)$_4$: 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.

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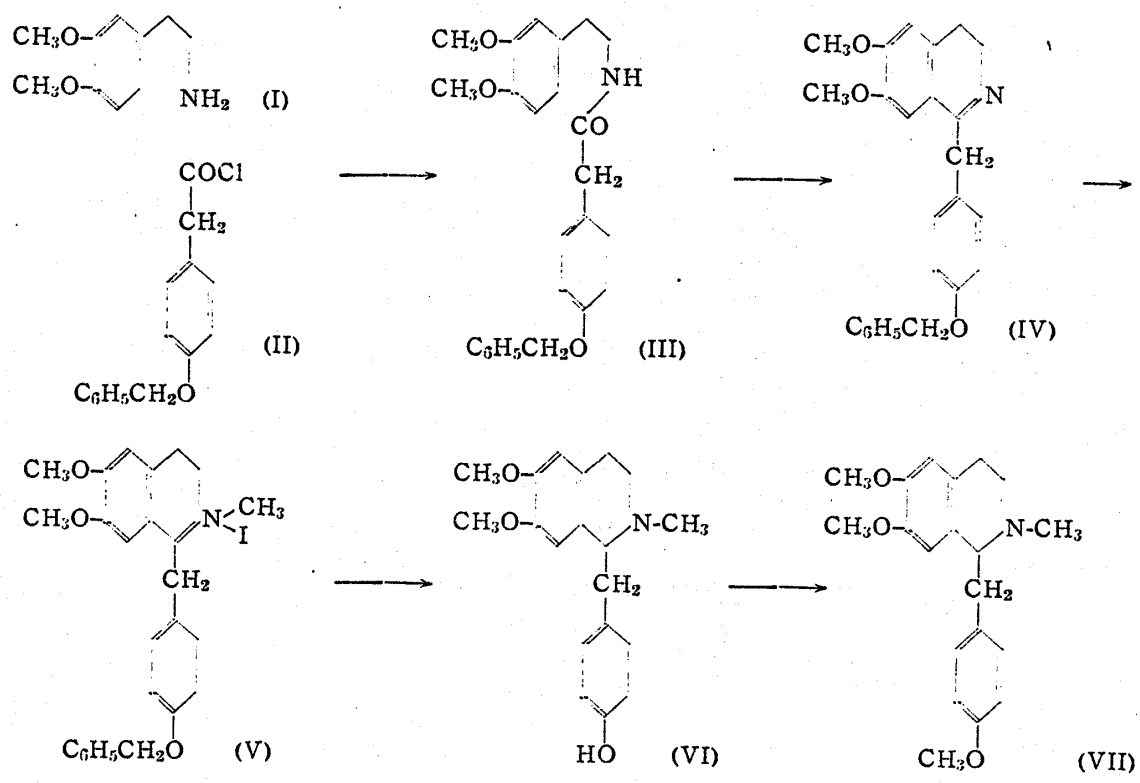
rt CII: This Bulletin, 1, 5 (1953).
Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, 71, 226, 1036 (1951); E. Fujita, F. ırai: *Ibid.*, 71, 1039, 1043 (1951); E. Fujita: *Ibid.*, 72, 213, 217 (1952); Y. Inubushi: *Ibid.*, 72,) (1952); Y. Inubushi, H. Niwa: *Ibid.*, 72, 762 (1952).
Tomita, F. Kusuda: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

authors synthesized *dl*-armepavine (VI) by a method different from that employed by Marion, as shown in the following schema:



