A NEW INDOLE ALKALOID FROM VOACANGA GRANDIFOLIA

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A NEW INDOLE ALKALOID FROM *VOACANGA GRANDIFOLIA*

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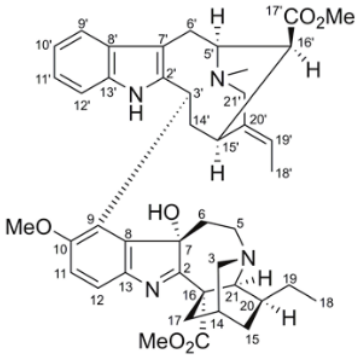
Abstract – A new bisindole alkaloid, voacalgine F (**1**), has been isolated from the bark of Indonesian *Voacanga grandifollia* (Miq.) Rolfe. Its structure was elucidated on the basis of 1D and 2D-NMR data analysis.

Voacanga is a small genus of the Apocynaceae family consisting of 12 species. Species of this genus are distributed mainly in the tropical Africa and Malysia, and have been reported to contain vobasine, eburnane, iboga, and aspidosperma type of monoterpene indole alkaloids.[1] Various activities have been reported for monoterpene indole alkaloids, such as cytotoxicity,[2] anti-melanogenesis,[3] anti-plasmodial,[4] and vasorelaxant activities.[5] In the search for new bioactive compounds from tropical plants,[3,5-8] alkaloid constituents of *V. grandifolia* bark were investigated and a new bisindole alkaloid voacalgine F (**1**) was isolated together with voacamine,[9-12] voacangine,[9] voacanginehydroxyindolenine,[13] and pagicerine.[14] The isolation and structure elucidation of **1** are reported herein.

[†]Dedicated to the celebration of the 77th birthday of Prof. Dr. Isao Kuwajima, Professor emeritus of Tokyo Institute of Technology



1

Voacalgine F (**1**) was obtained as yellow amorphous solid and the molecular formula was determined as $C_{43}H_{52}N_4O_6$ from the HRESIMS data (*m/z* 721.3978 $[M+H]^+$, calcd for $C_{43}H_{53}N_4O_6$, 721.3965). The IR absorptions (3430 and 1720 cm^{-1}) implied the presence of hydroxyl and carbonyl functionalities. Analysis of the ^{13}C-NMR data (Table 1) showed that the chemical shift of 21 carbon signals is highly similar to the vobasine unit of voacamine, suggesting the presence of a vobasine unit in **1**. The chemical shift of the other carbon signals is highly similar to that of voacangine hydroxyindolenine, except for downfield shift of C-9. These data suggested the structure of **1** as a new vobasine-iboga type of bisindole alkaloids as shown in Figure 1.

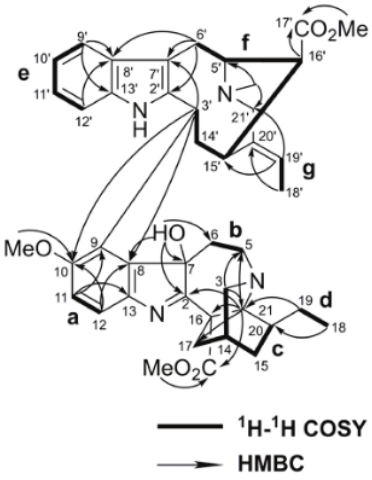


Figure 1. Selected 2D-NMR Correlations of **1**

The planar structure of **1** was further confirmed by 2D NMR analysis (^{1}H-^{1}H COSY, HSQC and HMBC, Figure 1). Analysis of ^{1}H-^{1}H COSY and HSQC data revealed the presence of 7 partial structure (**a**–**g**).

HMBC correlations of 7-OH to C-2, C-6, C-7 and C-8, H-11 to C-9 and C-13, and H-12 to C-8 and C-10 confirmed the presence of a 7-hydroxyindolenine moiety and the connection of C-6 and C-7. HMBC cross-peaks of H_3-18 to C-20 suggested the connectivity of C-19 and C-20, and the HMBC correlations of H_2-3 to C-5 and C-21, H_2-19 to C-21, H-21 to C-2, C-5, C-16, C-17 and a carbonyl (δ_C 174.4), and a methyl (δ_H 3.73) to δ_C 174.4 completed the structure of the iboga unit. HMBC cross-peaks of H-3' to C-7', H_2-6' to C-2', C-7', and C-8', H-9' to C-8' and C-13', and H-12' to C-8' suggested the presence of an indole unit and the connectivity of partial structure **f** to the indole unit. HMBC cross-peaks of H_3-18' to C-20', and H-19 to C15' and C-21' revealed the connectivity of partial structures **f**, **g**, and C-21' through C-20'. HMBC correlations of a methyl (δ_H 2.61) to C-5' and C-21' established the connections between C-5' and C-21' through a nitrogen atom, and HMBC cross-peaks of H-16' to C-17', and another methyl (δ_H 2.49) to C-17' suggested the presence of a methoxycarbonyl moiety at C-16'. Finally, the two units were confirmed to be connected by C-9 to C-3' bond by the HMBC correlations of H-3' to C-8 and C-10.

