Structure of the *Bis*-Indole Alkaloids Tabernaemontabovine and Tabernaemontavine – A Revision

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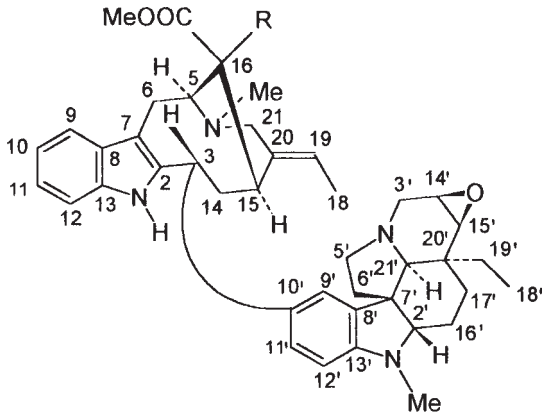
Abstract. The structures of the *bis*-indole alkaloids tabernaemontabovine (**1**) and tabernaemontavine (**2**) have been revised on the basis of APT, ^{1}H-^{1}H COSY, gradient-selected HSQC and gradient-selected HMBC spectra.

Tabernaemontana bovina Lour. [1] is used in the traditional medicine of Vietnam. Especially the roots are applied for the treatment of fever and jaundice [2]. Recently, we reported the structural elucidation of the novel indole alkaloids 3-oxomehranine and 14α,15β-dihydroxy-*N*-methylaspidospermine [3] as well as the *bis*-indole alkaloids tabernaebovine and methylenebismehranine [4], isolated besides a series of already known members from aerial parts of *T. bovina*. In addition, we proposed structures for two further new *bis*-indole alkaloids, named tabernaemontabovine and tabernaemontavine, from the same plant source [5]. More detailed NMR studies led to structure revisions of both compounds, now correctly represented as alkaloids **1** and **2**, respectively, with a vobasinyl substructure.



1 R = H

2 R = $^{17}CH_2OH$

Results and Discussion

The elemental composition of tabernaemontabovine (**1**) was shown to be $C_{41}H_{50}N_4O_3$ by high-resolution mass spectrometry [5].

The ^{1}H and ^{13}C NMR signals of **1** (Table 1) and the structure of the alkaloid were assigned on the basis of APT, ^{1}H-^{1}H DQF COSY, gradient-selected HSQC and gradient-selected HMBC spectra. Chemical shifts and coupling constants $J_{H,H}$ of **1** for the molecule half containing C-2' to C-21' were practically identical with those of analogous atoms of tabernaebovine and methylenebismehranine [4] indicating the identical mehranine substructure [5]. A detailed analysis of the HMBC spectrum for the molecular part of **1** containing C-2 to C-21 revealed several correlations that were not in agreement with the earlier proposed structure. Furthermore, some correlations between atoms were unfortunately derived from equivocal data of the ^{1}H-^{1}H COSY and HMBC spectra (overlapping or nearly isochronous signals). However, the ^{13}C chemical shifts ($CDCl_3$) of tabernaemontabovine (**1**) for C-2 to C-21 (including OMe, C=O, NMe, Table 1) agreed very well with those of the vobasinyl part of conoduramine [6] except for C-2, C-3 and C-14, which represent the nearest neighbourhood of the connection between both molecule parts. The ^{1}H NMR spectra of **1** and 19'(*R*)-hydroxyconodurine [6] were also very similar except for H-3 and NH, although **1** was measured in $CDCl_3$ and 19'(*R*)-hydroxyconodurine in DMSO-d_6. All unequivocal correlations from the ^{1}H-^{1}H COSY and HMBC spectra were in complete accordance with this vobasinyl structure and the 3,10'-bond. Corresponding couplings for **1** were detected between H-3/H-14A, H-5/H-6A, H-5/H-6B, H-5/H-16, H-6A/H-6B, H_3-18/H-19, H-3/C-7, H-3/C-14, H-3/C-15, H-3/C-11', H-5/C-7, H-5/C=O, H-6A/C-5, H-6A/C-7, H-6A/C-8, H-6A/C-16, H-6B/C-5, H-6B/C-7, H-6B/C-8, H-9/C-8, H-9/C-11, H-9/C-13, H-14A/C-3, H-14A/C-15, H-16/C-5, H-16/C-6, H-16/C-14, H-16/C-15, H-16/C=O, H_3-18/C-21 (4 bonds), H-19/C-15, H-19/C-18, H-19/C-21, H-21A/C-5, H-21A/C-15, H-21A/NMe, NH/C-3, NH/C-7, NH/C-8, OMe/C=O, H-9'/C-3, H-11'/C-3. The above-mentioned data unambiguously confirmed the structure of tabernaemontabovine as **1**, in which a vobasine and a mehranine substructure are connected *via* a C-3/C-10' bond.

