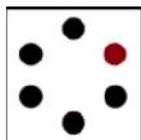


**HETEROCYCLES**  
An  
International  
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for  
Reviews  
and  
Communications  
in  
Heterocyclic  
Chemistry

Volume 81  
Number 9  
September 1  
2010

WILEY  
ISSN 0361-0316



The Japan Institute of Heterocyclic Chemistry Publication

# HETEROCYCLES

An International Journal for Reviews and Communications in Heterocyclic Chemistry  
Web Edition ISSN: 1881-0942

Published online by The Japan Institute of Heterocyclic Chemistry



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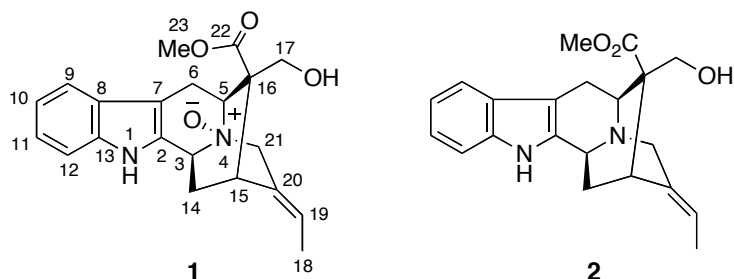
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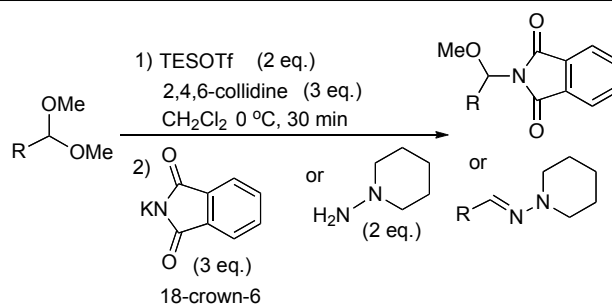
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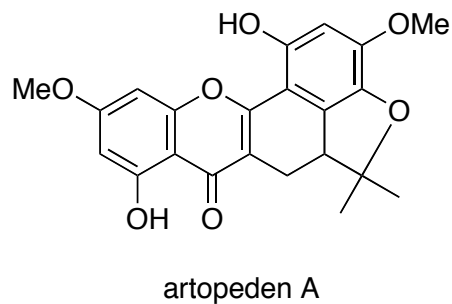
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HETEROCYCLES, Vol. 79, 2009, pp. 1107 - 1112. © The Japan Institute of Heterocyclic Chemistry  
Received, 6th October, 2008, Accepted, 27th November, 2008, Published online, 8th December, 2008.  
DOI: 10.3987/COM-08-S(D)65

## INDOLE ALKALOIDS FROM THE LEAVES OF *ALSTONIA SCHOLARIS*

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Abdul Rahman,<sup>c</sup> Wiwied Ekasari,<sup>c</sup> Aty Widyawaruyanti,<sup>c</sup> Gunawan  
Indrayanto,<sup>c</sup> Noor Cholies Zaini,<sup>c</sup> and Hiroshi Morita<sup>a,\*</sup>

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**Abstract** – A new indole alkaloid, akuammidine-*N*-oxide (**1**) was isolated from the leaves of *Alstonia scholaris* (Apocynaceae) together with akuammidine (**2**), and the structure was elucidated by NMR spectral analysis and chemical correlation. Akuammidine (**2**) showed a moderate antiplasmodial activity.

## INTRODUCTION

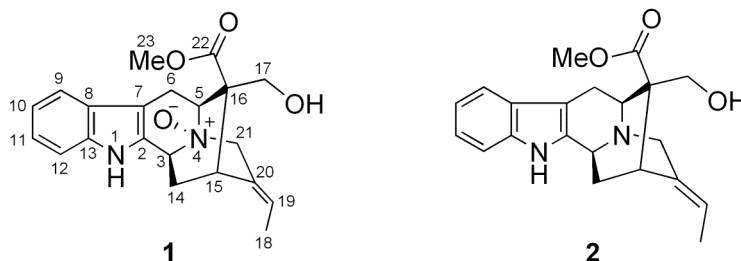
The genus *Alstonia* and *Kopsia* (Apocynaceae), which are widely distributed throughout tropical Asia, are noted for producing variety of indole alkaloids with useful biological activities.<sup>1</sup> Recent investigation of extracts from the leaves of *Alstonia angustiloba*,<sup>2</sup> *Kopsia flavida*,<sup>3</sup> and *Kopsia arborea*<sup>3</sup> resulted in the isolation of some new indole alkaloids with antiplasmodial and vasorelaxant activities. In this paper, we report the isolation and structure elucidation of a new indole alkaloid, akuammidine-*N*-oxide (**1**) from the leaves of *Alstonia scholaris*, and antiplasmodial activity of isolated indole alkaloids.

