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Voastrictine, a novel pentacyclic quinolinic alkaloid from *Tabernaemontana*

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Abstract—A novel pentacyclic quinolinic alkaloid, voastrictine, was obtained from *Tabernaemontana corymbosa* and its structure elucidated by spectroscopic analysis. © 2001 Elsevier Science Ltd. All rights reserved.

Plants of the genus *Tabernaemontana* are notable for being rich sources of a variety of indole and bisindole alkaloids.[1,2] In recent years, a number of new alkaloids of unusual structures have been reported from plants of this genus.[3–7] The Malayan species *Tabernaemontana corymbosa*, for instance, provided several bisindole alkaloids of the vobasinyl-iboga type, which were found to reverse multidrug-resistance (MDR) in vincristine-resistant KB cells.[6] The same plant also provided several alkaloids, characterized by novel molecular skeletons, including the hexacyclic indole, tronoharine **1**.[7] We have now obtained another unusual alkaloid, voastrictine **2**, characterized by a novel pentacyclic carbon skeleton, incorporating a quinoline chromophore.

Voastrictine **2** was obtained as a colourless oil, with $[\alpha]_D$ +321 (*c* 0.23, $CHCl_3$). The UV spectrum showed absorption maxima at 209, 231, 283, 294, 307, and 321 nm (log ε 4.37, 4.32, 3.40, 3.36, 3.27, and 3.19, respectively), which do not correspond to indole or dihydroindole derivatives, but are suggestive of a quinoline chromophore.[8] This was confirmed by the observation of an acid-induced bathochromic shift, which resulted in the merging of the middle bands (289, 294, 307 nm), to give a new band at 308 nm (log ε 3.40).[8,9] The IR spectrum showed a band at 3185 (broad) which is assigned to an OH function. The EIMS showed a molecular ion at m/z 292 which was also the base peak, and which analyzed for $C_{19}H_{20}N_2O$ requiring 11 degrees of unsaturation.[10] The ^{13}C NMR spectrum (Table 1) gave a total of 19 separate carbon resonances (one methyl, four methylenes, eight methines, and six quaternary carbons) in agreement with the molecular formula. The ^1H NMR spectrum (Table 1) showed signals due to four contiguous aromatic hydrogens of a benzenoid residue (δ 8.48, 7.98, 7.61, 7.54), a low field one-hydrogen singlet at δ 8.41 which does not undergo exchange, and signals characteristic of an ethylidene side chain (δ 5.26, qd, 1.84, dd).

The HMQC spectrum showed that the low field hydrogen singlet at δ 8.41 correlates with the carbon resonance at δ 150.8, indicative of an imine function (CH=N). This is also consistent with the absence of any NH signal in the ^1H NMR spectrum. The remaining two quaternary carbon signals in the lower field region (δ 130.5, 146.8), after discounting the aromatic, ethylidene, and imine signals, are due to the presence of a tetrasubstituted double bond which must be part of the quinoline chromophore. Of the eight upfield signals, the methyl resonance at δ 12.8 and a low field signal at δ 76.9 attributable to an oxygenated quaternary carbon atom are immediately apparent. The COSY and HMQC spectral data showed the presence of NCH_2CH_2, $NCHCH_2CH$, and $NCH_2C{=}CH(CH_3)$ partial structures, revealing at once the three fragments branching from *N*(4). The aromatic H(9) resonance at δ 8.48 is relatively deshielded, which is due to its proximity to the C(7) hydroxyl function. The observed paramagnetic deshielding of H(9) in fact indicates that the C(7) hydroxyl group is in the α-configuration.[11]

The construction of the entire molecule from the linking of the various substructures so far unravelled, is based on the HMBC data (Table 1, Fig. 1). The observed two-bond heteronuclear correlations from the