3,4-Dimethoxy-ω-nitrostyrene was produced via veratraldehyde[5] starting with vanillin, and by reducing it with lithium aluminum hydride, 3,4-dimethoxyphenylethylamine (I) was synthesized. Subsequently, by condensing with 4-benzyloxyphenylacetyl chloride (II), this was converted into the acid amide (III), m.p. 116°, which was cyclized by the action of phosphoryl chloride in toluene by the Bischler-Napieralski reaction, and led to 1-(4′-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IV), m.p. 101° (hydrochloride, m.p. 210.5°). In this connection, it has been announced in several reports[6] that 1-benzyl-3,4-dihydroisoquinolines are unstable in alkali solution and are oxidized into 1-benzoyl compounds. So far as the present substance was concerned, the hydrochloride, obtained by treating in hydrochloric acid solution after cyclization, was quite identical with the one which was regenerated from the free base obtainable by treating once with caustic alkali after cyclization, and no oxidation such as that mentioned above was observed. The dihydroisoquinoline (IV) was converted into its methiodide (V), m.p. 199°, which was then reduced and simultaneously debenzylated with zinc dust and hydrochloric acid, and the product thus obtained was recrystallized from a mixture of a small quantity of acetone and ether, yielding *dl*-armepavine (VI) as beautiful prisms, m.p. 166°. The data and the properties of this substance coincide well with those described by Marion, *et al.* This was dissolved in a small quantity of methanol, to which an ethereal solution of excess diazomethane was added, and allowed to stand for several days at a room temperature. Then the crude crystals obtained by the treatment of the above product were purified by chromatography and recrystallized from ether and petroleum ether, whereupon O-methylarmepavine (VII) was obtained as white needles, m.p. 62.5~63°. By admixture of this substance with *dl*-O,O,N-

5) "Org. Syntheses", Coll. Vol. II, 629.
6) J. S. Buch, R. D. Haworth, W. H. Perkin: J. Chem. Soc., 125, 2176 (1924); A. Lindenmann: Helv. Chim. Acta, 32, 69 (1949).

trimethylcoclaurine (VII), m.p. 62°, derived from *dl*-coclaurine in our laboratory, no depression of the melting point could be recognized, ascertaining these two substances to be identical. Thus, it has been clarified that the description of the *dl*-type of the substance (VII) by Marion as m.p. 92° was an error.

A part of the expenses for this research was defrayed by the Scientific Research Funds provided by the Ministry of Education for which the authors express their profound gratitude.

Experimental[7]

(1) 3,4-Dimethoxy-ω-nitrostyrene — 3.32 g. of veratraldehyde was dissolved in 9 cc. of methanol and 1.6 g. of nitrostyrene was added. Meanwhile, 0.2 g. of methylamine hydrochloride was dissolved in a small quantity of methanol, and stirred well with the corresponding quantity of sodium carbonate and filtered. The filtrate was added to the above-mentioned solution, and sealed tightly and kept in a dark place at a room temperature. After 24 hrs., the deposited yellow plate crystals were filtered immediately, and washed first with a mixture of methanol and ether, and subsequently with sufficient ether. Yield, 3.6 g. (86.7%), m.p. 145°.

(2) 3,4-Dimethoxyphenylethylamine (I) — The apparatus and the operation were the same as those described for the synthesis of isococlaurine[8]. A solution of 2.08 g. of nitrostyrene and 40 cc. of purified anhydrous dioxane were added dropwise to a well-stirred mixture of 2 g. of $LiAlH_4$ and 150 cc. of anhydrous ether over a period of 2 hrs. After the addition, warming and stirring were continued for further 3 hrs. on a water bath at 40~50°, after which the bath was replaced with an ice-water bath and the contents were decomposed under vigorous stirring by the successive addition of 3 cc. of water, 3 cc. of 20% NaOH, and 2 cc. of water. The upper ether-dioxane layer was separated by decantation from the lower precipitates of inorganic salts, which were filtered by suction, and washed well with ether. The ether-dioxane layer was dried over anhydrous potassium carbonate. After removing the ether, the dioxane solution of the amine (I) was obtained. To this solution was added a saturated methanolic solution of 1.3 g. of oxalic acid, whereupon the oxalate deposited at once. Recrystallized from methanol to m.p. 178°. Yield, 1.5 g. (55.9%).

