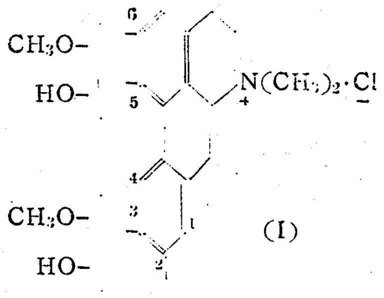
15. **Fuyuki Kusuda:** Studies on the Alkaloids of Menispermaceous Plants. CIV.[1] Alkaloids of *Cocculus laurifolius* DC. (Suppl. V[2]). The Structure of Laurifoline Chloride. (2)*.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto***)

In the preceding paper[2] of this series, M. Tomita and Kusuda reported on the investigation of laurifoline chloride, a new phenolic quaternary base of *Cocculus laurifolius* DC., in which they clarified by the degradation of its methyl ether iodide by the Hofmann method that O,O-dimethyllaurifoline iodide should have the same structure as O,O-dimethylboldine methiodide (glaucine methiodide), and assigned formula (I) to laurifoline chloride. However, confirmatory evidence on the location of the two phenolic hydroxyl groups lacked at that time, and on the ground that this base gave a green coloration with ferric chloride solution and caused no peculiar coloration on being alkalized, it was suggested that the two hydroxyl groups are not present in a vicinal form, and that this base might have the same structure as boldine methochloride or its isomeride distinguishable from the former by the arrangement of the hydroxyl groups. This time, the author carried out the same Hofmann degradation on O,O-diethyllaurifoline iodide as described in the previous paper, and examined its decomposition product, with the result that the location of the two hydroxyl groups in laurifoline has been determined. The results obtained are reported herein.



(I)

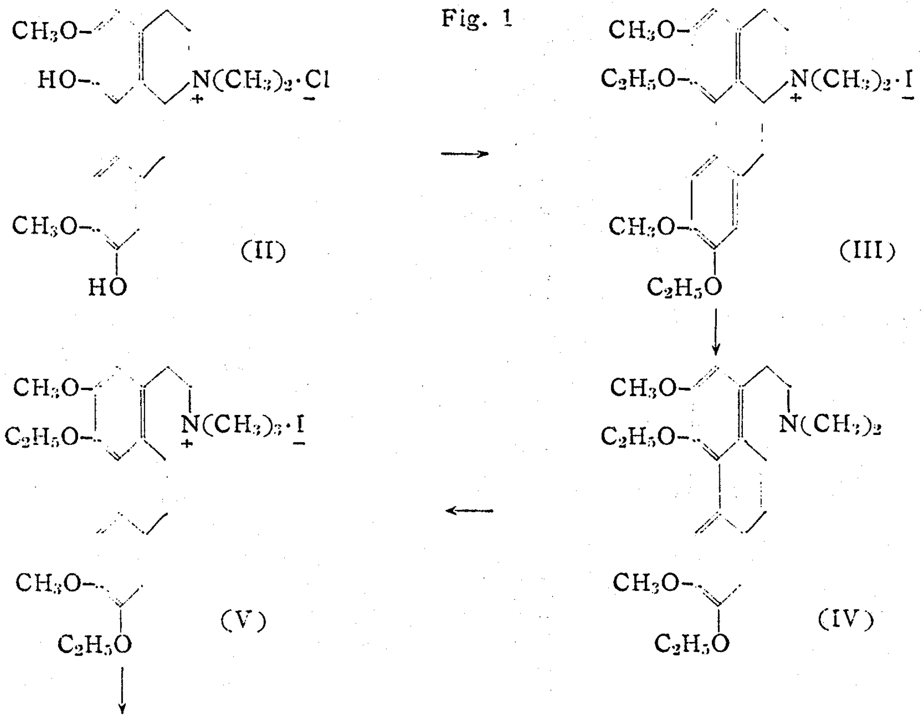


Fig. 1

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* M. Tomita: Studies on the Alkaloids of Menispermaceous Plants. CIV.

