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TWO NEW ALKALOIDS FROM BULBS OF *LYCORIS SQUAMIGERA*

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Abstract – A new crinine-type alkaloid, squamigine, and a norbelladine-type alkaloid were isolated from the bulbs of *Lycoris squamigera* (Amaryllidaceae), together with sixteen known alkaloids. Their structures were determined by spectroscopic analyses.

INTRODUCTION

Amaryllidaceae alkaloids having structural diversity as well as significant pharmacological activities, such as acetylcholine esterase inhibitory activity and antineoplastic activity, have been extensively studied for many years.[1-3] Galanthamine,[4,5] one of the principal Amaryllidaceae alkaloids, is a potential therapeutic agent for the treatment of Alzheimer's disease. To discover new alkaloids, we investigated constituents in the bulbs of *Lycoris squamigera* (Amaryllidaceae) that is widely distributed in Japan, and our efforts resulted in the isolation of two new alkaloids, squamigine (**1**) and 2*R*-hydroxy-*O*,*N*-dimethylnorbelladine (**2**) (Figure 1). In this paper, the structure elucidation of these new compounds is described.

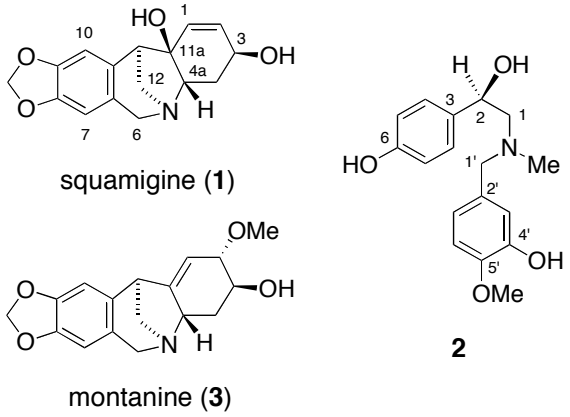


Figure 1. Structures of new alkaloids **1** and **2**, and known alkaloid **3**

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

RESULTS AND DISCUSSION

The bulbs of *L. squamigera* Maxim. (5.4 kg, wet weight) were extracted with MeOH to give the MeOH extract (464.4 g). The crude alkaloidal fraction (2.93 g) obtained by a conventional procedure from the MeOH extract was purified by repeated chromatography to afford new alkaloids squamigine (**1**, 4.0 mg) and 2*R*-hydroxy-*O*,*N*-dimethylnorbelladine (**2**, 18.6 mg) together with sixteen alkaloids categorized into the following types, i.e., galanthamine type: galanthamine, norgalanthamine,[6-8] sanguinine,[9,10] lycoramine,[7,11,12] and *O*-demethyllycoramine;[11] lycorine type: lycorine,[12-14] pseudolycorine,[15] and haemanthamine;[16,17] crinine type: 11-hydroxyvittatine,[18-20] haemanthidine,[20,21] montanine (**3**),[19] tazettine,[22] and 6-*O*-methylpretazettine;[23] and other types: ismine,[24,25] lycoricidine,[26,27] and narciclasine.[28,29]