The leaves of *A. scholaris* were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with saturated Na<sub>2</sub>CO<sub>3</sub>, were extracted with CHCl<sub>3</sub>. Water-soluble materials were extracted with BuOH. BuOH-soluble materials were subjected to an ODS column (H<sub>2</sub>O/MeOH 1:1 → 0:1) and the fractions eluted by H<sub>2</sub>O/MeOH (1:1) were subjected to silica gel columns (CHCl<sub>3</sub>/MeOH 1:0 → 7:3 and CHCl<sub>3</sub>/MeOH 1:0 → 5:1) to afford compound **1** (0.001%). CHCl<sub>3</sub>-soluble materials were subjected to

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<sup>†</sup>Dedicated to Dr. John Daly, National Institutes of Health scientist emeritus.

an LH-20 column (CHCl<sub>3</sub>/MeOH = 1:1) and an amino silica gel column (hexane/EtOAc 8:1 → 1:1 and then CHCl<sub>3</sub>/MeOH 1:0 → 0:1) to give akuammidine<sup>4</sup> (**2**, 0.04%).



## RESULTS AND DISCUSSION

Compound **1** { $[\alpha]_D^{23}$  -39 (*c* 1.0, MeOH)} showed the pseudomolecular ion peak at  $m/z$  369 (M+H)<sup>+</sup> in ESIMS, and the molecular formula, C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>, was established by HRESIMS [ $m/z$  369.1828, (M+H)<sup>+</sup> Δ +1.4 mDa]. IR spectrum suggested the presence of NH (3400 cm<sup>-1</sup>) and ester carbonyl (1720 cm<sup>-1</sup>) groups. The <sup>13</sup>C NMR (Table 1) spectrum of **1** disclosed twenty-one carbon signals due to one ester carbonyl ( $\delta_C$  172.5), five *sp*<sup>2</sup> quaternary carbons ( $\delta_C$  138.7, 134.0, 131.8, 127.2, and 104.5), one *sp*<sup>3</sup> quaternary carbon ( $\delta_C$  54.4), five *sp*<sup>2</sup> methines ( $\delta_C$  122.7, 120.9, 120.3, 119.0, and 112.3), three *sp*<sup>3</sup> methines ( $\delta_C$  72.8, 67.9, and 29.6), four *sp*<sup>3</sup> methylenes ( $\delta_C$  71.6, 68.0, 31.7, and 20.9), one methyl ( $\delta_C$  13.1), and one methoxy group ( $\delta_C$  52.2). <sup>1</sup>H and <sup>13</sup>C signals for **1** were assigned by detailed analysis of the HSQC spectrum. The <sup>1</sup>H-<sup>1</sup>H COSY spectrum revealed connectivities of C-5 to C-6, C-9 to C-12, C-3 to C-14, C-14 to C-15, and C-18 to C-19 (Figure 1). HMBC correlations of H-3 ( $\delta_H$  4.59) to C-2 ( $\delta_C$  134.0), H-5 ( $\delta_H$  3.17) to C-3 ( $\delta_C$  67.9) and C-7 ( $\delta_C$  104.5), H<sub>2</sub>-6 ( $\delta_H$  3.51) to C-2 and C-7, H<sub>2</sub>-14 ( $\delta_H$  2.41 and 2.96) to C-20 ( $\delta_C$  131.8), and H-15 ( $\delta_H$  3.35) to C-21 ( $\delta_C$  71.6) revealed the presence of a dehydroquinolizidine ring (C-2 to C-7, C-14 to C-15, C-20 to C-21, and N-4). Low field chemical shifts at C-3, C-5, and C-21 around N-4 atom [ $\delta_C$  67.9, 72.8, and 71.6, respectively] suggested that **1** was *N*-oxide form at N-4. The presence of the piperidine ring (C-5, C-3, C-14 to C-16, and N-4) was deduced from the HMBC correlations of H<sub>2</sub>-14 to C-16, and H<sub>2</sub>-6 to C-16. Connection between indole ring (C-2, C-7 to C-13 and N-1) and dehydroquinolizidine ring was deduced from the HMBC correlations of H-9 ( $\delta_H$  7.44) to C-7. Structure of methyl 3-hydroxypropanoate moiety (C-16 to C-17, C-22, and C-23) was elucidated from HMBC correlations of H-5 to C-17 and C-22 ( $\delta_H$  172.5), H-15 to C-17, and H<sub>3</sub>-23 ( $\delta_H$  2.98) to C-22. The HMBC cross-peaks of H<sub>3</sub>-18 ( $\delta_H$  1.73) to C-20 indicate the ethylidene side chain at C-20. Thus, the gross structure of **1** was assigned as sarpagine-type skeletal system with an N-4 oxide.

