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140. Tatsuo Nakasato and Shozo Nomura : Studies on the Alkaloids of Lauraceous Plants. IV.*2 The Structure of Laurolitsine.

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A new phenolic base had been isolated from the leaves of *Neolitsea sericea* (BLUME) KOIDZ., a domestic plant of the Lauraceae family, and was named laurolitsine. As described in the previous paper, this compound was first obtained as a crystalline picrolonate, m.p. 239°(decomp.). The free base did not crystallize and it came from benzene solution as a colorless amorphous powder, m.p. 138~140°(swelling at 115~118°), and was positive to the Feigl test for aliphatic secondary amines with sodium nitroprusside and acetaldehyde. The authors proposed tentatively the following formula for this compound and presumed laurolitsine might be a phenolic secondary base belonging to the aporphine series.

$$C_{18}H_{19}O_4N = C_{16}H_{10}(OH)_2(OCH_3)_2 \ (>NH)$$

O,O-Dimethyllaurolitsine, an oily substance regenerated from its crystalline picrolonate, was acetylated with acetic anhydride and pyridine to a neutral compound, m.p. 184°, in a good yield. The analysis agreed with its N-acetyl derivative, $C_{22}H_{25}O_5N$, and the ultraviolet absorption spectrum still had the characteristic peaks of aporphine derivatives. Thus, it was confirmed that laurolitsine is a secondary base.

The acetylation of laurolitsine also gave a neutral compound, m.p. 152~154°, which was optically active and had the formula, $C_{24}H_{25}O_7N$, corresponding to O,O,N-triacetyllaurolitsine. Its ultraviolet spectrum is shown in Fig. 1, and infrared spectrum had the absorption maxima at 1767, 1749 (ester CO), 1641 ($>NCOCH_3$), and 1207 cm^{-1} (phenolic acetate) as represented in Fig. 2.

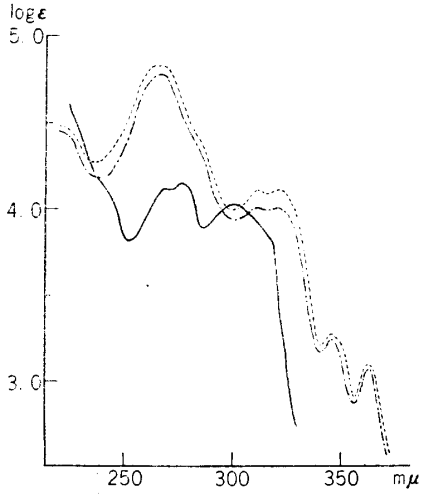

Fig. 1. Ultraviolet Absorption Spectra (in EtOH)
——— O,O,N-Triacetyllaurolitsine
-·-·-·- O,O-Diethyllaurolitsine methine methiodide
····· O,O-Dimethylboldine methine methiodide

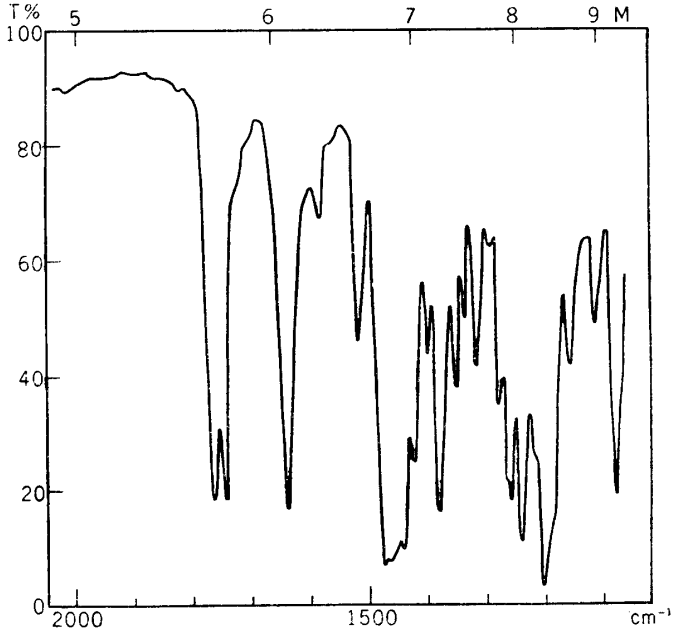

Fig. 2. Infrared Absorption Spectrum of O,O,N-Triacetyllaurolitsine (in Nujol)

