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Alkaloids from *Kopsia dasyrachis*

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Abstract

A total of 32 alkaloids were obtained from the stem extract of *Kopsia dasyrachis*, of which ten are new, viz., kopsiflorine *N*(4)-oxide, 11-methoxykopsilongine *N*(4)-oxide, kopsifine, decarbomethoxykopsifine, kopsinarine, 11,12-methylenedioxykopsine, dasyrachine, rhazinicine, (+)-19(*R*)-hydroxyeburnamine and (−)-19(*R*)-hydroxyisoeburnamine.

Keywords: Kopsia dasyrachis; Apocynaceae; Stem; Indole alkaloids

1. Introduction

Kopsia dasyrachis Ridl. is one of ca. 17 *Kopsia* species that are found in Malaysia and it occurs in Sabah, Malaysian Borneo (Markgraf, 1972). Plants of this genus have yielded many new alkaloids which possess intriguing carbon skeletons, as well as interesting bioactivities (Awang, Sevenet, Hadi, David, & Pais, 1992; Kam, Yoganathan, & Chuah, 1994; Kam, Yoganathan, & Chuah, 1995; Kam, Yoganathan, Koyano, & Komiyama, 1996c; Kam, Yoganathan, & Li, 1996d). A previous study of the leaf alkaloids of *K. dasyrachis* from Borneo yielded three new indoles, viz., kopsidasine, kopsidasine *N*-oxide and kopsidasinine (Homberger & Hesse, 1982), and, in addition, kopsirachine, which is constituted from the union of catechin and two units of skytanthine (Homberger & Hesse, 1984). We have now carried out a detailed chemical study of the stem of this species and wish to report the full alkaloidal composition, including the isolation of 10 new alkaloids (Kam & Subramaniam, 1998).

2. Results and discussion

Extraction of alkaloids from the stem in the usual manner (Kam & Tan, 1990) furnished a basic fraction, which on extensive chromatography, yielded a total of 32 alkaloids, as well as the lignan, syringaresinol. The alkaloids were kopsiflorine (**1**) (Crow & Michael, 1962; Gilbert, 1965), kopsilongine (**2**) (Crow & Michael, 1962; Gilbert, 1965; Feng, Kan, Potier, Kan, & Lounasmaa, 1983; Zheng, Zhou, & Huang, 1989; Kam & Sim, 1998), kopsamine (**3**) (Crow & Michael, 1962; Gilbert, 1965; Feng et al., 1983; Zheng et al., 1989; Kam & Sim, 1998), kopsamine *N*(4)-oxide (**4**) (Zheng et al., 1989; Kam & Sim, 1998), 11-methoxykopsilongine (**5**) (Feng et al., 1983; Zheng et al., 1989; Kam & Sim, 1998), kopsinine (**6**) (Feng et al., 1983), kopsinine *N*(4)-oxide (**7**) (Thomas, Achenbach, & Biemann, 1966), pleiocarpine (**8**) (Homberger & Hesse, 1982), 12-methoxypleiocarpine (**9**) (Kam & Sim, 1998), 11,12-methylenedioxykopsinaline (**10**) (Feng et al., 1983), tetrahydroalstonine (**11**), pleiocarpamine (**12**), 16-hydroxymethylpleiocarpamine (**13**) (Kan, Deverre, Sevenet, Quirion, & Husson, 1995), kopsine (**14**) (Battersby & Gregory, 1963; Guggisberg, Hesse, von Philipsborn, Nagarajan, & Schmid, 1966; Guggisberg, Gorman, Bycroft, & Schmid, 1969), *N*-carbomethoxy-5,22-dioxokopsane (**15**) (Achenbach & Biemann, 1965), (+)-eburnamonine (**16**) (Kam, Tan, & Chen, 1993; Kam, Arasu, & Yoganathan, 1996a), (+)-isoeburnamine (**17**) (Kam et al., 1993, 1996a), leuconoxine (**18**) (Abe & Yamauchi, 1994; Kam & Sim, 1998), paucidactine B (**19**) (Kam, Yoganathan, & Chen, 1996b), (−)-norpleiomutine (**20**), (−)-demethylnorpleiomutine (**21**), (+)-kopsoffinol (**22**) (Kan-Fan, Sevenet, Husson, & Chan, 1985), kopsiflorine *N*(4)-oxide (**23**), 11-methoxykopsilongine *N*(4)-oxide (**24**), kopsifine (**25**), decarbomethoxykopsifine (**26**), kopsinarine (**27**), 11,12-methylenedioxykopsine (**28**), dasyrachine (**29**), rhazinicine (**30**), (+)-19(*R*)-hydroxyeburnamine (**31**) and (−)-19(*R*)-hyd-

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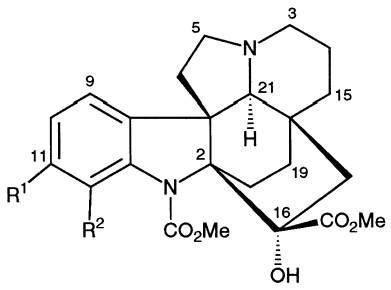
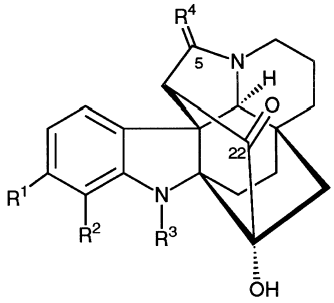
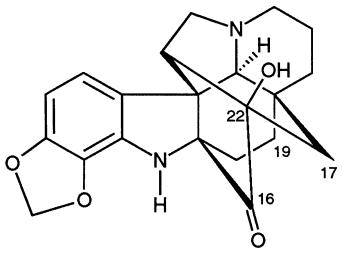


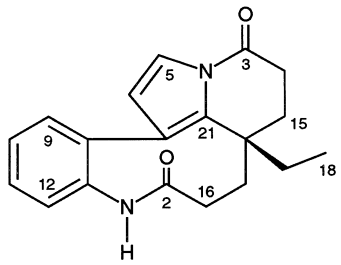


1 $R^1 = R^2 = H$,
2 $R^1 = H$, $R^2 = OMe$
3 R^1, $R^2 = OCH_2O$
4 R^1, $R^2 = OCH_2O$, $N(4)\rightarrow O$
5 $R^1 = R^2 = OMe$
23 $R^1 = R^2 = H$, $N(4)\rightarrow O$
24 $R^1 = R^2 = OMe$, $N(4)\rightarrow O$

14 $R^1 = R^2 = H$, $R^3 = CO_2Me$, $R^4 = H_2$
25 $R^1, R^2 = OCH_2O$, $R^3 = CO_2Me$, $R^4 = O$
26 R^1, $R^2 = OCH_2O$, $R^3 = H$, $R^4 = O$
27 $R^1 = R^2 = OMe$, $R^3 = CO_2Me$, $R^4 = O$
28 $R^1 = R^2 =$ OCH_2O, $R^3 = CO_2Me$, $R^4 = H_2$



