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ALKALOIDS OF STEM AND ROOTBARK OF *TABERNAEMONTANA DICHOTOMA*

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Key Word Index—*Tabernaemontana dichotoma*; Apocynaceae; indole alkaloids; new dimeric alkaloids; 3′*R*/*S*-hydroxytabernamine; 3′*R*/*S*-hydroxy-N_4-demethyltabernamine; N_4-demethyltabernamine; 3′*R*/*S*-hydroxy-N_4-demethylervahanine A and B; new monomeric alkaloid; 3,19*R*-oxidocoronaridine.

Abstract—During chemical investigation for compounds possessing biological activity in the stem and rootbark of *Tabernaemontana dichotoma*, 22 alkaloids were isolated. Ten monomeric alkaloids were identified, viz. (−)-apparicine, coronaridine, 3-oxocoronaridine, 3-ketopropylcoronaridine, 19*R*-heyneanine, 3-ketopropyl-19*R*-heyneanine, ibogamine, isomethuenine, perivine and vobasine. Two of the monomeric alkaloids isolated were new, one was identified as 3,19*R*-oxidocoronaridine and the other one is not yet identified. The other ten alkaloids isolated were dimeric compounds, three were identified as tabernamine, voacamine and 3′*R*/*S*-hydroxyvoacamine. Five of the dimers were new alkaloids related to tabernamine and ervahanine type structures and identified as 3′*R*/*S*-hydroxytabernamine, 3′*R*/*S*-hydroxy-N_4-demethyltabernamine, N_4-demethyltabernamine and 3′*R*/*S*-hydroxy-N_4-demethylervahanine A and B. The remaining two alkaloids are partially characterized.

INTRODUCTION

The rootbark and stembark of *Tabernaemontana dichotoma* are used in traditional medicine in Sri Lanka for healing wounds caused by snake bites and the bites of centipedes [1, 2]. The aqueous and ethanol extracts of both the plant parts showed strong antimicrobial activity against Gram-positive, Gram-negative bacteria, a yeast and a fungus. A similar activity was found for the crude tertiary alkaloid fractions of these extracts from the stembark and rootbark [3]. Kupchan *et al.* [4] isolated coronaridine and heyneanine and Schnoes *et al.* [5] isolated voacristine hydroxyindolenine from the rootbark of *T. dichotoma*. Voacamine was shown to be present in the stembark extract of this plant by TLC comparison with an authentic sample [6].

In continuation of our studies on the biologically active compounds from this species we studied the alkaloids present in the root and stembark.

RESULTS AND DISCUSSION

TLC and HPLC analysis showed no qualitative differences in alkaloid content in extracts of stembark and rootbark. Therefore further studies were performed only on stembark material.

From the chloroform soluble fraction of the basified crude acetic acid extract of the stembark of *T. dichotoma* 22 alkaloids, 12 monomeric and 10 dimeric were isolated by means of LC and prep. TLC. Eight of the monomeric alkaloids, were also found in the other parts of the same plant [7–11]. They were identified by means of their spectral data and co-TLC with reference compounds as (−)-apparicine, coronaridine, 3-ketopropylcoronaridine, 19*R*-heyneanine, ibogamine, isomethuenine, perivine and vobasine. One of the monomeric alkaloids was also a known compound, although not previously found in this plant and identified as 3-oxocoronaridine (**1**) [12]. In Table 1 the ^{1}H NMR data of 3-oxocoronaridine are presented. Both the data and the interpretation differ on several points from those given by Feng *et al.* [13] (H-14, H-15a, H-15b, H-20). However the ^{13}C NMR data unambiguously prove the structure as 3-oxocoronaridine.

One of the isolated alkaloids showed UV maxima at 226, 286 and 293 nm, typical for an indole chromophore. The IR showed the presence of a carbomethoxy group (1710 cm^{-1}). The mass spectrum of this compound was similar to that of heyneatine [14] except that all peaks were 30 mu greater. Though this compound showed only one spot in six different TLC-systems, its ^{1}H NMR was highly complex and it seemed to be a mixture of several compounds related to heyneanine. Signals at δ4.28 and 4.25 pointed to the possibility of a 3-hydroxy-iboga type of compound. The mass spectrum could well explain the simultaneous presence of both 3*R*-hydroxy-19*R*-heyneanine and 3*S*-hydroxy-19*R*-heyneanine, as peaks at *m/z* 368 $[M-2]^+$, *m/z* 354 $[M-16]^+$ and *m/z* 353 $[M-17]^+$ which are typical for a 3-hydroxy-iboga alkaloid [15] are present. The intense peak at *m/z* 352 can be explained by the formation of an internal ether bridge resulting in a 3,19*R*-oxidocoronaridine structure. Reduction of the compound with sodium borohydride yielded only 19*R*-heyneanine, which further suggested that this alkaloid could be either 3*R*/*S*-hydroxy-19*R*-heyneanine (**4**, **5**) or 3,19*R*-oxidocoronaridine (**3**) or a mixture of the three compounds as all of these compounds will yield the same reduction product. Carbinolamines readily react with the alcohols and form alkoxy compounds, a behaviour commonly found for alkaloids such as pseudostrychnine, ajmaline and akagarine [16]. As the isolated alkaloid thus has a 3- as well as a 19-hydroxy group, the formation of an internal ether-bond should be

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Table 1. ^{1}H NMR chemical shifts for 3-oxo-coronaridine (1) and 3-ketopropyl-19*R*-heyneanine (2) (δ, $CDCl_3$)

