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## ISOQUINOLINE ALKALOIDS FROM NEOLITSEA A UREO-SERICEA STEM BARK(แอดคาคอยด์กลุ่ม isoquinoline จากเปลือกต้น Neolitsea aureo-sericea)

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ORIGINAL ARTICLE

## ISOQUINOLINE ALKALOIDS FROM *NEOLITSEA* *AUREO-SERICEA* STEM BARK

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### ABSTRACT

By means of column chromatography, four isoquinoline alkaloids of the aporphine, pavine and tetrahydrobenzylisoquinoline types were isolated from the stem bark of *Neolitsea aureo-sericea* Kosterm. The physical, chemical properties and spectroscopic data of those alkaloids have shown that they are isoboldine, bisnorargemonine, norcinnamolaurine and (+) - reticuline. Bisnorargemonine and norcinnamolaurine have never been reported to be found in genus *Neolitsea*. (Th. J. Pharm. Sci., Vol. 12 No. 4, 327-333 (1987) )

### KEY WORDS

*Neolitsea aureo-sericea* Kosterm., Lauraceae, isoquinoline alkaloids, aporphine, pavine, tetrahydrobenzylisoquinoline, isoboldine, bisnorargemonine, norcinnamolaurine, (+) - reticuline.

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## INTRODUCTION

*Neolitsea aureo-sericea* Kosterm. had been reported as one of new species of *Neolitsea* in Thailand (1). In Malaysia, Indonesia and India, the root and bark of *Neolitsea* spp. are applied for skin diseases (2). In Thailand, the medicinal uses are reported only in the genus *Litsea* but not in the *Neolitsea*. The *Neolitsea* plants are found to be rich in isoquinoline alkaloids, mainly aporphines, and also found proaporphines, oxoaporphines, tetrahydrobenzylisoquinolines. Other chemical constituents such as flavonoids, monoterpenes, sesquiterpenes, triterpenes, lignans, fatty acids and phytosterols are also occurred in this genus.

There are many reports on the pharmacological action of the isoquinoline alkaloids. Most of tetrahydrobenzylisoquinolines are displaying as smooth muscle relaxant whilst some are vasodilators. Aporphines act mostly on nervous system. Boldine has a mild sedative, diuretic, antiparasitic actions and increases the secretions of the liver and salivary glands. Isoboldine is the insect antifeedants. There is no previous report on the pharmacological action of pavin alkaloid (3). Other chemical constituents such as neoliacine, the germacranolide sesquiterpene dilactone was also reported to exhibit moderate cytotoxicity to HeLa cell culture *in vitro*(4).

Neither phytochemical nor pharmacological studies of *Neolitsea aureo-sericea* Kosterm. has been reported previously. This present work is led to the phytochemical studies, deeply on isoquinoline alkaloids.

## MATERIALS AND METHODS

**Materials** The stem bark of *Neolitsea aureo-sericea* Kosterm. was collected from Pakthongchai, Nakorn-Rachasima, Thailand. The plant material was identified by Mr. Weerachai Na Nakorn of the Royal Forest Department and Mrs. Jaree Bunsiddhi, Botany Section, Department of Medical Science, Bangkok.

Melting points were determined on Gallenkamp MFB 595 melting point apparatus and were uncorrected. Optical rotations were obtained on Perkin-Elmer 241 polarimeter. UV spectra were measured on double beam spectrophotometer, Hitachi 220A. IR spectra were determined on Shimadzu-440 using KBr disc. NMR ( $^1\text{H}$ ) spectra were recorded with Bruker WP 200 MHz Supercon FT spectrometer in DMSO- $d_6$  solution with TMS as internal reference. Mass spectra were obtained on Kratos MS 9/50 operating at 70 eV.

