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Processing of Nux Vomica (I)
Four New Alkaloids from the Processed Seeds of *Strychnos nux-vomica*

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In the course of our studies on the drug-processing of the seeds of *Strychnos nux-vomica* L. (Loganiaceae), four new alkaloids, isobrucine, isobrucine *N*-oxide, isostrychnine *N*-oxide and 2-hydroxy-3-methoxystrychnine, were isolated from the heat-treated seeds of *S. nux-vomica*, along with ten known alkaloids. The new alkaloids may be artifacts formed during the drug-processing.

Keywords——drug-processing; isobrucine; isobrucine *N*-oxide; isostrychnine *N*-oxide; 2-hydroxy-3-methoxystrychnine; *Strychnos nux-vomica*

Nux Vomica (馬銭子; ma-qian-zi in Chinese; machinshi in Japanese) is the dried seed of *Strychnos nux-vomica* L. (Loganiaceae). The drug is one of the important crude drugs in traditional Chinese medicine and used for improving blood circulation, removing blood stasis and relieving pains.[1] It is included as an ingredient in various prescriptions such as "shu-feng-ding-tong-pian (疏風定痛片)," "jian-hu-wan (健虎丸)," "jiu-fen-san (九分散)" *etc.* In Japan, Nux Vomica and its derivatives are registered in the Japanese Pharmacopoeia[2] and are used mostly for improving appetite and gastrointestinal disorders.

As the fresh seeds of *S. nux-vomica* contain extremely toxic alkaloids, such as strychnine and brucine[3-6] which cause strong convulsion in animals and humans, the seeds must be appropriately pretreated before being internally used. In China, the seeds are processed as described in the Chinese Pharmacopoeia,[1] and Sha *et al.*[7] reported that such processing of the seeds of *S. nux-vomica* resulted in significant decrease of the major alkaloid contents and of the toxicity of the seeds.

In the present paper, we describe the isolation and characterization of new alkaloids obtained from the processed seeds of *S. nux-vomica.*

Results and Discussion

The seeds of *S. nux-vomica* were parched for 3 min at 235°C in a sand bath according to the standard processing procedure described in the Chinese Pharmacopoeia.[1] The processed seeds were powdered and extracted with $CHCl_3$ under alkaline conditions. The extract was fractionated into basic and non-basic fractions in a usual manner. The basic fraction was subjected to repeated column-chromatography on silica gel to give four new compounds (**1–4**) along with strychnine, β-colubrine, brucine, pseudostrychnine, strychnine *N*-oxide, brucine *N*-oxide, novacine, icajine, vomicine and isostrychnine (isostrychnine I) which had been isolated from *S. nux-vomica* and related plants.[3-6] The structures of **1–4** were determined by spectroscopic means as described below.

Compounds **1** was obtained as colorless prisms, mp 197–199°C, $[\alpha]_D$ $-31°$. Its high resolution mass spectrum (HRMS) showed a molecular ion peak at m/z 394.1886, corresponding to the formula $C_{23}H_{26}N_2O_4$. The infrared (IR) spectrum showed the presence of a hydroxyl group (3430 cm^{-1}) and a lactam carbonyl (1635 cm^{-1}). The proton nuclear magnetic resonance (^1H-NMR) spectrum showed the pres-