** Yoshida-konoe-cho, Sakyo-ku, Kyoto. (楠田冬樹).

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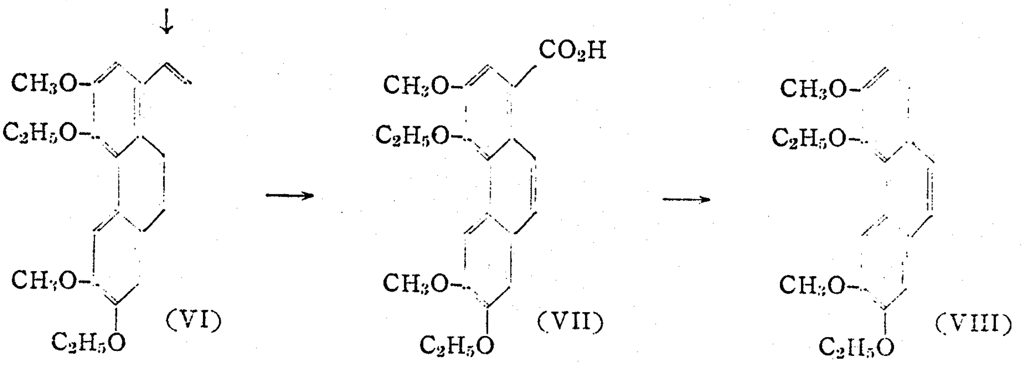
2) Suppl. IV: This Bulletin, 1, 5 (1953).



As shown in Fig. 1, laurifoline chloride (II) was converted by the action of ethyl iodide in the presence of alkali into O,O-diethyllaurifoline iodide (III), which was then subjected to the Hofmann degradation in two stages and yielded diethoxydimethoxyvinylphenanthrene (VI). This, on oxidation with potassium permanganate, followed by decarboxylation with quinoline-copper powder, was led to diethoxydimethoxyphenanthrene (VIII).

From a comparison of the data of the decomposition products (III) to (VIII) of each stage of this Hofmann degradation, with the analogous ones for the decomposition products of O,O-diethylboldine[3], an evident difference was recognized in the melting points of des-N-base (VI) and diethoxydimethoxyphenanthrene (VIII), as indicated in Table I. Thus, it has become clear that the two hydroxyl groups in laurifoline are not located at 2 and 6 positions of aporphine ring skeleton as those of boldine.

TABLE I

	Laurifoline chloride	Boldine
O-Ethyl ether methiodide (III)	m.p. 220°	resinous
Methine base (IV)	oil	oil
Methine methiodide (V)	m.p. 253~254°	m.p. 252~253°
Des-N-base (VI)	m.p. 126~127°	m.p. 112~113°
Diethoxydimethoxyphenanthrene-carboxylic acid (VII)	m.p. 199~200°	m.p. 202~203°
Diethoxydimethoxyphenanthrene (VIII)	m.p. 139~140°	m.p. 133~134°

On the other hand, among diethoxydimethoxyphenanthrenes are the following compounds so far synthesized by Späth, *et al.*[3], as shown in Table II, and it was noted that, of these, 4,7-diethoxy-3,6-dimethoxyphenanthrene was quite identical in the melting point with diethoxydimethoxyphenanthrene (VIII) obtained by the decomposition of laurifoline chloride by the author.

TABLE II

Compound	m.p.
3,7-Diethoxy-4,6-dimethoxyphenanthrene	133~134°
4,7-Diethoxy-3,6-dimethoxyphenanthrene	139~140
4,6-Diethoxy-3,7-dimethoxyphenanthrene	96~98

Consequently, the author carried out the Pschorr reaction by the method employed by Späth (*loc. cit.*), starting with 2-nitroisovanillin ethyl ether[4] and 3-ethoxy-4-methoxyphenylacetic acid[5], and synthesized 4,7-diethoxy-3,6-dimethoxyphenanthrene. The objective compound thus obtained showed m.p. 139~140°, quite identical with that described by

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[3] E. Späth, K. Tharrer: Ber., **66**, 904 (1933).
[4] R. Pschorr, W. Stöhrer: Ber., **35**, 4395 (1902); E. Späth, E. Bernhauer: Ber., **58**, 203 (1925).
[5] R.H.F. Manske, W.K. Ashford: J. Am. Chem. Soc., **73**, 5144 (1951).

Späth, and undepressed by admixture with the substance (VIII), m.p. 139~140°, derived from the natural laurifoline.

