acetone, deposited laurifoline chloride (V-base) as short pillars. They were collected, dissolved in a small portion of methanol, and by the addition of acetone on warming, recrystallized. The mother liquor, after evaporating to dryness under a reduced pressure, dissolved in approx. 50 cc. of water, decolorized by a small quantity of charcoal, and submitted to the mercuric chloride process. The manipulation described above was repeated, and further amounts of laurifoline chloride were obtained as colorless short pillars, m.p. 253°(decomp.); total yield, 1.3~1.5 g. The mother liquor perfectly separated from laurifoline chloride, after being made free from organic solvents, was dissolved in approx. 30 cc. of water, and saturated sodium picrate solution added. The deposited yellow precipitate was recrystallized from hot water, yielding yellow needles, m.p. 88°; yield, 0.3 g. (VI-base).

Trilobine (III-Base)—This base was obtained from benzene as colorless short pillars, m.p. 237°, and when mixed with trilobine, m.p. 237°, obtained from *Cocculus trilobus*, no melting point depression was observed. It gives a persistent blue color with conc. sulfuric acid and nitric acid (or potassium nitrate). $[\alpha]_D^{30}=+281.37°$ (0.0184 g. in 7 cc. $CHCl_3$, $l=0.5$ dm.). *Anal.* Calcd. for $C_{36}H_{36}O_5N_2$: C, 74.96; H, 6.29; N, 4.86. Found: C, 74.72; H, 6.27; N, 4.92.

Laurifoline chloride (V-Base)—It crystallizes in colorless short pillars, m.p. 253°(decomp., with effervescence), and is readily soluble in water, soluble in methanol and ethanol on warming, and insoluble in other organic solvents. The Gaebel methylenedioxy reaction and the Millon reaction were both negative. It gives a green coloration with ferric chloride solution. $[\alpha]_D^{24}=+26.32°$ (0.0798 g. in 7 cc. H_2O, $l=0.5$ dm.). *Anal.* Calcd. for $C_{20}H_{24}O_4NCl$: C, 63.57; H, 6.36; N, 3.71; OCH_3, 16.42; $N(CH_3)_2$, 7.95. Found: C, 63.05; H, 6.58; N, 3.22; OCH_3, 14.12; $N(CH_3)_2$, 9.36.

Laurifoline chloride was dissolved in a little water, and saturated sodium picrate solution added. The yellow precipitate which resulted was collected and recrystallized from hot water, yielding the picrate of yellow needles, m.p. 222°(decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_4N\cdot C_6H_2O_7N_3$: C, 54.73; H, 4.65; N, 9.82. Found: C, 54.56; H, 4.46; N, 9.63.

Summary

The authors made a systematic study of the alkaloids of *Cocculus laurifolius* DC., and as a result, clarified that besides coclaurine so far known, five other kinds of new bases were contained, as summarized in Table I.

(Received September 27, 1952)

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2. Masao Tomita and Fuyuki Kusuda: Studies on the Alkaloids of Menispermaceous Plants. CII[1]. Alkaloids of *Cocculus laurifolius* DC. (Suppl. IV). Structure of Laurifoline Chloride.

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

In the previous paper[1], the authors reported having isolated from *Cocculus laurifolius* DC. a new phenolic quaternary base, which was named laurifoline chloride, as a crystalline chloride, m.p. 325°(decomp.), and as a result of further studies on its chemical properties, propose, for the representation of this base, the following rational formula:

$$C_{20}H_{21}O_4NCl=C_{16}H_{10}\begin{cases}(OCH_3)_2\\(OH)_2\\>N(CH_3)_2\cdot Cl\\ \quad +\quad -\end{cases}$$

A concentrated sulfuric acid solution of laurifoline chloride is yellowish brown in color but on the addition of a drop of concentrated nitric acid, or a piece of potassium nitrate, a blue-green coloration develops which, on standing for a while, changes to a brown color. Apparently, this color

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1) Part CI: This Bulletin, 1, 1 (1953).

reaction is similar to that[2] of the alkaloid of the trilobine type possessing a diphenylene dioxide nucleus, but by a comparative observations, there exists some difference, namely that in the case of laurifoline chloride, a blue-green color becomes decolorized in a comparatively short time, whereas in that of the trilobine type, it persists for a long period of time. It was found that the color reaction of laurifoline chloride is quite identical with that caused by glaucine or boldine, an aporphine type alkaloid, described in the literature[3].