TABLE I. ^{13}C-NMR Spectral Data for New Alkaloids **1**–**4**

Carbon	$1^{a)}$	$2^{b)}$	$3^{b)}$	$4^{c)}$
1	105.8(d)	108.6(d)	126.9(d)	108.3(d)
2	146.2(s)	149.2(s)	124.7(d)	143.4(s)
3	149.1(s)	152.0(s)	131.6(d)	147.1(s)
4	99.5(d)	101.5(d)	116.7(d)	100.7(d)
5	135.2(s)	136.7(s)	142.9(s)	134.3(s)
6	125.1(s)	125.4(s)	130.5(s)	123.8(s)
7	52.4(s)	53.3(s)	52.9(s)	51.5(s)
8	67.6(d)	67.7(d)	66.8(d)	59.9(d)
10	167.7(s)	170.7(s)	171.2(s)	169.0(s)
11	36.7(t)	42.6(t)	42.9(t)	42.0(t)$^{d)}$
12	120.5(d)	124.0(d)	125.0(d)	77.0(d)
13	137.6(s)	132.5(s)	139.3(s)	47.8(d)
14	34.7(d)	34.9(d)	34.5(d)	31.1(d)
15	25.7(t)	25.1(t)	25.2(t)	26.2(t)
16	62.9(d)	81.5(d)	81.2(d)	59.5(d)
17	45.6(t)	44.3(t)	44.3(t)	41.8(t)$^{d)}$
18	52.7(t)	69.8(t)	68.4(t)	49.4(t)
20	53.9(t)	69.9(t)	68.7(t)	52.1(t)
21	142.2(s)	141.8(s)	140.8(s)	139.3(s)
22	126.7(d)	135.1(d)	136.8(d)	128.2(d)
23	57.9(t)	59.4(t)	59.4(t)	64.3(t)
OMe	56.1(q)	57.9(q)		55.8(q)
OMe	56.5(q)	57.5(q)		

The multiplicities in the proton off-resonance decoupled spectrum are represented as follows: s, singlet; d, doublet; t, triplet, q, quartet.

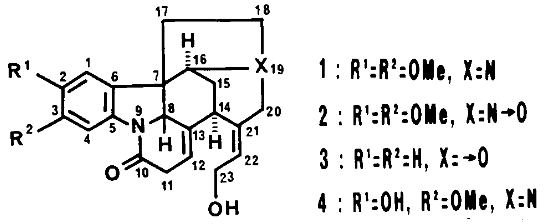
$^{a)}$measured in $CDCl_3$; $^{b)}$ measured in CD_3OD; $^{c)}$ measured in $CDCl_3$-CD_3OD; $^{d)}$ interchangeable.

ence of two vinyl protons (δ 5.85, 1H, m; δ 5.58, 1H, t, $J=6.3$ Hz) coupled with the vicinal methylene (δ 3.07) and hydroxy-bearing methylene (δ 4.3) protons, respectively, which were confirmed by double resonance experiments. The general spectral feature was quite similar to that of isostrychnine except for the signals due to two aromatic and two methoxy protons. The two aromatic protons appeared at δ 6.70 and 7.87 as singlets, suggesting that the two methoxy groups are located at C-2 and C-3 as in brucine. These findings suggested that **1** was an isomeric form of brucine, *i.e.* isobrucine. The ^{1}H-NMR and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral data proved this structure to be correct (TABLE I).

Compound **2**, white powder, $[\alpha]_D$ +34.2°, was shown to have molecular formula $C_{23}H_{26}N_2O_5$ by MS. The peak at *m*/*z* 410 indicated the presence of an additional oxygen atom as compared with **1**. The ^{1}H-NMR spectrum showed the presence of a propenol ($=C—CH_2—OH$) and β,γ-unsaturated lactam ($N—CO—CH_2—CH=$) moieties and suggested a brucine-type aromatic substitution pattern. In comparison of the spectrum with that of **1**, the proton signals (16-H, 18-H and 20-H) adjacent to N-19 shifted to the downfield. In addition, when compared with the ^{13}C-NMR spectrum of **1**, the signals for C-16, C-18 and C-20 shifted to the downfield by 18.6, 17.1 and 16.0 units, respectively (TABLE I). These findings led us to conclude that **2** is isobrucine *N*-oxide.

Compound **3**, white powder, $[\alpha]_D$ +15.1°, was shown to have the molecular formula $C_{21}H_{22}N_2O_3$ by HRMS. The ^{1}H-NMR spectrum was quite similar to that of **2** except for the signals in the aromatic region. The signal pattern in the aromatic region could be superimposed on that of isostrychnine. Compound **3** was thus concluded to be isostrychnine *N*-oxide.