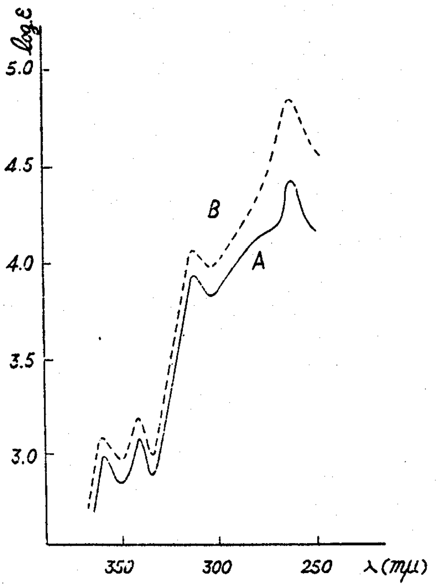
Furthermore, the ultraviolet absorption spectrum of the substance (VIII) exhibits the marked characteristic of the phenanthrene derivatives, as shown in Fig. 2.

From the foregoing experimental results, it has been determined that the two hydroxyl groups in laurifoline chloride exist at 2 and 5 positions of its molecule, and laurifoline chloride should be represented by formula (II).

Although a considerable number of the aporphine type bases have hitherto been isolated from the plant body, laurifoline is the first instance of the occurrence of the quaternary base of this type.

The author wishes to acknowledge his indebtedness to Prof. Dr. M. Tomita for his constant guidance during this study. The author also wishes to acknowldge that a part of the expenses for this study were defrayed by the Scientific Research Fund provided by the Ministry of Education.

Fig. 2



A —— 3, 4, 6, 7-Tetramethoxyphenanthrene (C_2H_5OH)

B - - - 4, 7-Diethoxy-3, 6-dimethoxyphenanthrene (C_2H_5OH)

Expenrimental⁶⁾

(A) Hofmann degradation of laurifoline chloride (II) (1) O,O-Diethyllaurifoline iodide (III)—1.3 g. of laurifoline chloride was dissolved in 18 cc. of 0.5*N*-methanolic potash, followed by 8 g. of ethyl iodide. The mixture was gently refluxed on a water bath for 2 hrs. After the reaction had been completed, deposited inorganic material was filtered off, and an excess of ethyl iodide and methanol removed, leaving a yellowish brown resinous substance. It was recrystallized from a mixture of methanol-acetone to colorless plates, m.p. 220°; yield, 1.7 g. *Anal.* Calcd. for $C_{24}H_{32}O_4NI \cdot H_2O$: C, 53.01; H, 6.31; N, 2.58. Found: C, 52.53; H, 6.27; N, 2.54.

(2) O,O-Diethyllaurifoline methine (IV)—To 1.6 g. of O,O-diethyllaurifoline iodide was added a solution of 14 g. of potassium hydroxide dissolved in 50 cc. of water. The content was heated on a water bath for 2.5 hrs. After the reaction had been finished, the depositing oily product was taken up in ether, and the aqueous layer was again heated on a water bath. After this manipulation was repeated three times, the ether solutions were combined, concentrated, and extracted with 5% hydrochloric acid. The hydrochloric acid solution was made alkaline with aqueous potassium hydroxide, and extracted with ether. The ether layer was washed with water and dried over anhydrous potassium carbonate. After removal of the solvent, a slightly yellow, oily substance was obtained; yield, 0.86 g. Attemps to crystallize it failed.

(3) O,O-Diethyllaurifoline methine methiodide (V)—0.86 g. of the above oily methine base was dissolved in 6 cc. of methanol, followed by 4 g. of methyl iodide. After gentle digestion for 1 hr., the methanol and excess methyl iodide were removed, and the residue was recrystallized from a mixture of methanol and acetone to colorless pillars, m.p. 253~254°; yield, 0.81 g. *Anal.* Calcd. for $C_{25}H_{34}O_4NI$: C, 55.62; H, 6.36; N, 2.59. Found: C, 55.36; H, 6.34; N, 2.58.

