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Arboricine and arboricinine, unusual tetracyclic indole regioisomers from *Kopsia*

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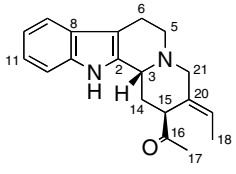
Abstract—A pair of unusual regioisomeric tetracyclic indoles of the corynantheine-type, arboricine and arboricinine were obtained from the Malayan *Kopsia arborea*. The structures were established by spectroscopic analysis and a possible biogenetic link between the alkaloids is presented.

Plants of the genus *Kopsia* (Apocynaceae) continue to provide novel indole alkaloids with intriguing carbon skeletons.[1–18] Recent examples of unusual alkaloids from *Kopsia* which are notable for possessing novel ring systems and which were postulated to derive from known monoterpenoid indole precursors through pathways involving deep-seated rearrangements and/or loss of key fragments include, inter alia, the cage indole arbophylline,[1] the three-nitrogen pentacyclic indole arboflorine,[2] the tetracyclic indole mersicarpine,[3] and the tetracyclic quinolinic alkaloid, mersilongine.[4] We now report the isolation and structure elucidation of another novel alkaloid from the leaf extract of *Kopsia arborea*, namely, arboricinine (**2**), representing an intriguing regioisomer of the new deplancheine-type indole alkaloid, arboricine (**1**).

Arboricine (**1**) was obtained after extensive chromatographic fractionation as colorless prisms, mp 126–128 °C, yield ca. 1.3 mg kg^{-1}, $[\alpha]_D$ −110 (*c* 0.14, $CHCl_3$). The UV spectrum (EtOH) showed typical indole absorptions at 225, 282, and 290 nm, while the IR spectrum showed bands at 3361 and 1702 cm^{-1}, corresponding to *N*H and ketone functionalities, respectively. The EI-mass spectrum showed a molecular ion at *m*/*z* 294 which analyzed for $C_{19}H_{22}N_2O$,[19] with other notable fragment ions at *m*/*z* 279 and 251, due to the loss of methyl and COMe, respectively. In addition, characteristic ions observed at *m*/*z* 156, 169, 170, and 184 are diagnostic of the corynantheine-type alkaloids.[20] The ^{1}H and ^{13}C NMR spectral data (Table 1) showed the presence of an unsubstituted indole ring, an indolic *N*H, an acetyl group, and an ethylidene side chain. The COSY and HMQC spectral data revealed partial structures consistent with a tetracyclic indole of the corynantheine-type, that is, *N*CH_2CH_2, *N*$CHCH_2CH$, and an isolated aminomethylene, corresponding to the C(5)–C(6), C(3)–C(14)–C(15), and C(21) fragments, respectively. The location of the acetyl substituent and the ethylidene side chain at C(15) and C(20),



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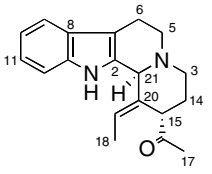

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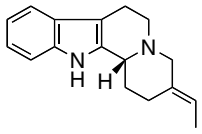

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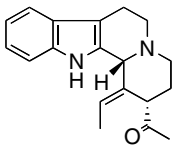

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Table 1. ^{1}H and ^{13}C NMR spectral data of **1** and **2**[a]

Position	1		2	
	δ_C	δ_H	δ_C	δ_H
2	134.0	—	130.8	—
3β	56.3	3.62 m	52.8	2.94 m
3α		—		3.03 m
5β	52.0	2.59 m	50.4	3.11 dt (11.3, 5.0)
5α		3.02 m		2.65 ddd (11.3, 8.2, 4.7)
6β	21.2	2.71 m	21.6	3.01 m
6α		3.05 m		2.82 dt (15.3, 4.7)
7	107.5	—	110.2	—
8	126.7	—	127.0	—
9	117.6	7.44 d (7.6)	118.2	7.48 d (7.6)
10	118.7	7.06 t (7.6)	119.2	7.08 ddd (7.6, 7.1, 1.2)
11	120.8	7.12 t (7.6)	121.6	7.14 ddd (7.9, 7.1, 1.3)
12	110.4	7.31 d (7.6)	110.6	7.30 d (7.9)
13	135.7	—	136.0	—
14α	29.5	1.55 br t (10)	25.6	2.31 dq (13.6, 2.3)
14β		2.69 m		1.94 m
15	47.8	3.59 m	49.5	3.79 dd (5.7, 1.7)
16	208.3	—	208.4	—
17	27.8	2.16 s	28.4	2.26 s
18	13.0	1.74 d (6.8)	13.3	1.76 dd (6.8, 1.3)
19	124.0	5.73 q (6.8)	123.4	5.61 q (6.8)
20	131.6	—	134.7	—
21β	61.2	2.98 m	61.2	—
21α		3.30 d (12.2)		4.07 br s
*N*H	—	8.36 br s	—	8.11 br s

