

Four New Indole Alkaloids from *Neolamarckia cadamba*[†]

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Phytochemical investigation on the leaves of *Neolamarckia cadamba* led to the isolation of four new indole alkaloids, spirocadambine (**1**), dehydratodihydrocadambine (**2**), nitrocadambines A and B (**3** and **4**). The structures and relative configurations were established by 1D and 2D NMR spectra. Spirocadambine (**1**) represents a new type of screw ring containing indole glucoalkaloids.

Keywords Rubiaceae, *Neolamarckia cadamba*, indole alkaloids, glucoalkaloids

Introduction

Indole alkaloids with diverse carbon skeletons have stimulated considerable interest and are arguably recognized as one of the most interesting nature products research fields.^[1] Our group has focused on investigating various natural indole alkaloids from Yunnan local medicinal plants in China for several years.^[2-7] The plant *Neolamarckia cadamba*, previously named *Anthoccephalus chinensis*, is a member of the tribe Neolamarckia in the family of Rubiaceae and it has been used traditionally in the “Dai” ethnopharmacy by the local ethnic people in Yunnan province of China to treat inflammation, fever and pruritus.^[9-11] Previously studies on chemical gradients had led to two novel amino acid containing indole alkaloids isolated from *N. Cadamba* (Roxb.) Bosser.^[8] This article reports our continuing research on the isolation and identification of four new indole alkaloids, named spirocadambine (**1**), dehydratodihydrocadambine (**2**), and nitrocadambines A and B (**3** and **4**) from the leaves of title plant. Among them, compound **1** was determined as a new type of screw ring containing indole glucoalkaloids, and compound **2** was assigned to be a novel compound possessing a 6/5/6/7/6 hexacyclic ring system.

Experimental

General experimental procedures

Solvents were distilled before use. Chromatographic purifications were carried out over silica gel (200–300 mesh; Qingdao Marine Chemical Inc., Qingdao, China), Sephadex LH-20 (40–70 μm, Amersham Pharmacia

Biotech AB, Uppsala, Sweden), and Lichroprep RP-18 gel (40–63 μm, Merck Darmstadt, Germany). Optical rotations: JASCO DIP-370 digital polarimeter. UV spectra were obtained on a Shimadzu UV 2401 PC spectrometer (Shimadzu; Kyoto, Japan); IR spectra were obtained on a Bruker Tensor 27 spectrometer (Bruker Optics Inc.; Ettlingen, Germany) with KBr pellets; MS were recorded on a VG Autospec-3000 or API QSTAR PULSAR LC-Q-TOF spectrometer (VG; Manchester, England); NMR spectra were recorded on a Bruker AM-400 (400 MHz/100 MHz), DRX-500 (500 MHz/125 MHz) and AV-600 (600 MHz/150 MHz) spectrometer (Bruker BioSpin AG; Fallanden, Switzerland).

Plant material

The leaves of *N. cadamba* (25 kg) were collected in Xishuangbanna, Yunnan Province of China, in July 2008. The plant was identified by Prof. Xun Gong, Chinese Academy of Science. A specimen of this plant (No. 0766725) was deposited in the Kunming Institute of Botany, Kunming, China.

Extraction and isolation

The air-dried leaves of *N. cadamba* (25 kg) were refluxed three times with 95% EtOH, and the residue was partitioned between EtOAc and acidic liquor at pH 3–4. After being basified to pH 10 with saturated Na₂CO₃, the aqueous layer was further extracted with EtOAc and *n*-BuOH, successively. The EtOAc soluble material was then subjected to ion-exchange chromatography to enrich the crude alkaloid. The crude alkaloid fraction (20 g) was then chromatographed on RP-18 silica gel, eluting

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with H₂O-MeOH (from 10 : 1 to 0 : 10) to afford five fractions (I—V). Fraction II (10 g) was purified by silica gel column chromatographies to afford compounds **1** (54 mg) and **2** (19 mg). Fraction IV (1.3 g) was purified by silica gel column chromatographies and Sephadex LH-20 to afford compounds **3** (3 mg) and **4** (5 mg).

