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Tetrahedron Letters 44 (2003) 1317–1319

TETRAHEDRON
LETTERS

Kopsifolines A, B, and C, indole alkaloids with a novel hexacyclic carbon skeleton from *Kopsia*

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Received 3 September 2002; revised 8 November 2002; accepted 15 November 2002

Abstract—Three indole alkaloids, viz., kopsifolines A, B, and C, characterized by a novel carbon skeleton, were obtained from a Malayan *Kopsia* species and the structures established by spectroscopic analysis. © 2003 Published by Elsevier Science Ltd.

The Malaysian members of the genus *Kopsia* have proven to be rich sources of novel as well as bioactive alkaloids.[1–13] In continuation of our systematic investigation of this group of plants,[1–11] we would like to report the structures of several new indole alkaloids, characterized by a novel hexacyclic skeleton which are found for the first time in this genus.[14]

Kopsifoline A **1** was obtained from the leaf extract as a colorless oil, with $[\alpha]_D$ −11 (*c* 0.43, $CHCl_3$). The UV spectrum showed absorption maxima at 213, 248, and 296 nm (log ε 4.26, 3.93, and 3.51, respectively), indicating the presence of a dihydroindole chromophore. The IR spectrum showed absorption bands at 3369 (broad) and 1710 cm^{-1}, which are assigned to OH/NH and ester functions, respectively. The EIMS of **1** showed a molecular ion at m/z 382, which analyzed for $C_{22}H_{26}N_2O_4$, requiring 11 degrees of unsaturation.[15] The ^{13}C NMR spectrum (Table 1) gave a total of 22 separate carbon resonances (two methyls, six methylenes, six methines, and eight quaternary carbons) in agreement with the molecular formula. The ^1H NMR spectrum of **1** (Table 1) showed the presence of two methoxy groups (an aromatic methoxy and a carbomethoxy), three contiguous aromatic hydrogens, two olefinic hydrogens, an NH, and an OH function. The methoxy substituent is placed at C(12) from examination of the aromatic carbon resonances[11] and from the HMBC spectrum. The COSY spectrum disclosed the same partial structures as those present in an aspidofractinine skeleton, for example, venalstonine **4**, which was also isolated. In fact the non-aromatic carbon shifts of kopsifoline A **1** bear a general resemblance when compared to that of venalstonine **4**,[16] except for changes involving carbons 2, 16, 17, 20, and 21, suggesting a different connection of the fragments. This is clearly indicated by the HMBC spectrum which showed the following long range (^3J) correlations: H(19) to C(16), H(17) to C(18), and H(18) to the ester carbonyl. These observed correlations represent a clear departure from that normally observed in aspidofractinine compounds, and clearly indicate that in kopsifoline A **1**, a novel carbon skeleton is present in which C(18) is now linked to C(16) instead of C(2) (see Fig. 1).

The presence of the hydroxyl group at position 2 is supported by the presence of an oxygenated quaternary carbon at δ 97.1, the significant downfield shift is due to it being linked to both a nitrogen as well as an oxygen atom. This is also supported by the observed HMBC correlations from H(6), H(17), H(18), and H(21) to C(2). The stereochemistry at C(21) is similar to that in aspidofractinine compounds from the observed NOE enhancement of H(9) and H(19α) on irradiation of H(21). This result also confirms the stereochemistry of the C(17) methylene bridge in the bicyclo [3.2.1] octane system constituting the C and F rings, as shown in **1**. The stereochemistry of the C(2)-hydroxyl substituent was deduced to be α from the observed enhancement of H(17β) on irradiation of H(6β).

Kopsifoline B **2** was obtained as a colorless oil with $[\alpha]_D$ −46 (*c* 0.66, $CHCl_3$). The IR and UV spectra were similar to that of **1**. The EIMS of **2** showed a molecular ion at m/z 400 which analyzed for $C_{22}H_{28}N_2O_5$, with a base peak at m/z 382, due to loss of a molecule of water.[17] The main difference from **1** is shown in the ^1H and ^{13}C NMR spectra which indicated loss of the 14,

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Keywords: alkaloids; indoles; NMR; plants.

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0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02616-3

Table 1. ^{1}H and ^{13}C NMR spectral data of **1**, **2**, and **3**[a]