(3) N-(3,4-Dimethoxyphenethyl)-4'-benzyloxyphenacetamide (III) — 3.9 g. of 4-benzyloxyphenylacetic acid was mixed with 17.5 cc. of anhydrous ligroine and 3.72 g. of phosphorus pentachloride and heated on a water bath at 60° for 10 mins. to effect uniform solution. When cooled, the acid chloride (II) readily deposited as white crystals. After cool, ligroine was added to this mixture, agitated well, the crystals were filtered by suction, washed with a small portion of cooled ligroine, and dissolved in absolute ether. Meanwhile, the free base, obtainable by the decomposition of 3.35 g. of the amine (I) oxalate with caustic alkali, was extracted thoroughly with ether, and salted out by saturation with potassium carbonate because of its high solubility in water. The ether extract was cooled well together with 75 cc. of 5% NaOH, and the above-mentioned ether solution of acid chloride was added dropwise under vigorous stirring. The resulting acid amide (III) appeared at once due to its low solubility in ether. After the addition, stirring was continued for 40 mins. at a room temperature. The ether layer was decanted and the ether was distilled off. All the products were extracted with chloroform, and successively washed with water, dil. HCl, and water. The chloroform was removed, leaving a light yellow oily substance. On standing overnight in a desiccator, the white crystalline mass appeared. Recrystallized from methanol, the acetamide was obtained as white needles, m.p. 116°. Yield, 4.5 g. (90%). *Anal.* Calcd. for $C_{25}H_{27}O_4N$: C, 74.07; H, 6.66. Found: C, 73.97; H, 6.58.

(4) 1-(4'-Benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (IV) — 0.5 g. of the acid amide (III), 3 cc. of anhydrous toluene, and 0.8 g. of phosphoryl chloride were mixed and gently boiled in an oil bath at 105~115° for 1.5 hrs. After cooling, the deposited product was separated from the toluene layer, washed with petroleum ether and the petroleum ether layer was discarded. The trace of the remaining petroleum ether and phosphoryl chloride were completely removed on a water bath in vacuo, leaving a black resinous substance. This was recrystallized first from acetone, and then from ethanol. The hydrochloride of the objective substance (IV) was gained as white scales, m.p. 210.5~211° (decomp.). Yield, 0.1 g. *Anal.* Calcd. for $C_{25}H_{25}O_3N \cdot HCl$: C, 70.83; H, 6.13. Found: C, 70.56; H, 6.14.

The acetone was removed from the mother liquor of recrystallization, the residue was dissolved in hot water, and after washing with ether, alkalized by caustic alkali and extracted with ether. After drying over anhydrous potassium carbonate, the ether was distilled off, yielding the free

7) All melting points are uncorrected. The microanalyses were carried out by Mr. K. Hozumi, Mr. K. Imaeda, and Miss H. Iwata, in the Microanalytical Laboratory of the Pharmaceutical Institute, University of Kyoto, to whom the authors express their thanks.

8) M. Tomita, H. Yamaguchi: J. Pharm. Soc. Japan, 72, 1219 (1952).

base (IV) as white needles. Recrystallized from ethanol containing water to m.p. 101°. *Anal.* Calcd. for $C_{25}H_{25}O_3N$: C, 77.51; H, 6.45. Found: C, 77.79; H, 6.75.

A small portion of this free base was dissolved in acetone, and conc. HCl was added. The solution was allowed to stand for several days in a desiccator, and deposited crystals. The hydrochloride, obtained by recrystallization from a mixture of methanol and ether, showed m.p. 210.5°, and on admixture with the above hydrochloride, obtained by the treatment in acid solution after the cyclizing reaction, no depression of the melting point was observed.

