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# Mersilongine, a novel tetracyclic quinolinic alkaloid from *Kopsia*

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**Abstract**—A novel quinolinic alkaloid, viz., mersilongine, incorporating a novel tetracyclic carbon skeleton was obtained from a Malayan *Kopsia* species. The structure was established by spectroscopic analysis and a possible pathway from a mersinine-type precursor is presented.
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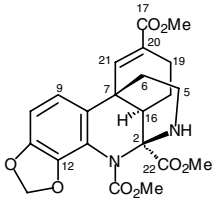
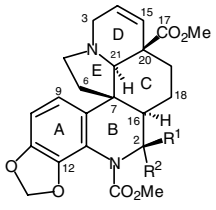
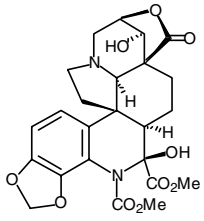
The genus *Kopsia* has proven to be a fertile source of structurally novel as well as biologically active alkaloids.[1–15] We have previously reported the presence of a new structural class of the monoterpenoid indole alkaloids, viz., the mersinines (**2**, **3**) and mersiloscine **4**, which are characterized by a novel pentacyclic carbon skeleton incorporating a tetrahydro-quinoline instead of an indole chromophore.[4] These alkaloids bear a resemblance to the *Melodinus* alkaloids, exemplified by meloscine **5** and epimeloscine **6**, although from a biogenetic viewpoint, they could well have arisen via an entirely different pathway.[16] We have subsequently confirmed the structure of the mersinines by an X-ray diffraction study[3] of mersinine A **2**, and now wish to report the structure of another unusual alkaloid obtained from the same plant.



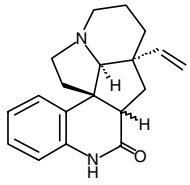
**1**



**2** $R^1 = CO_2Me$, $R^2 = OH$
**3** $R^1 = OH$, $R^2 = CO_2Me$



**4**



**5** H-16β
**6** H-16α

Mersilongine **1** was obtained from the basic fraction derived from the EtOH extract of the leaves after extensive chromatographic fractionation, as a colorless oil (yield ca. 8 mg kg$^{-1}$), with $[\alpha]_D$ +106 (*c* 0.17, $CHCl_3$). The UV spectrum (220, 250 shoulder, and 291 nm) was reminiscent of the mersinines and suggested the presence of a similar tetrahydroquinoline chromophore. The IR spectrum showed bands at 3356, 1751, and 1712 cm$^{-1}$, suggesting the presence of *N*H, ester, and carbamate/conjugated carbonyl functionalities, respectively. The EIMS of **1** showed a molecular ion at *m*/*z* 444, which analyzed for $C_{22}H_{24}N_2O_8$, requiring 12° of unsaturation, and indicating a highly oxygenated molecule.[17] The mass fragments, which were observed at *m*/*z* 412, 385, and 353, can be attributed to loss of MeOH, $CO_2Me$, and (MeOH + $CO_2Me$) fragments, respectively. The $^{13}C$ NMR spectrum (Table 1) gave a total of 22 carbon resonances (three methyls, five methylenes, four methines, and ten quaternary carbons) in agreement with the molecular formula. The $^1H$ NMR spectrum indicated an aromatic ring substituted by a methylenedioxy function at C(11) and C(12), from the characteristic pair of AB doublets at $\delta$ 5.91 and 6.02 ($\delta_C$ 100.9), three methoxy groups at $\delta$ 3.77, 3.86, and 3.82, and a vinylic-H at

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

| Position | $\delta_C$ | $\delta_H$ | Position | $\delta_C$ | $\delta_H$ |
|---|---|---|---|---|---|
| 2 | 77.3 | — | 18 | 19.5 | 1.51 m |
| 5 | 38.0 | 2.61 td (13, 3) | | | 2.07 m |
| | | 2.91 br dd (13, 6) | 19 | 24.1 | 2.07 m |
| 6*R* | 33.7 | 1.71 br d (13) | | | 2.59 m |
| 6*S* | | 1.99 td (13, 6) | 20 | 128.4 | — |
| 7 | 37.4 | — | 21 | 141.9 | 7.40 br s |
| 8 | 130.0 | — | 22 | 170.9 | — |
| 9 | 117.0 | 6.90 d (8.2) | 17-OMe | 51.8 | 3.77 s |
| 10 | 103.6 | 6.62 d (8.2) | 22-OMe | 53.4 | 3.86 s |
| 11 | 147.2 | — | *N*$CO_2$Me | 52.9 | 3.82 s |
| 12 | 139.2 | — | *N*$CO_2$Me | 153.9 | — |
| 13 | 122.2 | — | $OCH_2O$ | 100.9 | 5.91 d (1.5) |
| 16 | 43.5 | 1.91 br d (12.2) | | | 6.02 d (1.5) |
| 17 | 167.6 | — | | | |

