

Arboflorine, an Unusual Pentacyclic Monoterpenoid Indole Alkaloid Incorporating a Third Nitrogen Atom

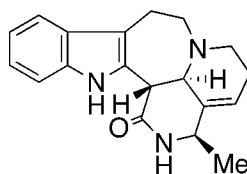
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ABSTRACT



arboflorine (3)

A new indole alkaloid, arboflorine, possessing a novel pentacyclic carbon skeleton and incorporating a third nitrogen atom was obtained from the Malayan *Kopsia arborea*. The structure was established by spectroscopic analysis, and a possible biogenetic pathway from a preakummicine-type precursor is presented.

Plants of the genus *Kopsia* have proven to be prodigious sources of indole alkaloids with unusual structures as well as useful biological activities.^{1–16} We previously reported

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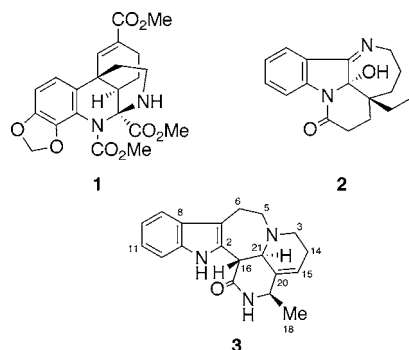
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the structures of several alkaloids characterized by novel carbon skeletons from *K. singaporensis*, such as the tetracyclic quinolinic alkaloid, mersilongine **1**,² and the novel tetracyclic dihydroindole, mersicarpine **2**.¹ The latter alkaloid was also found in *K. arborea*. These alkaloids are notable for possessing novel ring systems and are postulated to derive from known monoterpenoid indole precursors through pathways involving deep-seated rearrangements and loss of key fragments. Thus, mersilongine was proposed to be derived from a mersinine-type precursor via successive Grob fragmentation and retro-Michael elimination of acrolein, followed by an intramolecular primary amine–iminium ion reaction.² The mersinines in turn represent a new structural subclass derived from aspidosperma-type precursors.⁵ The novel carbon skeleton of mersicarpine **2** on the other hand was postulated to originate from a leuconolam/rhazinilam-type precursor, via a sequence involving formation of a dehydroleuconoxine derivative followed by subsequent rearrangement to a pentacyclic tertiary alcohol, incorporating a β -lactam unit.¹ The central 6–5–7 ring system present in

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mersicarpine as well as in the proposed key intermediate is also found in the halogenated marine alkaloids, chartellamides A and B, from the marine bryozoan *Chartelle papyracea*.¹⁷ We now report the structure and possible biogenetic origin of another unusual indole alkaloid from *K. arborea*, arboflorine **3**, characterized by a novel ring system and incorporating a third nitrogen atom. Previous examples of indole alkaloids from *Kopsia* incorporating a third nitrogen atom include the mersingines¹⁸ and the lahadinines.^{19,20}



Arboflorine, **3**, was obtained as a minor alkaloid from the basic fraction derived from the EtOH extract of the stem bark of *K. arborea* following repeated chromatographic fractionation (colorless oil, yield ca. 0.4 mg kg⁻¹, [α]_D +71 (*c* 0.07, CHCl₃)). The UV spectrum (EtOH) showed typical indole absorptions at 224, 283, and 291 nm, whereas the IR spectrum showed bands at 3393 and 1651 cm⁻¹, suggesting the presence of NH and lactam functionalities, respectively. The EIMS of **3** showed a molecular ion at *m/z* 307 (base peak), the odd mass indicating the presence of a third nitrogen. This was confirmed by HREIMS which revealed the molecular formula, C₁₉H₂₁N₃O, requiring 11 degrees of unsaturation.²¹ A prominent fragment peak due to loss of a methyl was seen at *m/z* 292.

The ¹³C NMR spectrum (Table 1) gave a total of 19 carbon resonances (one methyl, four methylenes, eight methines, and six quaternary carbons) in agreement with the molecular formula. The eight carbon resonances of the indole moiety could be readily assigned from considerations of their chemical shifts and were confirmed from examination of the HMBC spectrum. The quaternary carbon resonance at δ 171.4 was assigned to the lactam carbonyl, leaving two other downfield carbon signals (δ 133.6 and 120.8) which are attributed to a trisubstituted double bond. The ¹H NMR spectrum indicated an unsubstituted aromatic ring; two broad NH peaks at δ 9.74 and 6.11, the former due to the indolic nitrogen from the observed three-bond correlation to C(7) and C(8) in the HMBC spectrum; a vinylic H, seen as a broad doublet at δ 5.92; and a methyl doublet at δ 1.37. In addition,

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(21) HREIMS found *m/z* 307.1682 (calcd for C₁₉H₂₁N₃O, 307.1685).

