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Biomimetic oxidative transformations of pericine: partial synthesis of apparicine and valparicine, a new pentacyclic indole alkaloid from *Kopsia*

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Abstract—A new pentacyclic indole alkaloid of the pericine-type, valparicine, representing the first member of this sub-group, was obtained from a Malayan *Kopsia* species and the structure was established by spectroscopic analysis. A partial synthesis of valparicine and apparicine from pericine was carried out via the Potier–Polonovski reaction and the biogenetic implications are discussed.

In the course of our continuing studies of the genus *Kopsia*,[1–8] we obtained small amounts of a new alkaloid, valparicine **1**, from the stem–bark extract of *K. arborea*. The alkaloid was obtained following repeated chromatographic fractionation, as a colourless oil with $[\alpha]_D$ −40 (*c* 0.22, $CHCl_3$). The UV spectrum (EtOH) showed absorptions at 228 and 297 nm indicating the presence of an unsubstituted indolenine chromophore, which was also supported by the presence of the characteristic imine resonance at δ 186 in the ^{13}C NMR spectrum. The EIMS of **1** showed a molecular ion at *m/z* 276, which analyzed for $C_{19}H_{20}N_2$, differing from pericine **2**, another alkaloid also present, by loss of two hydrogens.[9] The ^{13}C NMR spectrum (Table 1) gave a total of 19 carbon resonances (one methyl, five methylenes, seven methines and six quaternary carbons) in agreement with the molecular formula. In addition to the six carbon resonances readily attributable to the aromatic moiety, and the imine resonance at δ 186.4, two other downfield quaternary resonances were observed at δ 139.2 and 144.6. The former was associated with an ethylidene side chain, as shown by the characteristic H signals at δ 5.52 (qd) and 1.78 (d). The other was associated with an exocyclic double bond, from the two broad singlets observed at δ 5.39 and 6.02, due to the hydrogens of the geminal C(22) (δ_C 116.4). The remaining quaternary carbon resonance at δ 65.1 was attributed to the indole C(7), which was supported by the observed three-bond correlations from H(9) to C(7) and from H(6) to C(2), C(8) in the HMBC spectrum.

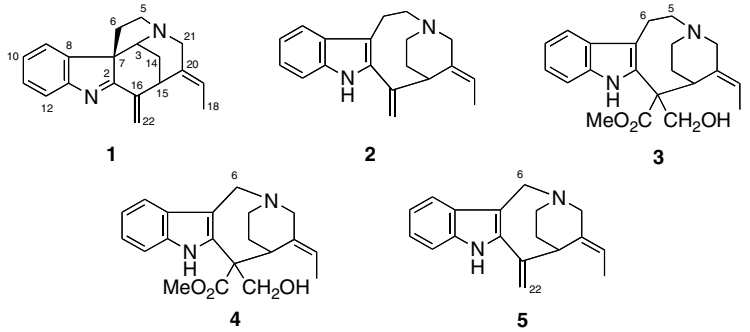

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Table 1. ^{1}H and ^{13}C NMR spectral data of **1**[a]

Position	δ_C	δ_H	Position	δ_C	δ_H
2	186.4	—	13	154.2	—
3	65.1	4.10 s	14	27.0	2.01 dt (14.2, 3.2)
5	56.5	3.23 ddd (11, 6.5, 4.1)			1.38 dt (14.2, 2.7)
		3.36 ddd (11, 9.2, 6.1)	15	37.3	3.85 s
6	36.7	1.97 ddd (12.9, 6.1, 4.1)	16	144.6	—
		2.42 ddd (12.9, 9.2, 6.5)	18	13.7	1.78 d (7)
7	65.1	—	19	119.8	5.52 qd (7, 1.3)
8	144.5	—	20	139.2	—
9	121.0	7.37 d (7.5)	21	54.5	3.77 dt (15.0, 1.6)
10	125.8	7.22 td (7.5, 1.0)			3.29 d (15.0)
11	127.9	7.34 td (7.6, 1.3)	22	116.4	5.39 s
12	120.7	7.61 d (7.6)			6.02 s

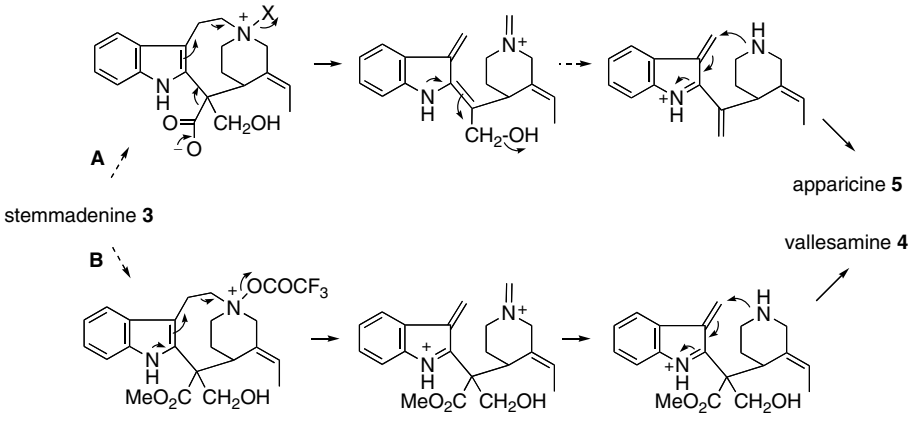
[a] $CDCl_3$, ^{1}H (400 MHz), ^{13}C (100 MHz); assignments based on COSY, HMQC and HMBC.

