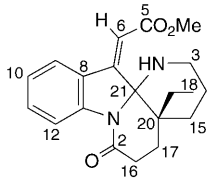
Secoleuconoxine and Oxopericine Derivatives from *Kopsia*

by **Kuan-Hon Lim** and **Toh-Seok Kam***

Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia
(phone: +603-79674266; fax: +603-79674193; e-mail: tskam@um.edu.my)

Two new indole alkaloids, *viz.*, arboloscine (**1**), the first example of a secoleuconoxine, and pericidine (**5**), an oxidized derivative of pericine (**6**), were obtained as minor alkaloids from the stem-bark extract of the Malayan *Kopsia* species, *K. arborea.* Their structures were established by spectroscopic analysis.

Introduction. – The genus *Kopsia* [1] is rich in indole alkaloids, and the Malaysian representatives in particular have proven to be rich sources of novel indoles with unusual or intriguing C-skeletons and interesting biological activity [2–17]. In continuation of our studies on the Malaysian members of this genus [2–15], we would like to report the structures of a secoleuconoxine derivative, arboloscine (**1**), as well as of pericidine (**5**), a new oxidized derivative of pericine (**6**), isolated from *K. arborea* BLUME [1].



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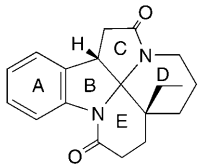

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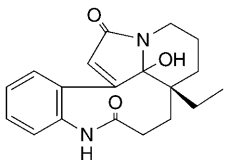

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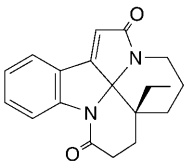

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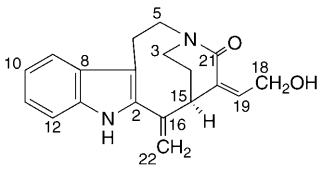

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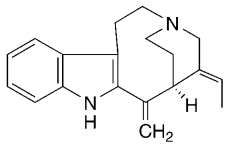

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Results and Discussion. – Arboloscine (**1**) was obtained from the stem-bark extract of *K. arborea* as a colorless, optically active oil. Its UV, IR, ^{1}H- and ^{13}C-NMR (*Table*), and MS data and their comparsion with those of similar known indole derivatives estab-

[1]) Trivial atom numbering; for systematic names, see the *Exper. Part.*

lished the structure of **1**. Arboloscine (**1**) represents the first example of a secoleuconoxine (see leuconoxine (**2**)). A possible origin is from a leuconolam (or epileuconolam) precursor **3** which on transannular cyclization leads to a didehydroleuconoxine derivative **4**. Hydrolytic cleavage of this followed by methylation furnishes **1**.

Table. *^{1}H- and ^{13}C-NMR Data for Compounds* **1** *and* **5** (400 MHz, $CDCl_3$)[a]). δ in ppm, J in Hz.

	1[1])			**5**[1])	
	δ(H)	δ(C)		δ(H)	δ(C)
C(2)	–	169.6	C(2)	–	135.7
CH_2(3)	2.78–2.81 (*m*), 3.21 (*td*, *J* = 12.6, 3.3)	40.3	CH_2(3)	2.97 (*ddd*, *J* = 13.2, 9.6, 6.4), 3.34 (*ddd*, *J* = 13.2, 9.2, 4.1)	44.9
C(5)	–	168.9	CH_2(5)	2.77 (*ddd*, *J* = 12.7, 7.9, 3.8), 4.38 (*ddd*, *J* = 12.7, 6.0, 4.4)	49.4
H–C(6)	6.51 (*s*)	110.4	CH_2(6)	2.84 (*ddd*, *J* = 14.4, 6.3, 3.8), 3.05 (*ddd*, *J* = 14.4, 7.9, 4.4)	21.5
C(7)	–	140.8	C(7)	–	110.5
C(8)	–	127.1	C(8)	–	127.8
H–C(9)	7.43 (*dd*, *J* = 7.6, 1)	120.4	H–C(9)	7.54 (*d*, *J* = 7.7)	118.3
H–C(10)	7.09 (*td*, *J* = 7.6, 1)	124.0	H–C(10)	7.11 (*td*, *J* = 7.1, 1.2)	119.8
H–C(11)	7.33 (*ddd*, *J* = 8.2, 7.6, 1)	130.9	H–C(11)	7.17 (*td*, *J* = 7.1, 1.2)	122.3
H–C(12)	8.35 (*d*, *J* = 8.2)	118.3	H–C(12)	7.29 (*d*, *J* = 7.8)	110.9
C(13)	–	142.5	C(13)	–	135.2
CH_2(14)	1.60–1.62 (*m*), 1.81–1.89 (*m*)	26.4	CH_2(14)	1.88–1.96 (*m*), 2.15 (br. *t*, *J* = 11.4)	28.5
CH_2(15)	2.49 (*dd*, *J* = 16.9, 9.9), 2.73–2.78 (*m*)	29.9	H–C(15)	3.62–3.65 (*m*)	47.0
CH_2(16)	1.42–1.44 (*m*), 1.62–1.65 (*m*)	30.3	C(16)	–	142.9
CH_2(17)	1.56 (*ddd*, *J* = 13, 7, 3), 2.68 (*ddd*, *J* = 13, 7, 1)	25.4		–	
Me(18)	0.82 (*t*, *J* = 7.5)	6.95	CH_2(18)	4.10 (*dd*, *J* = 14.3, 5.8), 4.27 (*dd*, *J* = 14.3, 6.5)	59.4
CH_2(19)	1.45–1.51 (*m*), 1.66–1.74 (*m*)	20.1	H–C(19)	6.09 (*dd*, *J* = 5.8, 6.5)	135.3
C(20)	–	36.8	C(20)	–	139.1
C(21)	–	88.1	C(21)	–	169.8
			CH_2(22)	5.40 (*t*, *J* = 1.5), 5.58 (*t*, *J* = 1.5)	122.7
			NH	8.12 (br. *s*)	