3-Oxocoronaridine					3-Ketopropyl-19R-heyneanine			
NH	*br s*	1H	8.30		*br s*	1H	7.81	
H-3					*m*	1H	1.90	
H-5a	*m*	1H	4.47–4.38		*m*	1H	3.29–3.40	
H-5b								
H-6a	*m*	3H	3.28–3.17		*m*	3H	3.10–3.25	
H-6b								
H-9	*br d*	1H	7.50	$J_{9,10}=7.5$ Hz	*br d*	1H	7.43	$J_{9,10}=7.5$ Hz
H-10	*ddd*	1H	7.15	$J_{10,11}=J_{10,9}=7.5$ Hz, $J_{10,12}=1.5$ Hz	*ddd*	1H	7.16	$J_{10,11}=J_{10,9}=7.5$ Hz, $J_{10,12}=1.5$ Hz
H-11	*ddd*	1H	7.10	$J_{11,10}=J_{11,12}=7.5$ Hz, $J_{11,9}=1.5$ Hz	*ddd*	1H	7.09	$J_{11,10}=J_{11,12}=7.5$ Hz, $J_{11,9}=1.5$ Hz
H-12	*br d*	1H	7.25	$J_{12,11}=7.5$ Hz	*br d*	1H	7.23	$J_{12,11}=7.5$ Hz
H-14	*m*	1H	2.60		*m*	1H	1.86	
H-15a	*dd*	1H	1.98	$J_{15a,15b}=13.1$ Hz, $J_{14,15a}=9.7$ Hz	*m*	1H	1.62	
H-15b	*m*	1H	1.37		*m*	1H	1.45	
H-17a	*dd*	1H	2.64	$J_{17a,17b}=13.3$ Hz, $J_{17a,14}=1.5$ Hz	*dd*	1H	2.63	$J_{17a,17b}=13$ Hz, $J_{17a,14}=1.2$ Hz
H-17b	*dd*	1H	2.31	$J_{17a,17b}=13.3$ Hz, $J_{17b,14}=3.8$ Hz	*d*	1H	2.10	
H-18	*t*	3H	0.98	$J_{18,19}=7.5$ Hz	*dd*	3H	1.26	$J_{18,19}=6.0$ Hz, $J_{18,21b}=2.2$ Hz
H-19	*m*	2H	1.54–1.43	$J_{18,19}=7.0$ Hz	*br qd*	1H	3.87	$J_{18,19}=6.5$ Hz $J_{19,20}=2.8$ Hz
H-20	*m*	1H	1.74		*m*	1H	1.40	
H-21a	*br s*	1H	4.53		*br s*	1H	4.11	
COOMe	*s*	3H	3.72		*s*	3H	3.71	
CH_2COMe					*s*	3H	2.11	
					dd	1H	2.76	$J_{1a,1b}=17$ Hz, $J_{1a,3}=8.5$ Hz
					dd	1H	2.66	$J_{1a,1b}=17$ Hz, $J_{1b,3}=4.5$ Hz

feasible as can be deduced from a Dreiding model. Taking into account the difference for the aromatic methoxy group the spectral data reported for such a 3,19-oxido-type compound by Gunasekera *et al.* [14] are identical to the alkaloid we found, although comparison of the ^{1}H NMR data are difficult as only a 60 MHz spectrum was reported in which only some characteristic signals were assigned. Considering the extreme complexities of the 300 MHz ^{1}H NMR spectrum and the fact that chromatographically only one compound can be observed, the alkaloid is thus believed to be 3,19*R*-oxidocoronaridine (**3**) in equilibrium with its open form, a mixture of 3*R*- and 3*S*-hydroxy-19*R*-heyneanine (**4**, **5**). Due to the presence of the various forms, the ^{13}C NMR was also extremely complex, showing a vast number of signals. In Table 2 the most important signals and their assignment based on the comparison with related compounds is given. The upfield shift for one of the resonances for C-18 at δ17.4 is explained by a γ-gauche interaction of this carbon with N_4 in the conformation with the 3,19-ether bridge. Also the upfield shifts observed for C-15 and C-21 if compared to related heyneanines, can be explained by similar interactions, supporting the presence of an ether bonded form of this alkaloid. This shifts observed for C-3 at δ95.9 and 85.6, respectively, confirm the presence of both a 3*R*- and a 3*S*-hydroxy derivative. The ether bonded form shows a signal at δ89.9 for C-3, which is more upfield than expected for an ether bonded C-3, however, the γ-gauche interaction of C-3 with C-18 contributes to the shifts with a shielding effect.

The spectral data of the other isolated monomeric compound were similar to that of 19*R*-heyneanine. The presence of an additional ketopropyl group at the 3 position was readily recognized in the ^{1}H NMR spectrum and the mass spectrum which showed $[M]^+$ at *m/z* 412. As the ketopropyl derivative of coronaridine was also found in the same extract, it is highly probable that this alkaloid is an artefact formed from acetone with the new alkaloid 3*R*/*S*-hydroxy-19*R*-heyneanine. Thus the alkaloid was identified as 3*R*/*S*-ketopropyl-19*R*-heyneanine (**2**).

From the isolated dimeric compounds three were identified by their spectral data and co-TLC as tabernamine (**6**) [17] voacamine (**12**) [18] and 3'*R*/*S* hydroxyvoacamine (**13**). According to UV, IR and ^{1}H NMR data three of the dimeric alkaloids have structures related to tabernamine. One of the dimeric alkaloids, showed UV maxima at 237, 287 and 295 nm and the IR indicated the presence of a carbomethoxy group (1710 cm^{-1}). The mass spectrum showed an $[M]^+$ at *m/z* 632 and furthermore fragments at *m/z* 630 $[M-2]^+$, 616 $[M-16]^+$, 615 $[M-17]^+$ and 614 $[M-18]^+$, characteristic of a 3-hydroxy-iboga type of alkaloid. In the ^{1}H NMR vobasinyl signals are observed. Furthermore at δ4.18 a broad singlet which integrates for 0.3 protons and at δ4.64 a multiplet (which

Table 2. ^{13}C NMR chemical shifts for 3-oxocoronaridine (1) and 3,19*R*-oxidocoronaridine 3 (in $CDCl_3$)

Carbon No.	Chemical shifts (δ) 3-Oxocoronaridine	3,19*R*-Oxidocoronaridine*
2	135.7	135.6
3	172.9	85.6/89.9/95.9
5	42.7	49.8†/50.6†
6	21.0	21.8‡
7	109.7	110.5
8	127.7	127.9
9	118.3	118.3
10	119.9	119.4
11	122.2	122.2
12	110.6	110.5
13	133.9	132.0
14	30.9	34.9/34.4/31.4§
15	35.4	22.7
16	55.5	52.8†/51.2†
17	35.7	35.7§
18	11.3	17.4/22.0‡
19	27.5	70.2/71.5
20	38.1	40.3‖/41.0‖
21	56.1	53.9†/53.3†
COOMe	52.9	52.8†
COOMe	175.8	174.9

*Only major signals are presented.
†‡§‖Interchangeable.

also includes the H-3 signal (*dd*) of the vobasinyl part) which integrates for 1.7 protons were observed. This also suggested the presence of a 3-hydroxy-iboga type of moiety in the molecule. Reduction of this alkaloid with sodium borohydride yielded tabernamine according to TLC comparison with the reference compound. Taking into account all these data it was concluded that this alkaloid is 3′*R*/*S*-hydroxytabernamine (**7**). Due to the presence of both epimers, a number of signals are doubled in the ^1H NMR, hampering its complete assignment.