29



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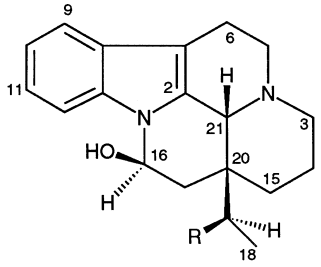
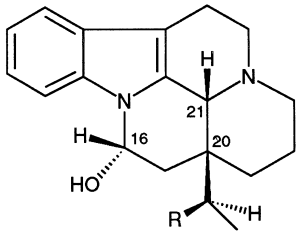


31 R = OH
33 R = H

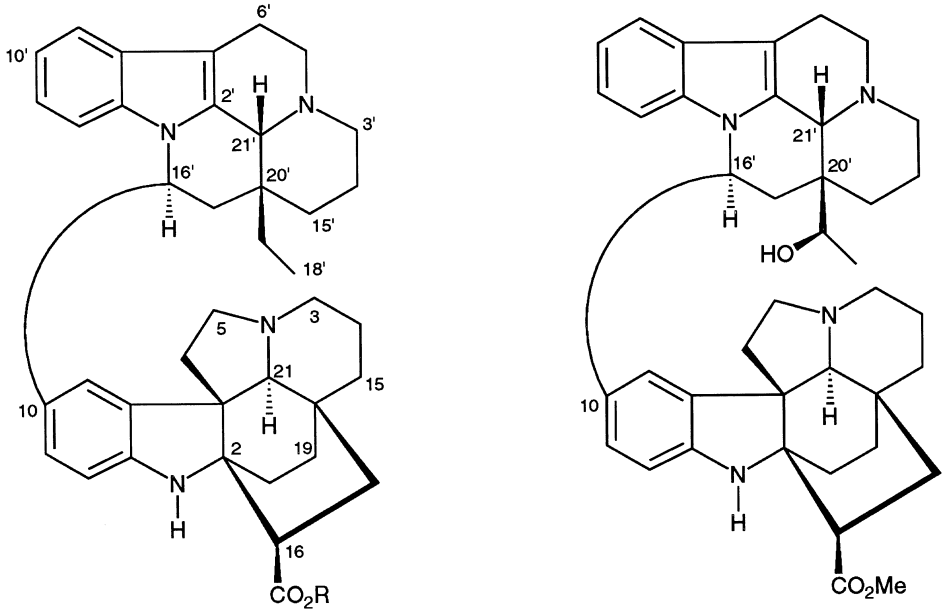


32 R = OH.
17 R = H

Structure 1.

roxy-isoeburnamine (**32**). The last 10 alkaloids (**23**–**32**) are new, while kopsamine (**3**) is the major alkaloid present in the stem. 12-Methoxypleiocarpine (**9**) and the novel hexacyclic indole, paucidactine B (**19**), were very recently reported by us from other *Kopsia* species (Kam et al., 1996b; Kam & Sim, 1998).

The aspidofractinine alkaloids, kopsiflorine, kopsilongine and kopsamine, were first reported from the Australian plant, *K. longiflora* (Crow & Michael, 1962). Although only partial structures were initially proposed in the early reports based on degradative studies, structures **1**–**3** (representing kopsiflorine, kopsilongine and kopsamine respectively) have been subsequently accepted as correct for these three alkaloids (Gilbert, 1965). Since high-field NMR spectral data are not available for kopsiflorine (**1**), the NMR data (Tables 1 and 2) are included in the present report; they are in agreement with the structure **1**. Although the *N*(4)-oxide of kopsamine has since been reported (Zheng et al., 1989), the corresponding *N*(4)-oxide of kopsiflorine (**23**) is new and



20 R = Me

21 R = H

22

Structure 2.

was readily identified based on the mass spectrum {strong $[M-16]^+$ fragment}, the characteristic downfield shift in the ^{13}C NMR spectrum for carbons 3, 5 and 21, when compared with the parent alkaloid **1** (Table 2), as well as its ready reduction to kopsiflorine (**1**). Similarly, compound **24** was readily identified as the *N*(4)-oxide of 11-methoxykopsilongine (**5**) by comparison of the mass spectrum and ^{13}C NMR spectral data with that of the parent alkaloid (**5**) (Table 2) (Feng et al., 1983).

Kopsifine (**25**), $[\alpha]_D$ +97° ($CHCl_3$, *c* 0.04), showed a $[M]^+$ at *m/z* 438 in the mass spectrum. The base peak was observed at *m/z* 410, which can be attributed to loss of CO or ethene from the $[M]^+$. HREIMS measurements (*m/z* 438.1425) gave the formula $C_{23}H_{22}N_2O_7$ (calcd 438.1427), which is also in agreement with the observation of 23 carbon resonances in the ^{13}C NMR spectrum. The UV spectrum is typical of a dihydroindole chromophore (λ_{max} 223, 250, 285 and 295 nm), while the IR spectrum showed the presence of hydroxyl (3295 cm^{-1}), five-membered ring ketone (1765 cm^{-1}) and carbamate and lactam carbonyl (1684 cm^{-1}) functions. The ^1H and ^{13}C NMR spectra (Tables 1–2) showed the presence of a methylenedioxy substituent at carbons-11 and -12 (a pair of aromatic AB doublets at δ_H 6.72 and 6.63 and another pair at δ_H 5.96, 5.94, δ_C 100.9) and the presence of a hydroxyl group was indicated by an OH resonance at δ 7.09. In addition, the presence of ketonic, carbamate and lactam carbonyl functions was confirmed by carbon resonances at δ_C 202.5, 155.3 and 164.3, respectively. Analysis of the NMR spectral data revealed an alkaloid of the kopsine-type. In addition to the ketonic carbonyl bridging carbons-6 and -16, another lactam carbonyl function is also present. This lactam carbonyl function was deduced to be at position 5, since its alternative placement at position 3 can be ruled out by the presence of the usual H(3) and C(3) resonances of kopsine-type compounds (e.g. **28**). This is also supported by the COSY spectrum which revealed the presence of a characteristic C(3)–C(14)–C(15) fragment. Similarly, position 21 can also ruled out by the presence of the H(21) resonance, which is seen as a doublet (*J* 2 Hz), as a result of W-coupling with H(17α). The location of the lactam function is therefore at position 5, which is entirely consistent with the spectral data. Firstly, H(6) is now seen as a conspicuous singlet at δ 2.91, while H(3β) has undergone a downfield shift to δ 4.22, as a result of the anisotropy exerted by the lactam carbonyl. Finally, these assignments are supported by the HMBC data which showed two-bond correlations from the H(6) singlet at δ 2.91 to C(5), C(7) and C(22), and three-bond correlations to C(8), C(16) and C(21). The H(21) signal showed, in addition to a two-bond correlation to C(7), five three-bond correlations to C(5), C(6), C(8), C(17) and C(19).

