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Mersicarpine, an unusual tetracyclic dihydroindole alkaloid incorporating a seven-membered imine ring

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Abstract—A novel dihydroindole derivative, viz., mersicarpine, incorporating a novel tetracyclic carbon skeleton, containing a seven-membered imine ring, was obtained from a Malayan *Kopsia* species. The structure was established by spectroscopic analysis and a possible biogenetic pathway from a leuconolam precursor is presented.

Plants of the genus *Kopsia*, which has a widespread distribution in tropical Asia including Malaysia, have proven to be a fertile source of alkaloids possessing novel carbon skeletons as well as interesting biological activities.[1–15] We have previously reported the presence of a new structural subclass of the monoterpenoid indole alkaloids, exemplified by mersinines A (**2**) and B (**3**).[4] We recently reported the structure of another novel tetracyclic quinolinic alkaloid, mersilongine (**4**), which we proposed to have originated from a mersinine-type precursor via successive Grob fragmentation, retro-Michael elimination of acrolein, followed by an intramolecular primary amine–iminium ion reaction.[1] We now report the structure and possible biogenetic origin of another curious dihydroindole derivative, mersicarpine (**1**), characterised by an unusual tetracyclic carbon skeleton, incorporating a seven-membered imine ring.

Mersicarpine (**1**) (which occurs as a minor alkaloid in the bark of *K. fruticosa* as well as *K. arborea*), was obtained from the basic fraction derived from the EtOH extract of the stem-bark following repeated chromatographic fractionation, as a colourless oil (yield ca. 2 and 0.3 mg kg^{-1} from *K. fruticosa* and *K. arborea*, respectively), $[\alpha]_D$ −18 (*c* 0.28, $CHCl_3$). The UV spectrum (EtOH) showed absorptions at 204, 239, 246, 266, 275 and 329 nm, which resembled those of a *N*-acyl dihydroindole chromophore (e.g. leuconoxine), but with additional bands, possibly due to additional conjugation to an imine function. The IR spectrum showed strong, broad bands at 3318 and 1654 cm^{-1}, suggesting the presence of OH and imine/lactam functionalities, respectively. The EIMS of **1** showed a molecular ion at *m*/*z* 284, which analysed for $C_{17}H_{20}N_2O_2$, requiring 9 degrees of unsaturation.[16] The base peak was observed at *m*/*z* 267, corresponding to loss of OH. The ^{13}C NMR spectrum (Table 1) gave a total of 17 carbon resonances (one methyl, six methylenes, four methines, and six quaternary carbons) in agreement with the molecular formula. The quaternary carbon resonances at δ 169.6 and 168.9 were assigned to lactam carbonyl and imine functionalities, respectively, in agreement with the IR spectrum. In addition, another quaternary carbon resonance, which was observed downfield at δ 93.8 was attributed to a carbon adjacent to both a nitrogen and oxygen atom. The ^1H NMR spectrum indicated an unsubstituted aromatic ring, a broad OH peak at δ 5.92, and an ethyl side chain.

The COSY and HMQC spectral data revealed two further partial structures, viz. $NCH_2CH_2CH_2$ and CH_2CH_2, in addition to the four contiguous aromatic hydrogens, and the ethyl side chain noted previously. The absence of an indole *N*H suggested that *N*(1) is associated with the lactam group, an inference, which was further supported by the observed downfield shift of H(12) due to deshielding by the proximate amide/lactam carbonyl linked to the indolic nitrogen.[17–21] In addition, the aromatic carbon and hydrogen shifts bear a striking similarity to those of epileuconolam,[22] suggesting a close structural affinity in that part of the molecule with **1**.

