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THREE ASPIDOFRACTININE-TYPE ALKALOIDS FROM *KOPSIA TEOI*

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Key Word Index—*Kopsia teoi*; Apocynaceae; stem-bark; aspidofractinine-type indole alkaloids.

Abstract—Novel alkaloids of the aspidofractinine-type, viz. kopsinol, kopsinginol and kopsinganol, were isolated in trace amounts from an ethanol extract of the stem-bark of *Kopsia teoi*.

INTRODUCTION

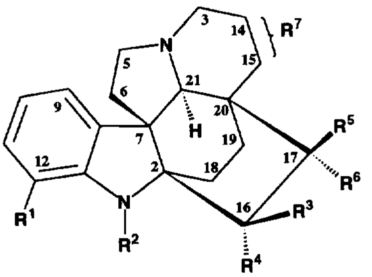
We have previously reported the presence of new aspidofractinine-type alkaloids from the stem-bark extract of *Kopsia teoi* L. Allorge [1, 2], one of about 17 species that occur in Malaysia [3, 4]. We have also reported the presence, in trace amounts, of novel indoles possessing new skeletal systems from examination of the leaf extracts [2, 5, 6]. We, now wish to report the full alkaloidal composition of the stem-bark extract, including further isolation of new alkaloids [2].

RESULTS AND DISCUSSION

The ethanol extract of the stem-bark furnished, in addition to kopsingine (**1**), kopsaporine (**2**), rhazinilam (**9**), rhazimol (**10**), akuammiline (**11**), kopsinginine (**3**), and 17-α-hydroxy-$\Delta^{14,15}$-kopsinine (**4**) [1, 2], several new alkaloids including kopsinol (**5**), kopsinginol (**6**) and kopsinganol (**7**) [2]. Compound **1** was by far the predominant alkaloid occurring in both the stem as well as the leaf extract and its structure has been recently confirmed by X-ray analysis [1]. Compound **5** is readily shown to be the N_1-decarbomethoxy derivative of **2** [1, 2] from its ^{1}H and ^{13}C NMR spectra (Table 1), which were similar to those of **2**, except for the absence of signals due to the urethane function. As in **1** and **2**, the stereochemistry of the 17-OH is deduced to be β from the W-coupling observed between H-17α and H-21 [1, 2].

Compound **6** shows a $[M]^+$ at *m/z* 294 consistent with the formula $C_{19}H_{22}N_2O$. The ^{1}H and ^{13}C NMR spectral data indicate a 17-hydroxylated aspidofractinine derivative resembling **4** [1, 2], except that the COOMe group at C-16 is now absent. This is supported by the observation of C-16 in the ^{13}C NMR spectrum, which is now a methylene shifted to higher field (δ_C 39.5). The corresponding H-16 signals appear at δ 2.30 (*dd*, $J = 14$ and 9 Hz, H-16α) and 2.41 (*ddd*, $J = 14$, 4 and 2 Hz, H-16β). The assignment is further confirmed by the observation of W-coupling between H-16β and H-18α (2 Hz). However, unlike **4**, the 17-OH is now β from the W-coupling observed between H-17α and H-21 (2 Hz).

Compound **7**, shows a $[M]^+$ at *m/z* 474 consistent with the formula $C_{24}H_{30}N_2O_8$, i.e. differing from **1** by 18 mu. The ^{1}H and ^{13}C NMR spectral data indicate that **7** is similar to **1**, except for the 14,15-double bond which is absent, being replaced instead by a hydroxyl group in ring E. Analysis of the COSY and HETCOR spectra indicates that the OH group can be *a priori* placed on C-3 or C-15. The ^{1}H and ^{13}C NMR shifts are, however, more consistent with hydroxyl substitution at C-15. Additional confirmation of this assignment is provided by the major oxidation product of **7**, which gave ^{1}H and ^{13}C NMR spectra consistent with the structure **8** (δ_{C15} 209.0). The stereochemistry of the 15-OH is deduced to be α, since irradiation of H-21 did



1 R^1 = OMe, R^2, R^3 = CO_2Me, R^4, R^5= OH, R^6 = H, R^7 = $\Delta^{14,15}$
2 R^1, R^6, = H, R^2, R^3 = CO_2Me, R^4, R^5 = OH, R^7 = $\Delta^{14,15}$
3 R^1 = OMe, R^2, R^3 = CO_2Me, R^4 = OH, R^5, R^6, = H, R^7 = $\Delta^{14,15}$
4 R^1, R^2, R^4, R^5 = H, R^3 = CO_2Me, R^6 = OH, R^7 = $\Delta^{14,15}$
5 R^1, R^2, R^6 = H, R^3 = CO_2Me, R^4, R^5 = OH, R^7 = $\Delta^{14,15}$
6 R^1, R^2, R^3, R^4, R^6 = H, R^5 = OH, R^7 = $\Delta^{14,15}$
7 R^1 = OMe, R^2, R^3 = CO_2Me, R^4, R^5 = OH, R^6 = H, R^7 = 15–αOH
8 R^1 = OMe, R^2, R^3 = CO_2Me, R^4, R^5 = OH, R^6 = H, R^7 = 15–oxo

