B–5, $CHCl_3$–MeOH (5:1)] showed one spot (*Rf*: 0.30). Purification from $CHCl_3$—*n*–hexane gave a colorless powder, mp 122—129° (sinters at 114°). *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot \frac{1}{2}H_2O$[17]: C, 71.38; H, 6.82; N, 4.63. Found: C, 71.26; H, 6.93; N, 4.64. IR cm^{-1} (KBr): ν_{OH} 3300—3540 (broad). NMR (ppm) ($CDCl_3$): 2.39 (6H, singlet, 2N–CH_3); 3.75 (6H, singlet, 2OCH_3); 6.15 (1H, C_8–H); 6.23 (1H, C_8–H); 6.45—7.13 (9H, aromatic protons).

Stereoisomeric Mixture of O,O,O-Trimethylmagnoline (II) (O,O,O-Trimethylbergamumine)——To a solution of 43 mg of synthetic magnoline mentioned above in 15 ml of EtOH was added a solution (50 ml) of an excess of CH_2N_2 in ether, and the mixture was allowed to stand at 3° for 48 hr. After filtration, removal of the solvent *in vacuo* in a current of N_2 afforded 40 mg of II as a brown syrup, whose dipicrate was recrystallized from $CHCl_3$—*n*–hexane to give a yellow powder, mp 143—145° (decomp.) (sinters at 127°). $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3ON_3 \cdot 1H_2O$[17] *Anal.* Calcd. for: C, 54.93; H, 4.88; N, 10.05. Found: C, 55.21; H, 4.51; N, 10.03. The IR spectrum (in $CHCl_3$) of this dipicrate was superimposable on that of the sample[13] obtained by methylation of natural dauricine, followed by treatment with picric acid.

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17) This was dried on P_2O_5 at 60° for 48 hr *in vacuo*.

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Synthesis of Stereoisomeric Mixture of Daurinoline (Studies on the Syntheses of Heterocyclic Compounds. CCXLIX[1])

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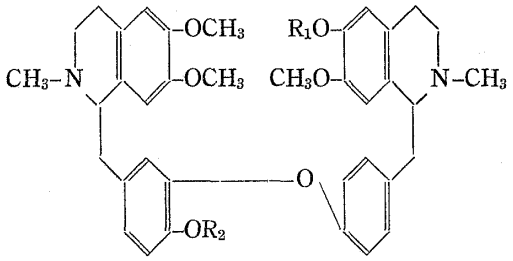
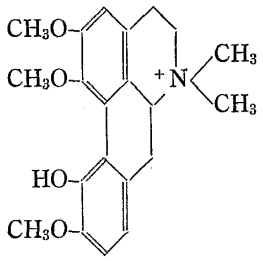
Daurinoline (II),[3] $C_{37}H_{42}O_6N_2 \cdot H_2O$, was isolated from *Menispermum dauricum* DC. (Japanese name "Kohmorikazura") as a minor new phenolic base of biscoclaurine type alkaloid, besides dauricine[4] (I) and menisperine[5] (V). This base was obtained as non-crystallizable, pale yellow powder, whose methylation with diazomethane gave the known O–methyldauricine (III). Futhermore, ethylation with diazoethane gave O,O–diethyldaurinoline, whose cleavage reaction with metallic sodium in liquid ammonia afforded D–(–)–O–ethylarmepavine as a non–phenolic base and D–(–)–6–ethoxy–1,2,3,4–tetrahydro–1–(4–hydroxybenzyl)–7–methoxy–2–methylisoquinoline as a phenolic base[3]. These facts confirmed the structure of daurinoline as II.

We now report the synthesis of the stereoisomeric mixture of daurinoline by the application of a Ullmann reaction between two tetrahydroisoquinoline derivatives, XII and XIII.

1) Part CCXLVIII: T. Kametani, H. Iida, and K. Sakurai, *Chem. Pharm. Bull.* (Tokyo), **16**, 1623 (1968).
2) Location: *a*) *No. 85, Kita–4–bancho, Sendai*; *b*) *No. 600, Kashiwagi–4–chome, Shinjuku, Tokyo.*
3) M. Tomita and Y. Okamoto, *Yakugaku Zasshi*, **85**, 456 (1965).
4) *a*) M. Tomita and S. Narita, *Yakugaku Zasshi*, **47**, 279 (1927); *b*) T. Kametani and K. Fukumoto, *J. Chem. Soc.*, **1964**, 6141.
5) M. Tomita and T. Kikuchi, *Chem. Pharm. Bull.* (Tokyo), **3**, 100 (1955).





menisperine (V)

dauricine (I): $R_1=CH_3$; $R_2=H$
daurinoline (II): $R_1=R_2=H$
O,O-dimethyldaurinoline (O-methyldauricine) (III): $R_1=R_2=CH_3$
O,O-dibenzyldaurinoline (IV): $R_1=R_2=CH_2Ph$

