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Tenuisines A, B and C, Novel Bisindoles with C_2 symmetry from *Kopsia Tenuis*

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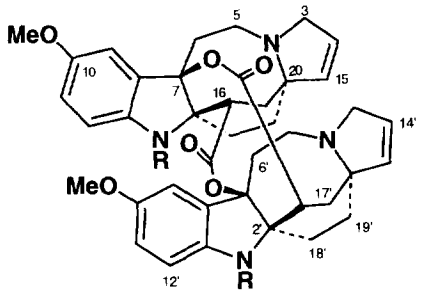
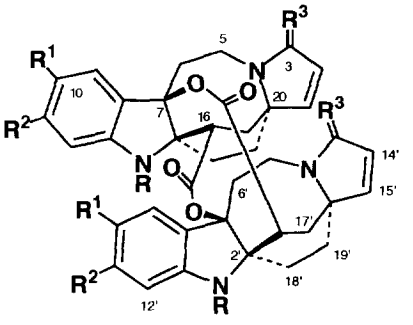
Abstract : Three new dimeric indoles viz., Tenuisines A, B and C possessing a novel carbon framework with a C_2 axis were isolated from Kopsia tenuis and their structures elucidated by spectral analysis. Copyright © 1996 Elsevier Science Ltd

Kopsia tenuis Leenh. & Steenis is one of about 17 *Kopsia* species that occur in Malaysia and is endemic to Sarawak, in North Borneo. Plants of this genus have yielded an impressive array of new natural products possessing novel carbon skeletons as well as useful bioactivities[1-3]. For instance we recently reported the structure and novel bioactivity of two new indoles *viz.*, pauciflorines A and B, isolated from the leaves of *Kopsia pauciflora* Hook. f., a species native to North Borneo, which have been found to be potent inhibitors of melanin biosynthesis[1(a)] and we have also reported the presence of the lundurines[1(c)], members of a new class of indoles having an unusual hexacyclic structure incorporating a cyclopropyl unit from *Kopsia tenuis*. We now wish to report new dimeric indoles of a novel structure type possessing a C_2 axis isolated from the leaves of the same plant.

Tenuisine A **1**, was obtained in amorphous form, $[\alpha]_D$ 77° ($CHCl_3$, *c* 0.76). Attempts to obtain single crystals were singularly unsuccessful resulting each time in light orange coloured plates which were found to be glasses. The EIMS of tenuisine A **1** showed the highest mass fragment at *m/z* 396 ($C_{22}H_{24}N_2O_5$) which was also the base peak. However, the FABMS of **1** clearly showed a MH^+ peak at *m/z* 793 with a significant fragment at *m/z* 397 corresponding to cleavage of the parent ion resulting in two equal halves. HRFABMS measurements gave the exact mass of the MH^+ ion as 793.3447 corresponding to the molecular formula $C_{44}H_{48}N_4O_{10}$ (calcd. MH^+, 793.3449). The UV spectrum showed absorption maxima at 206, 247 and 304 nm (log ε 4.46, 3.99 and 3.64 respectively) indicating presence of a dihydroindole chromophore and is

somewhat reminiscent of lundurine B[1(c)]. The ^1H and ^{13}C NMR spectral data (Tables 1 & 2) showed the presence of a methoxy substituent at carbon-10 (δ_H 3.77, δ_C 55.6), a CO_2Me function at N_1 (δ_C 152.5, broad H-12 doublet at δ 7.46), a low field quaternary carbon attributable to oxygenation at C-7 (δ_C 90.2), a lactone carbonyl (δ_C 177.3, IR 1750 cm^{-1}) and a 14,15-double bond which is part of a five membered ring (δ_H 5.70, 5.50; $J_{14\text{-}15}$ = 6 Hz; δ_C 126.6, 135.8). The ^1H and ^{13}C NMR spectra are also complicated by the existence of equilibrating conformers due to the carbomethoxy substituent on the indole nitrogen[4]. Thus although the ^1H NMR spectrum integrated for a total of 24 hydrogens, 2 pairs of identical signals, each pair integrating for one hydrogen each, are clearly seen for H-12 (δ_H 7.46, 7.92) and H-16 (δ_H 3.39, 3.27). In both cases the ratio of the major *versus* the minor conformer was constant at 1.7 : 1. The same is also true for H-18 although the signals are not sufficiently well resolved for determination of the relative proportions[5]. Increasing temperature led to a gradual broadening of these signals. The same behaviour was observed in the carbon spectrum where splitting of signals occurred for 10 of the carbon resonances (Table 2). Such behaviour shown by certain indole alkaloids bearing a urethane group in which two energetically favourable planar conformations result is well documented[4, 6]. 2-D H-H COSY and HMQC experiments revealed the remaining partial structures to be made up of two CH_2-CH_2 units corresponding to the C_5-C_6 and C_{18}-C_{19} fragments and a CH-CH_2 unit corresponding to the C_{16}-C_{17} fragment. The NMR spectral data resembles that of lundurine B **4** except that signals due to the cyclopropyl unit are now absent, instead signals attributable to a lactone function have taken its place. In fact, the spectral data for the non-aromatic portion of the molecule resembles that of lapidilectine B[2], in which the lactone function is part of a five-membered ring system involving carbons 7, 2 and 16 as shown in **5**. In the present case, HMBC experiments on **1** also show correlations between the lactone carbonyl