**Extraction and isolation** The dried powdered bark (3 kg) of *Neolitsea aureo-sericea* Kosterm. was extracted in a Soxhlet apparatus with petroleum ether (b.p. 60-80°C) for 48 hours. The defatted bark was extracted exhaustively with 95% ethyl alcohol at room temperature. The filtrate was concentrated under reduced pressure to sticky mass (311 g). This sticky mass (150 g) was acidified with 5% acetic acid solution (1 L). The acid solution was filtered and basified with strong ammonia solution and extracted with chloroform (8 × 200 ml). The extract were pooled and concentrated under reduced pressure to give dried yellowish-brown crude alkaloid NAA (31.35 g). The aqueous layer was further extracted with chloroform : methanol 2 : 1 (4 × 200 ml) and concentrated to give brown crude alkaloid NAB (10.52 g).

The crude alkaloid NAA (5 g) was isolated by silica gel chloroform : methanol 95 : 5 column chromatography.

**Table 1** Elution pattern of column chromatography

Fraction (50 ml)	Name of fraction	Compound
1-22	A	—
23-31	B	NA-1
32-37	C	NA-1* NA-2, NA-4
38-45	D	NA-1* NA-2, NA-3, NA-4
46-58	E	NA-2, NA-3, NA-4
59-78	F	NA-2* NA-3, NA-4*

\* main substance in the fraction

Compound NA-1 was purified by rechromatography (silica gel/chloroform) from Fraction B to give pale pink plates of aporphine alkaloid (180 mg).

Fraction E (2.18 g) was shown to contain mixture of alkaloids NA-2, NA-3 and NA-4. The information of Fraction E silica gel column chromatographic isolation was shown in Table 2.

**Table 2** Elution pattern of silica gel column chromatography

Fraction (20 ml)	Eluent	Name of fraction	Compound
1-30	Benz-EtOAc-MeOH	Ea	—
	8-4-2		
31-37	"	Eb	NA-3
38-85	"	Ec	NA-2, NA-3, NA-4
86-100	"	Ed	NA-2* NA-3, NA-4*
101-125	"	Ee	NA-2* NA-4*
126	MeOH	Ef	—

\* main substance in the fraction

Compound NA-3 was purified by column chromatography (silica gel/hexane-acetone 1-1) from Fraction Eb (0.06 g) to give colourless needles of tetrahydrobenzylisoquinoline alkaloid (12 mg).

Fraction Ee (0.21 g) contains mixture of alkaloids NA-2 and NA-4. They were isolated and purified by preparative thin layer chromatography (silica gel G/EtOAc-MeOH 1-1) to give 26 and 10 mg of isoquinoline alkaloids NA-2 and NA-4, respectively.

**COMPOUND NA-1** pale pink plates from methanol, mp. 121-2° C (uncorrected),  $[\alpha]_D^{25} + 53.65$  (c = 0.0233 g/ml, chloroform),  $C_{19}H_{21}NO_4$ , TLC : silica gel G (E.Merck) :  $CHCl_3$ -MeOH 9-1 (0.52), silica gel G (E.Merck) : benzene-EtOAc-MeOH 8-4-2 (0.35), silica gel G (E.Merck) : EtOAc-MeOH 1-1 (0.51), UV :  $\lambda$  max ( $CHCl_3$ ) 240, 280, 312, 320 nm, IR (KBr)  $\nu$  max ( $cm^{-1}$ ) = 3180, 2910, 1600, 1510, 1462, 1280, 1230, 1105, 1078, 1020, 810, 760,  $^1H$ -NMR ( $CDCl_3$ , 60 MHz)  $\delta$  2.52 (3H, s, N- $CH_3$ ), 3.90 (6H, s, 2xOCH<sub>3</sub>),

6.52 (1H, s, H-C3), 6.80 (1H, s, H-C8), 8.02 (1H, s, H-C11), MS : 70 eV,  $m/z$  (rel. int. %) 327 ( $M^+$ , 98), 326 (100), 312 (29), 310 (12), 296 (10), 284 (44), 269 (12), 253 (22), 252 (15).