A further isolated alkaloid showed in its mass spectrum an $[M]^+$ at *m*/*z* 602. The UV spectrum showed maxima at 232, 288 and 293 nm and the IR spectrum indicated the presence of a carbomethoxy function. The ^1H NMR spectrum was identical to that of tabernamine, except for the N–Me signal at δ2.62 which was missing. It was thus concluded that the unknown alkaloid was N_4-demethyltabernamine (**8**). Another isolated alkaloid was identified as the 3′-hydroxy compound of this alkaloid by means of its spectral data. It showed the characteristic mass spectral behaviour for this type of alkaloid. The ^1H NMR also indicated both the absence of the N_4-methyl group and the presence of two 3′-hydroxy epimers. Reduction of this alkaloid with sodium borohydride yielded a product which had the same TLC behaviour and colour reactions with spray reagents as N_4-demethyltabernamine. The alkaloid is thus identified as 3′*R*/*S*-hydroxy-N_4-demethyltabernamine (**9**).

A further alkaloid showed a $[M]^+$ at *m*/*z* 676 and the typical $[M-2]^+$, $[M-16]^+$, $[M-17]^+$ and $[M-18]^+$ fragments of 3-hydroxy-iboga alkaloids in the mass spectrum. The ^1H NMR spectrum showed the characteristic features of a vobasinyl moiety, with the exception of the N_4-methyl group, which was not observed. The alkaloid is thus derived from perivine instead of vobasine. Two carbomethoxy signals (δ3.64 and 2.45) but no methoxy signal were observed in the ^1H NMR placing the alkaloid in the ervahanine series [19]. From the shifts of the aromatic signals (δ6.98, *d* and 7.31, *s*) a 3,10′-bond between the two parts of the dimers was concluded. The alkaloid was thus identified as 3′*R*/*S*-hydroxy-N_4-demethylervahanine B (**11**). The ^{13}C NMR spectrum provided further evidence for this structure (Table 3), also confirming the presence of the two epimers (signals at δ93.9 and 83.1).

One more alkaloid was isolated with similar spectral data as 3′*R*/*S*-hydroxy-N_4-demethylervahanine B. As the

Table 3. ^{13}C chemical shifts for 3′*R*/*S*-hydroxy-N_4-demethylervahanine A (**10**) and B (**11**) (in $CDCl_3$)

Carbon No.	Chemical shifts (δ) **10**	**11**
2	137.0*	137.1†
3	45.4	45.3
5	61.5	60.2
6	24.6	24.6
7	110.7	110.6
8	129.7‡	129.6
9	117.7§	117.7‖
10	117.7§	117.7‖
11	121.7	121.8
12	109.8	109.8
13	134.3*	—
14	39.1	39.1
15	34.2	34.2
16	49.9	49.9
18	12.1	12.1
19	119.0	118.6
20	139.8*	139.9†
21	44.2	44.2
COOMe	50.0	50.1
COOCH$_3$	171.5	171.5
2′	137.4*	135.9†
3′	86.1/93.9	86.2/94.0
5′	51.2	51.2
6′	21.8	21.9
7′	110.9	109.4
8′	128.4‡	127.0
9′	117.0§	119.1‖
10′	137.4*	119.6‖
11′	122.7	140.0†
12′	110.8	110.8
13′	135.9*	135.7†
14′	34.4/30.8	34.4/30.8
15′	24.6	24.6
16′	52.6	52.6
17′	35.4	35.4
18′	11.7	11.6
19′	26.8	26.9
20′	37.9	37.6
21′	56.0	56.0
COOMe	53.3	53.4
COOMe	—	174.4

*†‡§‖Interchangeable.

R_f values of these two compounds were different in the TLC, the alkaloid was thought to be another derivative of the ervahanine series. Since in the ^{1}H NMR spectrum the aromatic part of this alkaloid was identical to that of tabernamine, which has a 3,11′-bond between the two parts of the dimer, the alkaloid was identified as 3′*R*/*S*-hydroxy-N_4-demethylervahanine A (**10**).

Three of the isolated alkaloids could only partly be characterized due to the small amounts obtained. 20A is a new dimeric indole alkaloid, which was also isolated independently from the root bark of *T. chippii* [15]. This alkaloid showed $[M]^+$ at *m/z* 600 with the major fragments at *m/z* 490, 182, 180 and 122 suggesting the presence of a vobasinyl-half. However the ^{1}H NMR data did not confirm this. For instance no N_4-methyl and no carbomethoxy group at δ2.65 and 2.45, respectively, were present and also other peaks characteristic for the vobasinyl-half were missing. Thus it seems to be the only dimeric alkaloid isolated from these two species lacking such a half. Other characteristic signals in the ^{1}H NMR spectrum were the presence of two doublets (J = 18 Hz, 1H each) at δ4.80 and 4.45 and two ethylidene side chains (J = 7 Hz, 3H each) at δ1.85 and 1.65. These and the M_r suggest a structure somewhat similar to vobparicine [20] although no vobasinyl-half in its normal configuration and conformation can be present. The structure elucidation of this alkaloid is in progress and will be reported in due course.

17C is another dimeric alkaloid which seemed to belong to the ervahanine series. The ^{1}H NMR showed most of the characteristic peaks of the vobasinyl part and the presence of two carbomethoxy groups. Due to the small amount available of this alkaloid it was not possible to elucidate the complete structure.