New alkaloid **1**, named squamigine, has the molecular formula $C_{16}H_{17}NO_4$ from the HR-FAB-MS spectrum (*m*/*z* 288.1237 $[MH]^+$). UV absorption bands at 292.0, 237.5, and 204.5 nm are similar to those of crinine-type alkaloids containing the methylenedioxyphenyl chromophore, such as montanine (**3**). The ^{1}H NMR spectrum showed signals assignable to two *p*-oriented aromatic protons [δ 6.63 (s, H-10), 6.55 (s, H-7)], two *cis*-olefinic protons [δ 6.12 (br-d, J = 10.4 Hz, H-2), 5.76 (br-ddd, J = 10.4, 1.5, 1.5 Hz, H-1)], two protons of methylenedioxy group [δ 5.94 (2H, s)], an oxymethine proton [δ 4.41 (br-dd, J = 10.8, 5.2 Hz, H-3)], and two benzylic methylene protons bearing a nitrogen atom [δ 4.28 and 3.83 (each d, J = 16.7 Hz, H_2-6)]. The ^{13}C NMR spectrum revealed 16 carbons, including eight sp^2 carbons, one methylenedioxy carbon at δ 101.0, one oxygenated quaternary sp^3 carbon at δ 82.9, one oxymethine carbon at δ 63.8, and one benzylic methylene carbon bearing a nitrogen atom at δ 62.1. ^{1}H-^{1}H COSY and HMQC analyses indicated a partial structure, -CH=CHCH(OH)CH_2CH- (C1–C4a). The HMBC correlation from H-2 and H-12 to the oxygenated quaternary carbon at δ 82.9 indicated that this carbon was C-11a (Figure 2). HMBC correlations from H-1 to C-3, from H-6 to C-12, and from H-6, H-11, and H-12 to C-4a were also observed. From the above data, this compound is deduced to be a 5,11-methanomorphanthridine derivative possessing olefin between C-1 and C-2 and two hydroxyl groups at C-3 and C-11a positions. NOE correlations of H-3/H-12 and H-6/H-4a indicated that the stereochemistry at C-3, C-4a, and C-12 methylene bridge was the same as that in montanine (**3**) and the tertiary hydroxyl group at C-11a had β orientation (Figure 3).

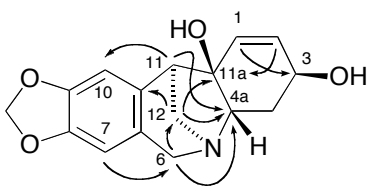


Figure 2. Selected HMBC correlations of **1**

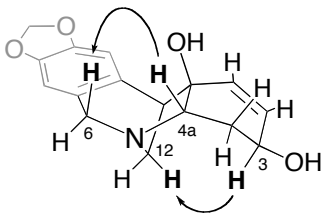


Figure 3. Selected NOE correlations of **1**

Therefore, the structure of squamigine was deduced to be formula **1**.

The HR-FAB-MS spectrum of new alkaloid **2** gave a protonated molecular ion peak at *m/z* 304.1551 ([MH]$^+$) that corresponded to the molecular formula $C_{17}H_{22}NO_4$ (*m/z* 304.1549). The ^{1}H NMR spectrum showed signals assignable to aromatic protons of *p*-substituted [δ 7.14 (H-4, 8) and 6.72 (H-5, 7) (each d, 2H)] and 1,2,4-trisubstituted benzene rings [δ 6.87 (d, H-3'), 6.80 (d, H-6'), 6.77 (dd, H-7')], a methoxy group on an aromatic ring at δ 3.87, an *N*-methyl group at δ 2.29, an oxymethine proton at δ 4.66 (dd), and two sets of methylene protons bearing a nitrogen atom [δ 3.62 (d) and 3.43 (d), δ 2.60 (dd) and 2.43 (dd)], the latter of which was coupled with the oxymethine proton. The ^{13}C NMR spectrum revealed 17 carbons, including three aromatic carbons bearing an oxygen function at δ 155.6, 145.9, and 145.5, and an oxymethine carbon at δ 69.2. In the HMBC spectrum, correlations between the oxymethine proton and carbons of C-4 and C-8 of the *p*-substituted benzene ring, and between methylene protons of C-1' and carbons of C-3' and C-7' of the trisubstituted benzene ring were observed (Figure 4) . NOE correlation between methoxy protons and H-6' indicated that the methoxy group was positioned at C-5' of the trisubstituted benzene ring. From these data, the structure of compound **2** was deduced to be 2-hydroxy-*O*,*N*-dimethylnorbelladine, which was already reported as a racemic synthetic compound.[30]