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

respectively, was clear from the observed correlations in the HMBC spectrum, namely, H(17) to C(15), H(14) to C(16), H(18) to C(20), and H(21) to C(19) (Fig. 1). The presence of the diagnostic Wenkert–Bohlmann bands in the IR spectrum at 2848, 2799, and 2739 cm^{-1} was consistent with an axial bridgehead hydrogen within a *trans*-quinolizidine skeleton.[21,22] Since on biogenetic grounds, C(15) is an invariant stereogenic center in the corynantheine alkaloids with H(15α), the stereochemistry of H(3) was assigned as β from the observed $J_{3-14\alpha}$ value of 10 Hz, requiring these hydrogens to be in a trans-diaxial arrangement, as well as from the observed NOEs

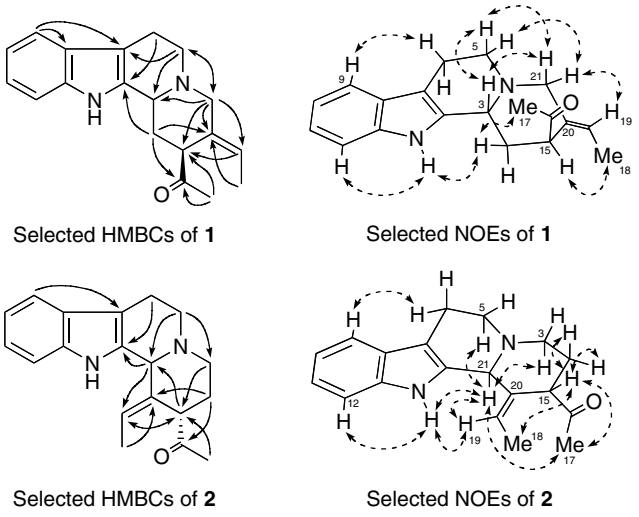


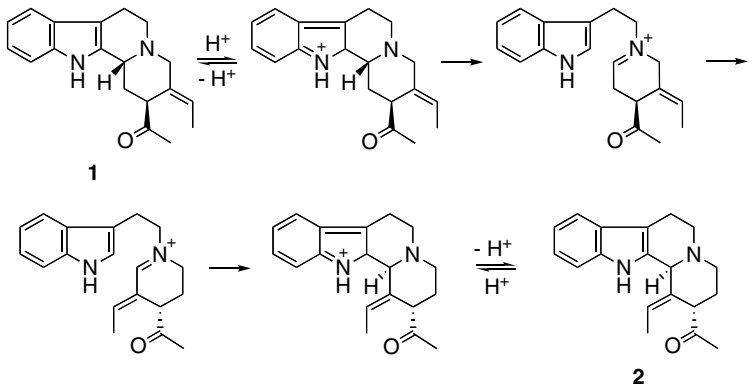
Figure 1. Selected HMBCs and NOEs of **1** and **2**.

for *N*H/H(14β), H(17)/H(14β), and H(15)/H(18) (Fig. 1), the latter NOE also confirming the *E* geometry of the C(19)–C(20) double bond. The configuration at C(3) is therefore similar to that in deplancheine (**3**),[23,24] and aboricine (**1**) is thus the 15β-acetyl derivative of deplancheine. This in itself would not constitute an unusual finding if not for the isolation of the regioisomeric alkaloid, arboricinine (**2**) from the same plant.