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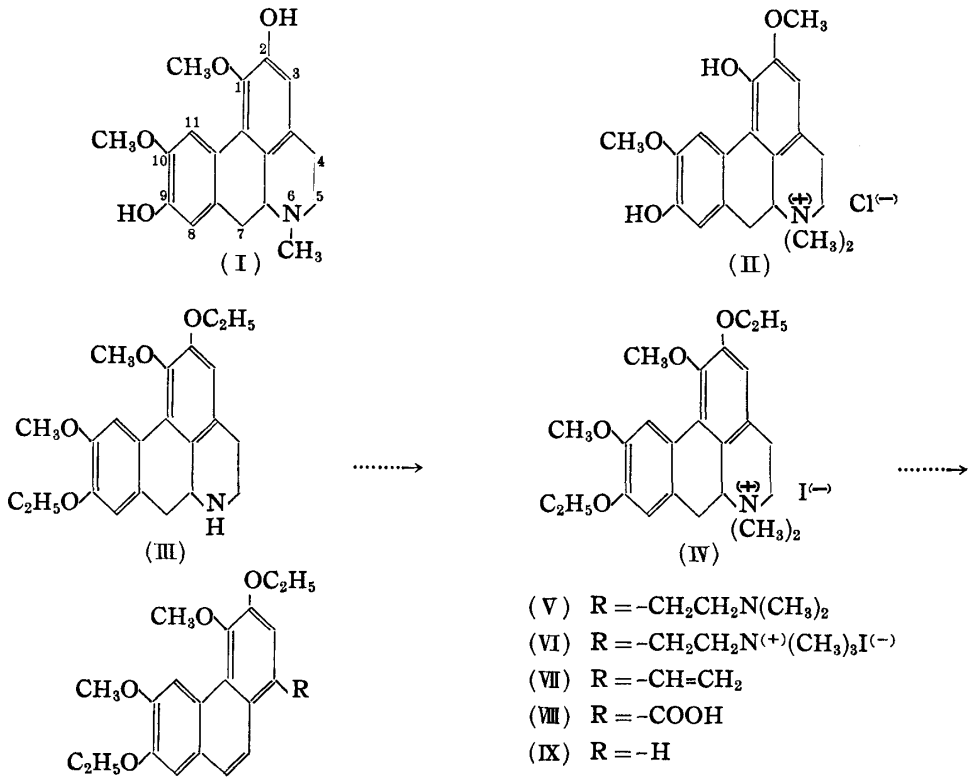
*2 Part III : Yakugaku Zasshi, **79**, 1267(1959).

The treatment of O,O-dimethyllaurolitsine with methyl iodide in a sealed tube in the presence of sodium hydrogen carbonate afforded an N-methyl methiodide. This compound was found to be identical with O,O-dimethylboldine methiodide (glaucine methiodide), as evidenced from a direct comparison of their ultraviolet and infrared spectra, and by the mixed melting point test. This fact revealed that four oxygen atoms of laurolitsine were located at 1, 2, 9, and 10 positions of the aporphine ring.

Among the aporphine-type alkaloids, only boldine[1,2] (I) and laurifoline chloride[3] (II) are known as the substances which have two methoxyl and two hydroxyl groups at 1, 2, 9, and 10 positions, and the configurations of these groups had been clarified by examination of the Hofmann degradation products of their diethyl ethers. Following the same procedure, this degradative reaction of O,O-diethyllaurolitsine (III) was examined as schematically shown below.



(V) R = $-CH_2CH_2N(CH_3)_2$
(VI) R = $-CH_2CH_2N^{(+)}(CH_3)_3I^{(-)}$
(VII) R = $-CH=CH_2$
(VIII) R = $-COOH$
(IX) R = $-H$

(III), which was prepared from laurolitsine and diazoethane, and gave neither crystals nor crystalline salts, was converted into O,O-diethyl-N-methyllaurolitsine methiodide (IV) and submitted to the Hofmann degradation without further purification of (IV). Only oxalate of the methine base (V) crystallized, which melted at 227~229° with effervescence. O,O-Diethyllaurolitsine methine methiodide (VI) showed no optical activity and its ultraviolet absorption spectrum was very similar to that of O,O-dimethylboldine methine methiodide (Fig. 1). Diethoxydimethoxyvinylphenanthrene (VII), produced by the same degradation procedure of (VI), was oxidized with potassium permanganate and decarboxylated with quinoline-copper powder to give diethoxydimethoxyphenanthrene (IX). (IV), colorless scaly crystals, m.p. 193~194°, was obtained by methylation of (III) with formic acid and formaldehyde, followed by treatment with methyl iodide.