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

Position	δ_C	δ_H	Position	δ_C	δ_H
2	169.6	—	16α	29.1	2.48 ddd
3	50.5	3.87 m			(18.5, 9.5, 3.5)
		3.87 m	16β		2.35 ddd
7	168.9	—			(18.5, 8.8, 7.8)
8	124.4	—	17α	25.4	1.89 dddd
9	122.2	7.66 br d (8)			(14, 9.5, 7.8, 1.5)
10	124.2	7.09 td (8, 1)	17β		1.65 m
11	133.2	7.39 td (8, 1)	18	6.8	0.74 t (7.5)
12	116.7	8.13 br d (8)	19	21.1	1.10 dq (14.5, 7.5)
13	146.5	—			1.32 dqd
14	22.9	1.65 m			(14.5, 7.5, 1.5)
		1.65 m	20	39.3	—
15α	34.3	2.07 m	21	93.8	—
15β		1.75 dt (14.3, 3.5)	21-OH	—	5.92 br s

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

The observed three-bond correlation from H(9) to the imine C(7) in the HMBC spectrum not only confirm the assignment of H(9), but also defines the location of the imine function. In addition, attachment of the propyl fragment to *N*(4) is supported by the H(3) to C(7) correlation, while the H(14) and H(18) correlations to the quaternary C(20) confirm the branching of the propyl and ethyl fragments from this carbon. The three-bond correlations from H(15) as well as H(19) to the oxygenated C(21) permit the assembly of the seven-membered imine-containing ring C. Since only a lactam carbonyl (which must be attached to the indolic nitrogen as noted above) remains as the only source of unsaturation, another ring remains to be assembled from the DBE value of 9. This is readily accomplished from the observed three-bond correlations from H(17) to C(2) and from H(16) to C(20). Other correlations from the HMBC spectrum are shown in Figure 1, which are in complete accord with the proposed structure. In addition, the large geminal coupling observed for the C(16) hydrogens ($J = 18.5$ Hz) is diagnostic of methylene hydrogens α to a carbonyl function, which provides further support for structure **1**.

The stereochemistry of the ethyl side chain is assumed to be similar to that in leuconolam, rhazinilam, and their congeners, which also occur in the stem-bark extract, on the grounds of a presumed close biogenetic relationship (vide infra). The NOESY and NOE difference experiments showed reciprocal NOE's between H(18) and H(15β), which in turn allowed the more deshielded signal to be assigned to H(15α). This is in agreement with the proposed α-face attachment of the hydroxyl substituent at C(21) {vide infra}, as H(15α) would then be expected to experience deshielding due to spatial proximity of the α-oriented OH.[4,21]

The structure of mersicarpine (**1**) represents a departure from the rhazinilam-leuconolam group of compounds, which coexist with **1** in the stem-bark extract of this plant. It appears to have lost the two-carbon tryptamine bridge corresponding to C(5) and C(6), normally present