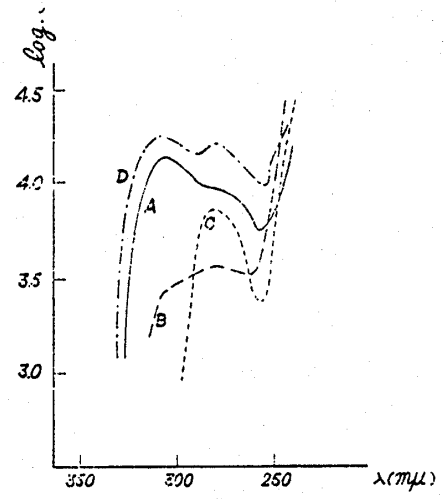
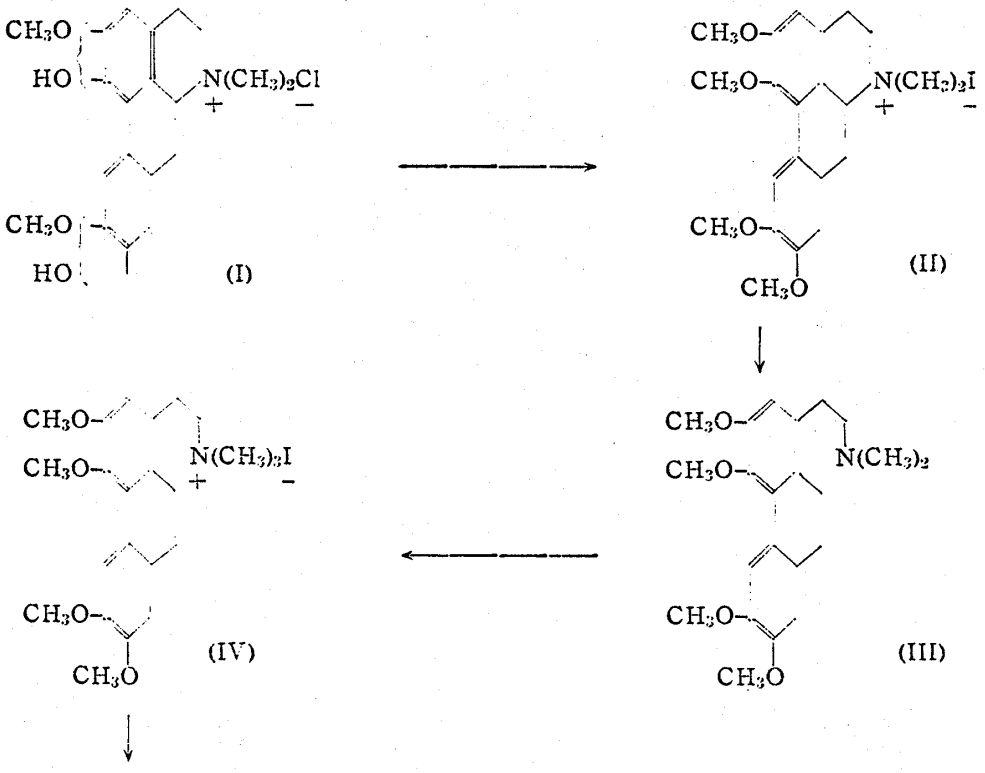


Fig. 1

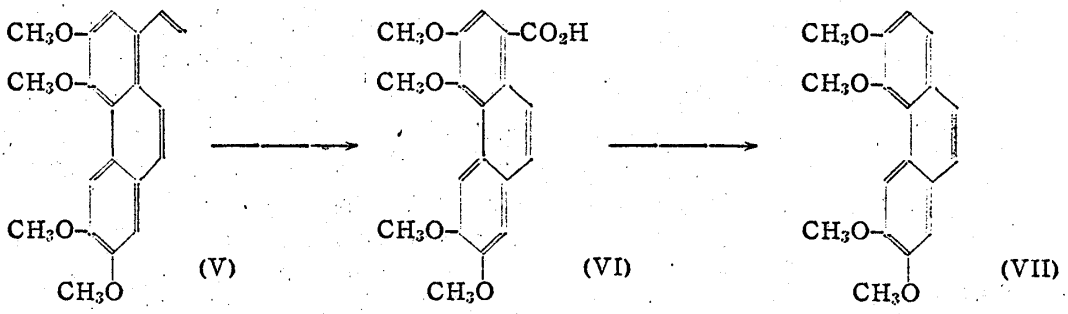
—— A Laurifoline chloride (in H_2O)
--- B Trilobine methochloride (in H_2O)
····· C Tubocurarine chloride (in H_2O)
-·-·- D Dicentrine (in C_2H_5OH)

Furthermore, comparison of the ultraviolet absorption spectrum of laurifoline chloride (A) with that of trilobine methochloride (B) showed that there is a great difference between the two as shown in Fig. 1, and the curve of the former also differs from that of tubocurarine chloride (C). Ultimately, it was found that the curve of laurifoline chloride (A) is well in agreement with that of one of the aporphine type bases, for instance, dicentrine[4] (D).