In Table I, the direct comparison is made between the properties of degradation

1) E. Merck : Mercks Jahresber., **36**, 110(1922).
2) Part I : Yakugaku Zasshi, **77**, 816(1957).
3) F. Kusuda : This Bulletin, **1**, 55(1953).

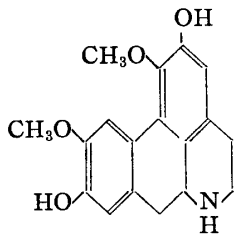
products (IV) to (IX) and those of O,O-diethylboldine reported by Späth, *et al.*[4] It was now clarified that they are in good agreement except the case of diethoxydimethoxyphenanthrene-carboxylic acid (VIII). (IX) derived from (VIII), however, showed a characteristic ultraviolet spectrum of phenanthrene derivative. Thus, the positions of the two phenolic hydroxyl groups in laurolitsine were assigned 2 and 9 in the aporphine ring, similar to the case of boldine, and this was confirmed further by the following experiments.

Table I.

	Laurolitsine, m.p.(°C)	Boldine,[4] m.p.(°C)
Diethyl ether methiodide (IV)	193~194	resinous
Methine base (V)	oil, (oxalate, 227~229)	oil
Methine methiodide (VI)	252~253	252~253
Des-N compound (VII)	111~112	112~113
Diethoxydimethoxy-phenanthrene-carboxylic acid (VIII)	192~193, 193 (vac.)	202~203 (vac.)
Diethoxydimethoxyphenanthrene (IX)	131 (picrate, 122)	133~134

The N-methylation of laurolitsine with formic acid and formaldehyde gave boldine which was identified by the mixed melting point test with the authentic specimen,[2] m.p. 161~162°. In addition, the degradation products of O,O-diethyllaurolitsine were proved to be identical with O,O-diethylboldine derivatives; no depression of the melting point occurred on the respective admixture of (IV), oxalate of (V), and (VI) with methiodide, methine oxalate, and methine methiodide derived from O,O-diethylboldine.

From the consideration of all available evidences, laurolitsine corresponds to desmethylboldine and is represented by the structure (X).



(X)

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Experimental

All m.p.s are uncorrected and analytical samples were dried over P_2O_5 at 80° *in vacuo*.

O,O-Dimethyl-N-acetyllaurolitsine—O,O-Dimethyllaurolitsine (70 mg.) prepared from the parent base and CH_2N_2 was dissolved in pyridine (2 cc.) and Ac_2O (1 cc.). The mixture was stood for 9 days at room temperature and distilled to dryness *in vacuo* below 30°. The solution of the residue in benzene was washed successively with 2*N* HCl, 0.5*N* NaOH, and water. After drying and evaporating benzene, the residue was crystallized from Et_2O to colorless needles, m.p. 184°.[5] Yield, 70 mg. *Anal.* Calcd. for $C_{22}H_{25}O_5N$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.66; H, 6.65; N, 3.68. UV λ_{max}^{EtOH} mμ (log ε): 282 (4.21), 302 (4.22).

O,O,N-Triacetyllaurolitsine—A mixture of laurolitsine (0.33 g.), pyridine (5 cc.), and Ac_2O (2 cc.) was allowed to stand for 15 days. Worked up as described above, a neutral material was obtained from Et_2O as colorless crystals, m.p. 152~154°. Yield, 0.25 g. $[\alpha]_D^{10}$ +293° (c=1.27, EtOH). *Anal.*

4) E. Späth, K. Tharrer: Ber., **66**, 904(1933).
5) O-Methyl-N-acetyllaurotetanine, m.p. 188~189°; E. Späth, F. Strauhal: Ber., **61**, 2395(1928).

Calcd. for $C_{24}H_{25}O_7N$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.17; H, 5.92; N, 3.23. UV λ_{max}^{EtOH} mμ (log ε): 268(4.11), 276(4.15), 300(4.02) (Fig. 1).

O,O,N-Trimethyllaurolitsine Methiodide—A solution of dimethyllaurolitsine (0.14 g.) in MeOH, MeI (1.5 cc.), and $NaHCO_3$ (0.2 g.) was heated at 80° for 1.5 hr. in a sealed tube, cooled, and filtered. The filtrate was evaporated to dryness and digested with hot benzene. The residue insoluble in benzene was crystallized from MeOH-AcOEt and then from EtOH to slightly green pillars, m.p. 219°, $[\alpha]_D^{23}$ +96.1°(c=0.487, EtOH). *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.13; H, 5.68; N, 2.82; $(OCH_3)_4$, 24.96. Found: C, 52.13; H, 5.73; N, 2.51; OCH_3, 23.59. UV λ_{max}^{EtOH} mμ(log ε): 284(4.16), 305(4.17).