Compound **4** was obtained as colorless prisms, mp>300°C, $[\alpha]_D$ −15.5°. The UV spectrum showed λ_{max} at 211, 263 and 304 nm in MeOH solution and the second peak shifted bathochromically to 272



1 : R¹=R²=OMe, X=N

2 : R¹=R²=OMe, X=N→O

3 : R¹=R²=H, X=→O

4 : R¹=OH, R²=OMe, X=N

Chart 1. Structures of New Alkaloids Isolated from the Processed Seeds of *S. nux-vomica*

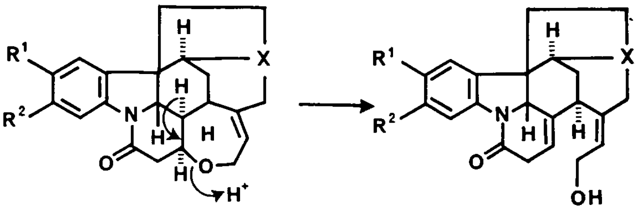


Chart 2. Possible Thermal Transformations of Strychnos Alkaloids into Ring-cleaved Compounds

Strychnine ($R^1=R^2=H$, X=N), brucine ($R^1=R^2=OMe$, X=N), strychnine *N*-oxide ($R^1=R^2=H$, X=N→O) and brucine *N*-oxide ($R^1=R^2=OMe$, X=N→O) may be converted to the corresponding ring-cleaved compounds.

nm in alkaline medium. No shift was observed in the spectra of brucine. The HRMS of **4** showed a molecular ion peak at *m/z* 380.1730, corresponding to the formula $C_{22}H_{24}N_2O_4$. The ^{1}H-NMR spectrum was quite similar to that of brucine except for the number of methoxy signals. Therefore, **4** was considered to be either 2-hydroxy-3-methoxy- or 3-hydroxy-2-methoxybrucine. In comparison of the ^{13}C-NMR with that of brucine,[8] the signal for C-1 shifted to the downfield by 2.4 units, while those for C-2, C-3 and C-4 shifted to the upfield by 3.0, 2.3 and 0.6 units, respectively. The appreciable shift of the C-1 signal (not of C-4) revealed that **4** was 2-hydroxy-3-methoxystrychnine.

When the alkaloid compositions of the processed and un-processed seeds were compared by means of thin-layer chromatography/densitometry, the amounts of the major alkaloids, strychnine and brucine, were significantly smaller in the processed seeds, but those of isostrychnine and compounds **1**–**4** were appreciably larger in the latter. Although the presence of isostrychnine in the fresh seeds of *S. nux-vomica* was reported by Galeffi *et al.*,[9] appreciable amounts of the ring-cleaved compounds may be produced by thermal reactions of strychnine, brucine and their *N*-oxides, as shown in Chart 2. Transformation of strychnine to isostrychnine by heat was reported by Bacovescu *et al.*[10] and Leuchs *et al.*,[11] but they did not report the transformations of brucine and related compounds into their respective isomeric forms. More detailed studies on the changes in their alkaloid profiles caused by the drug-processing will be published elsewhere.[12]

Experimental

Apparatus——^{1}H -and ^{13}C-NMR spectra were measured with JEOL GX-270 (^{1}H, 270 MHz) and JEOL FX-90Q (^{13}C, 22.5 MHz) spectrometers with tetramethylsilane (TMS) as internal standard. MS were measured with a JMS DX-300 mass spectrometer with an ionization voltage of 70 eV. UV spectra were taken on a Shimadzu UV-210A spectrometer. Optical rotation was measured with a JASCO DIP-360 automatic polarimeter. Melting points were measured on a Yanagimoto micromelting point apparatus and uncorrected.

Material——The seeds of *S. nux-vomica* were purchased from Koshiro Seiyaku Co. (Osaka, Japan).

Chemicals——Strychnine and brucine were purchased from Wako Pure Chemical Co. (Osaka, Japan). Brucine *N*-oxide, strychnine *N*-oxide and pseudostrychnine were purchased from Carl Roth K. G. (Karlsruhe, FRG).

Chromatography——Wako gel C-200 (Wako Pure Chemical Co., Osaka, Japan) was used for column chromatography. Merck Kieselgel 60 F_{254} plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, FRG) were used for TLC. The plates were developed with solvent systems: A, MeOH–H_2O (8:2); B, *n*-hexane–EtOAc–MeOH: Et_2NH (8:6:0.3:1.5) and sprayed with Dragendorff reagent.