From these experimental results, it is presumed that laurifoline chloride may be a quaternary base belonging to the aporphine group, and thus the Hofmann degradation of its O-methyl iodide was carried out. Laurifoline chloride was converted with methyl iodide in the presence of alkali into



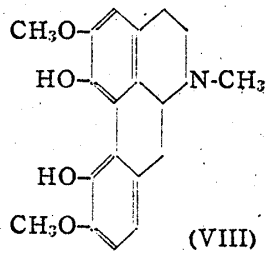
2) M. Tomita: J. Pharm. Soc. Japan, 52, 889 (1932); *ibid.*, 54, 893 (1934); M. Tomita, T. Tani: *ibid.*, 62, 468, 476, 481 (1942).
3) J. Gadamer: Arch. Pharm., 240, 94 (1902); *ibid.*, 249, 503, 641, 669 (1911).
4) M. Tomita, S. Shirai: J. Pharm. Soc. Japan, 62, 381 (1942).



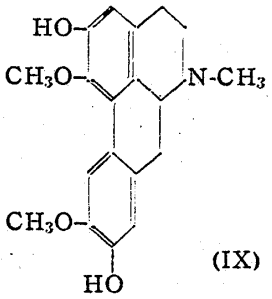
(V) (VI) (VII)

O,O-dimethyllaurifoline iodide (II), which was then subjected to the two-stage Hofmann degradation and, following the process shown in the schema, led to a neutral substance (VII).

On the other hand, according to the literature so far appeared, no quaternary bases belonging to the aporphine group have been discovered as yet, and only the tertiary bases of this type, corytuberine[5] (VIII) and boldine[6] (IX), having two methoxyl and two hydroxyl groups, have been described.



(VIII)



(IX)

The comparison of the data of the decomposition products (II) to (VII) of each stage obtained by the Hofmann degradation of laurifoline chloride (I) by the authors with those of the corresponding products of O,O-dimethylboldine[7] (glaucine) are given in the following Table I, where a perfect concordance is observed between the two series. In Table I, the methine base (III) derived from boldine was described as an oil, but the authors were able to obtain it in a crystalline form by taking much trouble.

TABLE I

	Laurifoline chloride (I)	Boldine (IX)
O,O-Dimethyl ether methiodide (II)	m.p. 221°	m.p. 221°
Methine base (III)	m.p. 66~67°	Oil
Methine methiodide (IV)	m.p. 278~279°	m.p. 276~280°
Des-N-base (V)	m.p. 143°	m.p. 143°
3,4,6,7-Tetramethoxy-phenanthrene-carboxylic acid (VI)	m.p. 215°	m.p. 213~214°
3,4,6,7-Tetramethoxy-phenanthrene (VII)	m.p. 124° (Picrate, m.p. 125°)	m.p. 124~125° (Picrate, m.p. 123~125°)

5) J. Dobbie, A. Lauder: J. Chem. Soc., 63, 485 (1893); J. Gadamer: Arch. Pharm., 240, 94 (1902); *ibid.*, 249, 503, 641 (1911).
6) K. Warnat: Ber., 58, 2768 (1925).
7) K. Warnat: Ber., 59, 85 (1926).

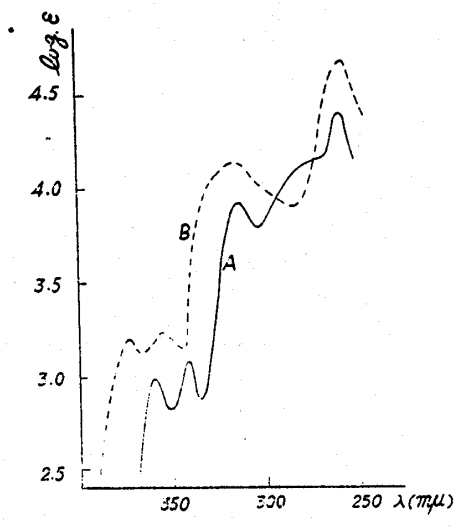


Fig. 2

A —— 3,4,6,7-Tetramethoxyphenanthrene (Degradation product of laurifoline chloride)