Table 1. ^{1}H and ^{13}C NMR spectral data for compounds **5**–**7***

	5		**6**		**7**	
Position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	70.3	—	65.1	—	75.9	—
3a	50.2	3.17 *dt* (15.6,2)	51.0	3.24 *br dt* (15.5, 2)	44.2	2.89 *td* (11,3)
3b	—	3.50 *ddd* (15.6, 4.5, 2)	—	3.56 *ddd* (15.5, 4.5, 2)	—	2.98 *dd* (11,6)
5a	49.0	2.62 *ddd* (12,8.5,4)	49.2	2.60 *ddd* (12,8.5, 4)	48.7	2.59 *ddd* (12,8.5, 4)
5b	—	2.92 *dd* (8.5, 6)	—	3.02 *dd* (8.5, 6)	—	2.70 *dd* (8.5, 6)
6a	40.0	1.52–1.88 m	37.1	1.42 *dd* (12, 4)	40.8	1.70 *dd* (12, 4)
6b	—	3.08–3.24 *m*	–	2.78 *td* (12, 6)	–	3.22 *td* (12, 6)
7	55.4	–	53.7	–	56.8	–
8	139.8	–	138.9	–	144.4	–
9	120.5	7.08 *dd* (7.5, 1)	120.9	7.03 *td* (7.5, 1)	111.9	6.83 *d* (8)
10	119.6	6.77 *td* (7.5, 1)	119.3	6.76 *td* (7.5, 1)	124.8	7.03 *dd* (8, 7)
11	127.0	7.05 *td* (7.5, 1)	127.2	7.04 *td* (7.5, 1)	113.0	6.82 *d* (7)
12	112.3	6.75 *dd* (7.5, 1)	111.3	6.69 *dd* (7.5, 1)	149.2	–
13	149.2	–	149.7	–	128.2	–
14a	128.8	5.98 *ddd* (10, 4.5, 2)	128.9	6.00 *ddd* (10, 4.5, 2)	33.7	1.77–1.89 *m*
14b	–	–	–	–	–	2.45–2.66 m
15	131.5	5.68 *dt* (10, 2)	132.5	5.68 *dt* (10, 2)	69.4	3.95 *m* (3.75, *dd*, 6,2 Hz)†
16a	81.6	–	39.5	2.30 *dd* (14, 9)	81.2	–
16b	–	–	–	2.41 *ddd* (14, 4, 2)	–	–
17	84.3	3.60 *dd* (6, 2)	72.6	3.78–3.89 *m*	83.1	*ca* 3.78
18a	27.6	1.52–1.88 *m*	30.8	1.12–1.32 *m*	26.9	1.29–1.47 *m*
18b	–	1.52–1.88 *m*	–	1.63–1.74 *m*	–	2.08 *br t* (12)
19a	26.8	1.22 *br t* (12)	27.6	1.12–1.32 *m*	21.2	1.29–1.47 *m*
19b	–	1.52–1.88 *m*	–	1.39–1.45 *m*	–	1.58–1.77 *m*
20	39.6	–	38.3	–	40.8	–
21	68.9	2.83 *d* (2)	69.6	2.79 *d* (2)	64.2	3.15 *d* (2)
16-OH	–	–	–	–	–	5.69 *s*
17-OH	–	8.22 *d* (6)	–	–	–	8.86 *d* (7)
Ar$O\underline{Me}$	–	–	–	–	55.9	3.83 *s*
$CO_2\underline{Me}$	51.9	3.83 *s*	–	–	51.7	3.79 *s*
$\underline{C}O_2Me$	170.5	–	–	–	171.9	–
$NCO_2\underline{Me}$	–	–	–	–	52.8	3.78 *s*
$N\underline{C}O_2Me$	–	–	–	–	155.4	–
N–H	–	3.31 *s*	–	–	–	–

*$CDCl_3$, 270 MHz; assignments based on COSY and HETCOR.
†δ in benzene-d_6.

not cause any NOE enhancement of H-15 (NOE irradiation of the H-17 signal is not feasible due to it being overlapped by the OMe signal at δ 3.78). Additional support for the proposed stereochemistry at C-15 is further provided by the observation that **7** is readily obtained by sodium borohydride reduction of kopsidine C [7, and unpublished data].

The new aspidofractinine alkaloids **5**–**7** are assumed to possess the same relative configuration as **1** at the remaining stereocentres, assuming that they share a common biogenetic origin.

EXPERIMENTAL

Plant material. Details of collection, deposition of voucher specimens, etc., have been reported earlier [1].