Compound **26**, $[\alpha]_D$ +52° ($CHCl_3$, *c* 0.07), was obtained in small amounts as a colourless oil. The mass spectrum showed an $[M]^+$ at *m/z* 380 which analysed for $C_{21}H_{20}N_2O_5$ (differing from kopsifine (**25**) by the substitution of NCO_2Me with H). Examination of the ^1H and ^{13}C NMR spectral data (Tables 1–2) revealed that while the ketone and lactam functions were intact, the

Table 1
^{1}H NMR data of compounds **1**, **5**, **23**–**30**[a]

H	**1**	**23**	**5**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
3	2.91 m	3.54 td (13, 5)	2.85 td (13, 3)	3.51 td (13, 5)	2.91 td (13, 4)	2.91 td (13, 4)	2.90 td (13, 4)	3.01 m	3.07 td (13, 4)	–
3	3.07 m	3.85 m	3.07 m	3.80 m	4.22 dd (13, 5)	4.23 dd (13, 5)	4.23 dd (13, 5)	3.01 m	3.19 dd (13, 5)	–
5	2.99 td (8.5, 4)	3.35 t (11)	2.94 td (8.5, 4)	3.34 t (11)	–	–	–	3.13 dd (10, 5)	3.18 d (10)	7.42 d (3)
5	3.14 td (8.5, 7)	3.85 m	3.07 m	3.80 m	–	–	–	3.51 t (10)	3.35 dd (10, 6)	–
6	1.57 ddd (14.5, 8.5, 7)	2.22 dd (15, 7.5)	1.75 m	2.41 dd (15, 7.5)	2.91 s	2.92 s	3.00 s	2.57 dd (10, 5)	2.31 d (6)	5.93 d (3)
6	2.08 ddd (14.5, 8.5, 4)	2.35 ddd (15, 11, 9)	2.16 ddd (14.5, 8.5, 4)	2.58 ddd (15, 11, 9)	–	–	–	–	–	–
9	7.31 dd (7.5, 1.5)	8.70 dd (7.5, 1.5)	6.92 d (8)	8.26 d (8)	6.72 d (8)	6.67 d (8)	6.89 d (8)	6.88 d (8)	7.04 d (8)	7.41 m
10	7.02 td (7.5, 1.5)	7.09 td (7.5, 1.5)	6.56 d (8)	6.61 d (8)	6.63 d (8)	6.35 d (8)	6.73 d (8)	6.61 d (8)	6.32 d (8)	7.41 m
11	7.15 ddd (8, 7.5, 1.5)	7.19 ddd (8, 7.5, 1.5)	–	–	–	–	–	–	–	7.37 m
12	7.50 brd (8)	7.47 brd (8)	–	–	–	–	–	–	–	7.28 d (8)
14	1.27 m	1.87 m	1.27 m	1.84 m	1.51 m	1.53 m	1.53 m	1.26 m	1.27 m	2.70 ddd (18, 4.5, 3.5)
14	1.85 m	1.87 m	1.80 m	1.84 m	1.65 m	1.63 m	1.61 m	1.79 m	2.05 qt (13, 5)	2.93 ddd (18, 13.5, 5)
15	1.31 td (14, 4)	1.46 td (14, 5)	1.24 td (14, 4)	1.43 td (14, 5)	1.46 m	1.46 m	1.43 td (14, 5)	1.34 m	1.34 td (13, 4)	1.73 ddd (13.5, 5, 3.5)
15	1.69 m	1.71 brdd (14, 1.5)	1.65 m	1.67 brdd (14, 1.5)	1.65 m	1.63 m	1.61 m	1.53 m	1.65 m	2.12 td (13.5, 4.5)
16	–	–	–	–	–	–	–	–	–	2.12 m, 2.40 m
17	1.43 brd (15)	1.47 brd (15)	1.41 brd (15)	1.46 brd (15)	1.61 brd (15)	1.50 brd (15)	1.61 brd (15)	1.58 brd (15)	0.96 d (14)	1.58 m
17	2.94 dd (15, 2)	3.05 dd (15, 3)	2.91 dd (15, 3)	2.95 dd (15, 3)	2.13 dd (15, 3)	1.99 dd (15, 3)	2.12 dd (15, 3)	2.39 dd (15, 3)	2.39 dd (14, 1.5)	2.44 m
18	1.43 m	1.52 ddd (13,11, 8)	1.48 ddd (13, 11, 8)	1.59 ddd (13, 11, 8)	1.70 m	1.75 m	1.68 m	1.68 ddd (14, 12, 5)	1.73 ddd (13, 11, 9.5)	0.74 t (7.5)
18	2.29 ddd (13, 11, 1.5)	2.42 ddd (13, 11, 1.5)	2.37 ddd (13, 11, 1.5)	2.50 ddd (13, 11, 1.5)	2.56 ddd (13.5, 12, 4.5)	2.09 td (13, 4.5)	2.52 ddd (13.5, 12, 4.5)	2.51 ddd (14, 12, 4)	1.89 ddd (13, 10, 1.5)	–
19	1.12 brt (11)	1.33 brt (11)	1.06 brt (11)	1.27 brt (11)	1.43 m	1.43 m	1.35 m	1.34 m	1.30 m	1.31 dq (14.5, 7.5)
19	1.72 m	1.94 td (11, 8)	1.67 m	1.88 td (11, 8)	1.80 td (12, 4.5)	1.73 m	1.77 m	1.56 m	1.56 m	1.47 dq (14.5, 7.5)
21	3.01 d (2)	3.69 brs	2.78 d (2)	3.52 brs	3.62 d (2)	3.66 brs	3.54 d (1.5)	3.02 d (2)	2.82 s	–
CO_2Me	3.75 s	3.78 s	3.76 s	3.80 s	–	–	–	–	–	–
NCO_2Me	3.96 s	3.99 s	3.92 s	3.93 s	3.82 s	–	3.77 s	3.81 s	–	–
OCH_2O	–	–	–	–	5.94 d (1.5) 5.96 d (1.5)	5.86 d (1.5) 5.91 d (1.5)	–	5.90 d (1.5) 5.93 d (1.5)	5.85 d (1.5) 5.89 d (1.5)	–
11-OMe			3.84 s	3.85 s	–	–	3.88 s	–	–	–
12-OMe			3.75 s	3.74 s	–	–	3.80 s	–	–	–
16-OH	7.32 s	7.73 s	6.67 s	6.94 s	7.09 brs	–	6.93 s	7.09 s	–	–
NH	–	–	–	–	–	–	–	–	4.03 brs	6.75 s

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

Table 2
^{13}C NMR data of compounds **1**, **5**, **23**–**30**[a]