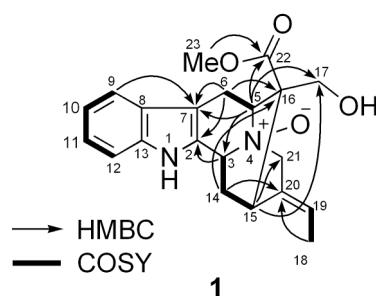


Figure 1. Selected 2D NMR correlations of **1**.

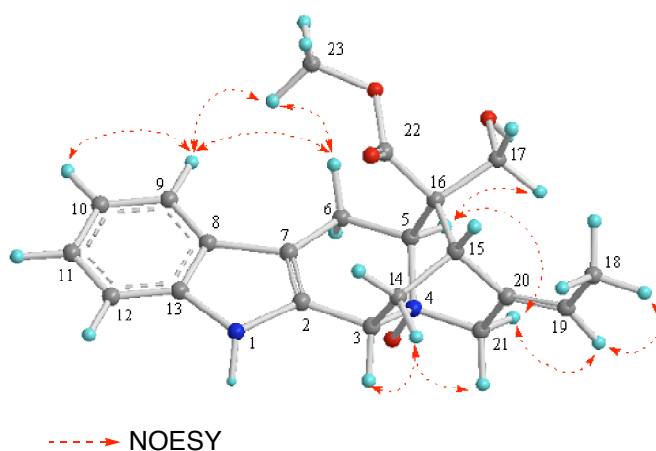


Figure 2. Selected NOESY correlations and relative stereochemistry for **1**

The relative stereochemistry of **1** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Figure 2). Configuration of C-16 was elucidated by NOESY correlations among H<sub>3</sub>-23, H-6, and H-9, and between H<sub>2</sub>-17 and H-5. NOESY correlations of H-19 to H-21 indicated the geometry of C-19 - C-20 double bond was *E*. Thus, the relative stereochemistry of **1** was assigned as shown in Figure 2.

Treatment of compound **1** with Na<sub>2</sub>SO<sub>3</sub> in aqueous MeOH afforded the reductive derivative, whose spectroscopic data and specific rotation were identical with akuammidine (**2**).<sup>4</sup> Thus, the absolute configuration of **1** was assigned as the same as **2**.

Malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions.<sup>5</sup> The emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites leads to the need for the development of new therapeutic agents against malaria.<sup>6</sup> Since some indole alkaloids from *Alstonia* species have already been reported on inhibitory activity against some parasites.<sup>7</sup> Akuammidine (**2**) showed a moderate *in vitro* antiplasmodial activity against *Plasmodium falciparum* (**2**: 32.6% inhibition at 10 μg/mL), whereas akuammidine-*N*-oxide (**1**) did not show (>10 μg/mL).<sup>8</sup>

Table 1.  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data [ $\delta_{\text{H}}$  (J, Hz) and  $\delta_{\text{C}}$ ] of akuammidine-*N*-oxide (**1**) in  $\text{CD}_3\text{OD}$  at 300K

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2		134.0
3	4.59 (d, 10.7)	67.9
5	3.17 (t, 29.6)	72.8
6a	3.51 (brd, 13.7)	20.9
6b	3.51 (brd, 13.7)	
7		104.5
8		127.2
9	7.44 (d, 7.9)	119.0
10	7.03 (t, 7.2)	120.3
11	7.10 (t, 7.2)	122.7
12	7.32 (d, 7.9)	112.3
13		138.7
14a	2.41 (d, 10.0)	31.7
14b	2.96 (d, 10.0)	
15	3.35 (d, 11.5)	29.6
16		54.4
17a	3.70 (d, 9.6)	68.0
17b	3.82 (d, 9.6)	
18	1.73 (d, 6.9)	13.1
19	5.55 (q, 6.9)	120.9
20		131.8
21a	4.00 (d, 15.8)	71.6
21b	4.45 (d, 15.8)	
22		172.5
23	2.98 (s)	52.2

## EXPERIMENTAL

**General Experimental Procedures.**  $^1\text{H}$  and 2D NMR spectra were recorded on a JEOL ECA600 spectrometer and chemical shifts were reported using residual  $\text{CD}_3\text{OD}$  ( $\delta_{\text{H}}$  3.31 and  $\delta_{\text{C}}$  49.0) as internal standards. HSQC experiments were optimized for  $^1J_{\text{CH}}=145$  Hz and HMBC experiments for  $^nJ_{\text{CH}}=8$  Hz. Mass spectra were recorded on a Micromass LCT spectrometer.