**COMPOUND NA-2** white amorphous powder, mp. 238-9° C (uncorrected),  $[\alpha]_D^{25}$ -214.20 ( $c = 0.0049$  g/ml, methanol),  $C_{19}H_{21}NO_4$ , TLC : silica gel G (E.Merck) :  $CHCl_3$ -MeOH 9-1 (0.37), silica gel G (E.Merck) : benzene-EtOAc-MeOH 8-4-2 (0.21), silicagel G (E.Merck) : EtOAc-MeOH 1-1 (0.50), UV :  $\lambda$  max ( $CHCl_3$ ) 288 292 nm,  $\lambda$  max ( $CHCl_3 + 0.1$  N HCl) 285, 290 nm, IR (KBr)  $\nu$  max ( $cm^{-1}$ ) = 3500, 2910, 1610, 1510, 1480, 1420, 1260, 760-780,  $^1H$ -NMR (DMSO, 200 MHz)  $\delta$  2.32 (3H, s, N- $CH_3$ ), 3.63 (3H, s,  $OCH_3$ ), 3.69 (3H, s,  $OCH_3$ ), 6.30 (1H, s, H-C10), 6.43 (1H, s, H-C4), 6.50 (1H, s, H-C1), 6.65 (1H, s, H-C7), MS : 70 eV,  $m/z$  (rel. int. %) 328 ( $M^+ + 1$ , 11), 327 ( $M^+$ , 53), 326 (44), 312 (7), 191 (24), 190 (100), 177 (4), 176 (3), 175 (10).

**COMPOUND NA-3** colourless needles from hexane, mp. 196-7° C,  $[\alpha]_D^{26} + 90.92$  ( $c = 0.0055$  g/ml, ethanol),  $C_{17}H_{17}NO_3$ , TLC : silica gel G (E. Merck) :  $CHCl_3$ -MeOH 9-1 (0.42), silica gel G (E.Merck) : benzene-EtOAc-MeOH 8-4-2 (0.41), silica gel G (E.Merck) : EtOAc-MeOH 1-1 (0.58), UV :  $\lambda$  max ( $CHCl_3$ ) 242, 288 nm,  $\lambda$  max ( $CHCl_3 + 0.1$  N HCl) 240, 285 nm,  $\lambda$  max ( $CHCl_3 + 0.1$  N NaOH) 240, 288 nm, IR (KBr)  $\nu$  max ( $cm^{-1}$ ) = 3410, 2900, 1600, 1480-1500, 1460, 1240, 1020, 600,  $^1H$ -NMR (DMSO, 200 MHz)  $\delta$  5.90 (2H, s,  $-OCH_2O-$ ), 6.59 (1H, s, H-C8), 6.67 (2H, d,  $J = 8.445$ , H-C2', H-C6'), 6.79 (1H, s, H-C5), 7.04 (2H, d,  $J = 8.405$ , H-C3', H-C5') 9.17 (1H, s, phen. OH), MS : 70 eV,  $m/z$  (rel.int.%%) 283 ( $M^+$ , 0.31), 282 (1.67), 177 (33), 176 (100), 146 (4) 118 (9), 107 (12), 91 (11), 77 (8), 65 (7).

**COMPOUND NA-4** yellow amorphous powder, mp. 125-6° C,  $[\alpha]_D^{25} = +55.00$  ( $c = 0.0001$  g/ml), ethanol),  $C_{19}H_{23}NO_4$ , UV :  $\lambda$  max ( $CHCl_3$ ) 242, 288 nm,  $\lambda$  max ( $CHCl_3 + 0.1$  N HCl) 240, 290 nm, IR (KBr)  $\nu$  max ( $cm^{-1}$ ) 3410, 2900, 1600, 1520, 1440, 1220-1280, 1130, 1020, 700, 600,  $^1H$ -NMR(DMSO, 200 MHz)  $\delta$  2.49 (3H, s, N- $CH_3$ ), 3.85 (6H, s,  $2 \times OCH_3$ ), 6.35 (1H, s, H-C8), 6.54 (1H, s, H-C5), 6.59 (1H, dd,  $J_o = 8.32$ ,  $J_m = 1.73$ , H-C2'), 6.74 (1H, d,  $J_o = 8.32$ , H-C3'), 6.75 (1H, d,  $J_m = 1.73$ , H-C6'), MS : 70 eV,  $m/z$  (rel.int.%%) 329 ( $M^+$ , 17), 328 (64) 327 (60), 326 (36), 312 (87), 193 (29), 192 (100), 177 (39).