B --- 3,4,5,6-Tetramethoxyphenanthrene (Synthetic product by Dr. M. Satomi)

When the substance (VII) and its picrate obtained by the authors were admixed with the specimens of 3,4,6,7-tetramethoxyphenanthrene[8], m.p. 124°, and its picrate, m.p. 123~125°, synthesized by Ochiai[9] and later by Satomi[10], respectively, no melting point depression occurred, and the identity of both were thereby confirmed. As shown in Fig. 2, the ultraviolet absorption spectrum of the substance (VII) is characteristic of that of the phenanthrene derivatives.

From the above experimental results, it has been confirmed that O,O-dimethyllaurifoline iodide should have the same structure as O,O-dimethylboldine methiodide (glaucine methiodide), represented by formula (II). Concerning the position of the two phenolic hydroxyl groups in the molecule of laurifoline chloride, no confirmatory evidence has been obtained thus far, and the particulars must depend upon further study. Yet, since laurifoline chloride gives merely a green coloration with ferric chloride, and even on alkalization no peculiar color results, it seems that the two hydroxyl groups should not be present in the vicinal-form on the same benzene nucleus, and that laurifoline chloride may be a quaternary base chloride represented by formula (I), probably having the same structure as boldine methochloride, or an isomer distinguished by the position of its hydroxyl groups. At any rate, the aporphine type alkaloids have so far been discovered from a large number of plants, but they are all confined to tertiary bases. This is the first instance of the occurrance of the alkaloid of this type as a quaternary base in plants. From the standpoint of the consideration of the formation mechanism of alkaloids in the plant body, it may be said that this fact also offers an important datum.

The authors wish to express their appreciation to Dr. H. Kondo and Dr. M. Satomi of the ITSUU Laboratory, Tokyo, for affording them a sample of 3,4,6,7-tetramethoxyphenanthrene-9-carboxylic acid for this study. The expenses for this study were defrayed by the Scientific Research Fund furnished by the Ministry of Education, for which the authors also wish to extend their gratitude.

Experimental[11]

Hofmann degradation of laurifoline chloride—(1) O,O-Dimethyllaurifoline iodide (II)—1.3 g. of laurifoline chloride was added to 11 cc. of 0.5 *N* methanolic potash, and followed by 7 g. of methyl iodide. After gentle digestion on a water bath for 2 hrs., potassium chloride was removed, and the excess of methyl iodide and methanol distilled off, leaving colorless pillars. Recrystallization was effected from methanol to m.p. 221°; yield, 1.3 g. Dried at room temperature in vacuo over phosphorus pentoxide. *Anal.* Calcd. for $C_{22}H_{28}O_4NI \cdot 1\frac{1}{2} H_2O$: C, 50.38; H, 5.96; N, 2.67; OCH_3, 23.67; $N(CH_3)_2$, 5.72. Found: C, 50.71, 50.10; H, 5.91, 5.73; N, 2.70, 2.39; OCH_3, 25.28; $N(CH_3)_2$, 4.86.

8) 3,4,6,7-Tetramethoxyphenanthrene-9-carboxylic acid, m.p. 210°, obtained from Dr. M. Satomi was decarboxylated by the usual method as described in the experimental part, and led to 3,4,6,7-tetramethoxyphenanthrene, m.p. 124°, and its picrate, m.p. 123~125°, quite identical with those described in the literature.

9) E. Ochiai: J. Pharm. Soc. Japan, **48**, 99 (1928).

10) M. Satomi: *Ibid.*, **72**, 834 (1952); Ann. Repts. ITSUU Lab. (Japan), **3**, 37 (1952).

11) All melting points are uncorrected. The authors' thanks are due to Mr. K. Hozumi and Mr. K. Imaeda for carrying out microanalyses herein reported.