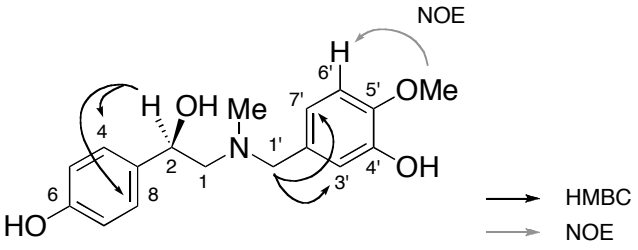
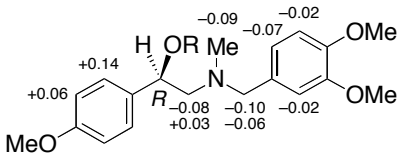


Figure 4. Selected HMBC and NOE correlations of **2**

The absolute configuration of the hydroxyl group at C-2 was determined by the modified Mosher's method[31] using (*S*)- and (*R*)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetyl] esters of **2** (Figure 5). Compound **2** was first treated with CH_2N_2 in MeOH to give trimethyl ether **4**. Reaction of **4** with (*R*)- or (*S*)-MTPA chloride in the presence of *N*,*N*-dimethylaminopyridine and Et_3N in CH_2Cl_2 gave (*S*)- or (*R*)-MTPA ester **5**, respectively. The $\Delta\delta_{(S-R)}$ values of the ^{1}H NMR chemical shifts for H-1 and *N*-Me were -0.08 and -0.09 ppm, while those for H-4, 8 and H-5, 7 were +0.14 and +0.06 ppm. The above results indicated that the absolute configuration at C-2 was *R* and therefore, compound **2** is 2*R*-hydroxy-*O*,*N*-dimethylnorbelladine.



4: R=H
5a: R=(*S*)-MTPA
5b: R=(*R*)-MTPA

$\Delta\delta = \delta$ (*S*)-MTPA $- \delta$ (*R*)-MTPA (ppm)

Figure 5. Structures of compounds **4**, **5a** and **5b**, and $\Delta\delta$ values of the MTPA esters (**5a** and **5b**)

EXPERIMENTAL

General

Optical rotation: JASCO P-1020. IR: JASCO FT/IR-230. ^{1}H and ^{13}C NMR spectra: JEOL JNM A-500 at 500 (^{1}H) and 125 (^{13}C) MHz, or JEOL JNM-ECP400 at 400 (^{1}H) and 100 (^{13}C) MHz, respectively. FAB-MS and HR-FAB-MS: JEOL JMS-HX110. TLC: Precoated silica gel 60 F_{254} plates (Merck, 0.25 mm thick). Column chromatography: Silica gel 60 [(Merck, 70-230 mesh (for open chromatography) or 230-400 mesh (for flash chromatography)], amino silica gel (Fuji Silysia Chemical, NH-DM1020). MPLC: C. I. G. prepacked column CPS-HS-221-05 (SiO_2).

Plant Material

The bulbs of *Lycoris squamigera* Maxim. (Amaryllidaceae) were harvested from the medicinal plant garden of Chiba University in May 2005, and identified by Dr. F. Ikegami, Chiba University. A voucher specimen was deposited at the Faculty of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation

The bulbs of *L. squamigera* (5.4 kg, wet weight) were extracted with MeOH (18.3 L, two times at rt and two times under reflux) to give the extract (464.4 g). The extract was suspended in 10% AcOH and filtered. The aqueous filtrate was extracted with *n*-hexane (1.3 L), rendered basic with Na_2CO_3, and then extracted with 5% MeOH/$CHCl_3$ (9 L) and *n*-BuOH (3 L) to give the crude alkaloid fraction (2.93 g) and the *n*-BuOH fraction (34.51 g), respectively. The crude base was roughly separated by SiO_2 flash column chromatography using $CHCl_3$/MeOH gradient to give 10 fractions: fr. A ($CHCl_3$, 2-5% MeOH/$CHCl_3$, 84 mg), fr. B (5%, 84 mg), fr. C (5-10%, 45 mg), fr. D (10%, 1342 mg), fr. E (10-20%, 453 mg), fr. F (30%, 31 mg), fr. G (50%, 48 mg), fr. H (50%, 34 mg), fr. I (MeOH, 78 mg), and fr. J (MeOH, 52 mg). Fr. I was purified by using a combination of amino silica gel open column chromatography (3-5% MeOH/$CHCl_3$), MPLC (25% MeOH/$CHCl_3$), and amino silica gel open column chromatography (4% MeOH/$CHCl_3$) to