C	1	23	5	24	25	26	27	28	29	30
2	74.3	73.6	74.6	74.7	74.9	71.9	76.8	75.3	70.8	176.4
3	47.4	65.5	47.5	65.8	40.7	40.8	40.7	46.4	47.2	167.9
5	50.2	65.2	50.2	65.6	164.3	164.7	164.2	53.8	46.9	116.6
6	37.0	34.3	37.4	34.0	59.0	59.6	58.3	53.5	51.9	114.6
7	57.3	58.7	57.1	58.9	52.6	53.6	53.2	59.7	58.3	121.9
8	139.7	137.0	133.7	132.8	128.6	127.1	128.8	131.8	130.5	137.1
9	122.1	126.0	116.3	121.2	115.1	115.2	116.6	115.4	117.2	130.0
10	123.9	124.6	107.3	108.0	105.2	100.5	109.7	105.1	100.4	128.9
11	127.2	128.0	153.1	153.4	149.9	148.9	154.0	149.0	148.4	127.8
12	115.3	114.6	137.8	137.0	136.1	132.6	140.9	135.7	131.1	127.5
13	140.1	139.8	135.6	133.6	123.9	132.4	134.8	123.9	127.9	137.1
14	16.9	19.4	17.9	19.6	19.3	19.5	19.4	15.3	17.1	29.0
15	35.6	33.4	35.8	33.7	32.6	33.0	32.6	33.2	36.0	31.7
16	74.4	73.6	75.7	74.0	83.1	82.3	83.1	82.2	217.3	28.2
17	41.6	40.6	41.7	41.1	39.3	37.6	38.7	44.0	39.2	33.6
18	23.6	22.5	24.7	23.8	18.8	20.1	19.8	19.6	26.4	7.9
19	32.2	32.7	32.4	33.1	31.8	32.8	32.0	32.3	34.7	29.7
20	32.2	34.1	32.0	34.2	32.8	34.7	32.6	34.9	34.4	38.2
21	67.8	84.4	68.3	85.2	65.4	65.6	65.5	69.6	66.6	133.2
22	–	–	–	–	202.5	204.6	202.3	214.0	82.4	–
CO_2Me	52.4	52.9	52.3	53.0	–	–	–	–	–	–
CO_2Me	173.0	172.9	173.2	173.1	–	–	–	–	–	–
NCO_2Me	53.3	53.5	53.3	53.5	53.8	–	54.1	53.6	–	–
NCO_2Me	156.8	157.0	157.4	158.0	155.3	–	155.9	155.6	–	–
OCH_2O	–	–	–	–	100.9	101.1	–	100.5	100.8	–
11-OMe	–	–	56.1	56.1	–	–	56.3	–	–	–
12-OMe	–	–	60.0	60.3	–	–	60.0	–	–	–

[a] 100 MHz, $CDCl_3$; assignments based on HMQC and HMBC.

resonances due to the carbamate group were absent in both the ^1H and ^{13}C NMR spectra, which in all other respects were similar to those of kopsifine (**25**). Compound **26** is therefore decarbomethoxykopsifine.

Another new oxo-kopsine derivative obtained is kopsinarine (**27**), $[\alpha]_D$ $+97^\circ$ ($CHCl_3$, *c* 0.25). The mass-spectrum showed an $[M]^+$ at *m/z* 454, which analysed for $C_{24}H_{26}N_2O_7$. The ^1H and ^{13}C NMR spectral data (Tables 1–2) are essentially similar to those of **25**, showing the presence of a lactam function at position 5, but differing from **25** in that the aromatic methylenedioxy substituent has been replaced by two methoxy groups (δ_H 3.80 and 3.88).

Compound **28**, $[\alpha]_D$ -13° ($CHCl_3$, *c* 0.18), was readily identified as 11,12-methylenedioxykopsine from its spectral data. The mass spectrum yielded a $[M]^+$ at *m/z* 424 (HRMS *m/z* 424.1635), which analysed for $C_{23}H_{24}N_2O_6$. The NMR spectral data (Tables 1–2) are similar in all respects to those of kopsine (**14**), except for the aromatic region, which indicated the presence of a methylenedioxy substituent at C(11) and C(12).

Dasyrachine (**29**), $[\alpha]_D$ $+17^\circ$ ($CHCl_3$, *c* 0.06), showed an $[M]^+$ at *m/z* 366 ($C_{21}H_{22}N_2O_4$), which was detected by both EI and API-LC mass spectrometry (MH^+ *m/z* 367). The ^{13}C NMR spectrum showed a total of 21 separate carbon resonances, in agreement with the formula derived from the $[M]^+$. The UV spectrum showed absorption maxima at 221, 243 and 281 nm, indicating a dihydroindole chromophore. The NMR spectral data (Tables 1–2) indicated the presence of a methylenedioxy substituent, the absence of carbamate or lactam functions, the presence of the characteristic H(21) of aspidofractinine-type alkaloids (δ 2.82), an oxygenated quaternary carbon (δ_C 82.4) and a ketonic function (δ_C 217.3). Application of COSY and HMQC methods revealed the presence of the same partial structures as in kopsine (**14**) and methylenedioxykopsine (**28**), viz. an isolated methylene, $CHCH_2$, CH_2CH_2 and $CH_2CH_2CH_2$ fragments. Comparison of the ^1H and ^{13}C NMR spectral data of **29** with those of 11,12-methylenedioxykopsine (**28**) (Tables 1–2), showed that although there were many similarities, some differences were noted in the chemical shifts of **29** compared with those of **28**. Of even greater significance was the observation that the HMBC data for **29** and **28** are different, suggesting a change in the structure. In methylenedioxykopsine (**28**), the ketonic C(22) showed heteronuclear correlations to H(5) and H(17), whereas, in the case of **29**, only correlations to H(17) were detected.

In **28**, the oxygenated quaternary carbon, C(16), showed correlations to H(6), H(18) and H(17), whereas in **29**, the same carbon, C(22), showed, in addition to the correlations to H(6) and H(17), a correlation to H(5), but not to H(18). These changes are consistent with an isokopsine-type carbon skeleton for dasyrachine (**29**) (Govindachari, Nagarajan, & Schmid, 1963; Guggisberg, Govindachari, Nagarajan, & Schmid, 1963). The carbonyl function is now at C(16), which is consistent with the observed three-bond correlations to both the H(17) in the HMBC spectrum and the noted absence of any correlation with H(5). The oxygenated quaternary carbon is now at C(22), which is consistent with the observed HMBC correlations with H(17) and H(6) $\{^2J\}$, as well as with H(5) $\{^3J\}$. Isokopsine has been obtained from kopsine via a thermally-induced acyloin rearrangement or by the action of dilute alkali (reflux) on kopsine or decarbomethoxykopsine, through which an equilibrium mixture of decarbomethoxykopsine and decarbomethoxy-isokopsine were obtained (Govindachari et al., 1963; Gilbert, 1965). Since kopsine, decarbomethoxykopsine and decarbomethoxy-isokopsine are known to occur in *K. fructicosa* (Guggisberg et al., 1963; Gilbert, 1965) and since the possible precursor of **29**, 11,12-methylenedioxykopsine (**28**) was isolated in this study, the possibility that **29** is an artifact formed from **28** cannot be completely discounted, although this is rendered unlikely under the mild conditions of the extraction procedure employed. This is further confirmed by the fact that attempted base-induced reaction of **28** (refuxing in 0.1 M NaOH for 8 h) resulted in the formation of the decarbomethoxylated derivative as the major product, with **29** detected only as a minor product (ratio 17:1).