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

$\delta$ 7.40. The three methoxy groups were deduced to be associated with conjugated ester, carbamate, and methyl ester functions from their respective carbon signals at $\delta$ 167.6, 153.9, and 170.9, respectively. Since an *N*H function is indicated by the IR spectrum, this must due to an *N*(4)-H. In addition to the signals due to the aromatic ring and the three carbonyl functions, the two remaining low field signals at $\delta$ 128.4 and 141.9, corresponding to a quaternary and a methine carbon, respectively, are due to a trisubstituted double bond constituting part of the α,β-unsaturated ester moiety. With these functionalities accounted for, a tetracyclic molecule is indicated from the molecular formula.

The COSY spectrum showed the presence of two main fragments, viz., $NHCH_2CH_2$ and $CHCH_2CH_2C{=}CH$. In the latter fragment, long-range allylic coupling was clearly seen in the COSY spectrum, although the vinylic-H appeared as a slightly broadened singlet. In the mersinine-type compounds, the quaternary C(2) resonance is found at ca. $\delta$ 87, due to it being adjacent to both a nitrogen and oxygen atom, as well as being substituted by a carbomethoxy group. In mersilongine, the quaternary C(2) resonance is observed at $\delta$ 77.3, shifted upfield by about 10 ppm, suggesting replacement of an adjacent oxygen by a nitrogen atom, compared to the mersinines.[18] The HMBC spectrum showed the same correlations, which established the six-membered ring B in the mersinines (Fig. 1).[4] This confirms the location of the methine C(16) within the quinolinic moiety. The $^{2}J$ and $^{3}J$ correlation from the lone vinylic-H to C(7) and C(16), and the three-bond correlations from H(18) to C(7), C(2), and C(20), indicated that the $CHCH_2CH_2C{=}CH$ fragment forms part of the six-membered ring linked to ring-B via C(16) and C(7). It only remains to link the $CH_2CH_2NH$ fragment to complete the tetracyclic ring system to reveal the structure of mersilongine as shown in **1**. The structure is characterized by a six-membered ring (C) contiguously fused to the quinolinic portion via C(7) and C(16), and bridged by a aminoethane unit from C(7) to C(2).

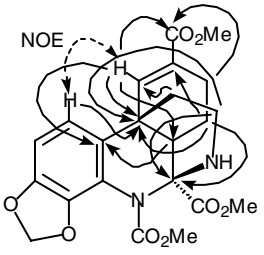
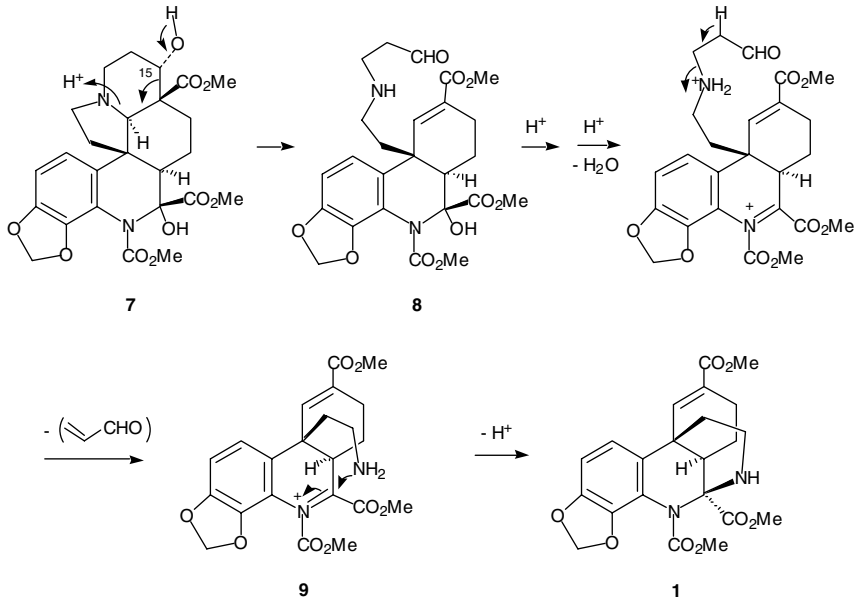