According to high-resolution mass spectrometry the elemental composition of tabernaemontavine (**2**) was shown to be $C_{42}H_{52}N_4O_4$ [5].

The ^{1}H and ^{13}C NMR signals of **2** (Table 1) and the structure of the alkaloid were assigned by means of APT, gradient-selected ^{1}H-^{1}H COSY, gradient-selected HSQC and gradient-selected HMBC spectra. As in the case of **1** chemical

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Table 1 ^{1}H and ^{13}C NMR data of compounds **1** and **2** [499.8/75.5 MHz, 2D: 499.8/125.7 MHz, $CDCl_3$, δ values, *J* (Hz) in parentheses, ^{1}H signals without multiplet specification taken from the 2D spectra]

Position	**1**		**2**	
	H	C	H	C
2	–	137.8	–	137.4 [a])
3	4.48 *dd* (13.0, 2.9)	44.7	4.48 *d* (11.9)	44.5
5	4.02 *td* (9.2, 2.4)	59.7	3.91 *t* (9.0)	59.9
6A	3.24 *dd* (14.6, 7.9)	19.3	3.27 *dd* (14.6, 8.2)	17.1
6B	3.45 *dd* (14.3, 10.7)		3.50	
7	–	110.4	–	110.4
8	–	129.8	–	130.0
9	7.54 *dd* (5.5, 2.4)	117.5	7.54 *m*	117.6
10	7.06	118.8	7.05	118.9
11	7.06	121.6	7.05	121.8
12	7.06	109.7	7.05	109.8
13	–	136.0	–	136.2
14A	1.84 *ddd* (15.3, 7.0, 3.4)	39.1	1.87 *ddd* (15.3, 6.7, 2.4)	39.0
14B	2.58		2.60	
15	3.74	33.6	3.47	35.8
16	2.70 *t* (3.4)	47.0	–	52.1
17	–	–	3.71 *m*	70.5
18	1.66 *dd* (6.7, 1.5)	12.2	1.65 *d* (5.8)	12.1
19	5.34 *q* (6.7)	118.6	5.40 *q* (6.4)	119.9
20	–	137.4 [a])	–	136.2
21A	2.91 *d* (14.0)	52.4	2.98 *d* (13.7)	51.9
21B	3.74		3.62 *d* (13.4)	
OMe	2.45 *s*	49.9	2.39 *s*	50.2
C=O	–	171.8	–	174.2
NMe	2.59 *s*	42.4	2.57 *s*	42.0
NH	7.44 *s*	–	7.43 *s*	–
2'	3.34 *dd* (10.7, 5.2)	73.2	3.34 *dd* (10.7, 5.2)	73.2
3α'	2.36 *d* (12.8)	53.1	2.35 *d* (12.8)	53.1
3β'	3.54 *dd* (11.9, 1.0)		3.55 *d* (13.1)	
5α'	2.22	53.6	2.22	53.6
5β'	3.19 *td* (7.9, 2.4)		3.20 *td* (7.9, 1.5)	
6α'	1.62	40.6	1.62	40.6
6β'	2.27		2.28	
7'	–	51.3	–	51.3
8'	–	137.2 [a])	–	137.3 [a])
9'	6.86 *d* (1.2)	121.1	6.84 *s*	121.2
10'	–	134.8	–	134.8
11'	6.81 *dd* (7.6, 1.4)	126.8	6.77 *d* (7.9)	126.9
12'	6.24 *d* (7.6)	106.4	6.23 *d* (7.6)	106.4
13'	–	149.1	–	149.2
14'	3.30 *d* (3.7)	53.1	3.31 *d* (3.4)	53.1
15'	2.84 *d* (4.0)	57.7	2.85 *d* (4.0)	57.6
16α'	1.07	20.0	1.08	20.0
16β'	1.72		1.73	
17α'	1.34 *dt* (14.0, 4.0)	24.5	1.36 *d* (15.6)	24.3
17β'	1.76		1.78 *dd* (14.0, 2.0)	
18'	0.53 *t* (7.5)	7.2	0.55 *t* (7.3)	7.3
19'	1.03	27.8	1.06	27.8
20'	–	34.6	–	34.6
21'	2.21	66.3	2.20	66.5
NMe'	2.70 *s*	31.7	2.70 *s*	31.7