Rhazinicine (**30**), $[\alpha]_D$ -208° ($CHCl_3$, *c* 0.13), showed an $[M]^+$ at *m/z* 308 in the mass spectrum. HRMS measurements yielded the formula $C_{19}H_{20}N_2O_2$. The base peak was observed at *m/z* 279, which is due to loss of an ethyl group. Other significant fragments were detected at *m/z* 251 $[M–CH_2CH_3–CO]^+$ and 223 $[M–CH_2CH_3–CH_2{=}CH_2–CO]^+$. This mass spectral fragmentation and the UV spectrum (λ_{max} 207, 229 and 275 nm), which is characteristic of rhazinilam-type compounds, indicated that **30** is a rhazinilam derivative (Goh, Ali, & Wong, 1989). The presence of a rhazinilam-type structure is further confirmed by the ^1H and ^{13}C NMR spectral data (Tables 1–2). The ^{13}C NMR spectrum indicated the presence of two lactam carbonyls, one of which (δ_C 176.4) is characteristic of C(2) of a rhazinilam derivative. The other lactam carbonyl is deduced to be at position 3, since the signals of the two pyrrole ring hydrogens, H(5) and H(6), are still observed in the ^1H NMR spectrum. Furthermore, the characteristic H(3) resonances of rhazinilam compounds are missing and the shifts due to both H(14), as well as C(14), are shifted downfield, consistent with C(14) being α to a carbonyl function. The H(6) signal was found at δ 5.93 as a doublet, with the characteristic pyrrole-H coupling of 3 Hz. The adjacent H(5) resonance was shifted downfield to δ 7.42 (cf. δ 6.51 in rhazinilam) due to the anisotropy of the C(3) carbonyl function. Based on the above observations, rhazinicine (**30**) is therefore 3-oxo-rhazinilam.

In addition to the other indole compounds, four alkaloids of the eburnane-type were also obtained. Two of these, (+)-eburnamonine (**16**) and (+)-isoeburnamine (**17**) have been previously obtained from other *Kopsia* species (Kam et al., 1993, 1996a), while the other two, **31** and **32**, are 19-hydroxy derivatives of (−)-eburnamine and (+)-isoeburnamine (**17**), respectively.

Compound **31** recrystallized from ethanol as colourless prisms, m.p. 246–248°C, $[\alpha]_D$ $+111^\circ$ ($CHCl_3$, *c* 0.09). The IR spectrum showed the presence of hydroxyl functions (3300 cm^{-1}), while the UV spectrum was typical of an indole chromophore, with absorption maxima at 201, 229, 283 and 291 nm. The EI-mass spectrum of **31** showed a $[M]^+$ at *m/z* 312 ($C_{19}H_{24}N_2O_2$), with other fragments observed at *m/z* 294 $[M–H_2O]^+$, 267 $[M–CH_3CHOH]^+$ and 249 $[M–H_2O–CH_3CHOH]^+$. The strong *m/z* 249 peak (base) is characteristic of eburnane-type alkaloids, such as eburnamine, isoeburnamine and 16-*O*-alkyleburnamine derivatives, and corresponds to successive losses of water, followed by the C(20) side-chain. The observation of the same peak in the present case afforded the first indication of the presence of a hydroxyethyl side-chain at C(20) in compound **31**. The ^1H and ^{13}C NMR spectral data (Tables 3 and 4) showed general similarity to eburnamine (**33**), except for the signals of the C(20) ethyl side-chain, which were replaced by a doublet at δ 1.24 and a quartet of doublets at δ 3.98, characteristic of a hydroxyethyl group. In addition, an oxymethine resonance was also observed at δ 78.3 in the ^{13}C spectrum corresponding to C(19) of **31**. The H(16) signal of **31** appeared as a doublet of doublets with coupling constants of 10 and 5 Hz, which are diagnostic of eburnane alkaloids belonging to the eburnamine series, as opposed to those belonging to the isoeburnamine (or epi-eburnamine) series (Kam et al., 1993). The configuration at the centres C(20) and C(21) are assumed to be similar to those of (+)-eburnamonine and (+)-isoeburnamine which were also obtained, assuming the eburnane alkaloids share a common biogenetic origin. The configuration of C(19), however, remains to be established and, since there were no suitable precedents, this was achieved by X-ray analysis (Fig. 1), which yielded the structure shown in **31**. The crystals of **31** are orthorhombic belonging to the space group $P2_12_12_1$, with $a=8.8420$ (5) Å, $b=12.3542$ (9) Å, $c=14.417$ (1) Å, $\alpha=\beta=\gamma=90^\circ$, $V=1574.9$ (2) $Å^3$; $D_X=1.318$ Mg m^{-3} and $Z=4$. The structure was solved by the direct method SHELXS86 (Sheldrick, 1990) and was refined by the full-matrix least squares method. The final *R*-factor was 0.0489. As shown in the perspective diagram of Fig. 1, compound **31** possesses a *cis*-C/D ring junction and, in

Table 3
^{1}H NMR data of compounds **20**--**22**, **31**, **32**[a]

H	**20**	**21**	**22**	H	**20**	**21**	**22**	H	**31**	**32**
3	3.05 m	3.02 m	3.10 m	3′	2.49 brt (13)	2.52 brt (13)	2.54 td (13, 4)	3	2.42 td (13, 4)	2.66 m
3	3.05 m	3.02 m	3.10 m	3′	2.62 m	2.67 m	2.62 brd (13)	3	2.57 m	2.66 m
5	3.05 m	3.02 m	3.10 m	5′	3.35 m	3.38 m	3.28 dd (14, 6.5)	5	3.28 ddd (13, 6.5, 1.5)	3.28 ddd (14, 6.5, 1.5)
5	3.35 m	3.38 m	3.42 m	5′	3.35 m	3.38 m	3.39 m	5	3.33 ddd (13, 11.5, 5)	3.33 ddd (14, 11.5, 5)
6	1.73 m	1.62 m	1.69 m	6′	2.62 m	2.67 m	2.63 m	6	2.57 m	2.59 ddt (16, 5, 1.5)
6	2.74 m	2.67 m	2.76 m	6′	3.05 m	3.02 m	3.01 m	6	2.97 dddd (16, 11.5, 6.5, 2.5)	3.00 dddd (16, 11.5, 6.5, 2.5)
9	7.17 s	7.27 s	7.15 s	9′	7.44 d (8)	7.46 d (8)	7.45 brd (8)	9	7.49 dd (7, 1.5)	7.50 brd (7.5)
10	–	–	–	10′	7.00 t (8)	7.02 t (8)	7.01 td (8, 1)	10	7.17 td (7, 1.5)	7.15 td (7.5, 1.5)
11	6.90 d (8)	6.95 d (8)	6.84 d (8)	11′	6.83 t (8)	6.86 t (8)	6.83 td (8, 1)	11	7.21 td (7, 1.5)	7.20 td (7.5, 1.5)
12	6.62 d (8)	6.78 d (8)	6.61 d (8)	12′	6.54 d (8)	6.50 d (8)	6.53 brd (8)	12	7.72 dd (7, 1.5)	7.40 brd (7.5)
14	1.27 m	1.40 m	1.31 m	14′	1.38 m	1.43 m	1.39 m	14	1.32 brd (13)	1.38 brd (14)
14	1.90 m	1.86 m	1.92 m	14′	1.77 m	1.82 m	2.26 qt (13, 4)	14	2.19 qt (13, 4)	2.24 m
15	1.30 m	1.32 m	1.31 m	15′	1.14 m	1.14 brt (13)	1.15 td (13, 4)	15	0.89 tdd (13, 4, 1)	1.75 td (14, 4)
15	1.62 brd (13)	1.62 m	1.59 brd (13)	15′	1.38 m	1.43 m	1.71 brd (13)	15	1.74 brd (13)	1.82 td (14, 4.5)
16	2.91 t (10)	2.84 t (10)	2.90 t (10)	16′	4.94 dd (11, 5)	4.99 dd (11, 5)	4.92 dd (11, 5)	16	5.59 dd (10, 5)	6.02 dd (5, 1)
17	1.38 m	1.62 m	1.39 m	17′	1.77 m	1.78 m	1.69 m	17	1.49 dd (14, 10)	1.85 dd (15, 5)
17	2.76 m	2.67 m	2.76 m	17′	2.11 m	2.18 m	1.92 dd (14, 4)	17	2.25 dd (14, 5)	2.02dd (15, 1)
18	1.26 m	1.43 m	1.25 m	18′	0.87 t (7.5)	0.86 t (7.5)	1.20 d (6.5)	18	1.24 d (6.5)	1.25 d (6.5)
18	1.92 m	2.01 m	1.92 m	19′	1.49 m	1.46 m	3.95 q (6.5)	19	3.98 qd (6.5, 1)	3.91 qd (6.5, 1)
19	1.26 m	1.43 m	1.25 m	19′	2.17 m	2.18 m	–	19	–	–
19	1.41 m	1.47 m	1.39 m	21′	4.03 brs	4.13 brs	4.36 brs	21	4.22 brs	4.18 brs
21	ca. 3.02	ca. 3.22	ca. 3.03							
CO_2Me	3.77 s	–	3.78 s							