Spirocadambine (1): Light yellow amorphous powder, $[\alpha]_D^{20} -293.85$ (*c* 0.013, MeOH). UV (MeOH) λ_{max} (log ε): 217.0 (4.39), 236.0 (4.48), 401.0 (3.58) nm; ¹H and ¹³C NMR data see Table 1; IR (KBr) ν_{max} : 3424, 2923, 1689, 1620, 1491, 1468, 1439, 1325, 1312, 1155, 1076, 753 cm⁻¹. HRTOFMS calcd for C₂₇H₃₄N₂O₁₁: 561.2085, found 561.2100 [M-H]⁺.

Dehydراisodihydrocadambine (2): Light yellow powder, $[\alpha]_D^{20} +8.20$ (*c* 0.030, MeOH). UV (MeOH) λ_{max} (log ε): 224.6 (4.54), 281.4 (3.90) nm; ¹H and ¹³C NMR data see Table 1; IR (KBr) ν_{max} : 3423, 2924, 1664, 1623, 1452, 1360, 1322, 1150, 1063, 1025, 997, 971, 941, 897, 817, 744 cm⁻¹. HRTOFMS calcd for C₂₆H₃₂N₂O₁₀: 532.2057, found 532.2054 [M]⁺.

Nitrocadambine A (3): White amorphous powder, $[\alpha]_D^{20} +11.50$ (*c* 0.020, MeOH). UV (MeOH) λ_{max} (log ε): 224.4 (4.41), 282.0 (3.80) nm; ¹H and ¹³C NMR data see Table 2; IR (KBr) ν_{max} : 3424, 2933, 1666, 1470, 1452, 1323, 1089, 1035, 742 cm⁻¹. HRTOFMS calcd for C₂₀H₂₃N₃O₃Na: 376.1637, found 376.1645 [M+Na]⁺.

Nitrocadambine B (4): Yellow powder, $[\alpha]_D^{20} +81.19$ (*c* 0.023, MeOH). UV (MeOH) λ_{max} (log ε): 224.6 (4.02), 282.4 (3.75) nm; ¹H and ¹³C NMR data see Table 2; IR (KBr) ν_{max} : 3425, 2927, 1690, 1639, 1453, 1319, 1306, 1230, 1134, 1102, 1078, 743 cm⁻¹. HRTOFMS calcd for C₂₁H₂₃N₃O₄: 382.1767, found 382.1768 [M+H]⁺.

Bioassays

The cytotoxicity of compounds **1**–**4** against A-549, MCF-7, HL-60, SW480 and SMMC-7721 human tumor cell lines was evaluated by the MTT method.^[12] In brief, cells were seeded in 96-well plates 12 h before treated by compounds, and then incubated at 37 °C for 48 h. After that, 20 μL of MTT (2.5 mg/mL) were added to each well and incubated for an additional 4 h. Then 100 μL detergent reagents were added in each well, followed by a further incubation at 37 °C overnight in the dark. The optical density was measured by BioTeck microplate reader.

Results and Discussion

Compound **1** was isolated as a light yellow amorphous powder. The molecular formula was determined to be C₂₇H₃₄N₂O₁₁ according to its negative HRTOFMS at *m/z* 561.2100 [M-H][−] (calcd 561.2085). Moreover, a fragment ion at *m/z* 399 was observed in negative FABMS corresponding to the [M-glucose][−] ion. The IR spectrum showed absorptions at 3424 cm⁻¹ for hydroxyl, 1689 and 1620 cm⁻¹ for carbonyl functionalities. ¹³C NMR and DEPT spectra showed the presence of 27 carbons, six of which were attributed to a glucosyl unit

