Available online at www.sciencedirect.com
SCIENCE DIRECT®
PERGAMON
Phytochemistry 63 (2003) 625–629
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

Conodurine, conoduramine, and ervahanine derivatives from *Tabernaemontana corymbosa*

Toh-Seok Kam*, Kooi-Mow Sim

Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

Received 18 September 2002; received in revised form 23 January 2003

Abstract

Four bisindole alkaloids, viz., 19′(*S*)-hydroxyconodurine, conodurinine, 19′(*S*)-hydroxyconoduramine, and 19′(*S*)-hydroxyervahanine A, in addition to conodurine and ervahanine A, were obtained from the leaf and stem-bark extracts of *Tabernaemontana corymbosa*. The structures of the new alkaloids were determined using NMR and MS analysis.

Keywords: *Tabernaemontana* species; Apocynaceae; Bisindole alkaloids

1. Introduction

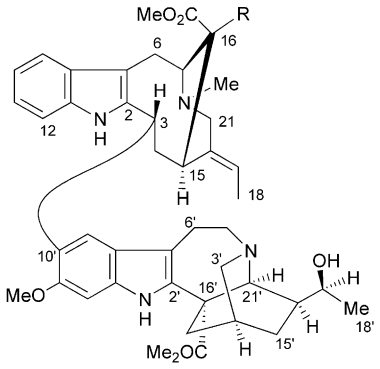
The genus *Tabernaemontana* (Apocynaceae) has a wide distribution (Leeuwenberg, 1991) and plants belonging to this genus are known to provide indole alkaloids of unusual structures, as well as novel bioactivity (Van Beek et al., 1984; Danieli et al., 1986; Kam, 1999). We have previously reported the structures of several new indole and bisindole alkaloids possessing novel carbon skeletons from the Malayan species, *T. corymbosa* Roxb. Ex Wall (Kam et al., 1998, 1999, 2000, 2001, 2003; Kam and Sim, 2001, 2002), including conodiparine A (**1**), a new vobasine-iboga bisindole which was found to reverse multidrug-resistance (MDR) in vincristine-resistant KB cells (Kam et al., 1998), and vobatricine (**2**), representing the first example of a bisindole of the vobasine-strychnan type (Kam et al., 2003). We now wish to report the structures of additional new bisindoles related to conodurine, conoduramine, and ervahanine, from the leaf and stem-bark extracts of this species.

2. Results and discussion

The stem-bark extract of *T. corymbosa* provided in addition to the known bisindoles, conodurine (**3**) and ervahanine A (**7**), the new derivatives, 19′(*S*)-hydroxyconodurine (**4**) and 19′(*S*)-hydroxyervahanine A (**8**), while the leaf extract provided the new bisindoles, conodurinine (**5**) and 19′(*S*)-hydroxyconoduramine (**6**). All six alkaloids showed UV spectra characteristic of an indole chromophore (see Experimental section, e.g., 19′(*S*)-hydroxyconodurine, λ_{max} 223, 286, 293 nm). Alkaloid **4** was obtained as a light yellowish oil, $[\alpha]_D$ −69° (*c* 0.12, $CHCl_3$). The IR spectrum showed bands due to NH (3376 cm^{-1}), OH (3228 cm^{-1}), and ester (1727 cm^{-1}) functions. The FABMS of **4** showed an MH^+ ion at *m*/*z* 721, 16 mass units higher than that of conodurine (**3**). HRFABMS gave the formula $C_{43}H_{52}N_4O_6$, suggesting the replacement of H with an OH, compared with **3**. In addition a peak due to the loss of H_2O was observed at *m*/*z* 703, indicating the presence of a hydroxyl group. The ^1H NMR spectrum of **4** (Table 1) was assigned using COSY, HMQC and HMBC techniques, and showed a close similarity with that of conodurine (**3**), revealing the presence of two indole NH, an unsubstituted indole ring (vobasinyl), another indole ring substituted at C(11′) and C(12′) (iboga), one aromatic methoxy group (iboga), two ester carbomethoxy groups, an *N*-methyl (vobasinyl), an ethylidene (vobasinyl), and a hydroxyethyl group (iboga). The ester methyl associated with the vobasinyl unit is unusually shielded (δ 2.53), which is in agreement with the configuration of C(16) which places the ester function in the shielding zone of the aromatic ring. The observation of the aromatic H(9′) and H(10′) of the