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

Table 4
^{13}C NMR data of compounds **20**–**22**, **31**, **32**[a]

C	20	21	22	C	20	21	22	C	31	32
2	66.8	66.5	66.9	2′	133.9	132.9	132.1	2	130.9	129.6
3	47.4	47.4	47.4	3′	44.4	44.2	43.8	3	43.7	44.4
5	50.8	50.4	50.9	5′	50.9	50.7	50.5	5	50.5	51.2
6	34.9	35.1	34.9	6′	17.0	16.9	17.0	6	16.7	17.0
7	58.1	58.4	58.2	7′	104.6	104.8	104.4	7	105.6	105.5
8	141.4	141.6	141.5	8′	128.4	128.4	128.4	8	128.6	129.1
9	120.0	120.7	120.2	9′	117.6	117.9	117.7	9	118.2	118.9
10	134.5	136.6	133.8	10′	118.9	119.3	119.2	10	120.4	120.6
11	125.1	125.4	125.2	11′	120.0	120.5	120.4	11	121.6	121.7
12	111.0	114.3	111.1	12′	112.1	112.0	112.3	12	112.1	110.2
13	148.5	146.7	148.7	13′	136.5	137.4	136.6	13	136.6	135.1
14	16.6	16.5	16.5	14′	20.7	20.3	21.4	14	21.2	21.9
15	36.3	36.0	36.4	15′	24.2	24.0	21.7	15	22.4	23.9
16	43.7	42.4	43.7	16′	55.9	56.0	55.9	16	76.5	74.5
17	33.0	33.4	32.2	17′	45.1	45.0	44.4	17	43.0	39.6
18	33.7	33.0	33.8	18′	7.4	7.5	17.5	18	17.6	17.8
19	33.8	34.1	33.9	19′	28.7	28.6	78.7	19	78.3	79.5
20	31.6	32.3	31.7	20′	34.9	35.1	37.4	20	39.5	37.4
21	67.9	68.5	68.0	21′	59.5	59.4	60.0	21	59.5	60.1
CO_2Me	51.9	–	52.0							
CO_2Me	174.7	177.4	174.7							

[a] 100 MHz, $CDCl_3$; assignments based on HMQC and HMBC.

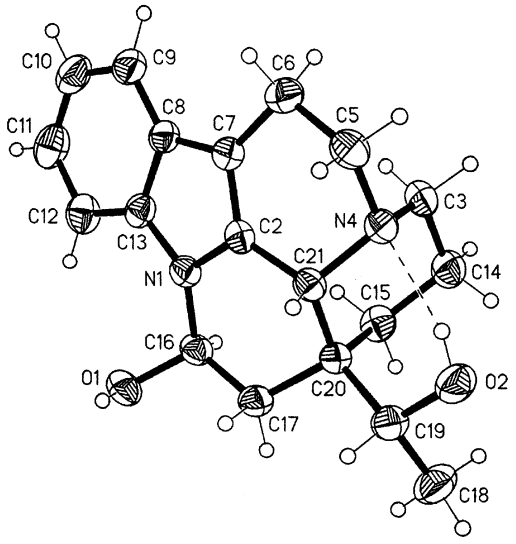


Fig. 1. X-ray structure of compound **31**.

addition, the C(19)–OH is intramolecularly H-bonded to the *N*(4) lone-pair electrons. Compound **31** is therefore (+)-19(*R*)-hydroxyeburnamine.

Compound **32** was obtained only in small amounts. The EI-mass spectrum showed an $[M]^+$ at *m*/*z* 312 (isomeric with **31**) and HREIMS measurements ($[M]^+$, *m*/*z* 312.1839) yielded the formula $C_{19}H_{24}N_2O_2$ (calcd 312.1838). Comparison of the NMR spectral data of **32** with those of **31** (Tables 3–4) and (+)-isoeburnamine (**17**) (Kam et al., 1993) indicated that **32** is the 19-hydroxy analogue of (+)-isoeburnamine (**17**). This was evident from the general similarity of the NMR data of **32** with those of (+)-isoeburnamine (**17**), except for the change in the signals due to the C(20) side-chain. The H(16) doublet of doublets of compound **32** showed coupling constants of 5 and 1 Hz, consistent with H(16β), which is characteristic of the pentacyclic eburnane compounds belonging to the isoeburnamine (or epieburnamine) series (Kam et al., 1993). The configuration at C(19) was assigned as *R*, i.e. similar to that in **31**, on the grounds that in the ^{1}H and ^{13}C NMR spectra of **32**, both the H(19) and C(19) resonances are similar when compared with those of **31** (Tables 3–4). Compound **32** is therefore (−)-19(*R*)-hydroxy-isoeburnamine.

In addition to the monomeric indoles, three *bis*indole alkaloids were also isolated, viz. (−)-norpleiomutine **20**, (−)-demethylnorpleiomutine **21**, and (+)-kopsoffinol **22**. High-field NMR spectral data for these compounds (Tables 3–4) are included, as they were previously not available (Kan-Fan et al., 1985). All three *bis*indoles are constituted from the union of eburnane and kopsinine units and we propose that all three compounds incorporate in common, eburnane units having the 20β, 21β-configuration, for the following reasons. Firstly, since the other two *bis*indoles present have eburnane units with the 20β, 21β-configuration, it would be extremely unlikely that a third odd *bis*indole should have a eburnane unit of the opposite configuration. Secondly, since all the monomeric eburnane compounds present in this plant (**16**, **17**, **31** and **32**) are of the 20β, 21β-configuration, it would be singularly unusual for kopsoffinol to incorporate a eburnane unit of the opposite configur-

ation. Lastly, considering that the likely precursor of the eburnane half in kopsoffinol, (+)-19(*R*)-hydroxyeburnamine **31**, was also obtained from this plant and its structure has been established by X-ray analysis (vide supra), the most likely structure of kopsoffinol is **22**, with the eburnane half corresponding to that of the monomeric precursor, **31**. The attachment of the kopsinine unit at C(16′) is now β {H(16′) α}, as required by the observed coupling constants for the H(16′) signal of 11 and 5 Hz for kopsoffinol (Kam et al., 1993).