(5) 1-(4'-Benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (V)—3,4-Dihydroisoquinoline (IV), produced from 0.5 g. of the acid amide (III) as described in (4), was dissolved in 2.5 cc. of methanol, and followed by 0.3 cc. of methyl iodide. The whole was refluxed for 1.5 hrs. on a water bath. After the reaction had been completed, methanol and excess of methyl iodide were distilled off. The residue was treated with warm ether, and the ether layer was discarded. The residual resinous substance was dissolved in acetone, and on cooling, the crystals deposited. Recrystallized from a mixture of acetone and methanol to m.p. 199°. Yield, 0.4 g. (61.5% from the acid amide). *Anal.* Calcd. for $C_{25}H_{25}O_3N \cdot CH_3I$: C, 58.98; H, 5.29. Found: C, 58.89; H, 5.44.

(6) *dl*-Armepavine (VI) — In a three-necked flask fitted with a stirrer and a reflux condenser was placed 1.3 g. of methiodide (V), 12 cc. of water, 28 cc. of 36% HCl, and 2 cc. of alcohol. The flask was boiled on a steam bath under stirring and then the content became a uniform solution. To this, 4.5 g. of zinc dust was added slowly over a period of 30 mins. After the addition, heating and stirring were continued for 1.5 hrs., after which time all the contents were filtered, diluted with a little water, and washed with ether. Subsequently, in a separating funnel, the solution, the upper layer of which was covered with ether, was basified by the addition of small portions of dilute aqueous ammonia. The mixture was shaken well every time the addition was made, to transfer the deposited free base completely to the ether layer, since once *dl*-armepavine crystallizes, it tends to be considerably insoluble in ether, and the extraction by ether becomes difficult. The ether layer was dried over anhydrous potassium carbonate, and the ether was distilled off. The residue was dissolved in a small quantity of methanol, and on standing in an ice box, crystallized. Yield, 0.4 g. (52%). The crystals were dissolved in a small amount of acetone and after the addition of ether, kept in an ice box, yielding pure *dl*-armepavine (IV) as prisms, m.p. 166°. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.84; H, 7.35. Found: C, 73.21; H, 7.40. The oxalate forms crystals of m.p. 212°.

(7) *dl*-O,O,N-Trimethylcoclaurine (*dl*-O-Methylarmepavine) (VII) — 0.1 g. of *dl*-armepavine (VI) was dissolved in a small quantity of methanol, to which an ethereal solution of diazomethane evolved from 3 g. of nitrosomethylurea was added, and allowed to stand for 5 days at a room temperature (25~28°). The ether and the excess of diazomethane were distilled off. The residue was dissolved in 7 cc. of 5% HCl, and after washing with ether, alkalized with caustic alkali, extracted with ether, and dried over anhydrous potassium carbonate. The ether was distilled off, leaving 90 mg. of a slightly yellow, oily substance. This was dissolved in the minimum amount of absolute ether, to which a few drops of petroleum ether (b.p. 29~50°) was added. On standing overnight in an ice box, the crude crystals deposited. They were dissolved in anhydrous benzene and purified by chromatography through an alumina column, yielding colorless crystals. They were recrystallized from a mixture of ether and petroleum ether, and *dl*-O-methylarmepavine (VII) deposited as white needles, m.p. 62.5~63°. This was washed with a cooled mixture of ether and petroleum ether (1:1). By admixture of this substance with *dl*-O,O,N-trimethylcoclaurine, m.p. 62°, derived from *dl*-coclaurine, no melting point depression was recognized.

Summary

The authors synthesized *dl*-armepavine (VI) and *dl*-O-methylarmepavine (VII) (*dl*-O,O,N-trimethylcoclaurine) from 3,4-dimethoxyphenylethylamine (I) and 4-benzyloxyphenylacetyl chloride (II) by the method different from that employed by Marion, *et al.*[4] As a result, it was clarified that the *dl*-type of the substance (VII) does not give m.p. 92°, as described by Marion, but gives m.p. 62.5~63°.

(Received September 27, 1952)