(Table 1). In addition to the sugar unit, the aromatic region of the ¹H NMR spectrum exhibited four aromatic signals (δ_H 6.67, 6.83, 7.38, 7.41), suggesting an *ortho*-disubstituted benzene ring. The majority of its 1D NMR data was in agreement with the isodihydrocadambine (**5**), which was also isolated from this plant.^[5,13] Compared with isodihydrocadambine (**5**), compound **1** contained an sp³ quaternary carbon (δ_C 75.3) and a ketone carbonyl group (δ_C 205.4). The HMBC relationship between H-10 (δ_H 6.67) and C-8 (δ_C 120.2), C-13 (δ_C 163.3) and the ketone carbonyl (δ_C 205.4), indicated that the ketone carbonyl group was connected directly to the benzene ring and was assigned at C-7. Furthermore, in the HMBC spectrum, the H-6 (δ_H 1.87) and H-3 (δ_H 2.32) were correlated to C-2 (δ_C 75.3) and C-7 respectively, together with the downfield chemical shift of C-2, suggesting the formation of rings B and C to make C-2 as a spiro atom center. Thus, the planar structure of compounds **1** was determined as a new type of screw ring containing indole glucoalkaloid. The relative configuration of compound **1** was determined by the coupling constants of the protons and 2D ROESY spectrum. The *J*-based configurational analysis indicated the glucose to be a β -configuration ($J_{\text{H}1' \cdot \text{H}2'} = 8.0$ Hz) and H-20 to be α -orientation ($J_{\text{H}21 \cdot \text{H}20} = 8.0$ Hz).^[13] The key ROESY cross-peaks of H-21 (δ_H 6.08)/H-14 β (δ_H 1.35), H-14 α (δ_H 1.28)/H-19 (δ_H 2.48), and H-19/H-3 (δ_H 2.32) suggested the α -orientation of H-19 and H-3, and the α -orientation of H-21. H-15 was determined to be at the same side with H-20 by comparison of the ¹H NMR data with isodihydrocadambine.^[13] The configuration of spiro atom C-2 was confirmed by the ROESY spectrum obtained in DMSO-*d*₆. The ROESY correlation of H-1 (δ_H 7.28)/H-6 α (δ_H 2.04) in the ROESY spectrum indicated the C-2-NH was α -orientation. Therefore, the structure of **1** was fully identified as shown in Figure 1, named as spirocadambine.

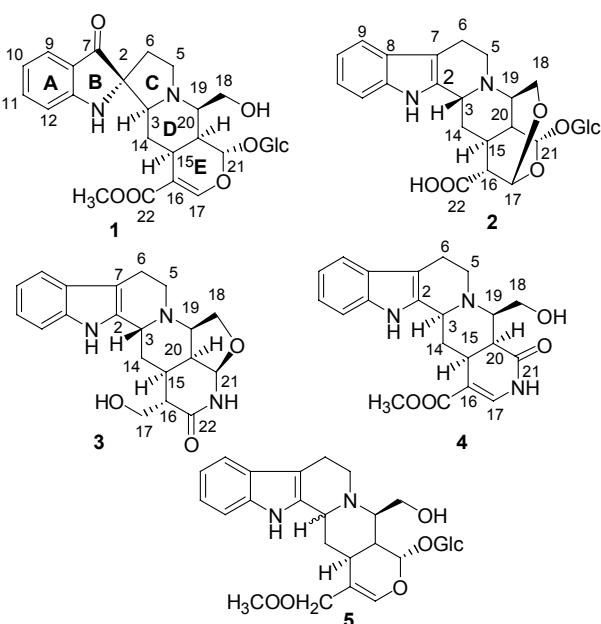


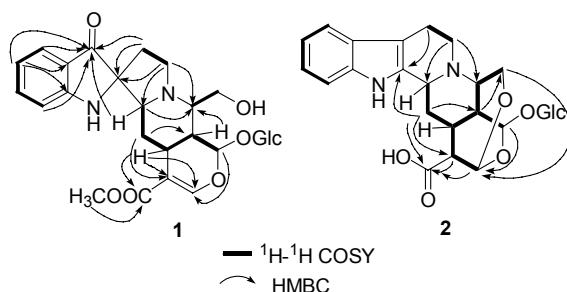
Figure 1 Structures of compounds **1**–**5**.