Hofmann Degradation of O,O-Diethyllaurolitsine. (1) **O,O-Diethyllaurolitsine (III)**—To a solution of laurolitsine (2.95 g.) in MeOH, an excess of diazoethane was added. After standing for 24 hr. in an ice-box, the reaction mixture worked up in the usual way to give (III) as a yellowish oil. Yield, 1.99 g.

(2) **O,O-Diethyl-N-methyllaurolitsine Methiodide (IV)**—a) A mixture of (III) (1.47 g.), MeI (6 cc.), $NaHCO_3$(1.3 g), and MeOH (20 cc.) was heated in a sealed tube and treated as in the case of O,O,N-trimethyllaurolitsine. The residue insoluble in Et_2O on digestion was brown and resinous which was subjected to the following reaction (3) without further purification.

b) One cc. each of 80% HCO_2H and 37% HCHO solution was added to 0.2 g. of (III). Heated at 100° for 2 hr., the mixture was diluted with water, and shaken with Et_2O. The aqueous layer was made alkaline with NaOH solution and extracted with Et_2O. The oily residue from the extract was chromatographed on alumina (eluted with 1:1 benzene-petr. ether). A solution of the eluate (0.13 g.) in Et_2O and an excess of MeI was stood for 3 hr. The resulting deposit was recrystallized from Me_2CO-AcOEt to give (IV) as colorless scales, m.p. 193~194°. Yield, 0.07 g. *Anal.* Calcd. for $C_{24}H_{32}O_4NI$: C, 54.86; H, 6.14. Found: C, 55.07; H, 6.23.

(3) **O,O-Diethyllaurolitsine Methine (V)**—A solution of the foregoing resinous residue in 25% methanol solution (50 cc.) was shaken thoroughly for 30 min. with moist silver oxide and filtered. MeOH was removed from the filtrate under a reduced pressure and the deposited resinous material was filtered off. The filtrate was diluted to 60 cc. with water, treated with KOH (18 g.), heated at 100° for 6 hr., cooled, and extracted with Et_2O. Evaporation of the dried extract left a yellowish oil (V). Yield, 1.24 g.

Oxalate: Colorless crystals from MeOH-EtOH, m.p. 227~229°(with effervescence). *Anal.* Calcd. for $C_{24}H_{31}O_4N(CO_2H)_2$: C, 64.05; H, 6.82; N, 2.87. Found: C, 63.76; H, 6.94; N, 2.87.

(4) **O,O-Diethyllaurolitsine Methine Methiodide (VI)**—A solution of (V) (1.1 g.) in MeOH (15 cc.) followed by MeI (2.5 cc.) was heated under reflux for 3 hr. After crystallization from MeOH, the methiodide (VI) was obtained as colorless fine needles, m.p. 252~253°. $[\alpha]_D^{23}$ ±0°(c=0.375, EtOH). Yield, 0.79 g. *Anal.* Calcd. for $C_{25}H_{34}O_4NI \cdot 1.5H_2O$: C, 53.00; H, 6.60; N, 2.47. Found: C, 52.99, 53.15; H, 6.62, 6.61; N, 2.38. UV λ_{max}^{EtOH} mμ(log ε): 265(4.78), 310(4.01), 321(4.01), 346(3.27), 364(3.08) (Fig. 1).

(5) **Des-N Compound (Diethoxydimethoxyvinylphenanthrene) (VII)**—To a solution of (VI) (0.72 g.) in 80% MeOH (50 cc.), an aqueous solution of NaOH (3 g.) was added and heated under reflux for 8 hr. The mixture was evaporated under a reduced pressure until free from MeOH and the separated material was taken up in benzene. The residue from the dried benzene solution was crystallized from Et_2O to give (VII) as colorless crystals, m.p. 111~112°. Yield, 0.31 g. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 74.97; H, 9.86. Found: C, 75.27; H, 7.04.

Diethoxydimethoxyphenanthrene-carboxylic Acid (VIII)—An aqueous solution of $KMnO_4$(0.76 g.) was added dropwise to (VII) (0.29 g.) in Me_2CO under stirring over a period of approx. 3 hr. The mixture was stirred for further 3 hr. and kept at 50° for 30 min. under agitation. After the reaction was completed, MnO_2 was dissolved by passing SO_2 gas and Me_2CO was removed under a reduced pressure. The resulting precipitate was taken up in Et_2O and the Et_2O solution was shaken with 5% Na_2CO_3. The alkaline layer was acidified with HCl and extracted with Et_2O. The residual acid (VIII) from the extract was crystallized from MeOH to yellow granules, m.p. 192~193° or 193°(vac.). Yield, 0.17 g. *Anal.* Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.85; H, 6.21.