## RESULTS AND DISCUSSION

The isolated Compound NA-1 was a major alkaloid, it gave positive test with Dragendorff's reagent (orange precipitate). The UV and MS showed that it is aporphine alkaloid. The IR spectrum showed hydroxyl group at  $3180\text{ cm}^{-1}$  and aromatic ring at  $1600, 1510\text{ cm}^{-1}$ . The  $^1H$ -NMR showed the presence of N-methyl (2.52), two methoxyls (3.90) and aromatic protons (6.52, 6.80, 8.02). The mass spectrum, molecular ion peak and base peak of NA-1 showed at  $m/z$  327 and 326, respectively. The main fragmentation pathway for NA-1 is consistent being the retro-Diels-Alder reaction as ring B is broken and loss of  $CH_2NCH_3$ .

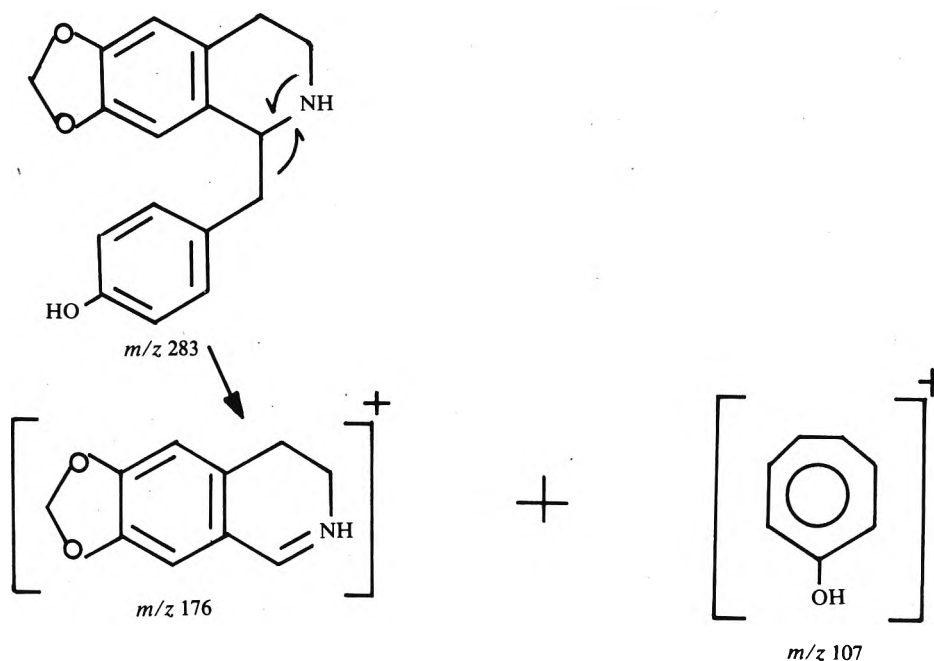
The isolated Compound NA-1 is identified as a known aporphine alkaloid called isoboldine by comparison of its melting point, UV,  $^1H$ -NMR and MS spectra with the data of the isolated isoboldine from *Neolitsea fuscata* (Thwait.) Alston. (5).

The isolated Compound NA-2 also gave positive test with Dragendorff's reagent. From UV and mass spectral data, NA-2 is pavine alkaloid (6). The IR spectrum showed hydroxyl group at  $3500\text{ cm}^{-1}$  and aromatic ring-ortho substituted at  $1600, 1510, 760-780\text{ cm}^{-1}$ . The  $^1H$ -NMR spectrum showed signals corresponding to N-methyl (2.32), two methoxyls (3.63, 3.69) and aromatic protons (6.50, 6.43, 6.65, 6.30). The mass spectrum showed the base peak (190) and molecular ion peak (327). The fragmentation of NA-2 proceeds essentially by only one pathway, resulting in formation of the N-methylisoquinolium ion ( $m/z$  190) and loss of the N-methyl radical to give isoquinolium ion ( $m/z$  175).