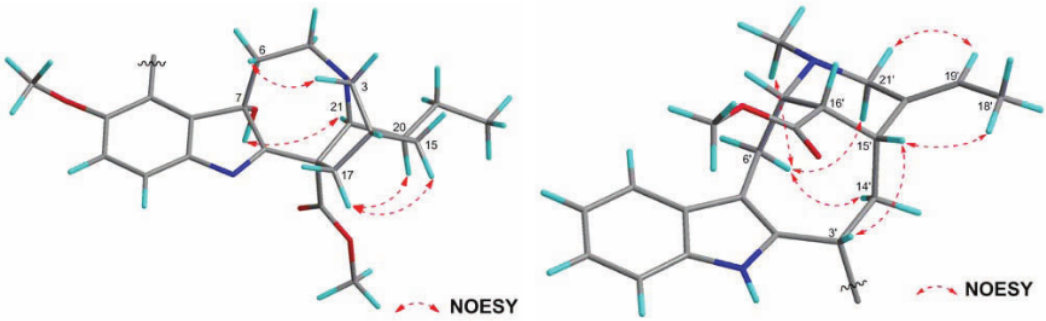


Figure 2. Selected NOESY Correlations of Each Indole Unit in **1**

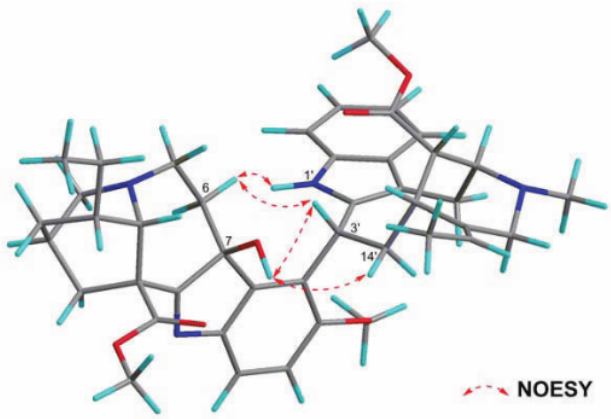


Figure 3. Selected NOESY Correlations Between Two Indole Unit of **1**

The relative configuration of **1** was assigned using the ^{1}H-^{1}H coupling constant values, ^{1}H NMR chemical shift and NOESY correlations. The orientation of 7-OH and H-21 was assigned as α from the NOESY correlation 7-OH/H-21. The relative configuration C-14, C-16, C-20, C-21, C-3' and C-5' was assigned to be the same as in voacamine based on the NOESY correlations shown in Figure 2. The orientation of the methoxycarbonyl at C-16' was deduced from the highly shielded ^{1}H NMR chemical shift of the methoxy group (δ_H 2.49), and the configuration of the C-19'-C-20' was determined to be *E* from the NOESY correlation of H-19'/H_2-21'. Finally the relative configuration of the total molecule was deduced from the NOESY correlations of H-6a/NH and H-3', 7-OH/H-3' and H-14'a (Figure 3).