[a]) Assignments based on COSY and HMQC.

The UV spectrum of **1** showed absorption maxima at 210, 247, 265, and 321 nm (log ε 3.83, 4.14, 3.99, and 3.38, resp.), which resembles that of an *N*-acyldihydro-1*H*-indole such as leuconoxine (**2**) [18], but with additional bands due possibly to extended conjugation to an α,β-unsaturated ester function (*vide infra*). The IR spectrum showed bands at 3312, 1726, and 1662 cm^{-1} due to NH, ester, and lactam functions, respectively. The ^{13}C-NMR resonances observed at δ 168.9 and 169.6 confirmed the presence of the ester and lactam functionalities, respectively. The EI-MS of **1** showed a molecular ion at *m*/*z* 340 (23% rel. intensity), with other fragments observed at *m*/*z* 325 (9%) and 284 (62%), due to loss of Me and C_3H_4O, respectively, while the base peak was observed at *m*/*z* 56 due to $C_3H_4O^{+\cdot}$. With softer ionization

(LSI-MS), the $[M+H]^+$ ion was observed as the base peak at m/z 341, and HR-LSI-MS yielded the formula $C_{20}H_{24}N_2O_3$. The ^{13}C-NMR spectrum (*Table*) gave a total of 20 separate C-resonances (2 Me, 6 CH_2, 5 CH, and 7 quaternary C-atoms), in agreement with the molecular formula. After accounting for the six aromatic resonances and the ester and lactam carbonyl resonances noted previously, two olefinic signals due to a trisubstituted C=C bond were seen at δ 140.8 and 110.4, the downfield shift of the former signal being characteristic of the C(β) of an α,β-unsaturated carbonyl function. The ^{1}H-NMR spectrum of **1** (*Table*) showed the presence of an unsubstituted indole chromophore, an ethyl side chain, a methyl ester group (δ 3.83), and an isolated olefinic H-atom (δ 6.51). The ^{1}H-NMR spectrum is somewhat similar to that of the diazaspirocyclic alkaloid leuconoxine (**2**), with the characteristically deshielded H–C(12) due to anisotropy by the proximate C=O group [18]. The affinity with **2** is further reinforced by the presence of the characteristic quaternary C-atom resonance at δ 88.1 corresponding to the spirocyclic C(21). There are, however, several notable differences in the NMR data of **1** and **2**. Firstly, an MeO signal associated with a methyl ester function is present at δ 3.83, which is absent in the spectrum of **2**. Likewise the olefinic signal at δ 6.51 present in the spectrum of **1** is also absent in that of **2**. On the other hand, the signals of CH_2(6) as well as the characteristc *d* due to the adjacent H–C(7) of **2** are not seen in the spectrum of **1**. Analysis of the COSY and HMQC data revealed the presence of some fragments of **1** which are also present in **2**, such as the $NCH_2CH_2CH_2$ and CH_2CH_2 moieties, corresponding to the C(3)–C(14)–C(15) and C(16)–C(17) units, respectively. Conspicuously absent in **1** is the $CHCH_2$ fragment corresponding to the C(7)–C(6) unit of **2**. Since the lactam moiety associated with the indole N-atom remains intact from the HMBC data, as are the fragments associated with rings B, D, and E of **2**, the ester group in **1** must be in some way associated with an altered ring C. Furthermore, since the degree of unsaturation for both compounds are the same (DBE, 10), but an additional C=C bond is present in **1** compared to **2**, the loss of one ring is indicated. Further clues to the structure of **1** are provided by the heteronuclear correlations from the HMBC spectrum (*Fig.*) which indicated cleavage of the N(4)–C(5) bond, resulting in a secoleuconoxine as shown in **1**. The observed correlation from H–C(9) to the quaternary olefinic C-atom at δ 140.8 indicated that this C-atom corresponds to C(7). The two-bond correlation from the olefinic H-atom to C(7) and the three-bond correlations to C(8) and the spirocyclic C(21) are consistent with the branching of the exocyclic C=C bond of the acrylic ester moiety from C(7). Finally, the NOE observed between the aromatic H–C(9) and the olefinic H–C(6) not only provides additional confirmation for the structure assignment, but also reveals the geometry of the C=C bond as (*Z*) (*Fig.*).