The isolated Compound NA-2 is identified as a known pavine alkaloid named bisnorargemonine by comparison of its melting point,  $^1H$ -NMR and MS spectra with the data of the isolated bisnorarge-

monine from *Argemone hispida* Gray and *A. munita* Dur. & Hilg. subsp. *rotundata* (Rydb.) G.B.Ownb. (7), (8).

The isolated Compound NA-3 is tetrahydrobenzylisoquinoline alkaloid. The IR spectrum showed amine at  $3410\text{ cm}^{-1}$  and aromatic ring at  $1600, 1460\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  showed signals of a methylenedioxy group (5.9), two aromatic protons, C-5 and C-8 of ring A (6.79, 6.59) and four aromatic protons, C-2', C-3', C-5', C-6' of ring B (6.67, 7.04). The mass spectrum showed base peak and molecular ion peak at  $m/z$  176 and 283, respectively. The main fragmentation pathway for NA-3 is shown below.



Compound NA-3 is identified as a tetrahydrobenzylisoquinoline alkaloid named norcinnamolaurine. The melting point, UV,  $^1\text{H-NMR}$  and MS spectral data of NA-3 are in full agreement with those of norcinnamolaurine isolated from *Cinnamomum* sp. (9).

The isolated Compound NA-4 is also tetrahydrobenzylisoquinoline alkaloid. The IR spectrum showed hydroxyl group at  $3410\text{ cm}^{-1}$  and aromatic ring at  $1600, 1520\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum showed the presence of N-methyl proton (2.49), two methoxyls (3.85) and aromatic protons of C-2', C-3', and C-6' of ring B (6.59, 6.74, 6.75). The mass spectrum showed the base peak ( $m/z$  192) and molecular ion peak ( $m/z$  329). The fragmentation is the same pathway as NA-3.

The optical rotation and  $^1\text{H-NMR}$  of NA-4 correspond with the data of (+) -reticuline isolated from *Thalictrum revolutum* Tops (10). From the various spectroscopic evidences, it is consistent established that Compound NA-4 is (+) - reticuline.

Concerning the chemotaxonomic point of view, in subtribe Litseinae, the morphological difference among genus *Litsea* and *Neolitsea* are very slight. This phytochemical work investigated the presence of bisnorargemonine and norcinnamolaurine in genus *Neolitsea*. While, both of these alkaloids have never been found in *Litsea*. Chemotaxonomically, this supports the classification of genera *Litsea* and *Neolitsea* in subtribe Litseinae.

Further pharmacological studies of the alkaloids, isoboldine, reticuline, norcinnamolaurine and especially bisnorargemonine should be done.

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65010<sup>a</sup> Alkaloids  
65010<sup>a</sup> *Neolitsea aureo-sericea*  
69011<sup>a</sup> Isoquinoline! 25ph  
แอลคาลอยด์ในกลุ่ม isoquinoline จากเปลือกต้น

### *Neolitsea aureo-sericea*

✓ 6 3007200

ผ่องพรรณ ศรีพงษ์ ภ.ม.\*  
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#### บทคัดย่อ

โดยการใช้กรรมวิธีทางคอลัมน์โครมาโทกราฟี ทำให้สามารถแยกแอลคาลอยด์ในกลุ่ม isoquinoline ซึ่งมี 3 กลุ่มย่อย คือ aporphine, pavine และ tetrahydrobenzylisoquinoline ได้ 4 ชนิด จากเปลือกต้น *Neolitsea aureo-sericea* Kosterm. จากคุณสมบัติทางกายภาพ เคมี และข้อมูลทางสเปกโตรสโคปี สามารถพิสูจน์เอกลักษณ์ของแอลคาลอยด์เหล่านี้ได้เป็น isoboldine, bisnorargemonine, norcinnamolaurine และ (+)-reticuline ซึ่ง bisnorargemonine และ norcinnamolaurine ยังไม่เคยมีรายงานว่า พบในพืชสกุล *Neolitsea* มาก่อน (ไทยเภสัชสาร ปีที่ 12 (4): หน้า 327-333 (2530))

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