3. Experimental

3.1. Plant material

Plant material was collected from Sabah, Malaysia and was identified by Dr K.M. Wong. Voucher specimens are deposited at the Herbarium of the Sabah Forest Department, Sandakan, Sabah, Malaysia.

3.2. Extraction and isolation

Extraction of alkaloids was carried out in the usual manner, as described in detail elsewhere (Kam & Tan, 1990). Essentially, ground stem material was exhaustively extracted with 95% EtOH at room temp. The EtOH extract was then concd under red. press., partitioned into dil. HCl, basified with concd NH_3 soln and the liberated alkaloids were then taken up into $CHCl_3$ to give a basic fr. The alkaloids were isolated by repeated fractionation using CC and centrifugal TLC on silica gel. Solvent systems used for chromatography were $CHCl_3$ with increasing proportions of MeOH (CC) and Et_2O, Et_2O–hexane, EtOAc, $CHCl_3$–MeOH, EtOAc–MeOH (centrifugal TLC). The yields (g kg^{-1}) of the alkaloids (**1**–**32**) from the stem extract were: **1** (0.028), **2** (0.003), **3** (0.689), **4** (0.026), **5** (0.012), **6** (0.033), **7** (0.004), **8** (0.095), **9** (0.005), **10** (0.004), **11** (0.006), **12** (0.007), **13** (0.003), **14** (0.001), **15** (0.001), **16** (0.004), **17** (0.002), **18** (0.002), **19** (0.002), **20** (0.002), **21** (0.003), **22** (0.005), **23** (0.005), **24** (0.002), **25** (0.007), **26** (0.001), **27** (0.004), **28** (0.003), **29** (0.001), **30** (0.002), **31** (0.005) and **32** (0.003).

3.3. *Kopsiflorine* N*(4)-oxide (**23**)*

$[\alpha]_D$ −57° ($CHCl_3$, *c* 0.32). UV (EtOH), λ_{max} (log ε) 206 (4.38), 242 (4.04), 278 (3.23) and 284 (3.20). EIMS, *m*/*z* (rel. int.): 428 [M^+, $C_{23}H_{28}N_2O_6$] (5), 412 (100), 394 (23), 353 (59), 321 (15), 282 (15), 265 (10), 229 (11), 180 (18) and 109 (22). ^1H and ^{13}C NMR: see Tables 1–2.

3.4. *Reduction of kopsiflorine* N-*oxide (**23**) to kopsiflorine (**1**)*

Compound **23** (5 mg) was stirred in aq. $FeSO_4$ (3%, 1 ml) at 80°C for 0.5 h. The mixt. was then extracted with $CHCl_3$ and chromatography over silica gel gave kopsiflorine (**1**) (2 mg, 42%).

3.5. *11-Methoxykopsilongine* N*(4)-oxide (**24**)*

$[\alpha]_D$ −11° ($CHCl_3$, *c* 0.13). UV (EtOH), λ_{max} (log ε) 223 (4.44), 252 (3.86), 282 (3.12), 289 (3.12). EIMS *m*/*z* (rel. int.): 488 ([$M]^+$, $C_{25}H_{32}N_2O_8$) (4), 472 (100), 457 (45), 413 (33), 395 (37), 342 (20), 289 (17), 180 (17), 124 (20), 109 (39). ^1H and ^{13}C NMR: Tables 1–2.

3.6. *Kopsifine (**25**)*

$[\alpha]_D$ +97° ($CHCl_3$, *c* 0.04). UV (EtOH), λ_{max} (log ε) 223 (4.41), 250 (3.94), 285 (3.16), 295 (3.10). EIMS *m*/*z* (rel. int.): 438 $[M]^+$ (23), 410 (100), 381 (13), 366 (29), 338 (17), 326 (9), 281 (14), 197 (12), 149 (20). HREIMS, $[M]^+$ found *m*/*z* 438.1425, calcd for $C_{23}H_{22}N_2O_7$ 438.1427. ^1H and ^{13}C NMR: Tables 1–2.

3.7. *Decarbomethoxykopsifine (**26**)*

$[\alpha]_D$ +52° ($CHCl_3$, *c* 0.07). UV (EtOH), λ_{max} (log ε) 220 (4.72), 243 (4.23), 288 (3.51). EIMS, *m*/*z* (rel. int.): 380 $[M]^+$ (100), 352 (52), 324 (19), 268 (15), 240 (14), 224 (10). HREIMS, $[M]^+$ found *m*/*z* 380.1367, calcd for $C_{21}H_{20}N_2O_5$ 380.1372. ^1H and ^{13}C NMR: Tables 1–2.

3.8. *Kopsinarine (**27**)*

$[\alpha]_D$ +97° ($CHCl_3$, *c* 0.25). UV (EtOH), λ_{max} (log ε) 219 (4.66), 240 (4.15), 280 (3.32), 288 (3.30). EIMS, *m*/*z* (rel. int.): 454 $[M]^+$ (47), 426 (100), 394 (39), 366 (25), 335 (22), 268 (22), 224 (26), 167 (8), 124 (8). HREIMS, $[M]^+$ found *m*/*z* 454.1745, calcd for $C_{24}H_{26}N_2O_7$ 454.1740. ^1H and ^{13}C NMR: Tables 1–2.

3.9. *11,12-Methylenedioxykopsine (**28**)*

$[\alpha]_D$ −13° ($CHCl_3$, *c* 0.18). UV (EtOH), λ_{max} (log ε) 225 (4.61), 244 (4.20), 287 (3.41), 294 (3.39). EIMS, *m*/*z* (rel. int.): 424 $[M]^+$ (63), 396 (33), 326 (100), 282 (7), 267 (20), 239 (5), 128 (5), 110 (8). HREIMS, $[M]^+$ found *m*/*z* 424.1635, calcd for $C_{23}H_{24}N_2O_6$ 424.1634. ^1H and ^{13}C NMR: Tables 1–2.

3.10. *Dasyrachine (**29**)*

$[\alpha]_D$ +17° ($CHCl_3$, *c* 0.06). UV (EtOH), λ_{max} (log ε) 221 (4.34), 243 (3.93), 281 (3.06). EIMS, *m*/*z* (rel. int.): 366 $[M]^+$ (29), 293 (11), 281 (13), 268 (32), 231 (18), 181 (30), 131 (38). API-LCMS, $[MH]^+$ *m*/*z* 367. HREIMS, $[M]^+$

found m/z 366.1577, calcd for $C_{21}H_{22}N_2O_4$ 366.1579. ^1H and ^{13}C NMR: Tables 1–2.