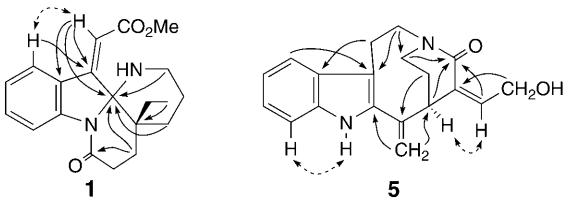

Figure. *Selected HMBC and NOEs of* **1** *and* **5** (→ = HMBC; ↔ = NOE)

Pericidine (**5**) was also obtained from the stem-bark extract of *K. arborea* as a colorless, optically active oil. Its structure was established similarly to **1**, including comparison with the known alkaloids apparicine and pericine (**6**) [19][20].The stemmadenine-type alkaloid pericine (**6**) was first isolated in 1982 from *Picralima nitida* cell suspension cultures [19] and subsequently (2002) from *Aspidosperma subincanum*, under the name subincanadine E [20], from which an oxidized derivative, pericin-15-ol (subincanadine D), was also obtained. Pericidine (**5**) represents the third member belonging to this small group of tetracyclic indoles characterized by the presence of the exocyclic C(16)=C(22) bond.

The UV spectrum of **5** showed typical indole absorptions at 223 and 283 nm (log ε 4.40 and 3.76, resp.), while the IR spectrum showed bands at 3387, 3275, and 1615 cm^{-1} due to NH, OH, and lactam functions, respectively. The EI-MS of **5** showed a molecular-ion peak at *m*/*z* 308, with other fragments at *m*/*z* 290 and 277 (base peak), due to the loss of H_2O and CH_2OH, respectively. High-resolution MS yielded the formula $C_{19}H_{20}N_2O_2$. In agreement with this, the ^{13}C-NMR spectrum (*Table*) showed a total of 19 C-resonances (6 CH_2, 6 CH, and 7 quaternary C-atoms). The observation of a quartenary resonance at δ 169.8 and an oxymethylene at δ 59.4 confirms the presence of lactam and primary alcohol functions. The ^{1}H-NMR spectrum of **5** (*Table*) showed, in addition to the resonances due to NH (δ 8.12) and four aromatic H-atoms of an unsubstituted indole chromophore, a characteristic pair of 1-H *t* at δ 5.40 and 5.58 (J = 1.5 Hz), due to the geminal H-atoms of an exocyclic C=C bond, reminiscent of that in apparicine and pericine (**6**) [19][20] (in apparicine, 2 *s* are seen at δ 5.26 and 5.39 for CH_2(22), while in pericine, 2 *s* are at δ 5.35 and 5.36; in **5**, however, geminal coupling as well as allylic coupling to H–C(15) results in 2 *t*). The ^{1}H-NMR spectrum of **5** was in fact similar to that of pericine (**6**) which was also present, but with some differences. The most prominent is due to replacement of the ethylidene side chain by a hydroxyethylidene moiety. Thus in **5**, the Me(18) *t* of **6** is replaced by signals due to the geminal H-atoms of an oxymethylene at δ 4.10 and 4.27 (δ(C) 59.4), while the olefinic H–C(19) in **5** is now a *dd* at δ 6.09, as compared to a *q* at δ 5.62 in pericine (**6**). Another difference between **5** and **6** is the absence of signals due to CH_2(21) in **5**, suggesting that C(21) is the site of oxygenation. This is supported by the downfield shift of one of the H–C(5) of **5** to δ 4.38 (the other H–C(5) appears at δ 2.77), due to anisotropy by the C(21) lactam C=O; in pericine (**6**), both H–C(5) signals are at δ *ca.* 3.2. These observations suggest oxygenation at C(21) and C(18) in the structure of **5** which are in complete accord with the 2D-NMR data (*Fig.*). Thus the three-bond correlations from H–C(19), CH_2(3), and H–C(15) to the lactam C=O in the HMBC experiment are consistent with the placement of the lactam C=O at C(21). The geometry of the C(19)=C(20) bond is deduced to be (*Z*) from the observed NOE between the olefinic H–C(19) and H–C(15) (*Fig.*).