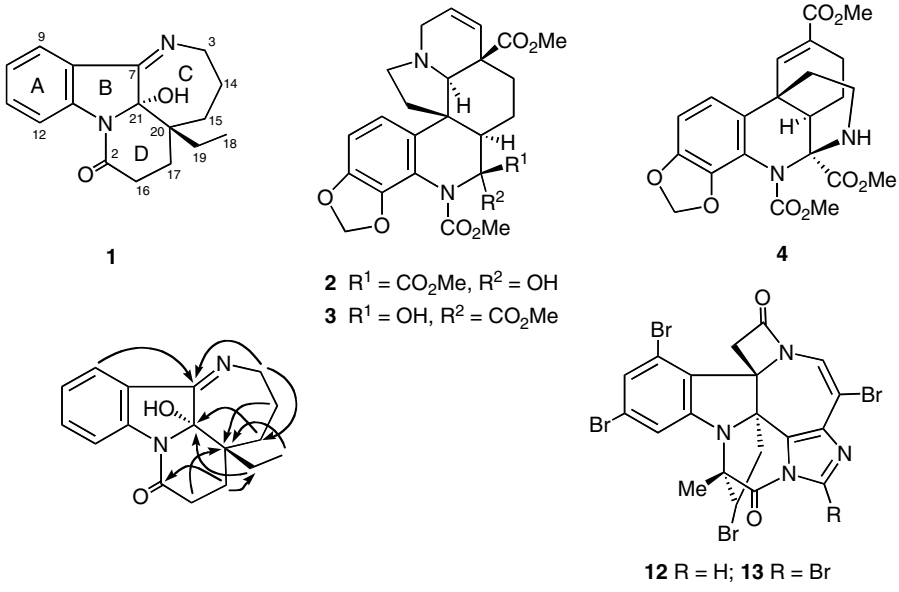
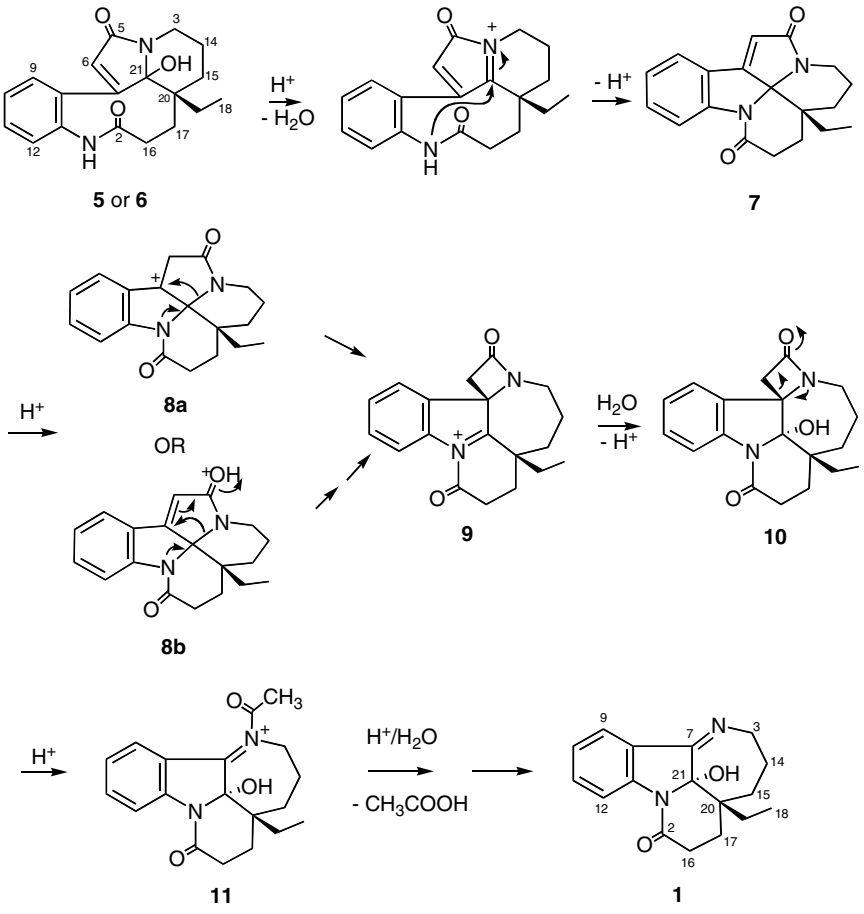


Figure 1. Selected HMBC of **1**.



Scheme 1.

in the other monoterpenoid indole alkaloids. In addition, the presence of the amide-containing ring D, suggested an affinity to leuconoxine, although a further rearrangement appears to have occurred leading to the loss of the two carbon chain and formation of the seven-membered imine-containing ring C. A possible biogenetic pathway to **1** is shown in Scheme 1, from leuconolam (**5**) {or epileuconolam (**6**)}, involving formation of a dehydroleuconoxine derivative **7**, from the transannular attack by the indolic nitrogen on the C(21) iminium ion of **5**. Protonation of **7** yields the tertiary benzylic carbocation **8a**, which then undergoes a 1,2-alkyl shift resulting in the iminium ion **9** (alternatively, **9** could also arise via a 1,2-alkyl shift from the protonated ketone **8b**). Nucleophilic attack by a molecule of water on **9**, which would be anticipated to occur from the less hindered α-face, gives the tertiary alcohol **10**, characterized by the presence of a β-lactam unit associated with *N*(**4**). Subsequent cleavage of the β-lactam unit, followed by hydrolysis of the resultant acyl imine salt **11**, yields the novel ring system of mersicarpine (**1**).[23] A search of the literature yielded strong support for such a pathway from an unexpected source. The halogenated marine alkaloids, chartellamide A (**12**) and B (**13**), from the marine bryozoan *Chartelle papyracea*, not only possess a structure displaying a remarkable resemblance to the 6–5–7 ring system of mersicarpine (**1**), but in addition incorporate a β-lactam unit, corresponding to that present in the proposed intermediate, **10**.[24] In the event, mersicarpine (**1**) represents the first member of this novel class of indole alkaloids from plants.

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