One of the isolated minor monomeric alkaloids gave a bright blue colour with the Fe^{3+} spray reagent and showed $[M]^+$ at *m/z* 324. Its ^{1}H NMR spectrum revealed this alkaloid to be a new alkaloid. The studies of the structure of this alkaloid are also in progress.

The present investigation together with the previous investigations [7–11] of *T. dichotoma* resulted in the isolation of 32 (Table 4) different indole alkaloids from the different plant parts. Stemmadenine which belongs to the biosynthetically less evolved group of alkaloids was found only in the seeds. The majority of the alkaloids isolated belong to the biosynthetically more evolved ibogan class. Perivine and vobasine, the most abundant alkaloids, belong to the biosynthetically least evolved corynanthean class. Most of the dimeric alkaloids isolated were a combination of these two classes. The most

Table 4. Alkaloids isolated from different parts of *T. dichotoma*

Alkaloid	L	S	F	SB	RB
Perivine	X		X	X	
Vobasine	X		X	X	
Isomethuenine	X		X	X	
Stemmadenine		X			
(−)-Apparicine	X		X	X	
16*S*-Hydroxy-16,22-dihydroapparicine	X				
Vallesamine			X		
O-Acetylvallesamine			X		
Voaphylline		X			
Voaphylline hydroxyindolenine	X	X			
12-Methoxyvoaphylline	X		X		
Tabersonine		X			
Coronaridine		X	X	X	X[4]
3-Ketopropylcoronaridine			X	X	
3-Oxocoronaridine				X	
19*R*-Heyneanine			X	X	X[4]
3-Ketopropyl-19*R*-heyneanine				X	
3,19*R*-Oxidocoronaridine				X	
19*R*-Iboxygaine	X				
Ibogamine		X		X	
Voacangine		X			
19*R*-Voacristine	X				
Voacristine hydroxyindolenine					X[5]
Dichomine	X		X		
Tabernamine				X	
Voacamine				X	
3′*R*/*S*-Hydroxyvoacamine				X	
3′*R*/*S*-Hydroxy-N_4-demethylervahanine B				X	
3′*R*/*S*-Hydroxy-N_4-demethylervahanine A				X	
3′*R*/*S*-Hydroxy-N_4-demethyltabernamine				X	
3′*R*/*S*-Hydroxytabernamine				X	
N_4-Demethyltabernamine				X	
Monogagaine				X	

L = leaves; S = seeds; F = fruits; SB = stembark; RB = rootbark.

common combination seems to be the perivinyl-iboga type instead of vobasinyl-iboga as found in other *Tabernaemontana* species. A number of new derivatives of the perivinyl-iboga type of dimeric compounds were found in the stembark of this species. Although methoxylation of the aromatic ring in the iboga part was not commonly found, hydroxylation of the 3'-position of this part was found abundantly in this species. The stembark of the plant seems to be rich in this type of compounds. Though no definite correlation could be seen (Scheme 1) between the degree of metabolic evolution and the plant part from which the alkaloid was isolated, it could clearly be seen that the dimeric alkaloids were only found in the stembark and rootbark of the plant but not in any other parts. As previous phytochemical investigations of many different species have shown that the genus *Tabernaemontana* contains primarily indole alkaloids of the corynanthean, ibogan and aspidospermatan classes and dimeric alkaloids which are a combination of these classes [20]. With respect to the present studies it can be concluded that the species investigated is a typical example of the genus *Tabernaemontana*.

Some preliminary studies were carried out to locate the alkaloids possessing antimicrobial properties by using the biogram technique with *Bacillus subtilis* as test organism. These studies revealed that the mixture of 3*R*/*S*-hydroxyheyneanine and 3,19*R*-oxidocoronaridine as the most active antimicrobial compounds found in the stembark extract. Furthermore the dimeric compounds tabernamine, 3'*R*/*S*-hydroxytabernamine, 3'*R*/*S*-hydroxy-N_4-demethyltabernamine and 3'*R*/*S*-hydroxy-N_4-demethylervahanine B also showed activity in these preliminary studies. Further studies are in progress.

EXPERIMENTAL

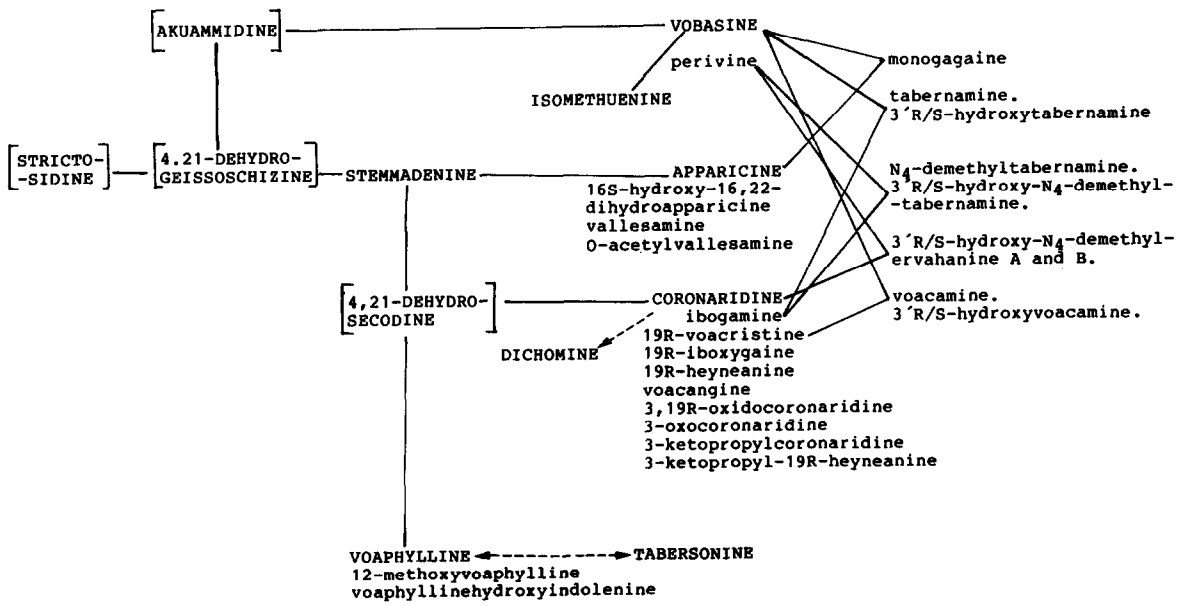
T. dichotoma Roxb. et Wall. was collected in Colombo, Sri Lanka and identified by Prof. S. Balasubramanium, Dept. of Botany, University of Peradeniya, Sri Lanka and Prof. F. Sandberg, Dept. of Pharmacognosy, Uppsala, Sweden. Voucher specimens are kept at the Dept. of Pharmacognosy, University of Uppsala, Sweden.