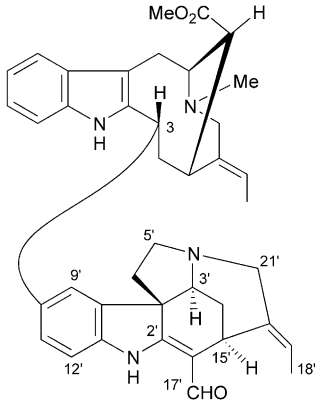
* Corresponding author. Tel.: +60-3-767-4266; fax: +60-3-767-4193.
E-mail address: tskam@um.edu.my (T.-S. Kam).

0031-9422/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0031-9422(03)00087-6

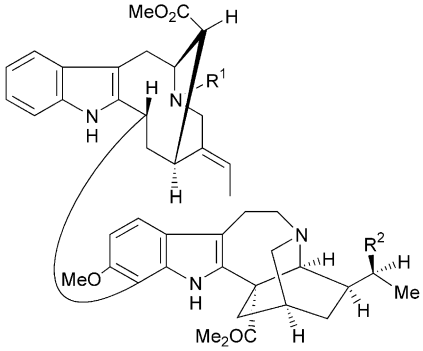


1 R = CH_2OH

6 R = H



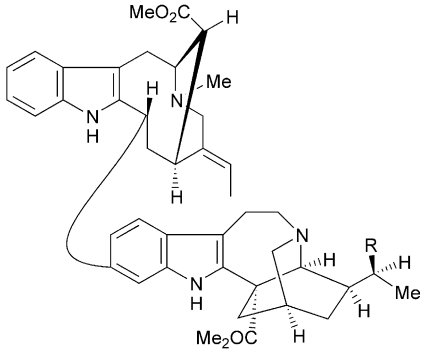
2



3 R^1 = Me, R^2 = H

4 R^1 = Me, R^2 = OH

5 R^1 = H, R^2 = OH



7 R = H

8 R = OH

iboga unit as a pair of AB doublets at δ 7.25 H(9′) and 6.84 H(10′) indicates substitution at C(11′) and C(12′) of the iboga moiety. Comparison of the NMR spectral data with those of conodurine and its derivatives (Takayama et al., 1994), indicated a similar pattern of substitution, with the attachment of the methoxy group at C(11′) and the vobasinyl unit at C(12′). Since only one H(3) is observed, the bisindole is therefore branched from C(3) of the vobasinyl unit to C(12′) of the iboga unit, which is also confirmed by the observed correlation from C(12′) to H(3) in the HMBC spectrum of **4**. The ^{1}H NMR spectrum of **4** is very similar to that of **3**, except for the presence of a C(20′) hydroxyethyl side chain (δ 4.05, *qd*, J = 6.3, 1.6 Hz, H(19′); 1.00, *d*, J = 6.3 Hz, CH_3-18′) in place of the C(20′) ethyl side chain in **3**. The presence of the hydroxyethyl group is further confirmed by the carbon resonances of C(19′) and C(18′) at δ 71.3 and 20.2, respectively. The configuration of C(19′) was readily deduced to be *S* from the chemical shift analogy of C(15′) and C(21′) with those of heyneanine (Wenkert et al., 1976). Alkaloid **4** is therefore 19′(*S*)-hydroxyconodurine. The 19′(*R*)-epimer was recently isolated from *T. subglobosa* (Takayama et al., 1994).

Conodurinine (**5**) was obtained as a light yellowish oil, $[\alpha]_D$ −55° (*c* 0.47, $CHCl_3$). The IR spectrum showed bands at 3379 and 1727 cm^{-1} due to NH/OH and ester functions, respectively. The FABMS of **5** showed an MH^+ at *m*/*z* 707, differing from **4** by 14 mass units. HRFABMS gave the formula $C_{42}H_{50}N_4O_6$, suggesting the replacement of a methyl group with H, compared with **4**. The ^{1}H and ^{13}C NMR spectral data of **5** showed a general similarity with those of **4**, indicating similar constitution from union of vobasinyl and iboga moieties, similar 11′-OMe substitution, and C(3) to C(12′) connection of the monomeric units, and the presence of a common hydroxyethyl side chain at C(20′) of the iboga unit. A prominent difference was the absence of the signals due to the *N*-methyl group in the NMR spectra of **5** when compared to **4**. The absence of the *N*-methyl substituent has caused the resonances of C(5) and C(21) to be shifted upfield from δ 59.5 and 52.0, respectively, in **4**, to δ 53.3 and 44.1, respectively, in **5**, a