3.11. Base-induced reaction of **28** (Govindachari et al., 1963)

A mixt. of **28** (10 mg) in 0.1 M aq. NaOH (5 ml) was refluxed for 8 h. H_2O was then added and the mixt. extracted with $CHCl_3$. The product mixt. was purified by passage through a short column of silica gel ($CHCl_3$). TLC (silica gel, 6% MeOH–$CHCl_3$) and ^1H NMR analysis showed the presence of *N*-decarbomethoxy-11,12-methylenedioxykopsine, with dasyrachine (**29**) detected as a minor product (ratio 17:1).

3.12. Rhazinicine (**30**)

$[\alpha]_D$ −208° ($CHCl_3$, *c* 0.13). UV (EtOH), λ_{max} (log ε) 207 (4.37), 229 (sh, 4.19), 275 (sh, 3.61). EIMS m/z (rel. int.): 308 $[M]^+$ (38), 279 (100), 251 (32), 237 (11), 223 (18), 195 (12). HREIMS, $[M]^+$ found m/z 308.1528, calcd for $C_{19}H_{20}N_2O_2$ 308.1525. ^1H and ^{13}C NMR: Tables 1–2.

3.13. (+)-19(R)-Hydroxyeburnamine (**31**)

M.p. 246–248°C, $[\alpha]_D$ +111° ($CHCl_3$, *c* 0.09). UV (EtOH), λ_{max} (log ε) 201 (3.86), 229 (4.02), 283 (3.42), 291 (3.31). EIMS m/z (rel. int.): 312 ($[M]^+$, $C_{19}H_{24}N_2O_2$) (14), 294 (25), 267 (18), 249 (100), 220 (10), 206 (37), 193 (13), 180 (10), 167 (18). ^1H and ^{13}C NMR: Tables 3–4.

3.14. X-ray diffraction analysis of **31**

A total of 4194 reflections were collected up to θ_{max} of 27.99° on a CAD4 diffractometer at 27° using MoK_α ($\lambda = 0.71073$ Å) on a crystal of dimensions $0.36 \times 0.36 \times 0.32$ mm. Data were collected by the ω–2θ method, 2679 observed reflections with $I > 2\sigma(I)$ and were corrected for Lorentz-polarization effect, but not for absorption. The structure was solved by using the direct method SHELXS86 (Sheldrick, 1990). All non-hydrogen atoms were refined anisotropically by full-matrix least squares refinement on an IBM 486 PC to $R = 0.0489$, $wR = 0.0872$ for the observed reflections, $w = [\sigma^2(F^2_o) + (0.0439P)^2]^{-1}$ where $P = (F^2_o + 2F^2_c)/3$. Hydrogen atoms were generated geometrically and were allowed to ride on their respective parent atoms. The atomic coordinates for the non-hydrogen atoms and their equivalent isotropic displacement parameters, calculated coordinates for the hydrogen atoms, anisotropic displacement parameters for the non-hydrogen atoms, a full list of bond distances and angles and the structure factor table are deposited as supplementary material at the Cambridge Crystallographic Data Centre.

3.15. (−)-19(R)-Hydroxyisoeburnamine (**32**)

$[\alpha]_D$ −16° ($CHCl_3$, *c* 0.18). UV (EtOH), λ_{max} (log ε) 203 (4.39), 229 (4.53), 282 (3.74), 292 (3.83). EIMS m/z (rel. int.): 312 $[M]^+$ (45), 294 (44), 267 (44), 249 (100), 220 (21), 206 (62), 193 (23), 180 (17), 167 (11). HREIMS, $[M]^+$ found m/z 312.1839, calcd for $C_{19}H_{24}N_2O_2$ 312.1838. ^1H and ^{13}C NMR: Tables 3–4.

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References

Abe, F., & Yamauchi, T. (1994). *Phytochemistry*, *35*, 169.
Achenbach, H., & Biemann, K. (1965). *Journal of the American Chemical Society*, *87*, 4944.
Awang, K., Sevenet, T., Hadi, A. H. A., David, B., & Pais, M. (1992). *Tetrahedron Letters*, *33*, 2493.
Battersby, A. R. & Gregory, H. (1963). *Journal of the Chemical Society*, 22.
Crow, W. D., & Michael, M. (1962). *Australian Journal of Chemistry*, *15*, 130.
Feng, X. Z., Kan, C., Potier, P., Kan, S. K., & Lounasmaa, M. (1983). *Planta Medica*, *48*, 280.
Gilbert, B. (1965). In R. H. F. Manske (Ed.), *The alkaloids* (Vol. VIII, p. 439). New York: Academic Press.
Goh, S. H., Ali, A. R. M., & Wong, W. H. (1989). *Tetrahedron*, *45*, 7899.
Govindachari, T. R., Nagarajan, K., & Schmid, H. (1963). *Helvetica Chimica Acta*, *45*, 433.
Guggisberg, A., Govindachari, T. R., Nagarajan, K., & Schmid, H. (1963). *Helvetica Chimica Acta*, *46*, 679.
Guggisberg, A., Hesse, M., von Philipsborn, W., Nagarajan, K., & Schmid, H. (1966). *Helvetica Chimica Acta*, *49*, 2321.
Guggisberg, A., Gorman, A. A., Bycroft, B. W., & Schmid, H. (1969). *Helvetica Chimica Acta*, *52*, 76.
Homberger, K., & Hesse, M. (1982). *Helvetica Chimica Acta*, *65*, 2548.
Homberger, K., & Hesse, M. (1984). *Helvetica Chimica Acta*, *67*, 237.
Kam, T. S., & Sim, K. M. (1998). *Phytochemistry*, *47*, 145.
Kam, T. S., & Subramaniam, G. (1998). *Natural Product Letters*, *11*, 131.
Kam, T. S., & Tan, P. S. (1990). *Phytochemistry*, *29*, 2321.
Kam, T. S., Tan, P. S., & Chen, W. (1993). *Phytochemistry*, *33*, 921.
Kam, T. S., Yoganathan, K., & Chuah, C. H. (1994). *Tetrahedron Letters*, *35*, 4457.
Kam, T. S., Yoganathan, K., & Chuah, C. H. (1995). *Tetrahedron Letters*, *36*, 759.
Kam, T. S., Arasu, L., & Yoganathan, K. (1996). *Phytochemistry*, *43*, 1385.
Kam, T. S., Yoganathan, K., & Chen, W. (1996). *Tetrahedron Letters*, *37*, 3603.

Kam, T. S., Yoganathan, K., Koyano, T., & Komiyama, K. (1996). *Tetrahedron Letters*, *37*, 5765.
Kam, T. S., Yoganathan, K., & Li, H. Y. (1996). *Tetrahedron Letters*, *37*, 8811.
Kan, C., Deverre, J. R., Sevenet, T., Quirion, J. C., & Husson, H. P. (1995). *Natural Product Letters*, *7*, 275.
Kan-Fan, C., Sevenet, T., Husson, H. P., & Chan, K. C. (1985). *Journal of Natural Products*, *48*, 124.
Markgraf, F. (1972). *Blumea*, *20*, 416.
Sheldrick, G. M. (1990). *Acta Crystallographica A*, *46*, 467.
Thomas, D. W., Achenbach, H., & Biemann, K. (1966). *Journal of the American Chemical Society*, *88*, 3423.
Zheng, J. J., Zhou, Y. L., & Huang, Z. H. (1989). *Acta Chimica Sinica (English Edn.)*, *2*, 168.