Table 1 ^1H and ^{13}C NMR data of compounds **1** and **2** in CD_3OD

Position	1		2	
	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}
2	—	75.3	—	136.3
3	2.32 m	74.0	4.26 m	51.1
5 α	2.37 m	51.8	2.80 m	50.5
5 β	3.27 m		2.97 m	
6 α	1.87 m		2.67 m	
6 β	2.16 m	35.6	2.85 m	22.7
7	—	205.4	—	108.2
8	—	120.2	—	128.3
9	6.83 d (8.3)	112.9	7.37 d (7.9)	118.5
10	6.67 t (8.3)	118.6	6.97 t (7.9)	119.7
11	7.38 m	139.1	7.04 t (7.9)	121.9
12	7.41 m	125.0	7.28 d (7.9)	111.8
13	—	163.3	—	138.1
14 α	1.28 m	29.0	1.76 dt (8.1, 2.3)	36.5
14 β	1.35 m		2.11 d (8.1)	
15	2.52 m	33.4	3.04 br s	23.6
16	—	111.7	2.85 m	54.1
17	7.43 s	154.3	5.49 m	97.3
18 α	3.93 m	64.0	3.65 m	59.5
18 β	3.83 m		4.17 m	
19	2.48 m	68.5	3.17 m	62.2
20	2.03 m	38.7	2.62 m	40.1
21	6.08 d (8.0)	97.5	5.65 m	96.3
22	—	168.6	—	176.9
OCH ₃	3.58 s	51.7		
1'	4.76d (8.0)	100.3	4.69 m	99.9
2'	3.21 m	74.8	3.28 m	74.8
3'	3.37 m	77.7	3.42 m	77.7
4'	3.18 m	72.0	3.31 m	71.5
5'	3.33 m	78.7	3.34 m	78.3
6'	3.59 m	63.4	3.68 m	62.8
	3.97 m		3.91 m	

Compound **2**, a light yellow powder, possessed the molecular formula $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_{10}$, as revealed by positive HRFOMS (m/z 532.2054 [M^+]). The IR spectrum showed an absorption band at 3423 cm^{-1} for hydroxyl. ^{13}C NMR and DEPT spectra of **2** were revealed the presence of 26 unique carbon atoms, six of which were assigned to a sugar unit (Table 1). The remaining 20 carbon atoms were further classified into four sp^2 quaternary carbons, four sp^2 methine groups, seven sp^3 methine groups, four sp^3 methylene groups and one carbonyl. The ^1D NMR data were very similar to those of isodihydrocadambine (**5**), with the lack of a methoxyl group and a double bond in **2**. The ^1H - ^1H COSY spectrum of **2** showed the connectivity of four fragments [H-3 (δ_{H} 4.26)—H-14 (δ_{H} 1.76)—H-15 (δ_{H} 3.04), H-20 (δ_{H} 2.62)—H-19 (δ_{H} 3.17)—H-18 (δ_{H} 3.65), H-15—

H-16 (δ_{H} 2.85)—H-17 (δ_{H} 5.49), H-20—H-21 (δ_{H} 5.65)], as indicated in Figure 2. The HMBC correlation of H-21/C-17, in combination with the downshift of C-17 (δ_{C} 97.3), C-21 (δ_{C} 96.3), revealed that C-17 was connected to C-21 through an oxygen atom. The HMBC correlation of H-18/C-17 indicated the connection of C-17 and C-18 via an oxygen atom to form a seven member ring. Meanwhile, the carbonyl group was connected to C-16 (δ_{C} 54.1) which was supported by HMBC correlation of H-15, H-16 and H-17 with C-22 (δ_{C} 176.9). The relative configuration of **2** was determined by ROESY cross-peaks of H-19/H-5 α (δ_{H} 2.80), H-5 β (δ_{H} 2.97)/H-3 and H-3/H-18 β established α -orientation of H-19, β -orientation of H-3 and CH₂-18. The relative configurations of H-15 and H-20 were assigned to be α -oriented on the base of literatures.^[14] Accordingly, the structure of **2** was elucidated as shown in Figure 1, and named dehydrosodihydrocadambine.