Table 1
^{1}H NMR spectral data for **4–6**, and **8** (400 MHz, $CDCl_3$)[a]

H	4	5	6	8
3	5.31 *dd* (13, 3)	5.33 *dd* (13, 3)	5.14 *br d* (13)	4.62 *dd* (13, 3)
5	4.10 *td* (9.5, 3)	4.25 *ddd* (10, 8, 3)	4.05 *ddd* (10, 8, 3)	4.03 *ddd* (10, 8, 3)
6	3.44 *m*	3.49 *dd* (15, 8)	3.27 *m*	3.25 *dd* (14.5, 8)
	3.44 *m*	3.60 *dd* (15, 10)	3.51 *dd* (14, 10)	3.49 *dd* (14.5, 10)
9	7.68 *br d* (7)	7.70 *br d* (7.8)	7.54 *br d* (7)	7.54 *dd* (8, 1.5)
10	7.13 *td* (7, 1)	7.14 *td* (7.8, 1)	7.05 *m*	7.04 *m*
11	7.08 *td* (7, 1)	7.08 *td* (7.8, 1)	7.05 *m*	7.04 *m*
12	7.02 *br d*	7.03 *dd* (7.8, 1)	7.05 *m*	7.04 *m*
14	1.93 *ddd* (15, 7, 3)	1.98 *ddd* (15, 7, 3)	1.98 *m*	1.93 *ddd* (15, 7, 3)
	2.66 *m*	2.74 *m*	2.54 *m*	2.65 *m*
15	3.83 *m*	3.92 *m*	3.76 *m*	3.74 *m*
16	2.76 *t* (3)	2.59 *t* (3)	2.72 *t* (3)	2.72 *t* (3)
18	1.67 *dd* (6.9, 1.7)	1.66 *dd* (6.8, 1.4)	1.66 *d* (6.5)	1.63 *dd* (6.5, 1.5)
19	5.32 *q* (6.9)	5.27 *q* (6.8)	5.32 *q* (6.5)	5.31 *q* (6.5)
21	2.91 *d* (13)	3.12 *d* (15)	2.93 *d* (13.5)	2.90 *d* (14)
	3.63 *br d* (13)	3.94 *br d* (15)	3.76 *m*	3.72 *br d* (14)
NH	7.70 *br s*	7.81 *br s*	7.66 *br s*	7.46 *br s*
CO_2Me	2.53 *s*	2.54 *s*	2.44 *s*	2.44 *s*
NMe	2.62 *s*	–	2.61 *s*	2.58 *s*
3′	2.73 *m*	2.44 *br d* (9)	2.78 *m*	2.71 *m*
	2.45 *br d* (9)	2.74 *m*	2.99 *m*	2.92 *m*
5′	3.00 *m*	2.95 *m*	2.99 *m*	3.06 *m*
	3.22 *m*	3.30 *m*	3.27 *m*	3.40 *m*
6′	2.94 *m*	2.95 *m*	2.78 *m*	3.06 *m*
	2.94 *m*	2.95 *m*	2.99 *m*	3.06 *m*
9′	7.25 *d* (8.7)	7.25 *d* (8.8)	6.91 *s*	7.35 *d* (8)
10′	6.84 *d* (8.7)	6.84 *d* (8.8)	–	6.97 *dd* (8, 1)
12′	–	–	6.80 *s*	6.99 *br* s
14′	1.58 *m*	1.56 *m*	1.98 *m*	1.96 *m*
15′	1.31 *m*	1.31 *m*	1.51 *m*	1.50 *m*
	1.68 *m*	1.67 *m*	1.88 *m*	1.86 *m*
17′	0.72 *ddd* (14, 4, 2)	0.70 *ddd* (14, 4, 2)	1.88 *m*	1.86 *m*
	1.74 *dt* (14, 2)	1.71 *dt* (14, 2)	2.62 *m*	2.51 *br d* (13.5)
18′	1.00 *d* (6.3)	0.99 *d* (6.3)	1.07 *d* (6)	1.06 *d* (6.3)
19′	4.05 *qd* (6.3, 1.6)	4.04 *qd* (6.3, 1)	4.09 *br q* (6)	4.12 *qd* (6.3, 1.5)
20′	1.26 *m*	1.25 *m*	1.40 *m*	1.41 *m*
21′	3.65 *br s*	3.64 *br s*	3.74 *br s*	3.80 *br s*
NH′	7.56 *br s*	7.52 *br s*	7.74 *br s*	7.72 *br s*
11′-OMe	3.98 *s*	3.98 *s*	3.97 *s*	–
CO_2Me'	3.72 *s*	3.71 *s*	3.68 *s*	3.69 *s*
19′-OH	–	6.35 *br s*	6.38 *br s*	–