General. MS were recorded at 70 eV and 12 eV with direct inlet. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ with 100 and 300 MHz instruments.

Extraction. Fresh stembark (10 kg) was macerated with 4% aq. HOAc and extracted twice with this solvent for 24 hr. The extracts were acidified with 1% HCl to pH 2 and Mayer's reagent was added until no more ppt was formed. The ppt was collected by filtration and dissolved in Me_2CO–MeOH–H_2O (6:2:1). The soln was passed over an Amberlite IRA-400 anion exchange resin (Cl^- form). The eluate was concd under red. pres. until the Me_2CO and MeOH were removed. The remaining H_2O phase, containing alkaloid chlorides, was basified with 25% NH_3 and extracted with $CHCl_3$. The $CHCl_3$ phase, containing tertiary alkaloids, was taken to dryness (6 g).

Isolation of alkaloids. Crude tertiary alkaloid mixture (6 g) was chromatographed over a silica gel column (silica gel 60 GF 254). The elution started with hexane, $CHCl_3$ was gradually added until the eluant was pure $CHCl_3$. Then MeOH was gradually added until the final eluant was pure MeOH. Fractions (20 ml) were collected and grouped according to the results of TLC analysis. From the combined fractions alkaloids were obtained pure with the aid of repeated prep. TLC. The following TLC systems were used for analysis and identification of alkaloids [21]. A. Cyclohexane–$CHCl_3$–Et_2NH, 6:3:1. B. Toluene–EtOH (satd with NH_3),* 19:1. C. $CHCl_3$–MeOH, 9:1. D. EtOAc–*iso*PrOH (satd with NH_3),* 17:3. E. petrol–*iso*PrOH (satd with NH_3),* 9:1. F. hexane–MeCOEt–Et_2NH, 8:1:1. * Prior to development the plates were placed in an atmosphere of NH_3 for 20 min. The plates precoated with silica gel 60 (0.25 and 0.5 mm, silica gel F 254 E. Merck), were developed in satd chambers. The alkaloids were detected by UV light at 254 and 366 nm, spraying with 0.2 M $FeCl_3$ in 35% $HClO_4$ (Fe^{3+}) and 1% $Ce(SO_4)_2$ in 10% H_2SO_4 (Ce^{4+}) followed by heating.

HPLC. Analyses were carried out on a Waters μPorasil column



Scheme 1. Plausible biogenetic interrelationship of the isolated alkaloids, according to Kisakürek and Hesse [11]. Intermediates which have not been isolated from this species are enclosed in square brackets.

(300 × 3.9 mm i.d.) with the solvent systems $CHCl_3$–MeOH–25% NH_3 (99:1:0.2) and hexane–$CHCl_3$ (99:1) at a flow rate of 1.0 ml/min. Detection wavelength was 280 nm.

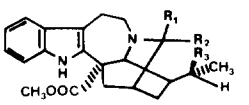
Reduction. Alkaloid (1 mg) was dissolved in 2 ml of EtOH–H_2O (7:1) and 5 mg of $NaBH_4$ was added to the soln which was then stirred for 2–3 hr at room temp. After reaction, 1–2 ml of H_2O was added to the reaction mixture which was then acidified with 4 M HCl. $KHCO_3$ was then added until the soln was basic and it was extracted twice with $CHCl_3$. The $CHCl_3$ phase was then evapd *in vacuo* to dryness.

Antibacterial activity. A preliminary assay for antibacterial activity of individual alkaloids was performed with the biogram technique [22] using *Bacillus subtilis* as test organism.

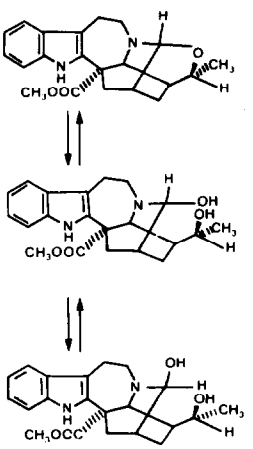
Physical data of alkaloids. Physical data of (−)-apparicine, coronaridine, 3-ketopropylcoronaridine, 19*R*-heyneanine, ibogamine, isomethuenine, perivine and vobasine are identical to those reported in previous publications [7–11].

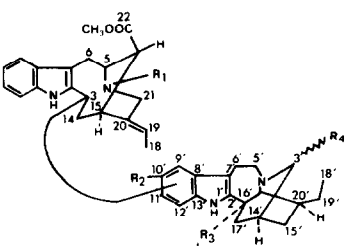
3-Oxocoronaridine (**1**). UV λ_{max}^{EtOH} nm (log ε): 224 (4.26), 285 (3.68), 293 (3.63). IR ν_{max}^{KBr} cm^{-1}: 3200, 2960, 2890, 1720, 1640, 1450, 1250, 1130, 730. MS *m/z* (rel. int., %): 352 $[M]^+$ (94), 229 (28), 214 (22), 197 (46), 195 (25), 154 (40), 143 (16), 138 (17), 124 (100); ^1H NMR: see Table 1; ^{13}C NMR: see Table 2. R_f values in TLC systems A and B were 0.25 and 0.27. A pale green colour was obtained with Fe^{3+} upon heating.

