

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

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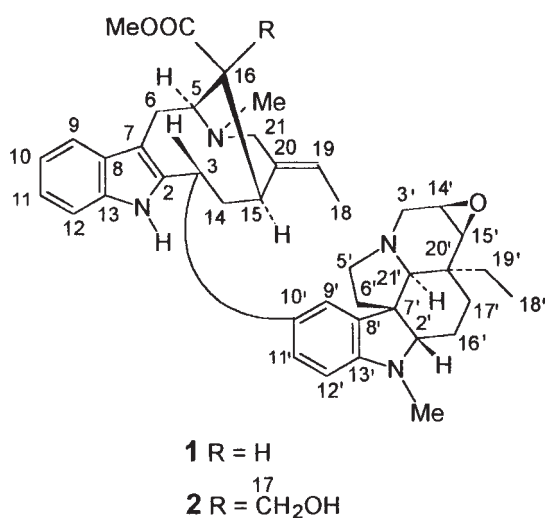
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Abstract. The structures of the *bis*-indole alkaloids tabernaemontabovine (**1**) and tabernaemontavine (**2**) have been

revised on the basis of APT, ^1H - ^1H 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 $14\alpha,15\beta$ -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 vobasinyll substructure.



Results and Discussion

The elemental composition of tabernaemontabovine (**1**) was shown to be $\text{C}_{41}\text{H}_{50}\text{N}_4\text{O}_3$ by high-resolution mass spectrometry [5].

The ^1H and ^{13}C NMR signals of **1** (Table 1) and the structure of the alkaloid were assigned on the basis of APT, ^1H -

^1H DQF COSY, gradient-selected HSQC and gradient-selected HMBC spectra. Chemical shifts and coupling constants $J_{\text{H,H}}$ 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 ^1H - ^1H 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 vobasinyll 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 ^1H 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 $\text{DMSO}-d_6$. All unequivocal correlations from the ^1H - ^1H COSY and HMBC spectra were in complete accordance with this vobasinyll 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, H₃-18/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, H₃-18/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 $\text{C}_{42}\text{H}_{52}\text{N}_4\text{O}_4$ [5].

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

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

^{a)} May be exchanged.

shifts and coupling constants $J_{\text{H,H}}$ of **2** for the molecule half containing C-2' to C-21' were practically identical with those of analogous atoms of tabernaebovine and methylenebis-mehranine [4] indicating again the identical mehranine sub-structure [5]. Similar as for **1** a careful analysis of the ^1H - ^1H COSY and HMBC spectra for the molecular part of **2** con-

taining 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 ^1H - ^1H COSY and HMBC spectra (overlapping or nearly isochronous signals). However, the ^{13}C and ^1H chemical shifts of tabernaemontavine (**2**)

for the molecular half containing C-2 to C-21 (Table 1) agreed very well with those of the vobasinyll part of conodiparine A [7] except for C-3, C-14 and H-3 (all spectra in CDCl₃). All unequivocal correlations from the ¹H-¹H COSY and HMBC spectra were in accordance with this vobasinyll 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, H₃-18/H-19, H₃-18/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, H₃-18/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 14 α ,15 β -dihydroxy-*N*-methylasspidospermine 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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