(2) **O, O-Dimethyllaurifoline methine (III)** — 1.2 g. of O, O-dimethyllaurifoline iodide was added to a solution of 12 g. of potassium hydroxide dissolved in 50 cc. of water. The mixture was boiled on a water bath for 3 hrs., and after cooling the deposited oily substance was taken up in ether. The aqueous layer remaining after the ether extraction was again heated on a water bath. After this manipulation was repeated three times, the ether solutions were combined and concentrated, yielding a yellow-brown oil. On addition of 5 cc. of 2% hydrochloric acid solution, this formed a hydrochloride, which was collected, dissolved in approx. 30 cc. of hot water, and discolored by charcoal. After filtration, the filtrate was made alkaline with 2% aqueous sodium hydroxide, and the resulting precipitate was taken up in ether. The ether solution was dried over anhydrous potassium carbonate, and the solvent removed, leaving a slightly yellowish oil. This was dissolved in approx. 50% aqueous methanol, and on standing, colorless needles, m.p. 66~67°, were obtained; yield, 0.52 g. The hydrochloride forms slightly orange scales, m.p. 256°, $[\alpha]_D^{28}=\pm 0°$ (0.0601 g. in 7 cc. methanol, $l=0.5$ dm.). *Anal.* Calcd. for $C_{22}H_{27}O_4N \cdot 1/2H_2O$: C, 69.79; H, 7.46; OCH_3, 32.79; $N(CH_3)_2$, 7.93. Found: C, 69.16; H, 7.42; OCH_3, 33.46; $N(CH_3)_2$, 7.51.

(3) **O, O-Dimethyllaurifoline methine methiodide (IV)** — 0.4 g. of the methine base was dissolved in 3 cc. of methanol, followed by 2 g. of methyl iodide, and the mixture was boiled gently with a reflux condenser on a water bath for 1 hr. After the reaction was completed, the excess of methyl iodide and methanol were removed, and the residue was recrystallized from methanol-chloroform (1 : 1) mixture. Colorless pillars, m.p. 278~279°; yield, 0.48 g. *Anal.* Calcd. for $C_{23}H_{30}O_4NI$: C, 54.01; H, 5.87. Found: C, 54.14; H, 5.73.

(4) **Des-N-substance (V) (Formation of tetramethoxyvinylphenanthrene)** — To a solution of 0.4 g. of the methine methiodide in 28 cc. of 80% hydrated methanol, heated on a water bath, was added a solution of 1.6 g. of sodium hydroxide dissolved in 4 cc. of 80% hydrated methanol. The content was boiled for 5 hrs., and after cooling, the deposited crystals were extracted with ether. The ether extract was once shaken with 3% hydrochloric acid solution to remove the basic material, washed with water, and after drying over sodium sulfate, the ether was removed. The residue was recrystallized from methanol to colorless rhombic pillars, m.p. 143°; yield, 0.18 g. *Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.03; H, 6.22. Found: C, 73.27; H, 6.49.

Trimethylamine formed as a by-product was caught in a hydrochloric acid solution, and treated with aurichloride solution. The chloroaurate which resulted was recrystallized from hot water to yellow needles, m.p. 241° (decomp.). In the case of the above ether extraction, a polymerization product (white amorphous powder) was obtained, m.p.>300°; yield, 0.07 g.

(5) **Oxidation of des-N-substance (Formation of tetramethoxyphenanthrene-carboxylic acid)** — To a solution of 0.15 g. of the des-N-substance in 20 cc. of acetone kept at 30° was added, dropwise under stirring, a solution of 0.33 g. of potassium permanganate dissolved in 16 cc. of water over a period of approx. 1 hr. Stirring was continued for further 6 hrs., and then after the temperature was raised to 50°, the content was heated under stirring for 30 mins. After the reaction was completed, manganese dioxide was dissolved by passing sulfur dioxide gas, and the acetone removed under a reduced pressure. The deposited crystals were taken up in ether, and the ether distilled off. The yellow brown oily residue was dissolved in 20 cc. of 5% aqueous sodium carbonate by warming. The solution was shaken once with ether to remove unreacted substance, and after acidification with hydrochloric acid, followed by further portions of ether. The ether solution was dried over anhydrous sodium sulfate and the ether distilled off. The residue was recrystallized from ethanol and gave slightly yellow short pillars, m.p. 215°; yield, 0.09 g. *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 66.86; H, 5.52.