[a] Assignments based on COSY and HMQC.

behaviour that has been previously noted in the related alkaloids conodiparines E and F (Kam et al., 2003). The C(3) to C(12′) connection of the bisindole was supported by the observed C(12′) to H(3) correlation in the HMBC spectrum of **5**, while the configuration of the oxymethine C(19′) was also (*S*), from the observed carbon shifts of C(15′) and C(21′) (vide supra) (Wenkert et al., 1976).

Alkaloid **6** was obtained as a light yellowish oil, $[\alpha]_D$ −43° (*c* 0.63, $CHCl_3$). The IR spectrum showed bands at 3391, 3253, and 1724 cm^{-1} due to NH, OH, and ester functions, respectively. The FABMS of **6** showed an MH^+ ion at *m*/*z* 721, and HRFABMS gave the formula $C_{43}H_{52}N_4O_6$. The ^{1}H NMR spectrum of **6** differs from that of the previous alkaloids in that the aromatic hydrogens of the iboga unit are observed as two singlets at δ 6.91 and 6.80, indicating a change in the attachment of the vobasinyl unit, which in **6** is from C(3) to C(10′). The attachment of the methoxy substituent is still at C(11′), from the characteristic upfield shift observed for H(12′), indicative of adjacent C(11′) oxygenation (Takayama et al., 1994). These conclusions were supported by the observed long range correlations from C(9′) to H(3) in the HMBC spectrum of **6**. The ^{1}H NMR and ^{13}C NMR spectral data of **6** in fact showed a general similarity when compared with those of 19′(*R*)-hydroxyconoduramine (Takayama et al., 1994). The chemical shifts of both alkaloids were very similar, except for H(19′) in the ^{1}H NMR spectrum, and C(15′) and C(21′) in the ^{13}C NMR spectrum, suggesting that

the two alkaloids are C(19′)-epimers. The observed shifts of C(15′) and C(21′) at δ 22.9 and 59.6, respectively, allowed the assignment of the C(19′) configuration as *S* (Wenkert et al., 1976). Alkaloid **6** is therefore 19′(*S*)-hydroxyconoduramine. The parent alkaloid, conoduramine, was however not obtained.

Alkaloid **8** was obtained as a light yellowish oil, $[\alpha]_D$ −105° (*c* 0.16, $CHCl_3$). The IR spectrum showed bands at 3365 and 1724 cm^{-1} due to NH/OH, and ester functions, respectively. The FABMS of **8** showed an MH^+ ion at *m*/*z* 691, which is 16 mass units higher than that of ervahanine A (**7**). HRFABMS gave the formula $C_{42}H_{50}N_4O_5$, indicating that **8** differs from ervahanine A (**7**), by replacement of H with OH. The presence of an OH function was also indicated by the observation of the $M-H_2O$ fragment (*m*/*z* 673) in the mass spectrum of **8**. The ^1H NMR spectrum of **8** showed another departure in the pattern of the aromatic resonances when compared to that of the previous alkaloids. The aromatic resonances of the iboga unit in **8** indicated the presence of three aromatic hydrogens, and comparison of the spectrum with the spectra of the tabernamines (Perera et al., 1985) and ervahanines (Feng et al., 1981), indicated attachment of the vobasinyl unit at C(11′), which is also consistent with the observed C(3) to H(10′), H(12′), and C(11′) to H(3) correlations in the HMBC spectrum of **8**. Comparison of the ^1H spectrum of **8** with that of ervahanine A (**7**), which was also obtained, showed in fact that the spectra were generally similar, except for the presence of a hydroxyethyl side chain at the iboga C(20′) in **8**, in place of an ethyl side chain in the case of **7**. The presence of the hydroxyethyl group was further confirmed by the carbon resonances of C(19′) and C(18′) at δ 71.3 and 20.3, respectively. The chemical shifts of C(15′) and C(21′) at δ 22.9 and 59.5, respectively, allowed assignment of the C(19′) configuration as *S* (Wenkert et al., 1976). Alkaloid **8** is therefore 19′(*S*)-hydroxyervahanine A.

