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Terengganensines A and B, Dihydroeburnane Alkaloids from *Kopsia terengganensis*

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Abstract : Five known indole alkaloids, (+)-quebrachamine, (-)-eburnamine, (+)-isoeburnamine, (-)-eburnaminol and (+)-larutensine, and two new alkaloids, terengganensines A **1** and B **2**, possessing a unique dihydroeburnane skeleton were isolated from the bark of *Kopsia terengganensis*. The structures of the new compounds were elucidated by spectral methods.
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The genus *Kopsia* (family Apocynaceae) is well known for its content in indole alkaloids, which often have revealed original structures. In continuation of our recent studies of this genus[1-4], we have undertaken[5] the investigation of a new species grown in Malaysia, *K. terengganensis* L. Allorge & C. Wiart.[6] Five known alkaloids were isolated from the bark, (+)-quebrachamine, (-)-eburnamine, (+)-isoeburnamine, (-)-eburnaminol and (+)-larutensine, together with two new ones named terengganensines A **1** and B **2**, which belong to a novel dihydroeburnane group.

The alkaloids were extracted using conventional methods and separated by chromatography on silica gel.

Terengganensine A **1**, $[\alpha]_D$ -25°, showed a $M^{+\cdot}$ peak at *m/z* 326.1627 (calcd. 326.1630) in the HREI mass spectrum corresponding to the molecular formula of $C_{19}H_{22}N_2O_3$. The UV spectrum exhibited maxima at 208, 236 and 284 nm (log ε 4.24, 3.89 and 3.34) indicating the presence of a dihydroindole chromophore. The molecular formula together with the lack of NH and ethyl groups in the NMR spectra suggested that alkaloid **1** possessed an eburnane skeleton bearing an oxidised ethyl chain as in the known eburnaminol **3** and larutensine **4**.[1] The ^1H and ^{13}C NMR spectra revealed only the six aromatic signals of an unsubstituted A ring. The aromatic C-7 and C-2 were replaced by quaternary sp^3 carbons, which resonated at δ 77.2 and δ 92.5, thus implying that the former was attached to an oxygen while the latter was linked to both a nitrogen and an oxygen. Analysis of the COSY and HMQC spectra showed the presence of the CH-21 at δ_H 2.30 (δ_C 65.7). The high field ^1H NMR chemical shift further confirmed that compound **1** was a dihydroindole alkaloid. Two spin systems corresponding to the methylenes at C-5, C-6 and C-3, C-14, C-15 were observed, along with two other

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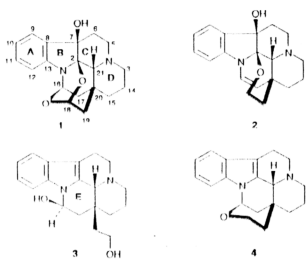
systems each corresponding to a methylene (C-19 and C-17) and an oxymethine (C-18 at δ 95.6 and C-16 at 77.6, respectively). The HMBC correlations H-18/C-2 and H-18/C-16 revealed the presence of an ether brigde C-18-C-16 similar to the one of larutensine together with the presence of a second oxygen bridge between C-2 and C-18. The cross peaks H-6/C-7, H-5/C-7, H-18/C-20 and H-19/C-20 confirmed that C-7 (δ 77.2) was attached to an OH and all the other observed HMBC correlations (Table 1) supported the formula depicted in **1** for terengganensine A.



The NOESY spectrum exhibited a cross peak between C-18 and C-21 thus confirming the usual *cis* D-E junction of the eburnane alkaloids. Formation of the two ether brigdes can take place only if all three C-16-O, C-18-O and C-2-O bonds lie on the same side. The B-C junction must also be *cis* in order to allow a chair conformation for ring C, which is *trans* fused with ring D. This is supported by the presence in the IR spectrum of Bohlman bands (2832, 2812 and 2785 cm^{-1}) characteristic of a *trans* fused quinoline system. Hence, ring D and E also can adopt chair conformations involving axial C_{16}-O and C_{20}-C_{19} bonds, which permit in addition to the axial C_2-O bond the closure of the oxygen rings. The overall conformation of alkaloid **1** is thus similar to the one previously observed for the hexacyclic eburnane larutensine **4**[1,7], while the pentacyclic eburnanes such as eburnaminol **3** possess C/D *cis* fused rings involving an equatorial β-OH[7].