afford squamigine (**1**, 4.0 mg). Fr. G was purified by MPLC (10% MeOH/$CHCl_3$) and amino silica gel open column chromatography (2% MeOH/$CHCl_3$) to afford 2*R*-hydroxy-*O*,*N*-dimethylnorbelladine (**2**, 18.6 mg). From the crude base, fourteen known alkaloids, galanthamine (196.8 mg), norgalanthamine (0.6 mg), sanguinine (2.4 mg), lycoramine (50.3 mg), *O*-demethyllycoramine (8.2 mg), lycorine (92.4 mg), pseudolycorine (7.5 mg), haemanthamine (3.4 mg), 11-hydroxyvittatine (1.9 mg), haemanthidine (8.4 mg), montanine (**3**, 92.6 mg), tazettine (2.4 mg), 6-*O*-methylpretazettine (8.5 mg), and ismine (6.8 mg), were isolated. From the *n*-BuOH fraction, three known alkaloids, pseudolycorine (17.1 mg), lycoricidine (12.7 mg), and narciclasine (39.2 mg), were obtained.

The ^{13}C NMR data of *O*-demethyllycoramine have not been reported elsewhere.

***O*-Demethyllycoramine**: ^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.7 (C-5a), 140.1 (C-6), 136.0 (C-8b), 128.0 (C-8a), 122.3 (C-8), 115.1 (C-7), 90.1 (C-4a), 65.6 (C-3), 60.4 (C-9), 54.0 (C-11), 46.9 (C-4b), 41.7 (*N*-CH_3), 31.5 (C-4), 31.1 (C-12), 27.6 (C-2), 23.6 (C-1).

Squamigine (1)

UV (MeOH) λ_{max} nm (log ε): 292.0 (3.27), 237.5 (3.23), 204.5 (4.15). IR ($CHCl_3$) ν_{max} cm^{-1}: 2961, 2927, 1482, 1095, 1036. FAB-MS (NBA) *m*/*z*: 288 $[MH]^+$. HR-FAB-MS (NBA/PEG) *m*/*z*: 288.1237 $[MH]^+$ (Calcd for $C_{16}H_{18}NO_4$: 288.1236). ^1H NMR (500 MHz, $CDCl_3$) δ: 6.63 (1H, s, H-10), 6.55 (1H, s, H-7), 6.12 (1H, br-d, *J* = 10.4 Hz, H-2), 5.94 (2H, s, -OCH_2O-), 5.76 (1H, br-ddd, *J* = 10.4, 1.5, 1.5 Hz, H-1), 4.41 (1H, br-dd, *J* = 10.8, 5.2 Hz, H-3), 4.28 (1H, d, *J* = 16.7 Hz, H-6α), 3.83 (1H, d, *J* = 16.7 Hz, H-6β), 2.98 (1H, dd, *J* = 11.8, 2.2 Hz, H-12), 2.90 (1H, m, H-4a), 2.85 (1H, d, *J* = 11.8, 1.5 Hz, H-12), 2.63 (1H, d, *J* = 2.2 Hz, H-11), 2.32 (1H, br-d, *J* = 12.6 Hz, H-4α), 1.64 (1H, ddd, *J* = 12.6, 10.8, 4.4 Hz, H-4β). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.6 (C-8), 146.1 (C-9), 136.9 (C-2), 131.0 (C-1), 128.8 (C-10a), 126.4 (C-6a), 109.9 (C-10), 107.2 (C-7), 101.0 (-OCH_2O-), 82.9 (C-11a), 68.1 (C-4a), 63.8 (C-3), 62.1 (C-6), 55.0 (C-12), 49.6 (C-11), 35.6 (C-4). CD (*c*=0.383 mmol/L, MeOH, 24 °C) Δε (λ nm): 0 (314), –0.4 (300), 0 (261), +0.4 (242), 0 (232), –5.9 (211).