3-Ketopropyl-19R-heyneanine (**2**). UV λ_{max}^{EtOH} nm (log ε): 224 (4.32), 284 (3.44), 296 (3.58). IR ν_{max}^{KBr} cm^{-1}: 3400, 2950, 2880,



	R_1	R_2	R_3	
1	=O		H	3-oxocoronaridine
2	$CH_2{\cdot}CO{\cdot}CH_3$	H	OH	3-Ketopropyl-19R-heyneanine





	R_1	R_2	R_3	R_4	
6	CH_3	H	H	H	Tabernamine (C_3-$C_{11'}$ bond)
7	CH_3	H	H	OH	3'-R/S-Hydroxytabernamine (C_3-$C_{11'}$ bond)
8	H	H	H	H	N_4-Demethyltabernamine (C_3-$C_{11'}$ bond)
9	H	H	H	OH	3'-R/S-Hydroxy-N_4-demethyltabernamine (C_3-$C_{11'}$ bond)
10	H	H	$COOCH_3$	OH	3'-R/S-Hydroxy-N_4-demethylervahanine A (C_3-$C_{11'}$ bond)
11	H		$COOCH_3$	OH	3'-R/S-Hydroxy-N_4-demethylervahanine B (C_3-$C_{10'}$ bond)
12	CH_3	OCH_3	$COOCH_3$	H	Voacamine (C_3-$C_{11'}$ bond)
13	CH_3	OCH_3	$COOCH_3$	OH	3'-R/S-Hydroxyvoacamine (C-$C_{11'}$ bond)

1705, 1450. MS *m/z* (rel. int., %): 412 $[M]^+$ (71), 396 (12), 368 (16), 354 (24), 353 (99), 349 (18), 336 (15), 229 (23), 228 (23), 214 (26), 208 (16), 194 (16), 182 (12), 180 (15), 170 (12), 154 (50), 144 (20), 143 (16), 130 (19), 108 (21). ^{1}H NMR: see Table 1. R_f values in TLC systems A and B were 0.29 and 0.27. With Fe^{3+} a pale grey colour was obtained upon heating.

3,19R-*Oxidocoronaridine* **3**. UV λ_{max}^{EtOH} nm (log ε): 226 (4.22), 286 (3.58), 293 (3.56). IR ν_{max}^{KBr} cm^{-1}: 3410, 2940, 2880, 1720, 1450. MS *m/z* (rel. int., %): 368 (3), 354 (9), 353 (28), 352 (100), 337 (13), 336 (6), 309 (15), 308 (12), 307 (12), 270 (28), 229 (25), 228 (12), 215 (25), 214 (70), 209 (11), 206 (10), 194 (11), 182 (15), 180 (17), 168 (9), 167 (22), 154 (45), 150 (20), 138 (37). ^{13}C NMR: see Table 2. R_f values in TLC systems A and B were 0.24 and 0.25. With Fe^{3+} a dark grey colour was obtained. Reduction with $NaBH_4$ yielded 19*R*-heyneanine.

Tabernamine **(6)**. UV λ_{max}^{EtOH} nm (log ε): 236 (4.52), 287 (4.02), 295 (4.00). IR ν_{max}^{KBr} cm^{-1}: 3440, 3290, 2940, 1720, 1450. MS *m/z* (rel. int., %): 616 $[M]^+$ (100), 436 (10), 194 (18), 182 (42), 181 (81), 180 (50), 137 (13), 136 (46), 135 (30), 124 (18), 123 (21), 122 (95). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.61 (1H, *br s*, N–H), 7.56 (*br d*, 1H, H-9, $J_{9,10}$ = 6.5 Hz), 7.53 (1H, *br s*, N–H'), 7.35 (1H, *br d*, H-9', $J_{9,10}$ = 8.0 Hz), 7.10–7.00 (3H, *m*, H-10, H-11, H-12), 7.05 (1H, *s*, H-12'), 6.96 (1H, *d*, H-10'), 5.36 (1H, *q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.62 (1H, *dd*, H-3, $J_{3,14a}$ = 13 Hz, $J_{3,14b}$ = 3 Hz), 4.08 (1H, *m*, H-5), 3.78 (1H, *m*, H-15), 3.74 (1H, *br d*, H-21b), 2.83 (1H, *br d*, H-21a), 2.76 (1H, *br t*, H-16, $J_{16,15}$ = 2.8 Hz, $J_{16,5}$ = 2.8 Hz), 2.62 (3H, *s*, N–Me), 2.45 (1H, *s*, COOMe), 1.65 (3H, *d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.88 (3H, *t*, H-18'). R_f in TLC systems A and B were 0.38 and 0.35. Pale blue green colour with Fe^{3+} was obtained upon heating.

3'R/S-*Hydroxytabernamine* **(7)**. UV λ_{max}^{EtOH} nm (log ε): 237 (4.84), 287 (4.34), 295 (4.31). IR ν_{max}^{KBr} cm^{-1}: 3440, 2940, 2880, 1710, 1450. MS *m/z* (rel. int., %): 632 $[M]^+$ (5), 630 $[M-2]^+$ (8), 616 $[M-18]^+$ (100), 614 $[M-16]^+$ (5), 437 (11), 306 (9), 225 (20), 194 (31), 182 (69), 181 (73), 180 (50), 136 (59), 135 (31), 122 (91). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.60 (1H, *br s*, N–H), 7.60–7.48 (2H, *m*, H-9, N–H'), 7.36 (1H, *br d*, H-9', $J_{9',10'}$ = 7.5 Hz), 7.10–6.92 (5H, *m*, H-10, H-11, H-12, H-10', H-12'), 5.30 (1H, *br q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.64 (1H, *dd*, H-3, $J_{3a,14a}$ = 13.0, $J_{3,14b}$ = 3.0 Hz), 4.18/4.16 (1H, *s*, H-3' *R* and *S*), 4.02 (1H, *m*, H-5), 3.78 (1H, *m*, H-15), 3.71 (1H, *br d*, H-21b), 3.38 (1H, *br dd*, H-6a, $J_{6a,6b}$ = 14.5 Hz, $J_{6a,5}$ = 10.5 Hz), 3.25 (1H, *dd*, H-6b, $J_{6b,6a}$ = 14.5 Hz, $J_{6b,5}$ = 8 Hz), 2.88 (1H, *br d*, H-21a, $J_{21b,21a}$ = 13.8 Hz), 2.70 (1H, *br d*, H-16), 2.58 (3H, *s*, N–Me), 2.45 (3H, *s*, COOMe), 1.64 (3H, *d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.89 (3H, *m*, H-18'). R_f in TLC systems A and B were 0.35 and 0.31. With Fe^{3+} a pale blue green colour was obtained. Reduction with $NaBH_4$ yielded tabernamine.

