Mersinines A and B and mersiloscine, novel quinolinic alkaloids from *Kopsia*

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Abstract—Three novel quinolinic alkaloids, viz., mersinines A and B and mersiloscine, were obtained from a Malayan *Kopsia* species and the structures established by spectroscopic analysis. © 2001 Elsevier Science Ltd. All rights reserved.

The Malaysian members of the genus *Kopsia* have proven to be rich sources of novel as well as bioactive alkaloids.[1–12] In continuation of our systematic investigation of this group of plants,[1–10] we would like to report the structures of several new pentacyclic quinolinic alkaloids related to the meloscine group, which are found for the first time in this genus.[13]

Mersinine A **1** was obtained from the leaf extract as colorless crystals (mp 204–205°C), with $[\alpha]_D$ −58 (CHCl₃, *c* 0.27).[14] The UV spectrum showed absorption maxima at 213, 239, and 289 nm (log ε 4.50, 4.10 and 3.82, respectively), consistent with a tetrahydroquinoline chromophore and reminiscent of some *Melodinus* alkaloids.[15–17] The IR spectrum showed

1   **2**   **3**

4

5 R¹, R², R³ = H, R⁴ = O, H-16β

6 R¹, R² = OCH₂O, R³ = CO₂Me,
     R⁴ = O, H-16α
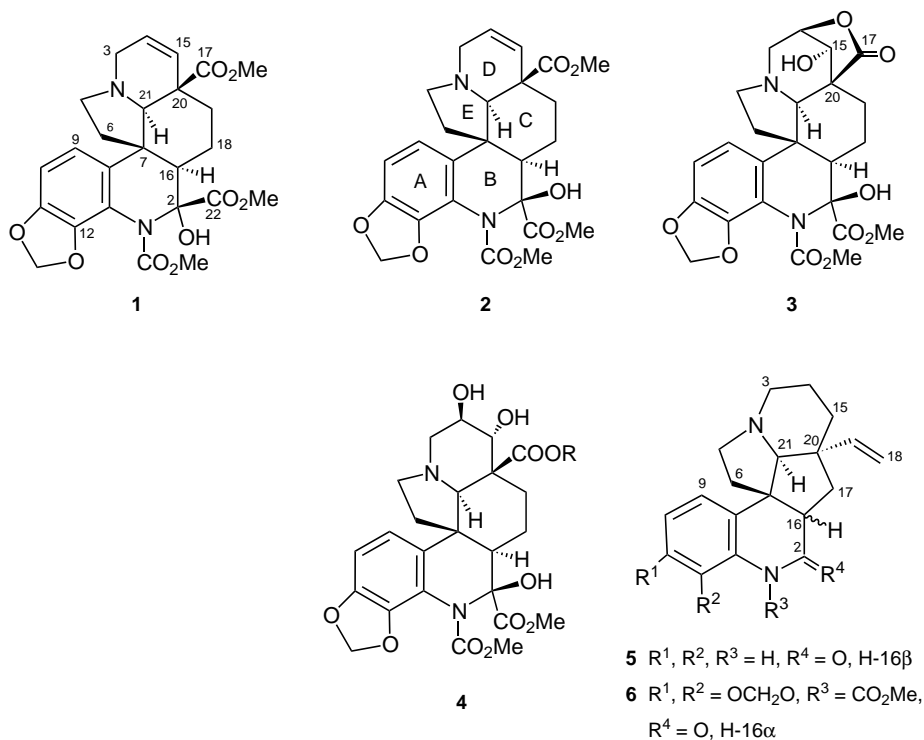
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absorption bands at 3523 (broad), 1739 and 1711 cm⁻¹, which are assigned to OH, ester and carbamate/ester functions, respectively. The EIMS showed a molecular ion at m/z 500, which analyzed for $C_{25}H_{28}N_2O_9$ requiring 13 degrees of unsaturation, and indicating a highly oxygenated molecule.[18] The ^{13}C NMR spectrum (Table 1) gave a total of 25 separate carbon resonances (three methyls, six methylenes, six methines and ten quaternary carbons) in agreement with the molecular formula. The ^{13}C NMR spectral data also confirmed the presence of carbamate and ester functions, in addition to a low-field quaternary resonance (δ 87.6) due to carbon-2, which is α to both a nitrogen and an oxygen atom. The ^{1}H NMR spectrum (Table 1) showed signals due to two adjacent aromatic hydrogens (AB doublets at δ 7.15, 6.62), two olefinic hydrogens (δ 5.95, 5.82), a methylenedioxy function (δ 5.96, 5.91), three singlets due to carbamate and ester methoxy groups (δ 3.82, 3.79, 3.63) and a broad OH singlet at δ 4.61 which undergoes exchange with D_2O.