**Figure 2** Selected ^1H - ^1H COSY (—) and HMBC (H \rightarrow C) correlations of compounds **1** and **2**.

Compound **3**, a white amorphous powder, showed a molecular-ion peak (M^+) at m/z 353 in the EI-MS spectrum. The molecular formula was determined as $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_3$ by positive HRFOMS at m/z 376.1645 ($[\text{M}+\text{Na}]^+$; calcd 376.1637), which indicated 11 degrees of unsaturation. The IR absorption of **3** indicated the presence of NH and/or OH (3424 cm^{-1}) and carbonyl (1667 cm^{-1}) groups. ^{13}C NMR and DEPT (Table 2) revealed 20 carbon signals due to four sp^2 quaternary carbons, four sp^2 methine groups, six sp^3 methine groups, five sp^3 methylene groups, and one carbonyl. The ^1H NMR signals at δ_{H} 7.34, 7.28, 7.00, and 6.92, together with ^{13}C NMR signals at δ_{C} 136.0, 135.9, 126.6, 120.2, 118.1, 117.3, 110.8, and 106.4 (Table 2) implied the presence of a 2-substituted indole-ring moiety. Extensive analysis of the NMR data of **3** revealed its structure to be close related to that of amicocadambines A.^[8] The only difference was the presence of an acidamide group to form the ring E, which was deduced by the HMBC correlations between H-17 (δ_{H} 3.83)/C-22 (δ_{C} 175.5), and H-21 (δ_{H} 5.11)/C-22 and the downshift of C-21 (δ_{C} 83.3). In addition, the downshift of C-17 (δ_{C} 56.8) and the molecular formula required a hydroxyl group at C-17.

The relative configuration of **3** was deduced by the ROESY analysis (Figure 3). The ROESY correlations of

Table 2 ^1H and ^{13}C NMR data of compounds **3** and **4**

Position	3 ^a		4 ^b	
	δ_{H} , (J in Hz)	δ_{C}	δ_{H} , (J in Hz)	δ_{C}
2	—	136.0	—	132.7
3	3.98, d (9.0)	45.9	4.42 s	56.9
5 α	2.68 m	48.9	3.00 m	48.8
5 β	3.10 m	48.9	3.68 m	48.8
6 α	2.57 m	21.3	2.50 m	17.8
6 β	2.72 m	21.3	3.08 m	17.8
7	—	106.4	—	108.9
8	—	126.6	—	128.6
9	7.34 d (8.0)	117.3	7.38 d (7.6)	118.6
10	6.92 t (8.0)	118.1	6.96 t (7.6)	119.8
11	7.00 t (8.0)	120.2	7.05 t (7.6)	122.1
12	7.28 d (8.0)	110.8	7.33 d (7.6)	112.1
13	—	135.9	—	137.7
14 α	1.57 m	29.5	1.85 dt (13.5, 4.5)	28.7
14 β	2.44 m	29.5	2.29 m	28.7
15	2.23 m	27.5	2.64 dd (13.5, 4.5)	31.8
16	2.47 m	43.7	—	112.8
17 α	3.83 m	56.8	7.18 s	136.5
17 β	4.04 m	56.8	—	136.5
18 α	3.72 m	64.8	3.97 dd (9.6, 2.8)	64.6
18 β	4.01 m	64.8	4.19 dd (9.6, 4.4)	64.6
19	3.86 m	61.7	3.05 m	56.1
20	2.66 q (8.0)	35.3	2.81 m	45.3
21	5.11 t (5.8)	83.3	—	173.8
22	—	175.5	—	168.2
OCH ₃		3.72 s		52.1

^a Data were recorded in DMSO-*d*₆ at 400 MHz (^1H) and 100 MHz (^{13}C). ^b Data were recorded in CD₃OD at 400 MHz (^1H) and 100 MHz (^{13}C).

H-3/H-16/H-5 β (δ_{H} 3.10), H-5 α (δ_{H} 2.68)/H-19 (δ_{H} 3.86)/H-20/H-15 and H-19/H-21 suggested that H-3 (δ_{H} 3.98) and H-16 (δ_{H} 2.47) were β -oriented, and H-15 (δ_{H} 2.23), H-19 (δ_{H} 3.86), H-20 (δ_{H} 2.66) and H-21 (δ_{H} 5.11) were α -oriented. Thus, the structure of **3** was assigned, and named nitrocadambine A.