2*R*-Hydroxy-*O*,*N*-dimethylnorbelladine (2)

$[\alpha]_D^{25}$ –46° (*c*=0.92, MeOH). UV (MeOH) λ_{max} nm (log ε): 280.0 (3.53), 226.5 (4.08), 206.0 (4.34). IR ($CHCl_3$) ν_{max} cm^{-1}: 3533, 3333, 1513. FAB-MS (NBA) *m*/*z*: 304 $[MH]^+$. HR-FAB-MS (NBA/PEG) *m*/*z*: 304.1551 $[MH]^+$ (Calcd for $C_{17}H_{22}NO_4$: 304.1549). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.14 (2H, d, *J* = 8.5 Hz, H-4, H-8), 6.87 (1H, d, *J* = 1.9 Hz, H-3'), 6.80 (1H, d, *J* = 8.2 Hz, H-6'), 6.77 (1H, dd, *J* = 8.2, 1.9 Hz, H-7'), 6.72 (2H, d, *J* = 8.5 Hz, H-5, H-7), 4.66 (1H, dd, *J* = 10.6, 3.4 Hz, H-2), 3.87 (3H, s, OCH_3), 3.62 and 3.43 (each 1H, d, *J* = 12.8 Hz, H_2-1'), 2.60 (1H, dd, *J* = 12.5, 10.6 Hz, H-1), 2.43 (1H, dd, *J* = 12.5, 3.4 Hz, H-1), 2.29 (3H, s, *N*-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.6 (C-6), 145.9 (C-5'), 145.5 (C-4'),

133.3 (C-3), 131.1 (C-2'), 127.4 (C-4, C-8), 120.7 (C-7'), 115.4 (C-3'), 115.3 (C-5, C-7), 110.6 (C-6'), 69.2 (C-2), 64.9 (C-1), 61.8 (C-1'), 55.9 (OCH_3), 41.6 (*N*-CH_3).

Methylation of compound 2 with CH_2N_2

An ether solution of freshly prepared CH_2N_2 was added to a solution of **2** (6.0 mg, 0.020 mmol) in MeOH (0.6 mL) and the reaction mixture was stirred at rt for 3 days. After addition of a few drops of AcOH, the solution was evaporated. The residue was purified by MPLC (10% MeOH/$CHCl_3$) to give trimethyl ether **4** (3.3 mg, y. 50%).

Trimethyl ether **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (2H, d, J = 8.7 Hz, H-4, H-8), 6.90 (1H, br-s, H-3'), 6.85 (2H, d, J = 8.7 Hz, H-5, H-7), 6.81 (2H, overlapped, H-6', H-7'), 4.76 (1H, d, J = 11.0 Hz, H-2), 3.873 (3H, s, OCH_3), 3.866 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.77 and 3.57 (each, 1H, d, J = 13.0 Hz, H_2-1'), 2.68 (1H, dd, J = 12.0, 11.0 Hz, H-1), 2.51 (1H, d, J = 12.0 Hz, H-1), 2.39 (3H, s, *N*-CH_3).

Preparation of (*S*)-MTPA ester 5a of trimethyl ether 4

To a solution of trimethyl ether **4** (1.1 mg, 0.0033 mmol), DMAP (1.6 mg, 0.016 mmol), and Et_3N (1.4 μL, 0.010 mmol) in dry CH_2Cl_2 (0.16 mL) was added (*R*)-MTPACl (1.9 μL, 0.010 mmol) and the reaction mixture was stirred at rt for 4.5 h under Ar. The reaction mixture was quenched with 3-[(dimethylamino)propyl]amine (1.3 μL, 0.010 mmol) and then evaporated. The residue was purified by silica gel open column chromatography ($CHCl_3$) and MPLC (30% AcOEt/*n*-hexane) to give (*S*)-MTPA ester **5a** (0.8 mg, y. 44%).