Examination of the NMR spectral data revealed a similarity with the stemmadenine-type alkaloid, pericine **2**, also present in the same plant, and first isolated in 1982 from *Picralima nitida* cell suspension cultures[10] and subsequently (2002) from *Aspidosperma subincanum* under the name, subincanadine E.[11] The major departure noted from the NMR data of **1** was the formation of a bond between C(3) to the indole C(7), and the change from an indole to an indolenine chromophore. The structure was entirely consistent with the 2-D NMR data. Valparicine **1** is a new alkaloid and represents the first member of the pericine-type alkaloids, characterized by a 16–22 exocyclic double bond, in which bond-formation has occurred between C(3) and C(7).

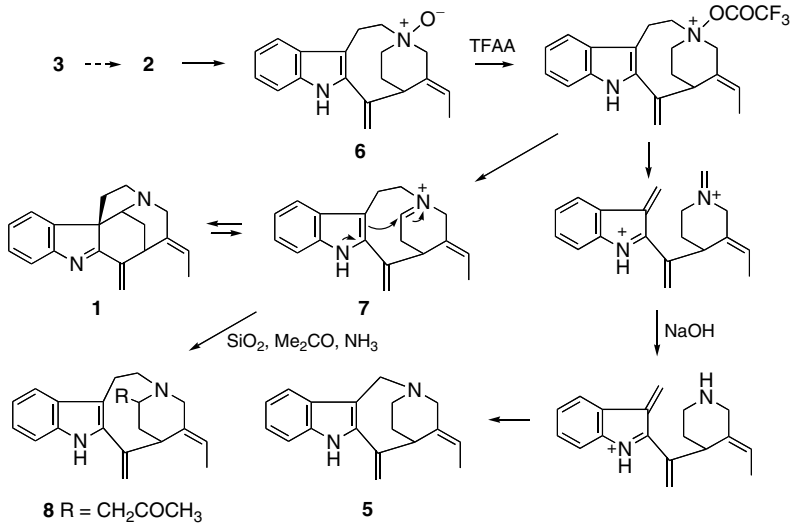
The biogenetic relationship between stemmadenine **3** and the 5-*nor*-indole derivatives, vallesamine **4** and apparicine **5** was first suggested by Kutney, who showed that the one-carbon bridge in apparicine was C(6), following excision of C(5) from the original two-carbon tryptamine bridge.[12,13] An attractive pathway from stemmadenine to apparicine was put forward by Potier and co-workers (Scheme 1, A), based on a route featuring the Potier–Polonovski fragmentation of the indole alkaloid *N*-oxide precursor.[14] A subsequent demonstration of the stemmadenine **3** to vallesamine **4** transformation by Scott et al. (Scheme 1, B) provided strong support for the Potier proposal, requiring, however a modification that the decarboxylation or deformylation step need not be synchronous with fragmentation to the iminium ion, although the earlier observation by Kutney of the incorporation of secodine into apparicine remains problematic.[15]

It occurred to us that pericine **2**, which was obtained as one of the major alkaloids in this study, might be a possible precursor to apparicine **5**, based on the Potier model for C-ring contraction (Scheme 2).

With sufficient amounts of the requisite precursor **2** to hand from the present study, it remained to obtain experimental support for this proposal. Thus pericine-*N*-oxide **6**, on treatment with trifluoroacetic anhydride in CH_2Cl_2 at −10 °C for 30 min, followed by hydrolysis (NaOH) gave two major products in relatively low yields, which were identified as apparicine (**5**, 5%) and valparicine (**1**, 4%). The structures of the two products were confirmed by comparison of their spectral data, $[\alpha]_D$ and TLC with those of authentic materials. In an attempt to optimize the yields, the various reaction parameters were varied, and after much experimentation, it was found that the overall yields could be raised to about 36% (**5**, 26%; **1**, 10%) by carrying out the reaction at 10 °C, with 4 equiv excess of TFAA added dropwise and at high dilution (100 ml CH_2Cl_2), for 10 min.



Scheme 1.



Scheme 2.

The formation of valparicine **1** is via the alternative cleavage of the *N*-oxide to the iminium ion **7**. This iminium ion is in equilibrium with valparicine **1** in protic media and can be trapped by $NaBH_4$.[16] Indeed when valparicine **1** was dissolved in MeOH and $NaBH_4$ was added, pericine **2** was the sole product isolated. The iminium ion **7** could also be trapped as the 3-acetonyl derivative **8**, on exposure of **1** to SiO_2 and acetone, in the presence of a trace quantity of concentrated ammonia.

The above partial synthesis of apparicine **5** via the Potier–Polonovski reaction has shown that pericine **2** can be considered as a viable intermediate in the biogenetic pathway to apparicine, deriving from stemmadenine **3** following deformylation or decarboxylation, and preceding one-carbon extrusion (Scheme 2). Such an alternative would be consistent with both the Kutney (one-carbon extrusion preceding decarboxylation unlikely)[13] and Scott (one-carbon extrusion and deformylation/decarboxylation steps not necessarily synchronous)[15] results. In addition it has also been shown that the new indole valparicine **1** is in all probability biogenetically related to pericine **2**. It is, however, somewhat puzzling that apparicine **5** was not detected among the many alkaloids obtained from this plant, although both **2** and **5** have been previously found in *A. subincanum*.[11]

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