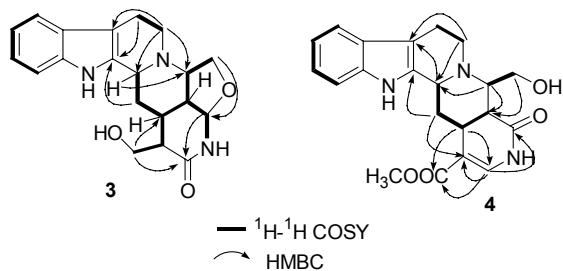


Figure 3 Selected ^1H - ^1H COSY (—) and HMBC (H→C) correlations of compounds **3** and **4**.

Compound **4** was obtained as a yellow powder. The molecular formula was determined as C₂₁H₂₃N₃O₄ from the positive-ion-mode HR-TOF-MS (*m/z* 382.1768

([M+H]⁺), calcd for C₂₁H₂₄N₃O₄: 382.1767), indicating 12 degrees of unsaturation. Its IR spectrum revealed the presence of NH and/or OH (3425 cm⁻¹) and C=O (1690 cm⁻¹) groups, while the UV spectrum showed absorption at 224 and 282 nm, suggesting the existence of conjugate groups. The ^{13}C NMR and DEPT spectra of **4** (Table 2) gave a total of 21 carbon atoms (five quaternary carbons, nine methine groups, four methylene groups, two carbonyls, and one methoxyl). The ^1D NMR spectra of **4** were similar to those of isodihydrocadambine (**5**). However, the signals due to a glucose in isodihydrocadambine were absent in **4**, and the presence of an additional carbonyl unit was observed in ^{13}C NMR spectrum of **4**. The HMBC correlations of H-19 (δ_{H} 3.05)/C-21 (δ_{C} 173.8), and H-20/C-21 indicated the carbonyl group of C-21 linked at C-20 (δ_{C} 45.3). An imino group placed between C-17 (δ_{C} 136.5) and C-21 was deduced from HMBC correlation between H-17 (δ_{H} 7.18)/C-21, the chemical shift of C-17, and the molecular formula of **4**. The above deductions were further confirmed by extensive 2D NMR experiments, including HSQC, COSY and HMBC (Figure 3). The relative configuration of **4** was determined to be the same as 3 α -isodihydrocadambine^[15] from ROESY analysis.

The potential biosynthetic pathway of compound **1** was proposed as shown in Figure 4. Compound **5** was considered to be a biogenetic precursor of compound **1**. The attachment of the hydroxyl group at position 7 in compound **5** leads to the rearrangement of ring B and C, which forms a unique screw ring at position 2.

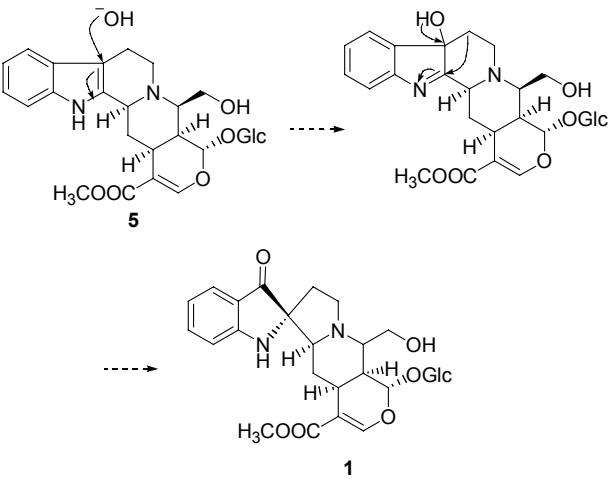


Figure 4 Proposed biosynthetic pathway of compound **1**.

All four compounds were tested for cytotoxic activities against the human tumor cell lines (A-549, MCF-7, HL-60, SW480, SMMC-7721). However, the results revealed that all four compounds were inactive against the above cancer cells with IC₅₀>40 μmol/L.

Conclusions

Four new indole alkaloids were isolated from the leaves of *Neolamarckia Cadamba* (Roxb.) Bosser. Among them, compound **1** was determined as a new

type of screw ring containing indole glucoalkaloids which is unique in natural products. Compound **2** was assigned to be a novel compound possessing a 6/5/6/6/7/6 hexacyclic ring system, and the cage-like ring system has increased the diversity of the chemical structure of indole alkaloids in nature.

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