Extraction and isolation.. Extraction of alkaloids was carried out in the usual manner as described in detail elsewhere [1] to give a total crude alkaloid yield of *ca* 6 g kg^{-1} for the stem-bark. Alkaloids were isolated by CC, prep. TLC and centrifugal TLC on silica gel. Solvent systems used for CC were $CHCl_3$-MeOH and Et_2O-EtOAc. Solvent systems used for prep. TLC and centrifugal TLC were Et_2O, Et_2O–EtOAc (20:1) and 1% MeOH in $CHCl_3$. The yields (g kg^{-1}) of the alkaloids from the stem extract were: **1** (1.7), **2** (0.08), **3** (0.0064), **4** (0.0096), **5** (0.005), **6** (0.003), **7** (0.268), **9** (0.041), **10** (0.038) and **11** (0.011).

Kopsinol (**5**). $[\alpha]_D = +82°$ ($CHCl_3$, *c* 0.022). UV (EtOH), λ_{max} nm (log ε): 211 (4.16), 245 (3.90), 292 (3.57). EIMS (probe) 70 eV, *m/z* (rel. int.): 368 [M^+] (100), 340 (11), 309 (8), 281 (10), 280 (25), 251 (38), 232 (22), 173 (31), 158 (39), 144 (38), 130 (29), 123 (28), 107 (20). ^{1}H and ^{13}C NMR: Table 1.

Kopsinginol (**6**). $[\alpha]_D = +288°$ ($CHCl_3$, *c* 0.016). UV (EtOH), λ_{max} nm (log ε): 210 (4.09), 245 (3.77), 288 (3.44). EIMS (probe) 70 eV, *m/z* (rel. int.): 294 $[M]^+$ (58), 251 (12), 250 (9), 249 (15), 158 (100), 144 (26), 130 (14), 107 (12). ^{1}H and ^{13}C NMR: Table 1.

Kopsinganol (**7**). $[\alpha]_D = +39°$ ($CHCl_3$, *c* 1.80). UV (EtOH), λ_{max} nm (log ε): 217 (4.56), 254 (4.07), 282 (3.38), 290 (3.35). EIMS (probe) 70 eV, *m/z* (rel. int.): 474 $[M]^+$ (67), 446 (14), 429 (23), 387 (35), 371 (28), 358 (20), 339 (13), 331 (17), 311 (13), 294 (20), 273 (14), 200 (14), 167 (11), 158 (11), 154 (11), 123 (12), 112 (17). ^{1}H and ^{13}C NMR: Table 1.

Oxidation of kopsinganol (**7**) *to kopsinganone* (**8**). Compound **7** was reacted with $CrO_3.2$ pyridine (1.1 equivalent) in CH_2Cl_2 at room temp. for 10 hr. The major product **8**, was obtained following standard work-up and chromatography over silica gel (Et_2O). EIMS (probe) 70 eV, *m/z* (rel. int.): 472 $[M]^+$ (100), 456 (5), 443 (10), 413 (20), 385 (25), 384 (30), 369 (12), 355 (35), 329 (20), 327 (20), 297 (15). $[\alpha]_D =$ +71° ($CHCl_3$, *c* 0.048). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.21–1.40 (*m*, H-18, H-19), 1.82 (*dd*, $J = 13$, 4 Hz H-6), 1.93–2.08 (*m*, H-19), 2.08–2.16 (*m*, H-18), 2.59–2.66 (*m*, 2 × H-14), 2.73–2.93 (*m*, H-5), 2.96–3.05 (*m*, H-5), 3.10 (*d*, $J = 2$ Hz, H-21), 3.26–3.42 (*m*, 2 × H-3, H-6), 3.78 (*s*, $NCO_2\underline{Me}$, $CO_2\underline{Me}$), 3.82 (*s*, 12-O$\underline{Me}$), 3.98 (*br*, *d*, $J = 5.4$ Hz, H-17), 5.73 (*s*, 16-OH), 6.78 (*d*, $J = 7$ Hz, H-11), 7.04 (*dd*, $J = 8$, 7 Hz, H-10), 6.84 (*d*, $J = 8$ Hz, H-9), 8.26 (*d*, $J = 7$ Hz, 17-OH). ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ 22.0 (C-19), 26.6 (C-18), 41.1 (C-6, C-14), 46.5 (C-3), 49.2 (C-5), 51.4 (C-20), 52.0 ($CO_2\underline{Me}$), 53.0 ($NCO_2\underline{Me}$), 56.1 (12-O$\underline{Me}$), 57.5 (C-7), 68.9 (C-21), 76.0 (C-2), 80.6 (C-16), 82.4 (17-OH), 112.3 (C-9), 113.0 (C-11), 125.1 (C-10), 128.4 (C-13), 143.6 (C-8), 149.5 (C-12), 155.4 ($N\underline{C}O_2Me$), 171.6 ($\underline{C}O_2Me$), 209.0 (C-15).

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