Table 1. ^{1}H (700 MHz) & ^{13}C (175 MHz) NMR Data of **1** in $CDCl_3$

	δ_H (J, Hz)	δ_C		δ_H (J, Hz)	δ_C
2		187.0	2'		136.7
3	2.85 (2H, m)	48.7	3'	5.28 (1H, d, 11.9)	36.7
5a	3.15 (1H, m)	49.2	5'	4.06 (1H, m)	59.5
5b	3.79 (1H, m)		6'a	3.20 (1H, m)	19.1
6a	2.24 (1H, td, 13.2, 3.6)	33.9	6'b	3.50 (1H, m)	
6b	2.52 (1H, br. d, 13.2)		7'		110.0
7		89.9	8'		130.1
8		141.2	9'	7.53 (1H, d, 7.4)	117.4
9		130.1	10'	7.06 (1H, t, 7.4)	118.9
10		158.0	11'	7.05 (1H, t, 7.4)	121.0
11	6.68 (1H, d, 8.3)	112.6	12'	7.09 (1H, d, 7.4)	109.7
12	7.27 (1H, d, 8.3)	119.8	13'		135.3
13		145.3	14'a	1.83 (1H, m)	33.6
14	1.98 (1H, br. s)	27.0	14'b	3.13 (1H, td, 13.6, 3.8)	
15a	1.15 (1H, d, 12.0)	32.1	15'	3.80 (1H, m)	33.1
15b	1.80 (1H, d, 12.0)		16'	2.75 (1H, br. s)	47.0
16		59.1	17'		171.6
17a	2.64 (1H, m)	34.0	18'	1.64 (3H, d, 6.8)	12.4
17b	2.70 (1H, d, 13.9)		19'	5.32 (1H, q, 6.8)	118.6
18	0.89 (3H, t, 7.0)	11.6	20'		138.1
19	1.45 (2H, m)	26.4	21'a	2.92 (1H, m)	52.4
20	1.41 (1H, m)	37.7	21'b	3.78 (1H, m)	
21	3.87 (1H, br. s)	58.8	17'-OMe	2.49 (s)	50.0
$\underline{C}O_2Me$		174.4	N-Me	2.61 (br. s)	42.4
$CO_2\underline{Me}$	3.73 (s)	53.3	NH	7.15 (s)	
10-OMe	3.39 (s)	56.5			
7-OH	4.15 (s)				

EXPERIMENTAL

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 automatic digital polarimeter. UV spectra were obtained on an Ultrospec 2100 pro spectrophotometer and IR

spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. High-resolution ESI MS were obtained on a LTQ Orbitrap XL (Thermo Scientific). ^{1}H and 2D NMR spectra were recorded on a Bruker AV700 spectrometer and chemical shifts were referenced to the residual solvent peaks (δ_H 7.26 and δ_C 77.0 for chloroform-*d*). Standard pulse sequences were employed for the 2D NMR experiments.

Plant Material. The barks of *V. grandifolia* were collected at Purwodadi Botanical Garden, Indonesia in 2008. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden. A voucher specimen has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.

Extraction and Isolation. The dried and powdered bark of *V. grandifolia* (300 g) was extracted successively with MeOH. Part of the extract (17.0 g of 28.4 g) was dissolved in 3% aqueous tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with saturated Na_2CO_3 (aq.) to pH 9 and was partitioned successively by $CHCl_3$ and *n*-BuOH. Part of the $CHCl_3$ soluble materials (5.0 g of 5.10 g) was subjected to an LH-20 column ($CHCl_3$/MeOH 1:1) to obtain 12 fractions.

Fraction 7 was fractionated by amino silica gel column chromatography (*n*-hexane/EtOAc, 1:0~1:1, $CHCl_3$/MeOH, 0:1~1:0) to obtain voacamine (100.8 mg, 0.032%). In addition, fraction eluted by $CHCl_3$/MeOH (80:1) was further separated by ODS HPLC (Inertsil ODS-3, 5 μm, 10 x 250 mm; 35% MeCN in 0.1% aqueous HCO_2H; flow rate 2 mL/min; UV detection at 254 nm) to obtain **1** (t_r 30 min., 2.7 mg, 0.001%).

Fraction 11 was separated by repeated amino silica gel column chromatography (*n*-hexane/EtOAc, 1:0~1:1, $CHCl_3$/MeOH, 0:1~1:0) and silica gel column chromatography ($CHCl_3$/MeOH, 0:1~1:0) to give voacangine (23.8 mg, 0.0043%), voacanginehydroxyindolenine (12.8 mg, 0.0079%), and pagicerine (3.6 mg, 0.0012%).

Voacalgine F (**1**): yellow amorphous solid; $[\alpha]_D^{22}$ -132 (*c* 1.0, MeOH); IR (KBr) ν_{max} 3430, 2940 and 1720 cm^{-1}; UV (MeOH) λ_{max} (ε) 225 (23400) and 290 (9000) nm; ^{1}H and ^{13}C NMR data (Table 1); ESIMS *m/z* 721 $(M+H)^+$; HRESIMS *m/z* 721.3978 ($M+H^+$; calcd for $C_{43}H_{53}N_4O_6$, 721.3965).

ACKNOWLEDGEMENTS

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