(*S*)-MTPA ester 5a: FAB-MS (NBA) *m*/*z*: 548 $[MH]^+$. ^{1}H NMR (500 MHz, CD_3CN) δ: 7.50 (2H, br-d, *J*=7.5 Hz, MTPA aromatic-H), 7.43 (1H, dddd, J = 7.5, 7.5, 1.4, 1.4 Hz, MTPA aromatic-H), 7.37 (2H, dd-like, *J*=7.5, 7.5 Hz, MTPA aromatic-H), 7.30 (2H, d-like, J = 8.7 Hz, H-4, H-8), 6.92 (2H, d-like, J = 8.7 Hz, H-5, H-7), 6.79 (1H, d, J = 8.2 Hz, H-6'), 6.77 (1H, d, J = 2.1 Hz, H-3'), 6.68 (1H, dd, J = 8.2, 2.1 Hz, H-7'), 6.15 (1H, dd, J = 8.7, 4.8 Hz, H-2), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.54 (1H, d, J = 13.1 Hz, H-1'), 3.40 (3H, br-s, MTPA-OCH_3), 3.35 (1H, d, J = 13.1 Hz, H-1'), 2.91 (1H, dd, J = 13.6, 8.7 Hz, H-1), 2.62 (1H, dd, J = 13.6, 4.7 Hz, H-1), 2.15 (3H, s, *N*-CH_3).

Preparation of (*R*)-MTPA ester 5b of trimethyl ether 4

To a solution of trimethyl ether **4** (2.5 mg, 0.0075 mmol), DMAP (3.7 mg, 0.030 mmol), and Et_3N (3.2 μL, 0.023 mmol) in dry CH_2Cl_2 (0.25 mL) was added (*S*)-MTPACl (4.3 μL, 0.023 mmol) and the reaction mixture was stirred at rt for 2 h under Ar. The reaction mixture was quenched with 3-[(dimethylamino)propyl]amine (3.8 μL, 0.030 mmol) and then evaporated. The residue was purified by MPLC (10% MeOH/$CHCl_3$ and then 30% AcOEt/*n*-hexane) to give (*R*)-MTPA ester **5b** (1.8 mg, y. 44%).

(*R*)-MTPA ester 5b: FAB-MS (NBA) *m*/*z*: 548 $[MH]^+$. ^{1}H NMR (500 MHz, CD_3CN) δ: 7.51 (2H, br-d, *J*=7.7 Hz, MTPA aromatic-H), 7.42 (1H, dddd, *J* = 7.7, 7.7, 1.4, 1.4 Hz, MTPA aromatic-H), 7.35 (2H, dd-like, *J* = 7.5, 7.5 Hz, MTPA aromatic-H), 7.16 (2H, d, *J* = 8.7 Hz, H-4, H-8), 6.86 (2H, d, *J* = 8.7 Hz, H-5, H-7), 6.81 (1H, d, *J* = 8.1 Hz, H-6'), 6.79 (1H, d, *J* = 1.8 Hz, H-3'), 6.75 (1H, dd, *J* = 8.1, 1.8 Hz, H-7'), 6.12 (1H, dd, *J* = 9.4, 4.1 Hz, H-2), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.64 (1H, d, *J* = 12.8 Hz, H-1'), 3.60 (3H, s, OCH_3), 3.55 (3H, br-s, MTPA-OCH_3), 3.41 (1H, d, *J* = 12.8 Hz, H-1'), 2.99 (1H, dd, *J* = 13.6, 9.4 Hz, H-1), 2.59 (1H, dd, *J* = 13.6, 4.1 Hz, H-1), 2.24 (3H, s, *N*-CH_3).

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