**Figure 1.** NOE and HMBC of **1**.

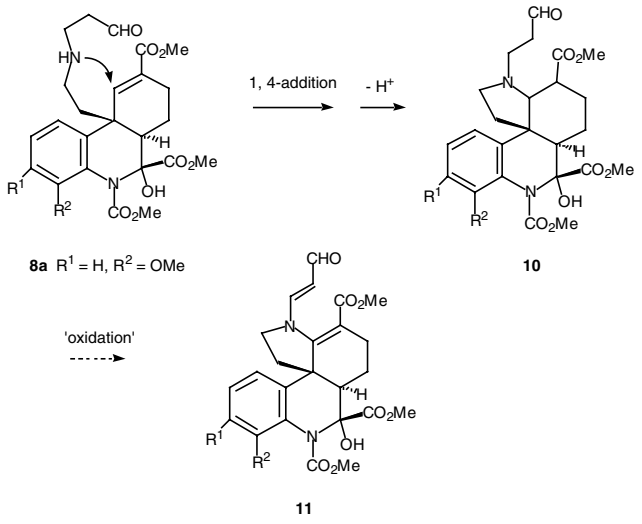
The proposed structure is in complete accord with all the spectral data including the COSY, HMBC, and NOE/NOESY data. For instance, the three-bond correlations from H(5) to C(2) and C(7), and from H(6) to C(21) are consistent with the branching of the aminoethane bridge from C(7) to C(2). NOESY as well as NOE difference experiments showed reciprocal NOE interactions between H(9)/H(21) and H(6*R*)/H(21), which are in agreement with the proposed structure. The stereochemistry of the aminoethane bridge is deduced to be β, on the basis of the observed NOE interactions, and this in turn fixes the relative configurations at C(7) and C(2), as well as that of C(16), which follows that of all the mersinine-type compounds discovered to date. In addition, it is also consistent with the proposed origin of **1** from a mersinine-type precursor (vide infra).

The structure of mersilongine **1** represents a departure from the mersinine group of compounds, which occur exclusively in this plant. It appears to have lost an entire ring (corresponding to ring D of the mersinines), and in addition, a rearrangement seemed to have occurred, resulting in cleavage of the *N*(4)–C(21) bond, and formation of a new bond, linking *N*(4) to C(2). A possible pathway to **1** is shown in Scheme 1 from a mersinine derivative **7** (which was also isolated from the leaf extract),[19] involving a concerted Grob-like fragmentation, initiated by the C(15) hydroxy group, followed by a retro-Michael elimination of an acrolein fragment. Finally, intramolecular capture of the iminium ion **9** via 1,2-addition by the appositely oriented $NH_2$ function of the aminoethane side chain, completes the formation of the aminoethane bridge, yielding the novel tetracyclic ring system of mersilongine **1**.



Scheme 1.

Mersilongine **1** represents an unusual alkaloid, characterized by an unprecedented, tetracyclic, quinolinic ring system. A possible route from the quinolinic mersinines has been presented above, involving a sequential Grob fragmentation, a retro-Michael reaction, and an intramolecular primary amine–iminium ion reaction. The proposed pathway also accounts for the isolation of another unusual *seco*-mersinine derivative **11** (a new compound also isolated from the leaf extract),[19] as shown in Scheme 2. The product from the Grob fragmentation **8a**, instead of undergoing protonation followed by elimination of acrolein in a retro-Michael reaction, undergoes intramolecular conjugate addition to the α,β-unsaturated ester moiety, leading to the tetracyclic intermediate **10**, which on subsequent oxidation (dehydrogenation) yields the *seco*-mersinine compound **11**, incorporating a vinylogous amide unit.



Scheme 2.

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