(6) **Decarboxylation of carboxylic acid (VI) (Formation of tetramethoxyphenanthrene (VII))** — A solution of 0.07 g. of the above carboxylic acid dissolved in 2.5 cc. of purified quinoline, mixed with 0.15 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 250~270°, and heating was continued for further 20 mins. at such a rate that the content boiled gently. After cooling, the content was diluted with 30 cc. of ether, and filtered to remove copper powder. The ether solution was shaken with ten portions of 10% hydrochloric acid solution, followed by two portions of 5% aqueous potassium hydroxide. The ether layer was washed with water, and after drying over anhydrous sodium sulfate, the ether was removed, leaving a reddish brown, viscous substance. When this was dissolved in approx. 20 cc. of anhydrous benzene, and purified through alumina column, a slightly yellowish solution with violet fluorescence was obtained, and the residue was recrystallized from methanol to almost colorless pillars, m.p. 124°; yield, 0.035 g. This substance gave violet fluorescence on irradiation of ultraviolet rays. *Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.45; H, 6.08. Found: C, 71.85; H. 5.81.

To a methanol solution of the above substance was added a saturated methanol solution of picric acid, and on standing for a while, the picrate crystallized to reddish needles, m.p. 125°.

(7) **Preparation of 3,4,6,7-Tetramethoxyphenanthrene** — 0.25 g. of 3,4,6,7-Tetramethoxyphenanthrene-9-carboxylic acid[8], m.p. 210°, furnished on decarboxylation by quite the same procedure as described above, slightly yellow pillars, m.p. 124°; yield, 0.16 g. *Anal.* Calcd. for

)$_4$: C, 72.45; H, 6.08. Found: C, 72.11; H, 5.82.
ıe picrate of this substance forms reddish needles, m.p. 123~125°. When these substances dmixed with the above substance (VII) and its picrate, respectively, no melting point depres- ıccurred, confirming them to be identical.

Summary

ıe authors clarified by the Hofmann degradation of laurifoline chloride, a quaternary ic base of *Cocculus laurifolius* DC., that O,O-dimethyllaurifoline iodide should have ıme structure as O,O-dimethylboldine methiodide (glaucine methiodide) (II), and ıed formula (I) for the representation of laurifoline chloride.

(Received September 27, 1952)

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3. **Masao Tomita and Hideo Yamaguchi**: Studies on the Alkaloids of Menispermaceous Plants. CIII.[1] Studies on the Syntheses of Coclaurine and Analogous Compounds. (5). Synthesis of *dl*-O,O,N-Trimethylcoclaurine.

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

ıcently, the cleavage reactions[2] by metallic sodium in liquid ammonia on many aurine alkaloids were carried out in our laboratory, and these bisected bases thus ıd were led to *d*- or *l*-1-(4′-methoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydro- ıoline, *viz.*, the substance corresponding to O,O,N-trimethylcoclaurine (VII). On ıer hand, *dl*-O,O,N-trimethylcoclaurine (VII) was derived from coclaurine[3]. From results, these three kinds of O,O,N-trimethylcoclaurines gave the following data:

d-O,O,N-Trimethylcoclaurine: m.p. 62°, $[\alpha]_D$: +83° (in $CHCl_3$).
l-O,O,N-Trimethylcoclaurine: m.p. 62°, $[\alpha]_D$: −83° (in $CHCl_3$).
dl-O,O,N-Trimethylcoclaurine: m.p. 62°, $[\alpha]_D$: ±0°.

ɔwever, Marion, *et al.*[4], in their report on the synthesis of *dl*-armepavine [1-(4′- ĸybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline] (VI), synthesized a ıce corresponding to our *dl*-O,O,N-trimethylcoclaurine (VII) by the methylation of ith diazomethane and described it as m.p. 92°. One of the authors (M. Tomita) Kusuda already pointed out this discrepancy[3] between ours and his. This time the s carried out the following study with a view to clarifying this point.
ıe synthetic method of *dl*-armepavine (VI) by Marion, *et al.*[4] was as follows: 1-(4′- ɜnzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide was converted on reduction inc dust and hydrochloric acid into its corresponding 4′-amino-N-methyl-tetrahydro- ıoline derivative, whose diazonium compound was then decomposed into (VI). The

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shida-konoe-cho, Sakyo-ku, Kyoto. (富田真雄, 山口秀夫).
rt CII: This Bulletin, 1, 5 (1953).
Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, 71, 226, 1036 (1951); E. Fujita, F. ırai: *Ibid.*, 71, 1039, 1043 (1951); E. Fujita: *Ibid.*, 72, 213, 217 (1952); Y. Inubushi: *Ibid.*, 72,) (1952); Y. Inubushi, H. Niwa: *Ibid.*, 72, 762 (1952).
Tomita, F. Kusuda: *Ibid.*, 72, 280, 793 (1952).
Marion, L. Lemay, V. Portelance: J. Org. Chem., 15, 216 (1950).