Table 1. ¹H and ¹³C NMR Spectral Data of **3**^a

position	δ_C	δ_H
2	131.7	
3 α	45.9	2.90 m
3 β		2.82 td (11.9, 3.8)
5 α	56.3	3.01 m
5 β		3.44 m
6	21.6	3.14 m
6'		3.14 m
7	113.0	
8	127.8	
9	117.6	7.48 d (7.8)
10	119.2	7.09 td (7.8, 1.2)
11	121.7	7.15 td (7.8, 1.1)
12	111.0	7.32 d (7.8)
13	134.2	
14 β	25.6	2.25 br d (16.5)
14 α		2.61 m
15	120.8	5.92 br d (2.7)
16	42.0	4.12 br d (9.4)
17	171.1	
18	18.1	1.37 d (6.4)
19	49.6	4.04 br q (6.4)
20	133.6	
21	59.2	4.30 br d (9.4)
NH (indole)		9.74 br s
NH (lactam)		6.11 br s

^a CDCl₃, 400 MHz.

a pair of AB doublets are seen at δ 4.30 and 4.12 with *J* = 9.4 Hz, and the observed carbon shift associated with the lower field doublet is at δ 59.2, indicating that this two-carbon CHCH fragment is branched from a nitrogen. This was also supported by the COSY and HMQC spectra which also revealed the presence of NCH₂CH₂, NCH₂CH₂CH=C, and CHCH₃ fragments, in addition to the four contiguous aromatic hydrogens.

Analysis of the ¹H and ¹³C shift values (Table 1) allowed recognition of the aminoethylene fragment as corresponding to the C(5)–C(6) unit, which was supported by the observed HMBC correlations from H(5) to C(7) and from H(6) to C(2), C(8). In a similar manner, the NCH₂CH₂CH=C and NCHCH fragments correspond to the C(3)–C(14)–C(15)–C(20) and C(21)–C(16) units, from the observed correlations from H(3) to C(5) and from H(5) to C(21), respectively. The observed correlations from H(21) to C(2) and from H(16) to C(7) allowed assembly of the seven-membered ring incorporating N(4), which is fused to the dihydroindole moiety. The attachment of the CHCH₃ fragment to the quaternary C(20) is indicated by the correlation from the methyl H(18) to C(20) and from H(15) to C(19). This left the lactam function to be inserted to complete the formation of the fifth ring as required by the molecular formula. The linkage of the lactam carbonyl to C(16) is shown by the two-bond correlation to this carbon from H(16) and three-bond correlations from the lactam NH to C(16) and C(20). The complete assembled structure is in complete agreement with the remaining HMBC data (Figure 1).

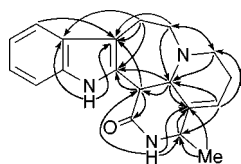


Figure 1. Selected HMBC of **3**.

The relative stereochemistry at the various stereogenic centers was established by NOE experiments (DNOE, NOESY; Figure 2). The observed NOE between H(21) and

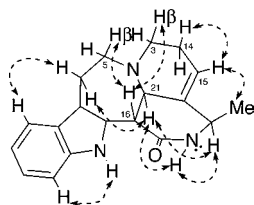


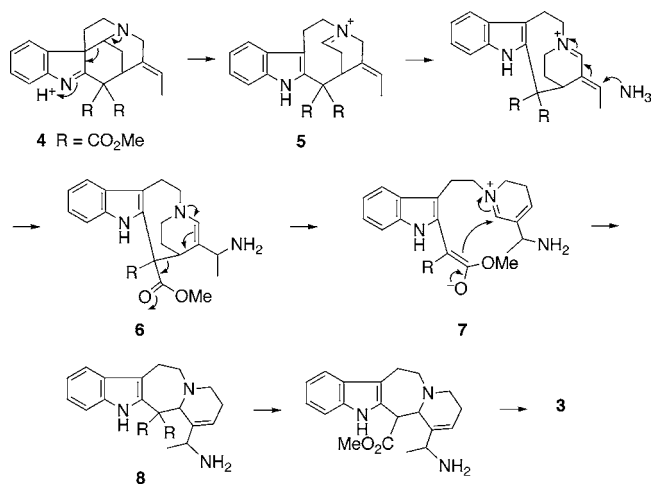
Figure 2. Selected NOEs of **3**.

H(19) requires both of these hydrogens to be syn with respect to each other. A NOE was not observed between H(16) and H(21) but was seen for H(16)/H(5 β) and H(16)/H(3 β). The stereochemistries of the C(3) hydrogens can be independently established from the observed trans-diaxial $J_{3\beta-14\alpha}$ coupling of 12 Hz and the NOE between H(14 β) and the olefinic H(15). In addition, the observed NOE between the lactam NH and both H(19) and H(21) allowed the stereochemistry of the nitrogen lone pair to be inferred. Other NOEs are in perfect agreement with the proposed structure as well as the relative configuration for arboflorine as shown in **3**.

The structure of arboflorine is notable on two counts. First, it represents a new subclass of monoterpene indoles with a novel pentacyclic carbon skeleton. A second and unusual feature is the incorporation of a third nitrogen atom embedded within a tryptamine-secologanin-derived monoterpene

indole. One possible pathway to arboflorine **3** is presented in Scheme 1.

Scheme 1. Possible Biogenetic Pathway to **3**



A plausible precursor is the diester derivative of preakua-mmicine, **4**, which undergoes a Grob-like fragmentation to the iminium ion, **5**.

Isomerization leads to a conjugated iminium ion, which on conjugate addition by ammonia gives the tetracyclic amine, **6**. A retrovinylogous Mannich reaction then follows to give the enolate **7**, which on subsequent ring closure via an intramolecular Mannich reaction gives the tetracyclic indole, **8**, with an amine-containing side chain. Decarboxylation, followed by aminolysis, leads to the novel ring system of arboflorine **3**.

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Supporting Information Available: NMR spectral data of arboflorine **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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