Terengganensine A **2**, $[\alpha]_D$ -19°, showed a $M^{+\cdot}$ peak at *m/z* 310.1675 (calcd. 310.1681) in the HREI mass spectrum corresponding to the molecular formula of $C_{19}H_{22}N_2O_2$. The NMR spectra were very close to the one of terengganensine A **1** except for the absence of the two oxymethines CH-16 and CH-18. Instead, an oxymethylene assigned to C-18 was observed at δ_H 3.70 and δ_C 61.6, together with two olefinic protons at δ 7.10 and 4.40. Obviously, there was only one oxygen bridge located between C-18 and C-2, which was supported by the HMBC correlation between H-18 and C-2. The olefinic protons corresponded to a Δ^{16} double bond showing typical ^1H chemical shift values[8]. The UV spectrum, which exhibited maxima at 228, 283 and 307 nm (log ε 3.74, 4.13, 3.60) further supported the presence of an *N*-arylenamine chromophore. Thus, terengganensine B possess the structure depicted in **2**. The similar C-21, C-2 and C-7 ^{13}C NMR shifts revealed a similar stereochemistry and conformation of the C, D and oxygen rings for both alkaloids **1** and **2**, which was

confirmed in the case of compound **2** by the observed NOESY correlations (Table 1) and the presence of Bohlman bands in the IR spectrum.

Since the known eburnane alkaloids, (-)-eburnamine, (+)-isoeburnamine, (-)-eburnaminol and (+)-larutensine, found in *K. terengganensis* all have the same absolute configuration at position 21, it is assumed that terengganensines A and B also have the same absolute configuration, as depicted in **1** and **2**.

Eburnane type alkaloids have previously been isolated from *Kopsia larutensis*[1,8,9], especially larutensine **4** which has an ether bridge between C-16 and C-18 like terengganensine A **1**. However, terengganensines A and B represent a new kind of eburnane alkaloids both possessing a dihydroindole skeleton, an oxygen bridge between C-18 and C-2, and an OH function at C-7.

Table 1. ^{13}C (62.5 MHz) and ^{1}H (400 MHz) NMR Data[a] for terengganensines A **1** and B **2**.

	1[b]				**2**[c]			
position	δ C[c]	δ H (*J* Hz)	HMBC	NOESY	δ C	δ H (*J* Hz)	HMBC[c]	NOESY[b]
2	92.5				89.7			
3	55.6	α 2.10 m β 2.95 m		3β,14α 5β	56.1	α 2.18 m β 2.85 m		3β 5β,14β
5	51.0	α 2.57 m β 2.30 m	6,7	5β,6β	52.1	α 2.55 m β 2.40 m	7,21 21	5β, 6β
6	36.5	α 2.00 m β 1.75 m	2,7		39.3	α 2.00 m β 1.60 m	2,7 5,8	6β
7	77.2				78.5			
8	135.8				137.8			
9	122.4	7.30 d (7.5)	11,13		122.9	7.15 d (7.5)	11,13	
10	121.2	6.92 dd (7.5,7.5)	8,12		121.1	6.78 dd (7.5, 7.5)	8,12	
11	128.8	7.20 dd (7.5,7.5)	9,13		129.7	7.18 dd (7.5,7.5)	9,13	
12	110.1	6.85 d (7.5)	8,10		108.0	6.82 d (7.5)	8,10	
13	145.2				142.5			
14	20.6	α 1.62 m β 1.90 m		14β 15β	23.3	α 1.60 m β 1.80 m	20	14β,15β 15β
15	35.2	α 1.90 m β 1.35 m	17,20 14,17,19,20	15β 21	37.4	α 1.80 m β 1.45 m	19,20 14,19,20	15β 21
16	77.6	5.45 dd (2,1.5)	2,20	17ab	127.4	7.95 d (7.5)	2,20	17
17	34.3	a 2.70 m b 1.85 m	19	17b	103.7	4.48 dd (7.5,1.5)	16,19,20,21	15α,19α
18	95.6	5.20 dd (2,2)	2,16,20	19αβ	61.6	3.70 m	2,19,20	19α,β
19	43.1	α 1.80 m β 1.95 m	20,21 18,20,21	21	40.8	α 1.38 m β 1.80 m	17,20 17,21	21
20	31.4				35.7			
21	65.7	2.30	2,5,15,20		65.0	2.35 br s		

[a]assignments based on 2D measurements, [b]in $CDCl_3$, [c]in CD_3OD.

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5. This work has been done in the framework of a collaborative program on Malaysian plants between CNRS (France) and the University of Malaya (Malaysia).
6. Bark of *K. terengganensis* L. Allorge & C. Wiart was collected in Dungun, Terengganu, Malaysia. Voucher specimens (KL 4432) identified by L. Allorge were deposited at the Muséum d'Histoire Naturelle in Paris and at the Herbarium of Department of Chemistry, University of Malaya.
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8. However, note that the H-16 NMR chemical shift value is slightly more shielded in the alkaloid **2** than in the indolic eburnane alkaloid eburnamenine (δ 5.05)[10], while H-17 resonated at somewhat lower field (δ 4.27 in eburnamenine). This may be explained by the resonance effect due to electron donation by the nitrogene lone pair, which is not trapped in the indolic aromatic system.
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