(4) Des-N-Base (VI) (Formation of diethoxydimethoxyvinylphenanthrene)—0.75 g. of the methine methiodide was dissolved in 25 cc. of methanol, diluted with 25 cc. of hot water, and shaken vigorously with freshly prepared silver hydroxide (from 3 g. of silver nitrate). The resulting silver salt was filtered off, and the filtrate was concentrated under a reduced pressure. The ammonium hydroxide thus obtained was heated at 100° for 10 mins. under a reduced pressure. After cooling, the residue was extracted with several portions of ether, and the insoluble white amorphous material removed. The ether solution was shaken with 3% aqueous hydrochloric acid to

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6) All melting points are uncorrected. The author wishes to express his thanks to Mr. K. Hozumi, Mr. K. Imaeda, and Miss H. Iwata in the Microanalytical Laboratory of the Pharmaceutical Institute, University of Kyoto, for performing the microanalyses reported herein.

remove the basic substance, and after being washed with water and dried over anhydrous potassium carbonate, the ether was distilled off, depositing orange pillars. They were recrystallized from methanol to slightly yellowish pillars, m.p. 126~127°; yield, 0.30 g. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 75.00; H, 6.82. Found: C, 75.03; H, 6.65.

(5) Oxidation of Des-N-Base (Formation of diethoxydimethoxyphenanthrene-carboxylic acid (VII))—To a solution of 0.25 g. of the des-N-base in 30 cc. of water, kept at 30°, was added dropwise under stirring during the course of about 1 hr. a solution of 0.5 g. of potassium permanganate in 25 cc. of water. After the addition, stirring was continued for an additional 6 hrs. Then the temperature was raised to 50°, and stirring and heating were continued for a further 30 mins. After the completion of the reaction, the resulting manganese dioxide was decomposed by a passage of sulfur dioxide, and the acetone removed by distillation under a reduced pressure. The depositing carboxylic acid was extracted by means of ether, and the ether distilled off. The yellowish brown, oily residue was dissolved by warming in 20 cc. of 5% aqueous sodium carbonate solution, and shaken once with ether to remove the unreacted material. The aqueous layer was then acidified with hydrochloric acid, and extracted with ether. The ether solution was washed with water, and after drying over anhydrous sodium sulfate the solvent was removed. Recrystallization of the residue from methanol yielded short orange pillars, m.p. 199~200°; yield, 0.11 g. *Anal.* Calcd. for $C_{21}H_{22}O_6$: C, 68.07; H, 5.99. Found: C, 67.48; H, 5.93.

(6) Decarboxylation of carboxylic acid (VII) (Formation of diethoxydimethoxyphenanthrene (VIII))—A mixture of 0.08 g. of the above carboxylic acid in 3 cc. of purified quinoline and 0.18 g. of copper powder was heated at 180~200° for 10 mins. After the evolution of carbon dioxide had ceased, the temperature was raised to 250~260°, and the mixture was boiled gently for a further 20 mins. After cooling, the content was diluted with about 30 cc. of ether, and filtered from copper powder. The ether solution was extracted with ten succesive portions of 10% aqueous hydrochloric acid solution followed by two portions of 5% aqueous potassium hydroxide solution. The ether layer was washed with water, dried over anhydrous sodium sulfate, and the ether removed, leaving a reddish brown syrupy product. This was dissolved in about 20 cc. of dehydrated benzene, and purified through an alumina column. On removal of benzene, a slightly yellowish solid remained, which was recrystallized from methanol to colorless pillars, m.p. 139~140°; yield, 0.04 g. *Anal.* Calcd. for $C_{20}H_{22}O_4$: C, 73.57; H, 6.79. Found: C, 72.78; H, 6.42.

(B) Synthesis of 4,7-diethoxy-3,6-dimethoxyphenanthrene (1) 4-Methoxy-5-ethoxy-6-nitro-α-(4′-methoxy-5′-ethoxyphenyl)-cinnamic acid—1.0 g. of sodium 3-ethoxy-4-methoxyphenylacetate was mixed well with 1.07 g. of 2-nitroisovanillin ethyl ether, and 5 cc. of acetic anhydride added. The mixture was heated at 110~120° for 30 hrs. Then the reaction mixture was treated with 10 cc. of water, and boiled for about 10 mins. After removal of the bulk of acetic acid, the residue was dissolved by warming in about 50 cc. of 5% aqueous ammonia, and filtered from insoluble material. The filtrate was shaken twice with ether to remove the unreacted materials, and then acidified with hydrochloric acid. The deposited yellow product was taken up in ether, and the ether extract was washed with water and dried over anhydrous sodium sulfate. Distillation of the solvent yielded yellow brown pillars. Recrystallized from methanol to yellow pillars, m.p. 165~166°; yield 0.97 g.