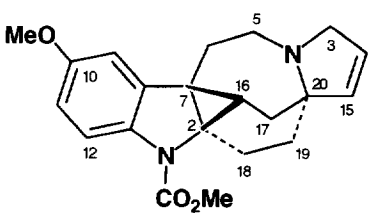




1 **R = CO_2Me**

2 **R = CO_2Me, R^1 = R^2 = OMe, R^3 = H_2**

3 **R = CO_2Me, R^1 = OMe, R^2 = H, R^3 = O**



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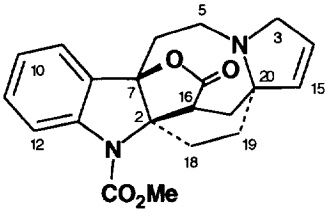

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Table 1. ^{1}H NMR Spectral Data for **1**[a]

Position	δ_H	Position	δ_H
3a, 3a'	3.13 br d (16)	16, 16'	3.39 m
3b, 3b'	3.80 m		3.27 m
5a, 5a'	2.87 m	17a, 17a'	2.02 br d (14)
5b, 5b'	3.20 dd (13, 8)	17b, 17b'	2.2 m
6a, 6a'	2.08 m	18a, 18a'	1.64 m
6b, 6b'	2.67 dd (16, 9)	18b, 18b'	2.60 m
9, 9'	6.90 br s		1.68 m
11, 11'	6.88 br d (8)		2.40 m
12, 12'	7.46 br d (8)	19a, 19a'	2.02 m
	7.92 br d (8)	19b, 19b'	2.06 m
14, 14'	5.70 br d (6)	10-OMe, 10-OMe'	3.77 s
15, 15'	5.50 m	NCO_2Me, NCO_2Me'	3.85 s

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

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

Position	δ_C	Position	δ_C
2, 2'	74.1	15, 15'	135.8
	73.7		135.6
3, 3'	61.5	16, 16'	44.7
5, 5'	47.2		45.7
6, 6'	29.8	17, 17'	38.5
7, 7'	90.2	18, 18'	21.5
	90.8		22.8
8, 8'	130.8	19, 19'	24.8
	129.4	20, 20'	67.1
9, 9'	109.8	10-OMe, 10-OMe'	55.6
10, 10'	155.9	NCO_2Me, NCO_2Me'	52.5
11, 11'	116.3	CO (urethane)	152.5
12, 12'	116.3		151.9
	116.5	CO (lactone)	177.3
13, 13'	134.4		176.9
14, 14'	126.6		
	126.8		

[a] $CDCl_3$, 67.5 MHz; assignments based on HMQC and HMBC.

and H-16 (^2J) as well as the C-17 hydrogens (^3J). However, since the FABMS clearly indicates a dimeric molecule and since the NMR data, discounting the added complication of conformational equilibration due to the urethane function, shows simplification of the spectra due to homotropic behaviour of the two halves (Tables 1 & 2), the existence of an element of symmetry is strongly indicated. This supposition is further confirmed when NMR experiments at 600 MHz resulted in essentially unchanged ^1H and ^{13}C NMR spectra. The presence of an element of symmetry is satisfied in the structure of tenuisine A as shown in **1** where the two identical monomeric units are connected *via* carboxyl linkages from C-16 of one half to C-7 of the other. Examination of models reveals that this structure results in the presence of a C_2 axis passing through the two halves, irrespective of the conformation adopted due to free rotation of the carboxyl linkages. This structure is also in accord with the 23 degrees of unsaturation deduced from the molecular formula, the additional one being contributed by the central 10-membered ring connecting the two halves (The C_2 axis passes in between the two monomers and is orthogonal to the approximate plane defined by the central 10-membered ring).

In addition to tenuisine A **1**, the related compounds tenuisines B **2** and C **3** are also obtained[7]. The tenuisines represent dimeric indoles of a novel structure type linked by carboxyl bridges and possessing a C_2 axis of symmetry giving rise to homotropic behaviour of the NMR spectra.

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References and Notes

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5. The H-18 signals corresponding to the two conformers are resolved at 600 MHz and gave the same ratio of major to minor conformers (1.7 : 1).
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7. Full details of compounds **1**, **2** and **3** will be reported subsequently elsewhere.

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