N_4-*Demethyltabernamine* **(8)**. UV λ_{max}^{EtOH} nm (log ε): 234 (4.80), 285 (4.28), 294 (4.18). IR ν_{max}^{KBr} cm^{-1}: 3420, 2940, 2880, 1710, 1600, 1460, 720. MS *m/z* (rel. int., %): 602 $[M]^+$ (38), 601 (21), 438 (8), 437 (13), 424 (12), 422 (11), 338 (16), 194 (16), 183 (21), 182 (64), 181 (85), 180 (71), 156 (25), 144 (24), 136 (42), 124 (29), 122 (100). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.86 (1H, *s*, N–H), 7.55 (2H, *m*, H-9, N–H'), 7.40 (1H, *br d*, H-9'), 7.10–6.94 (5H, *m*, H-10, H-11, H-12, H-10', H-12'), 5.28 (1H, *br q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.64 (1H, *dd*, H-3, $J_{3a,14a}$ = 13.0 Hz, $J_{3,14b}$ = 3.0 Hz), 4.22 (1H, *m*, H-5), 3.99 (1H, *m*, H-15), 3.85 (1H, *m*, H-21b), 2.56 (1H, *m*, H-16), 2.46 (3H, *s*, COOMe), 1.64 (3H, *d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.88 (3H, *t*, H-18'). R_f in TLC systems A and B were 0.34 and 0.33. A pale yellow colour was obtained with Fe^{3+}.

3'R/S-*Hydroxy-N_4-demethyltabernamine* **(9)**. UV λ_{max}^{EtOH} nm (log ε): 236 (4.87), 286 (4.30), 296 (4.27). IR ν_{max}^{KBr} cm^{-1}: 3420, 2940, 2890, 1720, 1460, 1220, 730. MS *m/z* (rel. int., %): 618 $[M]^+$ (8), 616 $[M-2]^+$ (22), 602 $[M-16]^+$ (8), 601 $[M-17]^+$ (7), 600 $[M-18]^+$ (10), 436 (12), 434 (8), 423 (11), 422 (10), 420 (18), 307 (7), 306 (8), 305 (11), 295 (6), 194 (77), 182 (50), 180 (51), 168 (11), 166 (20), 137 (88), 136 (100), 124 (70), 122 (72). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.57 (2H, *m*, N–H, H-9), 7.51 (1H, *s*, N–H'), 7.37 (1H, *d*, H-9', $J_{9',10'}$ = 8.0 Hz), 7.09–7.01 (5H, *m*, H-10, H-11, H-12, H-10', H-12'), 5.28 (1H, *q*, H-19, $J_{18,19}$ = 8.0 Hz), 4.65 (1H, *dd*, H-3, $J_{3,14a}$ = 13.5 Hz, $J_{3,14b}$ = 3.0 Hz), 4.23 (1H, *m*, H-5), 4.06 and 4.01 (1H, *br s*, H-3'*R* and *S*), 3.85 (1H, *m*, H-15), 2.57 (1H, *m*, H-16), 2.43 (3H, *s*, COOMe), 1.63 (3H, *d*, H-18, $J_{18,19}$ = 7.0 Hz), 0.88 (3H, *m*, H-18'). R_f in TLC systems A and B were 0.22 and 0.23. A purple red colour with Fe^{3+} upon heating was obtained. Reduction with $NaBH_4$ yielded N_4-demethyltabernamine.

3'R/S-*Hydroxy-N_4-demethylervahanine A* **(10)**. UV λ_{max}^{EtOH} nm (log ε): 230 (4.60), 288 (4.28), 293 (sh). IR ν_{max}^{KBr} cm^{-1}: 3420, 2950, 2840, 1720, 1640, 1450. MS *m/z* (rel. int.): 676 $[M]^+$ (4), 674 $[M-2]^+$ (14), 660 $[M-16]^+$ (8), 659 $[M-17]^+$ (8), 658 (7), 646 (6), 630 (10), 600 (6), 436 (10), 348 (18), 324 (12), 322 (28), 280 (26), 220 (64), 194 (72), 183 (17), 182 (100), 180 (95), 148 (78), 136 (98), 124 (42), 122 (95). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.80 (1H, *br s*, N–H), 7.56 (2H, *m*, H-9, N–H'), 7.38 (1H, *m*, H-10'), 7.07–6.98 (5H, *m*, H-10, H-11, H-12, H-9', H-12'), 5.30 (1H, *q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.65 (1H, *dd*, H-3, $J_{3,14a}$ = 13.5 Hz, $J_{3,14b}$ = 3.0 Hz), 3.63 (3H, *s*, COOMe'), 2.55 (1H, *s*, H-16), 2.45 (3H, *s*, COOMe), 1.62 (3H, *br d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.90 (3H, *m*, H-18'). R_f in TLC systems A and B were 0.15 and 0.17 and a brown colour with Fe^{3+} upon heating was obtained.

3'R/S-*Hydroxy-N_4-demethylervahanine B* **(11)**. UV λ_{max}^{EtOH} nm (log ε): 232 (4.67), 288 (4.18), 293 (sh, 4.17). IR ν_{max}^{KBr} cm^{-1}: 3430, 2940, 2880, 1710, 1450. MS *m/z* (rel. int.): 676 $[M]^+$ (4), 674 $[M-2]^+$ (22), 660 $[M-16]^+$ (16), 659 $[M-17]^+$ (13), 658 $[M-18]^+$ (12), 644 (8), 630 (8), 628 (6), 616 (20), 602 (21), 584 (14), 306 (67), 224 (88), 194 (80), 180 (54), 181 (58), 182 (100), 146 (80), 136 (97), 122 (98). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.82 (1H, *br s*, N–H) 7.61 (1H, *br s*, N–H'), 7.58 (1H, *m*, H-9), 7.31 (1H, *s*, H-9'), 7.09–6.96 (5H, *m*, H-10, H-11, H-12, H-11', H-12'), 5.30 (1H, *q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.66 (1H, *dd*, H-3, $J_{3,14a}$ = 13.5 Hz, $J_{3,14b}$ = 3.0 Hz), 4.38/4.08 (1H, *s*, H-3'*R*/*S*), 4.23 (1H, *m*, H-5), 3.82 (1H, *m*, H-15), 3.73 (1H, *br d*, H-21b, $J_{21b,21a}$ = 15.0 Hz), 3.15 (1H, *br d*, H-21a, $J_{21a,21b}$ = 15.0 Hz), 3.64 (3H, *s*, COOMe'), 2.56 (1H, *m*, H-16), 2.45 (3H, *s*, COOMe), 1.62 (3H, *br d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.88 (3H, *m*, H-18'). R_f in TLC systems A and B were 0.19 and 0.18. With Fe^{3+} a reddish yellow colour upon heating was obtained. ^{13}C NMR: see Table 3.