Processing of the seeds of *S. nux-vomica*——According to the procedure described in the Chinese Pharmacopoea,[1] sand (3 kg) in an ion pan was heated up to 235°C (the temperature at the bottom of the sand). The seeds of *S. nux-vomica* were then put into the sand, and parched for 3 min. The seeds foamed, turned dark yellow and swelled.

Extraction and isolation of strychnos alkaloids——Powder of the strychnos seeds (2.6 kg) processed as described above was soaked in aqueous ammonia (conc. NH_3–H_2O: distilled water=1:9 v/v; 1.7 *l*) for 10 h at room temperature. Chloroform (5 *l*) was added to the suspension and the mixture was kept for 5 d at room temperature. The $CHCl_3$ phase was separated and the residue was re-extracted three more times with $CHCl_3$ in a similar manner. The combined organic phases were evaporated *in vacuo* to give a $CHCl_3$ extract (195 g). A portion of the extract (193 g) was extracted with 8% citric acid (200 ml × 11). The combined aqueous phases were adjusted to pH 9–10 with 60% Na_2CO_3 and extracted with $CHCl_3$ (250 ml × 15). The combined $CHCl_3$ solutions were evaporated *in vacuo* to give a residue (70 g). A portion of the residue (68 g) was applied to a column of silica gel (75 cm × 8.5 cm ID). Successive elutions with hexane–$CHCl_3$–Et_2NH (10:1:0.3 and 2:8:0.3, v/v), hexane–$CHCl_3$-EtOH-Et_2NH (2.8:0.5:0.3 and 1:8:2.5:0.3) and MeOH gave fractions 1–2, 3–5 and 6, respectively. Each fraction was subjected to column chromatography, preparative thin-layer chromatography and crystallization to give the following compounds: pseudostrychnine (14 mg), vomicine (350 mg), icajine (9 mg) and novacine (25 mg) from fraction 1; strychnine (30 g), brucine (15 g) and β-colubrine (50 mg) from fraction 2; isostrychnine (25 mg) from fraction 3; strychnine *N*-oxide (25 mg) and brucine *N*-oxide (30 mg) from fraction 4; isobrucine (**1**: 30 mg), isobrucine *N*-oxide (**2**; 8.5 mg) and isostrychnine *N*-oxide (**3**; 9.5 mg) from fraction 5; 2-hydroxy-3-methoxystrychnine (**4**; 25 mg) from fraction 6.

Strychnine——Colorless needles, mp. 281–283°C (MeOH), $[\alpha]_D$ −142.9° (c=0.7; $CHCl_3$). MS *m/z*: 334 (M^+, 100%). The ^1H-NMR, ^{13}C-NMR, mass and UV spectral data were in agreement with those of an authentic sample.

β-Colubrine——Colorless needles, mp. 224–226°C (MeOH), $[\alpha]_D$ −77.4° (c=0.7, $CHCl_3$). MS *m/z*: 364 (M^+, 100%). The ^{13}C-NMR spectral data were in agreement with those described in the literature.[13]

Brucine——mp. 180–182°C (acetone), $[\alpha]_D$ −113.9° (c=0.6, $CHCl_3$). MS *m/z*: 394 (M^+, 100%). The UV, IR, ^1H-NMR and ^{13}C-NMR spectra were identical with those of an authentic sample.

Pseudostrychnine——Colorless orthorhombic crystals, mp. 244–246°C (MeOH), $[\alpha]_D$ −77.8°C (c=0.4, $CHCl_3$). MS *m/z*: 350 (M^+, 100%). The IR, ^1H-NMR and mass spectral data were in agreement with those of an authentic sample.