In all the six alkaloids (**3–8**), the signal of H(3) was observed as a doublet of doublet with $J=13$, and 3 Hz (or a broad doublet with $J=13$ Hz in the case of **6**), requiring H(3) and one of the H(14) to be *trans*-diaxial. This observation, coupled with the observed NOE interaction between H(3) and NH, confirmed the α attachment of the iboga unit at C(3) in these alkaloids.

3. Experimental

3.1. Plant material

Plant material was collected in Perak, Malaysia (May, 1996) and were identified by Dr. A.J.M. Leeuwenberg, Laboratory of Plant Taxonomy and Plant Geography, Agricultural University, Wageningen, The Netherlands. Herbarium voucher specimens (GK 604) are deposited at the Herbarium of the Department of Chemistry, University of Malaya, Malaysia, and at Wageningen.

3.2. Extraction and isolation

Extraction of the ground material was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid as has been described in detail elsewhere (Kam and Tan, 1990). The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH followed by rechromatography of appropriate partially resolved fractions using centrifugal TLC. Column chromatography of the basic fraction from the stem-bark gave essentially 11 fractions. Further fractionation of fractions 4 and 6 by centrifugal TLC gave **7** and **3**, respectively, while **4** and **8** were isolated from rechromatography of fraction 5. Column chromatography of the basic fraction from the leaves gave essentially seven fractions. Further fractionation of fractions 4 and 5 by centrifugal TLC gave **6** and **7**, respectively. Solvent systems used for centrifugal TLC were Et_2O, $CHCl_3$ (NH_3-saturated), Et_2O/MeOH (20:1), EtOAc/cyclohexane (1:1; NH_3-saturated). The yields (g kg^{-1}) of the alkaloids from the stem-bark were as follows: **3** (0.0013), **4** (0.0021), **7** (0.0060), and **8** (0.0011). The yields from the leaves are: **5** (0.0081) and **6** (0.0131).

3.2.1. 19′(*S*)-Hydroxyconodurine (**4**)

Light yellowish oil, $[\alpha]_D$ −69° ($CHCl_3$, *c* 0.12). UV (EtOH) λ_{max} (log ε) 223 (4.84), 286 (4.28), 293 (4.27) nm; IR (dry film) υ_{max} 3376, 3228, 1727 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; FABMS *m*/*z* 721 $[MH]^+$ (65), 703 (9), 661 (5), 337 (5), 194 (8), 182 (8), 180 (30), 136 (100), 122 (18); HRFABMS *m*/*z* 721.3970 (calc. for $C_{43}H_{52}N_4O_6+H$, 721.3965).

3.2.2. Conodurinine (**5**)

Light yellowish oil, $[\alpha]_D$ −55° ($CHCl_3$, *c* 0.47). UV (EtOH) λ_{max} (log ε) 224 (4.14), 286 (3.55), 293 (3.54) nm; IR (dry film) υ_{max} 3379, 1727 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; FABMS *m*/*z* 707 $[MH]^+$ (100), 689 (27), 180 (45), 168 (57), 136 (69), 122 (29); HRFABMS *m*/*z* 707.3979 (calc. for $C_{42}H_{50}N_4O_6+H$, 709.3914).