The COSY and HMQC spectral data showed the presence of NCH_2CH_2, $NCH_2CH=CH$, CH_2CH_2CH partial structures, as well as an isolated aminomethine corre-

sponding to H-21. Construction of the entire molecule from the linking of the fragments so far revealed is based on the HMBC data. The key observations from the HMBC spectrum which indicated the presence of a six-membered ring B (in contrast to the more common five-membered rings in dihydroindole derivatives), are the observed three-bond correlations from the quaternary C-7 to H-9, C-6, C-8, C-22 (CO_2Me) to H-16 and two-bond correlations from C-2, C-7 to H-16 (Fig. 1). The observed three-bond correlations from C-20 to H-14 and H-18, indicated that the two fragments $NCH_2CH=CH$ and CH_2CH_2CH are branched from the quaternary C-20, while the three-bond correlations from the ester carbonyl (C-17, δ 173.0) to H-15 and H-19 fix the location of the ester group at C-20. The remaining notable correlations from the quaternary C-7 to H-21 (isolated aminomethine), H-6, H-5 and from C-15, C-19 to H-21, complete the assembly of the ring system of mersinine A. The structure is entirely consistent with the full HMBC data as well as the results of NOE experiments. Irradiation of H-9 resulted in enhancement of the H-21 signal, while irradiation of H-21 in turn causes enhancement of H-9 as well as

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

Position	**1** δ_C	**1** δ_H	**2** δ_C	**2** δ_H	**3** δ_C	**3** δ_H
2	87.6	–	86.5	–	86.5	–
3a	49.6	3.57 ddd (18, 3, 2)	49.6	3.60 ddd (18, 3, 2)	45.2	3.10 dd (15, 3)
3b		3.97 dd (18, 5)	–	4.05 dd (18, 5)	–	3.60 d (15)
5a	53.8	2.98 t (8.5)	53.8	3.09 t (8.5)	52.1	3.20 m
5b	–	3.11 m	–	3.18 m	–	3.20 m
6a	30.4	1.62 dd (12.5, 6.5)	30.2	1.57 dd (12.5, 6.5)	29.7	1.63 m
6b	–	1.99 m	–	2.33 m	–	2.81 ddd (13.5, 10.5, 9.5)
7	45.6	–	45.3	–	46.1	–
8	136.6	–	136.6	–	135.1	–
9	115.8	7.15 d (8.2)	115.7	7.18 d (8.2)	116.5	7.20 d (8.2)
10	105.1	6.62 d (8.2)	104.4	6.62 d (8.2)	104.4	6.62 d (8.2)
11	146.8	–	146.7	–	146.8	–
12	140.2	–	139.1	–	139.0	–
13	118.0	–	118.1	–	119.0	–
14	131.7	5.95 ddd (9.5, 5, 2)	131.9	5.97 ddd (9.5, 5, 2)	76.7	4.46 dd (5.5, 3)
15	131.9	5.82 dd (9.5, 3)	132.1	5.86 dd (9.5, 3)	73.0	4.27 dd (5.5, 3.3)
16	52.9	2.14 dd (13,3)	49.2	2.08 dd (13, 3)	47.9	1.96 dd (13, 3)
17	173.0	–	173.1	–	178.6	–
17-OMe	51.6	3.63 s	51.7	3.66 s	–	
18α	21.5	1.78 dq (13, 3)	20.4	1.33 br d (13)	17.3	1.30 m
18β	–	1.34 br q (13)	–	1.85 qd (13, 3)	–	3.02 qd (13, 3)
19α	30.9	1.16 td (13, 3)	30.1	1.16 td (13, 3)	25.7	1.33 td (13, 3)
19β	–	2.39 dt (13, 3)	–	2.42 dt (13,3)	–	1.63 m
20	48.6	–	48.7	–	45.6	–
21	71.5	3.00 s	71.1	3.09 s	62.1	3.73 d
22	170.5	–	172.5	–	172.8	–
22-OMe	52.9	3.82 s	53.2	3.80 s	53.2	3.80 s
OCH₂O	101.1	5.91 d (1.5), 5.96 br s	101.1	5.92 d (1.5), 5.96 d (1.5)	101.1	5.92 d (1.5), 5.95 br s
2-OH	–	4.61 br s	–	5.08 br s		5.08 br s
15-OH	–	–	–	–	–	2.45 d (3.3)
NCO₂Me	155.4		154.4		[b]	
NCO₂Me	53.4	3.79 s	53.4	3.80 s	53.5	3.81 s

[a] CDCl₃, 400 MHz; assignments based on COSY, HMQC and HMBC.
[b] Not observed.

(⌒→ = HMBC)

Figure 1.

H-16, allowing the stereochemistry of H-16 to be assigned as α. The stereochemistry at the quaternary center (C-2) could be readily inferred, since the epimeric compound, mersinine B **2**, was also obtained. Mersinine B **2** (light yellowish oil)[19] showed very similar NMR spectral data when compared to that of **1**, except for the resonance of H-6, OH, and C-16 (Table 1). In addition, mersinine A **1** was smoothly and irreversibly converted to mersinine B **2** by the action of dilute alcoholic NaOH, indicating that compound **2** was the more stable epimer.[20] Examination of models confirmed that the less sterically congested structure has the hydroxyl substituent in the β-position.