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Experimental Part

General. CC = Column chromatography. Optical rotations: *Jasco DIP-370* digital polarimeter. UV Spectra: *Shimadzu UV-3101PC* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Perkin-Elmer 1600* FT-IR spectrophotometer in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Jeol JNM-LA-400* spectrometer at 400 and 100 MHz, resp.; $CDCl_3$ solns. with $SiMe_4$ as internal standard; δ in ppm, J in Hz. ESI-MS: *Perkin-Elmer API-100* instrument. Other MS measurements were carried out by Dr. *Noel Davies* at OIC Organic Mass Spectrometry, University of Tasmania, Tasmania, Australia.

Plant Material. Plant material was collected in Petaling Jaya, Malaysia, and was identified by Dr. *David Middleton*, Herbarium, Royal Botanic Garden, Edinburgh, 20A Inverleith Row, EH3 5LR Scotland. Herbarium voucher specimens (K 668) are deposited at the Herbarium, University of Malaya, Kuala Lumpur, Malaysia, and at Edinburgh.

Extraction and Isolation. Extraction of the ground stem-bark material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as described in detail elsewhere [21]. The alkaloids were isolated by initial CC (silica gel, $CHCl_3$ with increasing proportions of MeOH), followed by rechromatography of appropriate partially resolved fractions by using CC or centrifugal TLC. Initial CC of the basic fraction from the stem-bark provided essentially three fractions. Arboloscine (**1**; 1.04 mg kg^{-1}) was obtained from *Fr. 1*, after successive CC (SiO_2, MeOH/$CHCl_3$; 30% hexane/AcOEt, 0.5% NH_3), followed by centrifugal TLC (SiO_2, 30% hexane/AcOEt, NH_3-saturated). Pericidine (**5**; 1.61 mg kg^{-1}) was obtained from *Fr. 2* following CC (SiO_2, MeOH/$CHCl_3$) and centrifugal TLC (SiO_2; 30% hexane/AcOEt, NH_3-saturated).

Arboloscine (=*Methyl (2Z)-[(4a*R*)-4a-Ethyl-1,2,3,4,4a,5,6,7-octahydro-7-oxo-13*H*-indolo[1,2-*i*][1,8]naphthyridin-13-ylidene]acetate*; **1**): Colorless oil. $[\alpha]_D = +137$ ($c = 0.15$, $CHCl_3$). UV (EtOH): 210 (3.83), 247 (4.14), 265 (3.99), 321 (3.38). IR (dry film): 3312, 1726, 1662. ^{1}H and ^{13}C-NMR; *Table*. EI-MS: 340 (23, M^+), 325 (9, $[M-CH_3]^+$), 279 (21), 284 (62, $[M-C_3H_4O]^+$), 252 (26), 224 (55), 196 (21), 178 (24), 56 (100, $[C_3H_4O]^+$). LSI-MS: 341 (100, $[M+H]^+$), 309 (23), 273 (30), 235 (19), 219 (16), 195 (13). HR-LSI-MS: 341.1862 ($[M+1]^+$, $C_{20}H_{25}N_2O_3^+$; calc. 341.1865).

Pericidine (=*(5Z,6*R*)-1,6,7,8-Tetrahydro-5-(hydroxyethylidene)-7-methylene-2*H*-3,6-ethanoazonino[5,4-*b*]indol-4(5*H*)-one*; **5**): Colorless oil. $[\alpha]_D = +85$ ($c = 0.12$, $CHCl_3$). UV (EtOH): 223 (4.40), 283 (3.76). IR (dry film): 3387, 3275, 1615. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 308 (78, M^+), 290 (42, $[M-H_2O]^+$), 277 (100, $[M-CH_2OH]^+$), 262 (22), 250 (62), 234 (39), 220 (37), 206 (31), 194 (34), 180 (29), 168 (36), 154 (26), 40 (14). HR-EI-MS: 308.1521 ($C_{19}H_{20}N_2O_2^+$; calc. 308.1525).

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