Strychnine *N*-oxide——Colorless orthorhombic crystals, mp. 218–220°C (MeOH), $[\alpha]_D$ −9.2°C (c=0.7, $CHCl_3$). MS *m/z*: 350 (M^+, 33%). The ^{13}C-NMR spectral data were in agreement with those described in literature.[8,13]

Brucine *N*-oxide——Colorless plates, mp. 213–216°C (EtOH), $[\alpha]_D$ +16.4° (c=0.7, EtOH), MS *m/z*: 410 (M^+, 100%). The ^{13}C-NMR spectral data were in agreement with those reported.[13]

Novacine——Colorless needles, mp. 226–229°C (MeOH), $[\alpha]_D$ −43.5° (c=0.38, $CHCl_3$). MS *m/z*: 424 (M^+, 100%). The ^1H- and ^{13}C-NMR, mass and IR spectral data were identical with those reported.[14]

Icajine——Colorless needles, mp. 274–276°C (MeOH), $[\alpha]_D$ −7.9° (c=0.2, $CHCl_3$). MS *m/z*: 364 (M^+, 92%). The ^{13}C-NMR spectral data were in agreement with those reported.[13]

Vomicine——Colorless needles, mp. 285–287°C (MeOH), $[\alpha]_D$ +98° (c=1.2, $CHCl_3$). MS *m/z*: 380 (M^+, 100 %). On the basis of the ^1H- and ^{13}C-NMR, mass and IR spectra the compound was identified as vomicine.

Isostrychnine (isostrychnine I)——Colorless orthorhombic crystals, mp. 209–211°C (EtOH), $[\alpha]_D$ −6.9°C (c= 0.4, $CHCl_3$). MS *m/z*: 334 (M^+, 70%). The ^{13}C-NMR spectral data were in agreement with those reported.[8,13]

Isobrucine (1)——Colorless prisms, mp. 197–199°C (acetone), $[\alpha]_D$ −31.1° (c=0.3, $CHCl_3$). HRMS: Found, *m/z* 394.1886, Calcd for $C_{23}H_{26}N_2O_4$ (M^+): 394.1880. UV λ_{max} (MeOH) nm: 209(12800), 253(6800), 289(2000). IR ν_{max} (KBr) cm^{-1}: 1635 (lactam), 1502 (C=C). MS *m/z* (rel. int.): 394 (M^+, 100%), 376 (M^+-H_2O, 26%), 188 (49%), 138 (28%), ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.47 (1H, br d, J=13.9 Hz, 15-Hb), 2.15 (1H, dt, J=13.9, 3.4 Hz, 15-H_a), 2.24 (2H, m, 17-H_2), 2.86 (1H, m, 18-H_b), 2.94 (1H, d, J=14.7 Hz, 20-H_b), 3.03 (1H, t, J=3.2 Hz, 14-H), 3.07 (2H, d, J=6.3 Hz, 11-H), 3.18 (1H, m, 18-H_a), 3.39 (OH), 3.58 (1H, d, J=14.7 Hz, 20-H_a), 3.60 (1H, br s, 16-H), 3.86 (3H, s, OMe), 3.90 (3H, s, OMe), 4.28 (1H, s, 8-H), centered at *ca.* 4.3 (2H, AB in ABX type, 23-H_2), 5.58 (1H, t, J=6.3 Hz, 22-H), 5.85 (1H, m, 12-H), 6.70 (1H, s, 1-H), 7.87 (1H, s, 4-H).

Isobrucine *N*-oxide (2)——White powder, $[\alpha]_D$ +34.2° (c=0.0017, MeOH), UV λ_{max} (MeOH) nm: 208(16000), 262(5900), 301(3600), IR ν_{max} (KBr) cm^{-1}: 1638. MS *m/z* (rel. int.): 410 (M^+, 6%), 393 (M^+-OH, 66%), 364 (M-46, 100%), 256 (28%), 185 (38%), 149 (37%). ^1H-NMR (270 MHz, CD_3OD) δ: 1.54 (1H, dt, J=14.7, 2.4 Hz, 15-H_b), 2.41 (1H, m, 17-H_b), 2.59 (1H, dt, J=14.7, 3.4 Hz, 15-H_a), 2.72 (1H, m, 17-H_a), 3.31 (3H, m, 11-H and 20-H), 3.76 (1H, br s, 14-H), 3.84 (3H, s, OMe), 3.85 (2H, m, 18-H_2), 3.87 (3H, s, OMe), 4.03 (1H, br s, 16-H), 4.10 (1H, s, 8-H), 4.24 (1H, dd, J=14.2, 6.4 Hz, 23-H_b), 4.32 (1H, dd, J=14.2, 6.4 Hz, 23-H_a), 5.82 (1H, br t, J=6.4 Hz, 22-H), 6.06 (1H, dd, J=2.5, 2.5 Hz, 12-H), 7.20 (1H, s, 1-H), 7.79 (1H, s, 4-H).

