-3.26 m	-	-	-	-
7	56.4	-	59.4	-	60.0	-
8	144.2	-	136.6	-	131.3	-
9	111.8	6.82 dd (8, 1)	113.2	6.90 dd (7.3, 1)	115.4	6.87 dd (7.3, 1)
10	125.0	7.02 dd (8, 7)	126.8	7.12 dd (7.8, 7.3)	120.6	6.78 dd (7.8, 7.3)
11	113.2	6.76 dd (7, 1)	115.0	6.86 dd (7.8, 1)	110.6	6.68 dd (7.8, 1)
12	149.3	-	149.7	-	145.9	-
13	128.4	-	131.0	-	139.3	-
14a	128.6	5.95 ddd (10, 4.5, 2)	131.0	6.07 dt (10, 2)	32.6	1.52-1.62 m
14b	-	-	-	-	-	2.65-2.77 m
15	131.3	5.66 dt (10, 2)	128.6	5.60 dt (10, 2)	70.8	3.88-3.94 m
16	79.9	-	87.5	-	87.1	-
17	81.4	*ca.* 3.77	87.8	3.40 d (2)	88.7	3.87 d (2)
18a	27.1	1.40 ddd (13, 11, 7.5)	25.6	1.52-1.77 m	23.2	1.64-1.76 m
18b	-	2.10 br t (13)	-	2.17-2.30 m	-	2.04-2.14 m
19a	25.7	1.13 br t (13)	18.6	1.52-1.77 m	19.4	1.01-1.14 m
19b	-	1.69 ddd (13, 11, 7.5)	-	1.23-1.28 m	-	1.64-1.76 m
20	39.1	-	31.1	-	35.9	-
21	68.1	2.75 d (2)	62.2	3.65 d (2)	60.3	4.04 d (2)
16-OH	-	5.74 s	-	6.70 s	-	-
17-OH	-	8.11 d (6)	-	-	-	-
ArO<u>Me</u>	56.0	3.82 s	56.1	3.83 s	55.4	3.79 s
CO_2<u>Me</u>	52.9	3.78 s	-	-	-	-
<u>C</u>O_2Me	171.8		-	-	-	-
NCO_2<u>Me</u>	51.8	3.77 s	53.5	3.81 s	-	-
N<u>C</u>O_2Me	155.5	-	156.2	-	-	
CO	-	-	205.6	-	206.9	

[a] $CDCl_3$, 270 MHz; assignments based on COSY, COSYLR, HMQC and HMBC.

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References and Notes

1. Kam, T. S., Yoganathan, K. and Chuah, C. H., *Tetrahedron Lett.*, **1993**, *34*, 1819 - 1822.
2. Kam, T. S., Yoganathan, K., Chuah, C. H. and Chen Wei, *Phytochemistry*, **1993**, *32*, 1343-1346.
3. Compound **2**, kopsinitarine A, EIMS, *m/z* (rel. int.) : 422 [M^+] (100), 394 (31), 393 (63), 363 (14), 362 (15), 335 (22) and 307 (5.5). HREIMS, M^+ found 422.145, calcd. for $C_{23}H_{22}N_2O_6$ 422.147. UV (EtOH), λ_{max} (log ε) 215 (4.41), 245 (3.85) and 281 (3.06). ^1H NMR and ^{13}C NMR : see Table 1.
4. Compound **3**, kopsinitarine B, EIMS, *m/z* (rel. int.) : 364 [M^+] (100), 335 (52), 307 (7). HREIMS, M^+ found 364.1433, calcd. for $C_{21}H_{20}N_2O_4$ 364.1423. UV (EtOH), λ_{max} (log ε) 212 (4.60), 246 (3.90) and 290 (3.33). ^1H NMR ($CDCl_3$, 270 MHz) δ : 1.25 - 1.43 (*m*, H-19), 1.55 - 1.68 (*m*, H-18, H-19), 1.73 - 1.82 (*m*, H-18), 2.73 (*d*, *J* 4.9 Hz, H-6), 3.53 (*d*, *J* 2 Hz, H-21), 3.72 - 3.85 (*m*, 2 x H-3, H-17), 3.80 (*s*, 12-OMe), 5.16 (*d*, *J* 4.9 Hz, H-5), 5.61 (*dt*, *J* 10, 2 Hz, H-15), 6.05 (*dt*, *J* 10, 2.5 Hz, H-14), 6.71 (*dd*, *J* 7.8, 1 Hz, H-11), 6.79 (*dd*, *J* 7.8, 7.3 Hz, H-10) and 6.87 (*dd*, *J* 7.3, 1 Hz, H-9). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ : 19.4 (C-19), 26.2 (C-18), 32.3 (C-20), 47.5 (C-3), 55.3 (12-OMe), 56.6 (C-6), 59.7 (C-7), 62.1 (C-21), 68.1(C-2), 86.3 (C-16), 87.9 (C-17), 95.9 (C-5), 110.5 (C-11), 115.2 (C-9), 120.6 (C-10), 128.8 (C-15), 130.8 (C-14), 131.0 (C-8), 139.8 (C-13), 145.9 (C-12) and 207.0 (C-22).
5. Compound **4**, kopsinitarine C, EIMS, *m/z* (rel. int.) : 382 [M^+] (90), 354 (52), 353 (55), 337 (15) and 309 (12). HREIMS, M^+ found 382.1529, calcd. for $C_{21}H_{22}N_2O_5$ 382.1529. UV (EtOH), λ_{max} (log ε) 213 (4.49), 246 (3.80) and 290 (3.15). ^1H NMR and ^{13}C NMR : see Table 1.
6. The stereochemistry of the 15-OH in **4** is deduced to be α from the absence of NOE interaction between H-21 and H-15. The undue proximity of the H-15 and 17 resonances precluded irradiation of either of these proximate hydrogens.

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