3.2.3. 19′(*S*)-Hydroxyconoduramine (**6**)

Light yellowish oil, $[\alpha]_D$ −43° ($CHCl_3$, *c* 0.63). UV (EtOH) λ_{max} (log ε) 227 (4.22), 288 (3.62), 295 (3.64) nm; IR (dry film) υ_{max} 3391, 3253, 1724 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; FABMS *m*/*z* 721 $[MH]^+$ (94), 703 (10), 661 (5), 337 (9), 194 (15), 182 (15), 180 (70), 136 (100), 122 (48); HRFABMS *m*/*z* 721.3961 (calc. for $C_{43}H_{52}N_4O_6+H$, 721.3965).

Table 2
^{13}C NMR spectral data for **3–8** (100 MHz, $CDCl_3$)[a]

C	3	4	5	6	7	8
2	136.1	136.0	135.9	137.8	137.3	137.2
3	35.2	35.1	35.4	36.6	45.3	45.2
5	59.6	59.5	53.3	59.9	59.8	59.8
6	19.5	19.6	25.0	19.5	19.4	19.4
7	109.1	108.6	110.6	109.7	110.3	110.3
8	129.5	129.4	129.3	129.9	129.8	129.7
9	118.0	118.0	118.1	117.4	117.6	117.6
10	119.4	119.5	119.5	118.6	119.1	119.0
11	122.1	122.2	122.2	121.5	121.7	121.7
12	109.8	109.8	109.7	109.8	109.8	109.8
13	136.8	136.8	136.7	135.8	136.0	135.9
14	33.8	33.8	33.9	36.9	39.0	38.9
15	33.5	33.5	34.2	33.6	33.6	33.6
16	47.3	47.0	50.2	47.0	47.0	46.9
18	12.3	12.3	12.1	12.2	12.2	12.3
19	118.8	118.9	117.5	118.7	118.9	118.8
20	137.6	137.4	140.0	137.0	137.5	137.5
21	52.9	52.0	44.1	52.4	52.4	52.3
CO_2Me	50.0	50.1	50.0	49.8	49.9	49.9
$\underline{C}O_2Me$	171.7	171.7	171.5	171.3	171.8	171.8
$\overline{N}Me$	42.4	42.4	–	42.3	42.3	42.3
2′	136.0	135.2	135.2	134.4	136.8	135.9
3′	51.2	51.0	51.0	51.1	51.8	51.4
5′	52.4	52.3	51.9	52.1	53.0	52.1
6′	22.0	21.4	21.3	21.4	22.1	21.5
7′	110.0	110.0	108.5	109.7	110.2	109.7
8′	124.5	124.1	124.0	122.2	127.5	127.2
9′	117.1	117.1	117.0	117.8	118.7	118.7
10′	105.0	105.2	105.1	127.6	119.4	119.7
11′	152.0	152.2	152.2	153.1	139.9	140.3
12′	114.4	114.4	114.4	93.1	109.3	109.4
13′	135.1	135.1	135.1	134.9	135.7	135.8
14′	27.0	26.5	26.5	26.7	27.3	26.7
15′	31.8	22.7	22.6	22.9	32.0	22.9
16′	54.6	53.5	53.4	53.9	55.0	54.0
17′	34.7	35.2	35.1	36.9	36.4	36.9
18′	11.6	20.2	20.2	20.3	11.6	20.3
19′	26.5	71.3	71.3	71.3	26.7	71.3
20′	38.9	39.2	39.1	39.5	39.1	39.5
21′	57.6	59.6	59.5	59.6	57.2	59.5
CO_2Me'	52.3	52.7	52.7	52.8	52.5	52.9
$\underline{C}O_2Me'$	174.9	174.1	173.8	175.0	175.4	174.6
11′-OMe	56.9	56.8	56.7	55.9	–	–

[a] Assignments based on HMQC and HMBC.

3.2.4. 19′(S)-Hydroxyervahanine A (8)

Light yellowish oil, $[\alpha]_D$ −105° ($CHCl_3$, *c* 0.16). UV (EtOH) λ_{max} (log ε) 228 (4.75), 287 (4.22), 294 (4.19) nm; IR (dry film) υ_{max} 3365, 1724 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; FABMS *m*/*z* 691 $[MH]^+$ (50), 673 (8), 479 (12), 329 (90), 326 (32), 307 (25), 289 (20), 199 (35), 195 (12), 181 (30), 177 (76), 176 (100), 154 (90), 137 (68); HRFABMS *m*/*z* 691.3881 (calc. for $C_{42}H_{50}N_4O_5+H$, 691.3781).