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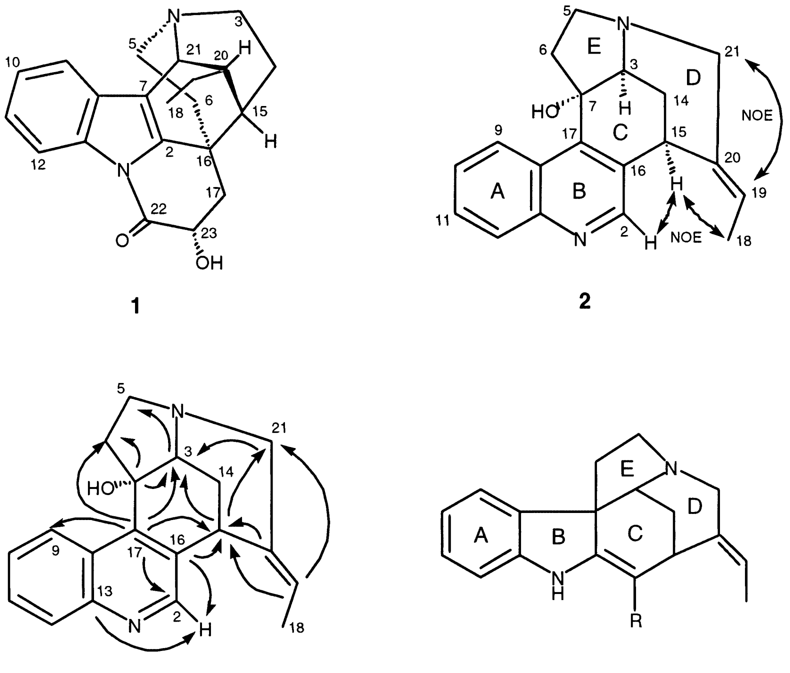
Table 1. ^{1}H and ^{13}C NMR spectral data of voastrictine **2**[a]

Position	δ_C	δ_H	HMBC		NOE[b]
			^2J	^3J	
2	150.8	8.41 s		15	15
3	67.2	3.31 t (3)	14	5, 6, 15, 21	5α
5α	52.9	3.09 dt (11, 9)	6	3	3
5β		2.53 m			
6α	40.8	2.61 ddd (14, 9, 2)			9
6β		2.76 dt (14, 9)			
7	76.9		3, 6	14, 2 (^4J)	
8	125.2			10, 12	
9	127.0	8.48 dd (8.5, 1)		11	6α, 10
10	126.3	7.54 td (8.5, 1)		12	9, 11
11	128.2	7.61 td (8.5, 1)		9	10, 12
12	129.8	7.98 dd (8.5, 1)	11	10	11
13	148.1			2, 9, 11	
14a	25.4	2.03 dt (13, 3)	3, 15		3, 15
14b		2.10 dt (13, 3)			
15	32.6	3.99 t (3)	14	2, 3, 19, 21	2, 14, 18
16	130.5		2, 15	14	
17	146.8			2, 3, 6, 9, 15	
18	12.8	1.84 dd (6.8, 1.8)	19		15, 19
19	118.7	5.26 qd (6.8, 1.8)	18	21	18, 21b
20	134.5		15, 19, 21	3, 18	
21a	52.5	2.55 dt (13, 1.8)		3, 5, 15, 19	
21b		2.83 d (13)			19

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

[b] NOEs of geminal hydrogens not indicated.



1

2

(= HMBC)

3

Figure 1.

hydroxyl-bearing C(7) to H(6) in the HMBC spectrum, allows connection of the C(6)–C(5) ethylene unit to C(7). Two-bond correlation from C(7) to H(3) and three-bond correlation from C(3) to H(5) complete the pyrrolidine ring E. Two-bond correlations from C(16) to the imine H(2), and three-bond correlations from C(17) to H(2), H(9), and from C(13) to H(2), confirm the six-membered ring B of the quinoline core. Three-bond correlations from C(17) to H(3), H(15), H(6) and two-bond correlation from C(16) to H(15) allow the six-membered ring C to be assembled. It only remains to link the ethylidene containing fragment to incorporate the fifth ring. This is readily achieved from the observed HMBC correlations from C(20) to H(15); C(19) to H(15), H(21); C(21) to H(3); and C(15) to H(21). The rest of the HMBC correlations are shown in Table 1 and are entirely consistent with the proposed structure.

Another noteworthy observation which is also consistent with structure **2** is the downfield shift of the doubly allylic H(15) at δ 3.99. The tricyclic C, D, E ring system of **2** in fact corresponds to the C, D, E rings of a strychnan-type alkaloid (e.g. **3**), which requires H(3) and H(15) to be *cis*. The NOE interaction between H(15) and H(18), H(2) is consistent with the α stereochemistry of H(15), while the observed H(15)/H(18) and H(19)/H(21) NOE interactions indicate that the geometry of the 19, 20 double bond is *E*.

Voastrictine **2** represents a tryptamine-monoterpene derived alkaloid, but possessing a quinoline instead of an indole/dihydroindole chromophore. Other examples include another *Tabernaemontana* alkaloid, voaharine, characterized by a 3-quinolone chromophore,[3,12] and the *Melodinus* alkaloids (e.g. meloscine), characterized by a 2-quinolone chromophore.[13] Voastrictine is probably derived from a strychnan-type precursor (e.g. **3**) and represents a new addition to the various skeletal classes of the monoterpenoid indole alkaloids.

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