Isostrychnine *N*-oxide (3)——White powder, $[\alpha]_D$ +15.1° (c=0.002, MeOH). HRMS: Found, *m/z* 350.1596, Calcd for $C_{21}H_{22}N_2O_3$ (M^+): 350.1563. UV λ_{max} (MeOH) nm: 209 (14900), 252(5700), 289(2200). IR ν_{max} (KBr) cm^{-1}: 3440 (OH), 1635 (lactam). MS *m/z* (rel. int.): 350 (M^+, 22%), 334 (M^+-16, 20%), 320 (34%), 318 (56 %), 303 (42%), 292 (49%), 235 (41%), 219 (100%). ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.64 (1H, dt, J=15.1, 2.4 Hz, 15-H_b), 2.61 (1H, m, 17-H_b), 2.63 (1H, d, J=15.1, 15-H_a), 2.76 (1H, m, 17-H_a), 3.02, 3.07 (2H, ABq, J=7.3 Hz, 20-H), 3.11 (1H, d, J=6.4 Hz, 11-H_b), 3.86 (1H, br s, 14-H), 4.09 (1H, m, 18-H), 4.26 (1H, m, 23-H_b), 4.35 (1H, m, 23-H_a), 4.32 (1H, d, J=6.4 Hz, 11-H_a), 4.44 (1H, br s, 16-H), 5.93 (1H, t, J=5.9 Hz, 22-H), 6.12 (1H, m, H-12), 7.22 (1H, dt, 1.0 *ca.* 7.3 Hz, H-2), 7.35 (1H, dt, 1.0 *ca.* 7.3, H-3), 7.59 (1H, d, *ca.* 7.3 Hz, H-1), 8.08 (1H, d, J=7.3 Hz, H-4).

2-Hydroxy-3-methoxystrychnine (4)——mp. >300°C ($CHCl_3$-MeOH), colorless prisms. $[\alpha]_D$ −15.5° (c=0.0007, MeOH). HRMS: Found, *m/z* 380.1730, Calcd for $C_{22}H_{24}N_2O_4$ (M^+): 380.1724. UV λ_{max} (MeOH) nm: 211 (11900), 263(5500), 304(4100); +NaOH: 213, 272, 303. IR ν_{max} (KBr) cm^{-1}: 3400 (OH), 1650 (lactam), 1495

(C=C). MS m/z (rel. int.): 380 (M^+, 100%). ^{1}H-NMR (270 MHz, $CDCl_3$-CD_3OD) δ: 1.33 (1H, m, 13-H), 1.55 (1H, br d, 15-H_a), 1.90 (1H, m, 17-H_2), 2.40 (1H, dt, $J=14.7$, 4.4 Hz, 15-H_b), 2.66 (1H, dd, $J=17.6$, 2.9 Hz, 11-H_a), 2.85 (1H, d, $J=14.6$ Hz, 20-H), *ca.* 2.93 (1H, m, 18-H_a), 3.08 (1H, dd, $J=17.6$, 8.3 Hz, 11-H_b), *ca.* 3.2 (1H, m, 18-H_b), 3.26 (1H, br s, 14-H), 3.34 (3H, s, Me), 3.75 (1H, br d, $J=14.6$ Hz, 20-H_b), 3.88 (1H, d, $J=10.3$ Hz, 8-H), 4.10 (1H, dd, $J=13.0$, 3.9 Hz, 23-H), 4.18 (1H, dd, $J=13.0$, 4.0 Hz, 23-H), 4.36 (1H, dt, $J=8.3$, 3.2 Hz, 12-H), 4.42 (1H, br s, 16-H), 6.03 (1H, br t, 22-H), 6.72 (1H, s, 1-H), 7.72 (1H, s, 4-H).

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