Diethoxydimethoxyphenanthrene (IX)—A mixture of (VIII) (0.15 g.), purified quinoline (3 cc.), and Cu powder (0.21 g.) was heated at 200~210° for 15 min., further to 260° for 20 min., and then cooled, to which benzene (50 cc.) was added. The filtered solution was washed with 10% HCl, 5% NaOH, and water, successively. The residue from the dried benzene solution was chromatographed on alumina and benzene eluate gave yellowish crystals, which was recrystallized from MeOH to (IX) as yellowish white needles, m.p. 131°. Yield, 0.1 g. *Anal.* Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.24; H, 6.80. UV λ_{max}^{EtOH} mμ(log ε): 260(4.80), 312(3.99), 342(3.21), 360(3.15).

Picrate: Chocolate-colored needles (from Et_2O-petr. benzine), m.p. 122°.

N-Methylation of Laurolitsine—Laurolitsine (0.3 g.) was heated with 80% HCO_2H (3 cc.) and 37% HCHO solution (3 cc.) on a water bath for 2 hr., and worked up in the usual way. The material obtained as a phenolic fraction was chromatographed on alumina (eluted with 2:1 benzene-AcOEt),

and the eluate was crystallized from benzene to colorless asteroids, in only 0.03 g. yield, m.p. 160~161°, alone and on admixture with an authentic sample of boldine.[2] $[\alpha]_D^{18}$ +128°(c=0.39, EtOH). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47. Found : C, 70.31; H, 6.58.

Methylation of Boldine—a) O,O-Dimethylboldine Methiodide (Glaucine Methiodide) : On reaction of MeI with dimethyl ether of boldine, the methiodide was obtained from MeOH as biscuit-colored needles, m.p. 219°, undepressed on admixture with a sample of O,O,N-trimethyllaurolitsine methiodide. UV and IR spectra of the two were identical. *Anal.* Calcd. for $C_{22}H_{28}O_4NI$: C, 53.13; H, 5.68. Found : C, 52.79; H, 5.80.

b) O,O-Dimethylboldine Methine Methiodide : A mixture of boldine (0.41 g.), MeI (2 cc.), and *N*/3 methanolic KOH (15 cc.) was heated at 85° for 3 hr. in a sealed tube, then cooled and concentrated to dryness under a reduced pressure. The residual product, washed with a small amount of water, was crystallized from MeOH to biscuit-colored needles, m.p. 269°. Yield, 0.29 g. *Anal.* Calcd. for $C_{23}H_{30}O_4NI$: C, 54.01; H, 5.91; $(OCH_3)_4$, 24.27. Found : C, 53.94; H, 5.92; OCH_3, 23.71. UV λ_{max}^{EtOH} $m\mu$ (log ε) : 265(4.82), 311(4.10), 320(4.11), 345(3.26), 362(3.09) (Fig. 1).

Hofmann Degradation of O,O-Diethylboldine. (1) O,O-Diethylboldine Methiodide—Diethylboldine prepared from boldine (0.38 g.) and CH_3CHN_2 could not be crystallized by any means. A solution of this base in Et_2O and an excess of MeI was left to stand for 3 hr. The precipitated solid was recrystallized from Me_2CO (more effectively from AcOEt) to colorless pillars, m.p. 193~194°, undepressed on admixture with a sample of (IV). *Anal.* Calcd. for $C_{24}H_{32}O_4NI$: C, 54.86; H, 6.14. Found : C, 54.63; H, 6.20.

(2) O,O-Diethylboldine Methine—The above methiodide (0.25 g.) was treated as in the case of (V). The methine base from this reaction also did not crystallize.

Oxalate : Colorless crystals (from MeOH-EtOH), m.p. 227~229°(with efferv.), alone and on admixture with a sample of oxalate of (V). *Anal.* Calcd. for $C_{24}H_{31}O_4N \cdot (CO_2H)_2$: C, 64.05; H, 6.82. Found: C, 63.19; H, 6.98.

(3) O,O-Diethylboldine Methine Methiodide—An ethereal solution of the above methine with MeI produced a white precipitate which was crystallized from MeOH to colorless needles, m.p. 252°, undepressed on admixture with a sample of (VI).

Summary

The structure of laurolitsine, a new phenolic base of *Neolitsea sericea* (Blume) Koidz., was established as represented by formula (X).

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