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Tronocarpine, a novel pentacyclic indole incorporating a seven-membered lactam moiety

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Abstract

A novel pentacyclic indole alkaloid, tronocarpine, incorporating a seven-membered lactam unit, was obtained from the stem-bark extract of *Tabernaemontana corymbosa* and its structure elucidated by spectral analysis. © 2000 Elsevier Science Ltd. All rights reserved.

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Plants of the genus *Tabernaemontana* are notable for producing a great variety of indole alkaloids.[1,2] In recent years many new indoles and bisindoles with novel molecular skeletons, as well as interesting bioactivities, have been reported from plants of this genus.[1–4] The Malayan species, *Tabernaemontana corymbosa* previously yielded new chippiine-type derivatives, as well as vobasinyl-iboga bisindoles which were notable for their ability to reverse multidrug resistance in vincristine-resistant KB cells.[5,6] The same plant has also provided minor amounts of an indole alkaloid, tronoharine, which possesses a novel hexacyclic carbon skeleton.[7] We now wish to report the structure of another minor alkaloid, tronocarpine **1**, characterized by a novel pentacyclic carbon skeleton, incorporating a seven-membered lactam ring (Fig. 1).

Tronocarpine was obtained as a colourless oil, $[\alpha]_D$ +231 (CH_2Cl_2, *c* 0.08). The UV spectrum showed absorption maxima at 226, 290, and 296 nm (log ε 4.30, 3.71, and 3.72, respectively) due to an indole chromophore. The IR spectrum showed absorptions at 3315 (OH/NH), 1661 (broad, various carbonyl functions), and 1633 (olefinic) cm^{-1}. The EIMS showed a molecular ion at *m/z* 336 which was also the base peak, with other major fragments observed at *m/z* 320 (M–O), 278, 221,180, and 144. HREIMS measurements gave the molecular formula $C_{20}H_{20}N_2O_3$ requiring 12 degrees of unsaturation.[8] The ^{13}C NMR spectrum (Table 1) gave a total of 20 separate carbon resonances (one methyl, four methylenes, seven methines, and eight quaternary carbons) in agreement with the molecular formula, and in addition confirmed the presence of ketonic (δ 198.2, conjugated) and lactam (δ 174.5) carbonyl functions, oxymethine (δ 80.5), and a trisubstituted double bond (δ 137.9, 139.7).

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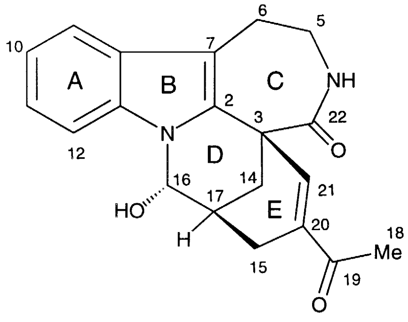
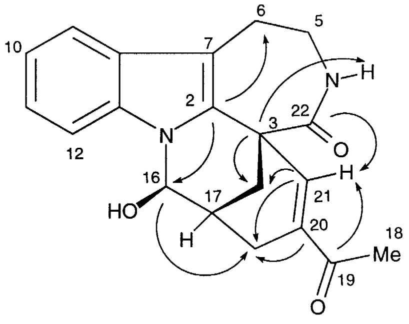


1a



1b (⌒ = HMBC)

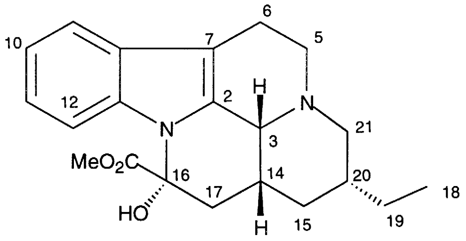


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Fig. 1.

The ^{1}H NMR spectrum indicated the presence of an unsubstituted indole moiety, an NH function, an acetyl group, and a deshielded vinylic hydrogen (δ 7.05). The substantial downfield shift of this olefinic resonance is characteristic of a β-proton of an α,β-unsaturated carbonyl moiety. The IR absorption and ^{13}C NMR resonance for the lactam carbonyl function suggested either a six- or seven-membered lactam. The COSY and HMQC spectral data revealed the presence of CH_2CH_2NH and $CH(OH)CH(CH_2)CH_2$ partial structures, while the presence of the CH=C–$COCH_3$ enone fragment is indicated by the three-bond correlation from the acetyl carbonyl, C(19), to the vinylic H(21) in the HMBC spectrum. The CH_2CH_2NH fragment is branched from the aromatic C(7), and corresponds to the C(6)–C(5)–*N*(4)H substructure, as indicated by the observed three-bond correlation from C(2) to H(6). Likewise, the observed three-bond correlation from the quaternary centre C(3) to the lactam NH suggests that C(3) is attached to the aromatic C(2) to provide a seven-membered lactam moiety fused to the indole portion at C(7) and C(2) as shown in **1**. The observed heteronuclear correlations from C(2) to H(16), C(3) to H(14), and C(20) to H(15), allowed the second $CH(OH)CH(CH_2)CH_2$ fragment to be connected, i.e. C(16) to *N*(1), C(14) to C(3) and C(15) to C(20), respectively. This leaves the enone unit which can be connected as shown in **1**, from the observed three-bond correlations from C(21) to H(14), H(15), and from C(22) to H(21).

The bridging of the six-membered D and E rings by the C(14) methylene group requires both the C(3)–C(21) and C(17)–C(15) bonds to be *cis*. The observed NOE interactions between H(16) and H(12), H(15α or 15β) allow the relative configuration of C(16) to be fixed. The other NOE interactions are summarized in Table 1 which are in agreement with the gross structure of tronocarpine. The stereochemistry of the C(14) methylene bridge determines the absolute configuration of tronocarpine, but it is not possible based on the present results to distinguish between the two enantiomers **1a** or **1b**.

The structure of tronocarpine represents a new addition to the various skeletal classes of the monoter-

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

Position	δ_C	δ_H	HMBC ^2J	HMBC ^3J	NOE[b]
2	127.4			6, 16	
3	43.9		14, 21	NH	
5a	40.8	3.23 ddt (14.7, 7, 3.5)			NH
5b		3.72 dddd (14.7, 12.7, 7, 3.5)			21
6a	25.2	2.63 ddd (16, 12.7, 3.5)			
6b		2.86 dt (16, 3.5)			9
7	110.9		6		
8	128.2			10, 12	
9	118.2	7.45 ddd (8, 1.1, 0.8)		11	6b, 10
10	120.6	7.17 ddd (8, 7, 1.1)		12	9, 11
11	122.8	7.26 ddd (8, 7, 1.1)		9	10, 12
12	110.6	7.49 ddd (8, 1.1, 0.8)	11	10	11, 16
13	135.9			9, 11	
14a	25.4	2.15 dd (14, 3.6)			15b
14b		2.67 dt (14, 2)			
15a	26.3	2.28 dd (19, 1.8)		21	16
15b		2.79 ddd (19, 9, 1.6)			14a
16	80.5	5.67 br s	17	15	12, 15a, 17
17	32.8	2.84 m			16
18	25.2	2.18 s			
19	198.2			21	
20	137.9		15	17	
21	139.7	7.05 m		14, 15	5b
22	174.5			21	
NH		6.01 t (7)			5a

[a] $CDCl_3$, 400 MHz. [b] NOE's of geminal hydrogens not indicated.

penoid indole alkaloids. It is probably biogenetically related to the tacaman group of alkaloids (exemplified by tacamine **2**)[9,10] which are unique to *Tabernaemontana*, although in the present investigation no tacaman-type alkaloids were detected.

Acknowledgements

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