Arboricinine (**2**) was obtained as a colorless oil (yield ca. 1.1 mg kg^{-1}), $[\alpha]_D$ −18 (*c* 0.14, $CHCl_3$). The mass spectrum showed that it was an isomer of arboricine (**1**) (M^+ *m*/*z* 294),[25] while the UV and IR spectra were similar to that of **1**. The IR spectrum also showed similar Wenkert–Bohlmann bands indicating the presence of a *trans*-quinolizidine skeleton.[21,22] Despite some similarities, there were however significant differences in the MS fragmentation, ^{1}H and ^{13}C NMR spectral data (Table 1). In the case of **2**, although the *m*/*z* 156 and 169 fragment ions were observed, the *m*/*z* 170 and 184 ions previously seen in the spectrum of **1**, were not detected.

The ^{1}H and ^{13}C NMR spectra showed some differences from those of **1** and definitive and unambiguous assignments required the application of the standard array of 2-D techniques. The COSY and HMQC data revealed the presence of different partial structures compared to those present in **1**. Thus, although the C(5)–C(6) unit appeared intact (with essentially similar chemical shifts), an isolated aminomethine was now present, as well as an NCH_2CH_2CH fragment. A strong NOE was observed in the case of **2** between the indolic *N*H and the vinylic H(19), which was not the case with **1**, although the H(18)/H(15) NOE seen for **1**, was also observed for **2**. The HMBC data (Fig. 1) also revealed certain clear differences in **2** when compared with **1**. The key observations concerned the change in the location of the ethylidene function relative to the indole ring. The observed three-bond correlations from H(5) and H(15) to the aminomethine, and from the aminomethine–H to C(19) and C(2) (two bond correlation), indicate that the aminomethine was linked to C(2), as well as to the quaternary C(20) from which the ethylidene side chain was branched. These observations sufficed to allow the assembly of the structure of arboricinine as shown in **2**, revealing a structure regioisomeric with **1** in which the principal changes have occurred in ring D. The structure was consistent with the extensive HMBC as well as NOE/NOESY data (Fig. 1). In particular, the observed strong NOE between the vinylic H(19) and the indolic *N*H becomes intelligible in the light of the rearranged ring D.

Arboricinine (**2**) is therefore a regioisomer of arboricine (**1**) and appears to have been derived from **1** following cleavage of the C(2)–C(3) bond, followed in succession by rotation about the C(5)–*N*(4) bond, isomerization to the C(21)–*N*(4) iminium ion, and finally, cyclization by bond formation between C(21) and C(2). A possible pathway based on these considerations is shown in Scheme 1, which leads to the numbering system adopted for **2**.[26]



Scheme 1. Possible biogenetic pathway to **2**.

Based also on this presumed origin, as well as the *trans*-quinolizidine configuration required by the Wenkert–Bohlmann bands,[21,22] the relative configuration of arboricinine is as shown in structure **2**, in which the configuration of C(21) {cf. C(3) in **1**}, C(15), and *N*(4) are inverted compared to those in arboricine (**1**). The relative stereochemistries of H(21) and H(15) were determined to be α and β, respectively (thus ruling out the alternative stereoisomer **4**), based on the observed NOEs between H(21)/H(17) and H(21)/*N*H. Although from a biogenetic viewpoint, somewhat similar processes have been proposed to link some of the monoterpenoid indole alkaloid classes (e.g., stemmadenine/preakuammicine to condylocarpine),[27,28] this is to the best of our knowledge, the first instance where such a regioisomeric relationship, arising from a rotated ring D, has been found in a pair of alkaloids of the same structure class and from the same plant.

Both **1** and **2** showed no appreciable cytotoxicity against drug-sensitive and vincristine-resistant KB cells as well as Jurkat cells (IC_{50} >25 μg/ml in all cases), but showed a moderate ability to reverse multidrug resistance in vincristine-resistant KB (VJ300) cells (IC_{50} 10.8 and 9.2 μg/ml for **1** and **2**, respectively, in the presence of 0.1 μg/ml of vincristine).

Acknowledgments

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