Mersiloscine **3** was obtained as a colorless amorphous solid, with $[\alpha]_D$ −50 (CHCl$_3$, c 0.04). The UV spectrum was similar to that of the previous two compounds, while the IR spectrum showed absorption bands at 3491 (broad, OH), 1747 (broad, lactone and ester) and 1703 (carbamate) cm^{-1}. The EIMS showed a molecular ion at m/z 502 which analyzed for $C_{24}H_{26}N_2O_{10}$ (DBE 13).[21] The ^{1}H and ^{13}C NMR spectral data of **3** (Table 1) showed a basic similarity with that of compounds **1** and **2** except for some notable differences. Firstly, the signals due to the 14,15 double bond and one ester methoxy function (20-CO$_2$Me) are absent in both the ^{1}H and ^{13}C NMR spectra of compound **3**. Instead H-14 and H-15 are now oxymethines, appearing at δ 4.46 and 4.27, respectively (δ_c 76.7 and 73.0, respectively) and a new signal due to OH is seen at δ 2.45 (exchanged with D$_2$O). In addition, the ^{13}C NMR spectrum of **3** shows the presence of a lactone carbonyl resonance at δ 178.6 (in place of the ester carbonyl resonance in compounds **1** and **2**). Since there is no unsaturation in the piperidine ring D, but the DBE remains unchanged, additional ring formation must have occurred in compound **3**, which takes the form of a γ-lactone unit incorporating carbons 14, 15, 20 and 17. This proposal is also supported by the observed three-bond correlations from the lactone carbonyl (C-17) to H-14 and H-21 in the HMBC spectrum of **3**. Another significant difference is the downfield shift of H-18β from δ 1.85 in **2** to δ 3.02 in **3**, which is caused by the anisotropic effect of the proximate lactone carbonyl function. This observation in fact allows the assignment of the C-20 to C-17 bond as β, since the alternative structure (in which the lactone unit is α with respect to the general plane defined by the molecule) would result in the placement of H-19α instead, within the anisotropic

influence of the lactone carbonyl function. On the assumption that the lactone **3** is formed from a hypothetical hydroxy ester/acid precursor such as **4**, which is in turn derived from oxidation of the olefin **2**, it would be reasonable to conclude that the stereochemistry of the ester group at C-20 in these closely related compounds (i.e. **1**, **2**, **3**) is β. Irradiation of H-21 causes enhancement of H-19α (in addition to H-16 and H-9). Irradiation of H-19β in turn, causes enhancement of H-15 and vice-versa, from which the stereochemistry of the C(15)–OH can be established as α.

The relative stereochemistry at C-2 in the epimeric compounds **1** and **2** have been assigned as discussed earlier based on steric grounds. Compounds **2** and **3** show strikingly similar C(2)–OH shift in ^{1}H NMR (ca. δ 5.1) which are distinct from the C(2)–OH shift in compound **1** (δ 4.61), from which it is reasonable to infer that the former compounds (**2**, **3**) possess the same relative configuration at C-2 (S). A similar trend is indicated in the carbon shifts of C-16 (ca. δ 49 in **2** and **3** c.f. δ 53 in **1**). Additional support for this assignment is also provided by the paramagnetic deshielding of H-18 (α or β) by the proximate C(2)–OH group.[22] The stereochemistry of the C-18 hydrogens can be independently assigned from consideration of the vicinal coupling constants and from NOE experiments. In compound **1**, in which the C(2)–OH group is α, H-18α experiences deshielding due to spatial proximity of the α-oriented OH (H-18α δ 1.78, H-18β δ 1.34), whereas in compounds **2** and **3**, the same effect operates on H-18β instead, which is deshielded to ca. δ 1.8 (H-18α ca. 1.3). In compound **3**, this paramagnetic deshielding due to OH is reinforced by additional deshielding from anisotropy of the lactone carbonyl (vide supra).

The mersinines and mersiloscine are pentacyclic quinolinic alkaloids which are related to the *Melodinus* alkaloids as exemplified by meloscine **5**.[20] Compounds of this structural class (of which to date only 16 members are known), have not been previously encountered outside the genus *Melodinus*. Of the known compounds, nine are aspidosperma-derived monomers, characterized by a dihydroquinolone chromophore,[20,23–26] four are bis-indoles incorporating a scandine-derived monomeric unit,[27] while lanceomigine[28] and its congeners[16,17] represent yet another variation of the meloscine skeleton, incorporating a tetrahydro- or dihydroquinoline core. The novel ring system in the present group of compounds can be considered as having arisen from an epimeloscine-type precursor (e.g. **6**), via scission of the C(16)–C(17) bond, followed by bond formation between C(18) and C(16). Compounds of this type are found for the first time in the genus *Kopsia*.

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