[a]) May be exchanged.

shifts and coupling constants $J_{H,H}$ of **2** for the molecule half containing C-2' to C-21' were practically identical with those of analogous atoms of tabernaebovine and methylenebismehranine [4] indicating again the identical mehranine substructure [5]. Similar as for **1** a careful analysis of the ^{1}H-^{1}H COSY and HMBC spectra for the molecular part of **2** containing C-2 to C-21 revealed several couplings which were not in accordance with the earlier proposed structure, for which, in addition, some correlations were unfortunately derived from ambiguous data of the ^{1}H-^{1}H COSY and HMBC spectra (overlapping or nearly isochronous signals). However, the ^{13}C and ^{1}H chemical shifts of tabernaemontavine (**2**)

for the molecular half containing C-2 to C-21 (Table 1) agreed very well with those of the vobasinyl part of conodiparine A [7] except for C-3, C-14 and H-3 (all spectra in $CDCl_3$). All unequivocal correlations from the ^1H-^1H COSY and HMBC spectra were in accordance with this vobasinyl structure and the 3,10'-bond. Corresponding couplings for **2** were detected between H-3/H-14A, H-3/H-14B, H-5/H-6A, H-5/H-6B, H-6A/H-6B, H-14A/H-14B, H-14A/H-15, H-14B/H-15, H_3-18/H-19, H_3-18/H-21B (homoallyl coupling), H-21A/H-21B, H-3/C-10', H-5/C-15, H-6A/C-2, H-6A/C-5, H-6A/C-7, H-6A/C-8, H-6B/C-2, H-6B/C-7, H-6B/C-8, H-9/C-11, H-14A/C-15, H-15/C-14, H-15/C-19, H-17/C-5, H-17/C-15, H-17/C=O, H_3-18/C-19, H-19/C-15, H-19/C-18, H-21A/C-5, H-21A/C-15, H-21A/C-19, NH/C-8, OMe/C=O, H-9'/C-3, H-11'/C-3. The structure of tabernaemontavine as **2** followed from the above-discussed data.

In the circular dichroism spectra of **1** and **2** 8 Cotton effects were observed [5]. They corresponded with each other concerning the signs and, especially the long wave-length effects, reflected therefore the same configurations at C-3. Alkaloids of the mehranine type occur in both enantiomeric forms [8]. Based on the X-ray analysis of (–)-mehranine hydrobromide [9] the absolute configurations of (–)-mehranine, 3-oxomehranine, and 14α,15β-dihydroxy-*N*-methylaspidospermine have been assigned [3]. Biogenetic considerations suggested that also both novel *bis*-indole alkaloids **1** and **2**, isolated from the same plant species, have identical steric structures with regard to the molecule halves containing the atoms C-2' to C-21'.

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