	1		**2**		**3**[b]	
Position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	97.1	–	97.4	–	97.1	–
3α	53.0	2.83 dt (16, 2)	47.2	2.45 td (13, 2)	54.2	2.62 dd (12, 2)
3β		3.53 ddd (16, 5, 2)	–	2.96 ddd (13, 5, 2)	–	2.99 m
5α	53.9	2.38 ddd (12, 8, 7)	53.3	2.35 q (9)	53.2	2.37 q (8)
5β	–	3.24 t (8)	–	3.12 t (9)	–	2.99 m
6α	34.8	1.40 dd (13, 7)	31.9	1.34 m	34.7	1.33 dd (12, 8)
6β	–	3.05 ddd (13, 12, 8)	–	3.02 dt (13, 9)	–	2.99 m
7	56.2	–	61.1	–	61.5	–
8	138.6	–	137.5	–	136.9	–
9	114.7	6.75 dd (8, 1)	114.6	6.80 br d (8)	114.4	6.74 br d (8)
10	119.4	6.69 t (8)	119.7	6.71 t (8)	119.8	6.65 t (8)
11	109.4	6.65 dd (8, 1)	109.5	6.65 br d (8)	109.8	6.60 br d (8)
12	143.0	–	143.1	–	142.8	–
13	135.9	–	135.9	–	135.8	–
14	125.4	5.72 ddd (10, 5, 2)	31.0	1.75 dq (13, 2)	69.7	3.70 br s
14		–		1.99 tdd (13, 5, 2)		–
15	132.8	5.47 dt (10, 2)	73.4	3.67 br s	75.0	3.45 d (2)
16	60.0	–	56.4	–	55.9	–
17α	38.1	1.86 dd (13, 1)	35.2	1.54 br d (12)	32.7	1.60 br d (13)
17β		2.23 dd (13, 1)		2.53 br d (12)		2.47 br d (13)
18a	29.5	1.71 m	29.5	1.58 m	27.7	1.51 m
18b	–	1.71 m	–	1.58 m	–	1.51 m
19α	35.1	1.26 m	34.2	1.34 m	33.9	1.25 m
19β	–	1.52 m	–	1.58 m	–	1.51 m
20	44.8	–	46.8	–	45.1	–
21	75.6	2.48 br s	70.0	2.70 br s	71.3	2.68 br s
CO_2Me	176.3	–	176.1	–	176.6	–
CO_2Me	52.0	3.75 s	52.0	3.74 s	52.0	3.69 s
12-OMe	55.3	3.82 s	55.3	3.83 s	55.3	3.77 s
2-OH	–	2.99 br s	–	–	–	–
NH	–	5.98 br s	–	5.93 br s	–	5.82 br s

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC and HMBC.

[b] A few drops of CD_3OD added.

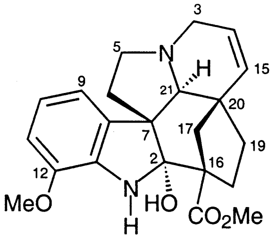
15-double bond, which is also consistent with the DBE value of 10 for **2**. Instead, an oxymethine function is indicated from the observed shift at δ 3.67 (δ_C 73.4) corresponding to C(15). This is also supported by the replacement of the *N*$CH_2CH{=}CH$ fragment of **1** by a *N*CH_2CH_2CHOH fragment in **2** as revealed by COSY and HMQC experiments. The stereochemistry of the C(15)-hydroxyl function was determined from the NOESY spectrum which showed interactions between H(15)/H(17α), indicating that the stereochemistry of the OH substituent is α.

Kopsifoline C **3**, $[\alpha]_D$ +87 (*c* 0.08, $CHCl_3$), showed a molecular ion at m/z 416 in the mass spectrum, which analyzed for $C_{22}H_{28}N_2O_6$, differing from **2** by replacement of H(14) with an OH.[18] As in **2**, the mass spectrum of **3** also showed a base peak at m/z 398 due to loss of a molecule of water. The ^{1}H and ^{13}C NMR spectral data were generally similar to that of **2**, except for the resonances due to the piperidine ring D. The piperidine ring was shown to have incorporated two oxymethines (δ_C 69.7, 75.0) associated with a 1,2-diol function. The corresponding H resonances were observed at δ 3.70 and 3.45, corresponding to H(14) and H(15), respectively. The stereochemistry at C(14) and C(15) were established from the H(14-15) coupling constant and from the NOESY spectrum. The J_{14-15} value of 2 Hz indicated that H(14) and H(15) were not *trans*-diaxially disposed. The NOESY spectrum showed correlations between H(15β)/H(17α), H(14α)/H(3β), H(3α). These results are consistent with both H(14) and H(15) being oriented equatorially in a six-membered ring.

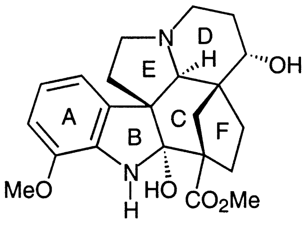
The kopsifolines represent a new family of indole alkaloids with an unprecedented carbon skeleton, in which C(18) is linked to C(16) instead of to C(2), as in aspidofractinine compounds.[19]

Acknowledgements

We would like to thank the University of Malaya and IRPA for financial support, and Professor G. Pattenden, School of Chemistry, University of Nottingham, United Kingdom, for mass-spectral measurements.



1



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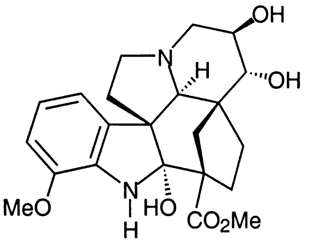

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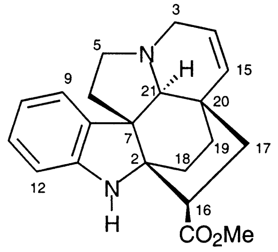

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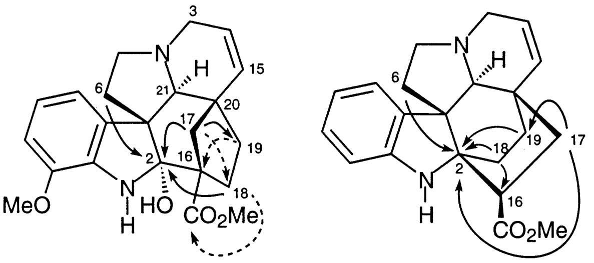

Figure 1. Selected HMBC correlations for **1** and **4**. - - - - → seen in **1** only.

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18. HREIMS found *m*/*z* 416.1919 (calcd for $C_{22}H_{28}N_2O_6$, 416.1947).
19. A kopsifoline-type structure constitutes one of the monomeric units of the novel bisindole, tenuiphylline, recently obtained by us from *Kopsia tenuis* (Ref. 7).