**Plant Material.** The leaves of *Alstonia scholaris* were collected in Purwodadi Botanical Garden, East Java, Indonesia in 2006. A voucher specimen is deposited at the Purwodadi Botanical Garden, Indonesia.

**Extraction and Isolation.** The leaves of *A. scholaris* (500 g) were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with saturated aqueous  $\text{Na}_2\text{CO}_3$ , were extracted with  $\text{CHCl}_3$ . Water-soluble materials were extracted with BuOH. BuOH-soluble materials were subjected to an ODS column

(H<sub>2</sub>O/MeOH 1:1 → 0:1) and the fractions eluted by H<sub>2</sub>O/MeOH (1:1) were subjected to silica gel columns (CHCl<sub>3</sub>/MeOH, 1:0 → 7:3 and CHCl<sub>3</sub>/MeOH, 1:0 → 5:1) to afford compound **1** (0.001%).

CHCl<sub>3</sub>-soluble materials were subjected to an LH-20 column (CHCl<sub>3</sub>/MeOH, 1:1) and an amino silica gel column (hexane/EtOAc, 8:1 → 1:1 and then CHCl<sub>3</sub>/MeOH, 1:0 → 0:1) to give akuammidine<sup>4</sup> (**2**, 0.04%).

**Akuammidine-*N*-oxide (1):** colorless amorphous solid;  $[\alpha]_D^{23}$  -39 (*c* 1.0, MeOH); IR (film)  $\nu_{\max}$  3400, 2940, 2360, 1720, and 1630 cm<sup>-1</sup>; UV (MeOH)  $\lambda_{\max}$  270 ( $\epsilon$  1000) and 205 ( $\epsilon$  5000) nm; <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1); ESIMS *m/z* 369 (M+H)<sup>+</sup>; HRESITOFMS *m/z* 369.1828 [(M+H)<sup>+</sup>, calcd for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>, 369.1814].

**Chemical conversion of akuammidine-*N*-oxide (1) into akuammidine (2).** To a solution of akuammidine-*N*-oxide (**1**, 0.2 mg) in aqueous MeOH (0.2 mL) was added Na<sub>2</sub>SO<sub>3</sub> (1.0 mg) and the mixture was kept at rt for 30 min. After evaporation, the residue was applied to a silica gel column (CHCl<sub>3</sub>/MeOH, 4:1) to give a compound (0.15 mg), whose spectroscopic data and  $[\alpha]_D$  value were identical with those of natural akuammidine (**2**).

**Antiplasmodial Assay.** Human malaria parasites were cultured according to the method by W. Trager *et al.*<sup>8</sup> The antimalarial activity of the isolated compounds was determined by the procedure described by Budimulja *et al.*<sup>8</sup> In brief, Stock solution of the samples were prepared in DMSO (final DMSO concentrations of < 0.5%) and were diluted to the required concentration with complete medium (RPMI 1640 supplemented with 10% human plasma, 25 mM HEPES and 25 mM NaHCO<sub>3</sub>) until the final concentration of samples at well culture plate were: 10; 1; 0.1; 0.01; 0.001 µg/mL. The malarial parasite *P. falciparum* 3D7 clone was propagated in a 24-well culture plate in the presence of a wide range of concentrations of each compound. The growth of the parasite was monitored by making a blood smear fixed with MeOH and stained with Geimsa solution. The antimalarial activity of each compound was expressed as an IC<sub>50</sub> value, defined as the concentration of the compound causing 50% inhibition of parasite growth relative to an untreated control.

The percentage of growth inhibition was expressed according to following equation : Growth inhibition % = 100 - [(test parasitaemia/control parasitemia) × 100. Chloroquine: IC<sub>50</sub> = 0.0061 µg/mL.

## ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and grants from the Research Foundation for pharmaceutical Sciences and The Open Research Center Project. We also acknowledge the financial support provided by Assessment Service Unit, Faculty of Pharmacy, Airlangga University.



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