Voacamine **(12)**. UV λ_{max}^{EtOH} nm (log ε): 225 (4.49), 286 (3.94), 294 (3.92). IR ν_{max}^{KBr} cm^{-1}: 3400, 2940, 2860, 1720, 1450. MS *m/z* (rel. int.): 704 $[M]^+$ (12), 701 (10), 674 (5), 645 (2), 524 (2), 522 (3), 510 (8), 428 (10), 300 (7), 278 (18), 194 (24), 182 (100), 180 (90), 136 (42), 124 (15),122 (12). R_f values in systems A and B 0.48 and 0.40, respectively. With Ce^{4+} a pale blue colour, and with Fe^{3+} a blue green colour were obtained.

3'R/S-*Hydroxyvoacamine* **(13)**. UV λ_{max}^{EtOH} nm (log ε): 225 (4.09), 288 (3.62), 295 (3.63). IR ν_{max}^{KBr} cm^{-1}: 3420, 2930, 2870, 1710, 1640, 1450. MS *m/z* (rel. int.): 720 $[M]^+$ (5), 718 $[M-2]^+$ (8), 704 $[M-16]^+$ (44), 702 $[M-18]^+$ (18), 700 (7), 646 (9), 522 (14), 510 (41), 208 (32), 194 (27), 182 (100), 180 (77), 136 (49), 122 (87), 124 (25). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.71 (1H, *br s*, N–H), 7.52 (2H, *m*, H-9, N–H'), 7.09–7.02 (4H, *m*, H-10, H-11, H-12, H-9'), 6.91 (1H, *s*, H-12'), 6.75 (1H, *s*, H-11'), 5.20 (1H, *q*, H-19, $J_{18,19}$ = 7.0 Hz), 5.14 (1H, *br dd*, H-3), 4.00 (3H, *br s*, aromatic OMe), 3.64 (3H, *s*, COOMe'), 2.70 (3H, *br s*, N–Me), 2.45 (3H, *s*, COOMe), 1.69 (3H, *br d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.90 (3H, *m*, H-18'). R_f values in TLC systems A and B were 0.43 and 0.42 and a blue green colour with Fe^{3+} upon heating was obtained. Reduction with $NaBH_4$ yielded voacamine.

17*C*. UV λ_{max}^{EtOH} nm (log ε): 231 (4.67), 288 (4.18), 293 (sh, 4.17). IR ν_{max}^{KBr} cm^{-1}: 3400, 2900, 2860, 1710, 1450. MS *m/z* (rel. int.): 688 (11), 674 $[M]^+$ (27), 658 (16), 632 (15), 600 (27), 394 (11), 338 (11),

337 (23), 296 (11), 280 (20), 195 (10), 180 (20), 168 (12), 156 (11), 154 (24), 138 (14), 136 (39), 124 (25). ^{1}H NMR (300 MHz, $CDCl_3$): δ7.66 (1H, *br s*, N–H), 7.54 (1H, *m*, H-9), 7.48 (1H, *s*, N–H'), 7.35 (1H, *d*, H-9'), 7.02–7.10 (3H, *m*, H-10, H-11, H-12), 6.98 (1H, *s*, H-12'), 6.04 (1H, *dd*), 5.42 (1H, *q*, H-19, $J_{18,19}$ = 6.5 Hz), 4.60 (1H, *dd*, H-3, $J_{3,14a}$ = 13.5 Hz, $J_{3,14b}$ = 3.0 Hz), 3.67 (3H, *s*, COOMe'), 2.71 (1H, *s*, H-16), 2.46 (3H, *s*, COOMe), 1.67 (3H, *br d*, H-18, $J_{18,19}$ = 6.5 Hz), 0.89 (3H, *d* of *m*, H-18'). R_f values in TLC systems A and B were 0.49 and 0.48. With Fe^{3+} a grey colour upon heating was obtained.

20*A*. UV λ_{max}^{EtOH} nm: 224, 287, 294. IR ν_{max}^{KBr} cm^{-1}: 3440, 2960, 1720, 1620, 1450. MS *m/z* (rel. int.): 600 $[M]^+$, 490, 262, 250, 194, 182, 180, 168, 166, 154, 136, 124, 122. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.52 (1H, *s*, N–H), 7.39–6.55 (7H, aromatic), 5.70 (1H, *q*, H-19, $J_{18,19}$ = 6.5 Hz), 5.25 (1H, *q*, H-19'), 4.80 (1H, *d*), 4.45 (1H, *d*), 3.45 (3H, *s*, COOMe), 2.45 (3H, *s*), 1.85 (3H, *d*), 1.65 (3H, *d*).

25*B*. UV λ_{max}^{EtOH} nm (log ε): 229 (3.89), 295 (3.64), 328 (3.62). IR ν_{max}^{KBr} cm^{-1}: 3430, 2940, 2890, 1660, 1600, 1450, 730. MS *m/z* (rel. int.): 324 $[M]^+$, 229, 194, 182, 180, 154, 126, 124. ^{1}H NMR (300 MHz, $CDCl_3$): δ8.82 (1H, *s*, N–H), 7.18–6.83 (4H, aromatic), 4.20 (1H, *br s*), 3.78 (3H, *s*), 3.25 (2H, *m*), 3.16 (1H, *br s*), 0.72 (3H, *t*).

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