(2) 4-Methoxy-5-ethoxy-6-amino-α-(4′-methoxy-5′-ethoxyphenyl)-cinnamic acid—To a mixture of a solution of 4.5 g. of ferrous sulfate in 12 cc. of water, and 12 cc. of concentrated aqueous ammonia, heated on a water bath, was added gradually a solution of 0.9 g. of the above nitro compound dissolved by warming in 18 cc. of 5% aqueous ammonia. The reaction took place with effervescence. Heating was continued for a further 40 mins., and the reaction mixture filtered. The residue was extracted thoroughly with about 40 cc. of hot water, and the extract and the filtrate obtained above were combined. Then this solution was transferred to a dropping funnel, covered with ether, and neutralized cautiously by the gradual addition of 10% hydrochloric acid. The deposited amino acid was extracted with ether, and the ether solution was washed with water and dried with anhydrous sodium sulfate. Removal of the solvent left a yellowish brown, crystalline powder, m.p. 124~140°; yield, 0.70 g. This substance resisted efforts at crystallization. When it was forced to recrystallize from methanol, a portion of it yielded colorless needle-shaped crystals, m.p. 195~196°, which we probably a carbostyril derivative resulting from the elimination of one molecule of water.

(3) 4,7-Diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid and 4,5-diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid—0.63 g. of the above crude amino acid was dissolved in 16 cc. of methanol, 7 cc. of 2*N* sulfuric acid added, and the solution was cooled to -5° with ice and sodium chloride, after which 3 cc. of *N* sodium nitrate was added, drop by drop under stirring, to the reaction mixture. This solution was allowed to stand, under cooling with moderate stirring. Then 1.7 g. of copper powder was added in small portions to the solution, and the mixture was agitated at room temperature, by which vigorous evolution of nitrogen gas occurred. The reaction mixture was kept standing for 30 mins. longer, and after being warmed on a water bath at 70° for 20 mins., diluted with approx. 70 cc. of water, made alkaline with ammonia, and filtered from copper powder. The copper powder separated was extracted with further 30 cc. of 5% aqueous ammonia, and the extract was filtered. The combined filtrates were introduced into a dropping funnel, covered with ether, and after acidification with hydrochloric acid, the acid thus deposited was taken up in ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate, and concentrated to approx. 20 cc. Upon standing, a brown amorphous powder appeared. Recrystallized from methanol, a slightly brownish crystalline powder (4,7-diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid), m.p. 205~207°, was obtained. Yield, 0.24 g. The ethereal mother liquor was freed from the solvent, and the residue was recrystallized from methanol depositing yellow pillars (4,5-diethoxy-3,6-dimethoxyphenanthrene-9-carboxylic acid), m.p. 176~178°; yield, 0.10 g.

(4) **4,7-Diethoxy-3,6-dimethoxyphenanthrene**—0.15 g. of the above carboxylic acid of m.p. 205~207° was dissolved in 6 cc. of purified quinoline, and 0.4 g. of copper powder was added. The same procedure as described in the case of the substance (VIII) was applied to this decarboxylation reaction, and yielded colorless pillar-shaped crystals, m.p. 139~140°; yield, 0.08 g. This substance was undepressed by admixture with the substance (VIII), m.p. 139~140°, obtained by the decomposition of the natural laurifoline chloride. *Anal.* Calcd. for $C_{20}H_{22}O_4$: C, 73.57; H, 6.79. Found: C, 73.69; H, 6.80.

Summary

A study was made of the constitution of laurifoline chloride, a new phenolic quaternary base of *Cocculus laurifolius* DC. The ethyl ether iodide of laurifoline was subjected to the Hofmann degradation and led to diethoxydimethoxyphenanthrenes, which was confirmed by synthesis to be identical with 4,7-diethoxy-3,6-dimethoxyphenanthrene. Thereby, the structure of laurifoline chloride was established as being represented by formula (II).

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