Acknowledgements

We would like to thank Dr. A.J.M. Leeuwenberg, Laboratory of Plant Taxonomy and Plant Geography, Agricultural University, Wageningen, The Netherlands, for identification of plant material, Dr. K. Komiyama of The Kitasato Institute, Japan, for mass spectra, and the University of Malaya and IRPA for financial support.

References

Danieli, B., Palmisano, G., 1986. Alkaloids from *Tabernaemontana*. In: Brossi, A. (Ed.), The Alkaloids, Vol. 27. Academic Press, Orlando, pp. 1–130 (Chapter 1).

Feng, X.Z., Kan, C., Husson, H.P., Potier, P., Kan, S.W., Lounasmaa, M., 1981. Nouveaux alcaloides indoliques dimeres de type voacamine extraits D′ *Ervatamia hainanensis*. J. Nat. Prod. 44, 670–675.

Kam, T.S., 1999. Alkaloids from Malaysian flora. In: Pelletier, S.W. (Ed.), Alkaloids: Chemical and Biological Perspectives, Vol. 14. Pergamon, Amsterdam, pp. 285–435 (Chapter 2).

Kam, T.S., Sim, K.M., Lim, T.M., 1999. Tronoharine, a novel hexacyclic indole alkaloid from a Malayan *Tabernaemontana*. Tetrahedron Lett. 40, 5409–5412.

Kam, T.S., Sim, K.M., Lim, T.M., 2000. Tronocarpine, a novel pentacyclic indole incorporating a seven-membered lactam moiety. Tetrahedron Lett. 41, 2733–2736.

Kam, T.S., Sim, K.M., Lim, T.M., 2001. Voastrictine, a novel pentacyclic quinolinic alkaloid from *Tabernaemontana*. Tetrahedron Lett. 42, 4721–4723.

Kam, T.S., Sim, K.M., 2001. Dippinines A-D, new iboga-derived indole alkaloids from *Tabernaemontana*. Heterocycles 55, 2405–2412.

Kam, T.S., Sim, K.M., Koyano, T., Toyoshima, M., Hayashi, M., Komiyama, K., 1998. Conodiparines A-D, new bisindoles from *Tabernaemontana*. Reversal of vincristine-resistance with cultured cells. Bioorg. Med. Chem. Lett. 8, 1693–1696.

Kam, T.S., Sim, K.M., 2002. Vobasonidine and vobatricine, novel bisindole alkaloids from a Malayan *Tabernaemontana*. Helv. Chim. Acta 85, 1027–1032.

Kam, T. S., Sim, K. M., Pang, H., 2003. New bisindole alkaloids from a Malayan *Tabernaemontana*. J. Nat. Prod. 66, 11–16.

Kam, T.S., Tan, P.S., 1990. Plumeran alkaloids from *Kopsia profunda*. Phytochemistry 29, 2321–2322.

Leeuwenberg, A.J.M., 1991. Tabernaemontana. The Old World Species, Royal Botanic Gardens, Kew.

Perera, P., Sandberg, F., Van Beek, T.A., Verpoorte, R., 1985. Alkaloids of stem and rootbark of *Tabernaemontana dichotoma*. Phytochemistry 24, 2097–2104.

Takayama, H., Suda, S., Chen, I.S., Kitajima, M., Aimi, N., Sakai, S., 1994. Two new dimeric indole alkaloids from *Tabernaemontana subglobosa*. Chem. Pharm. Bull. 42, 280–284.

Van Beek, T.A., Verpoorte, R., Baerheim Svendsen, A., Leeuwenberg, A.J.M., Bisset, N.G., 1984. *Tabernaemontana* L. (Apocynaceae): a review of its taxonomy, phytochemistry, ethnobotany and pharmacology. J. Ethnopharmacol. 10, 1–156.

Wenkert, E., Cochran, D.W., Gottlieb, H.E., Hagaman, E.W., Filho, R.B., Matos, F.J.A., Madruga, M.I.L.M., 1976. ^{13}C-NMR spectroscopy of naturally occurring substances. XLV. Iboga alkaloids. Helv. Chim. Acta 59, 2437–2442.