Chart 1

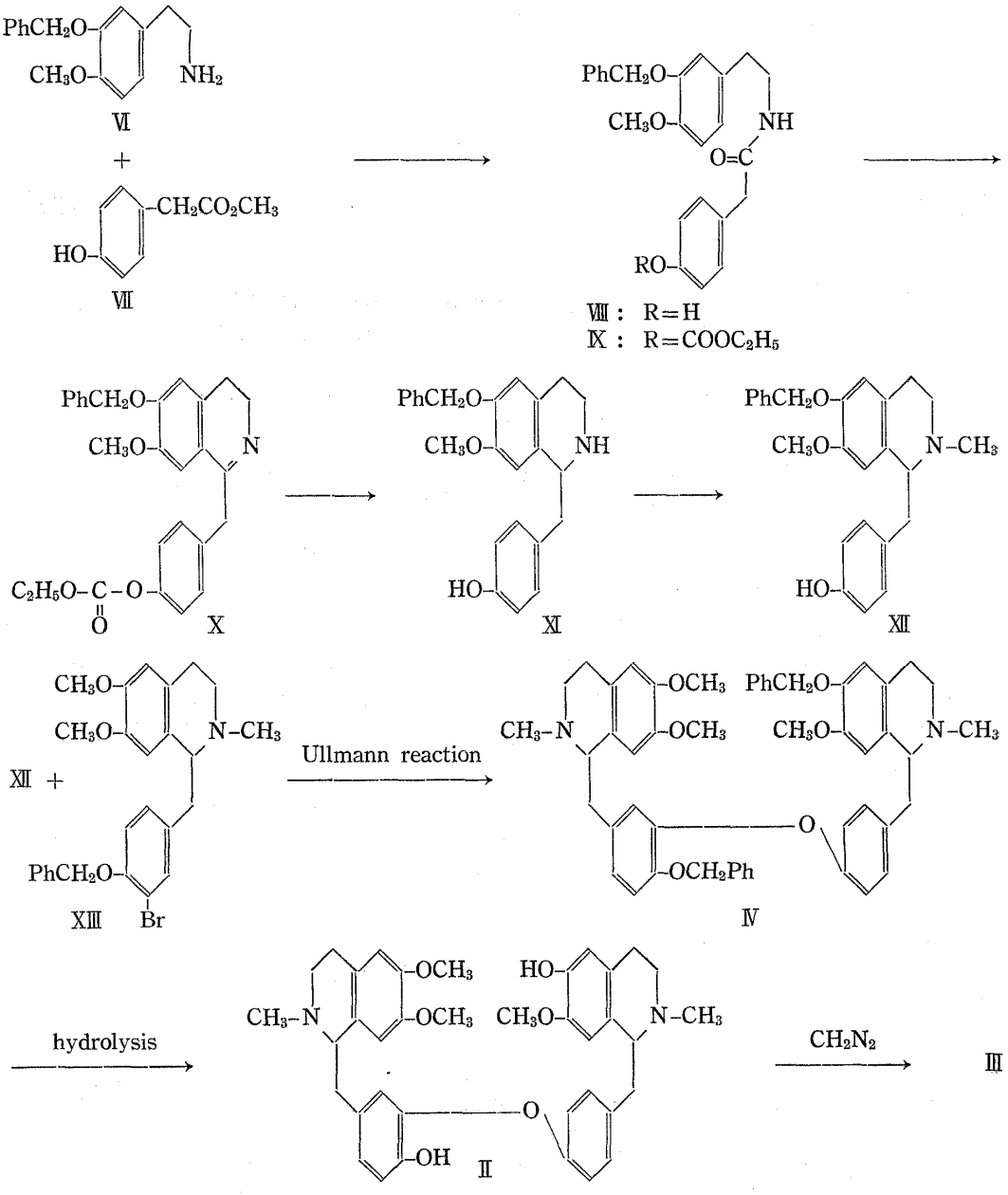


Chart 2

Condensation of 3-benzyloxy-4-methoxyphenethylamine (VI) with methyl 4-hydroxyphenylacetate (VII) in a current of nitrogen at 180° gave the amide (VIII), which was ethoxycarbonylated to give the amide (IX). Bischler-Napieralski reaction of IX gave the 3,4-dihydroisoquinoline derivative (X), which was converted into the 1,2,3,4-tetrahydroisoquinoline derivative (XI) by sodium borohydride reduction. Methylation of XI with 37% formalin and sodium borohydride in chloroform-methanol afforded the compound (XII).

Ullmann reaction between the above compound (XII) and 1-(4-benzyloxy-3-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XIII)[6] afforded a viscous substance, which was chromatographed on alumina and then silicic acid to afford O,O-dibenzyldaurinoline (IV). The NMR spectrum of IV showed the signals of three methoxyl groups at 6.20, 6.43, and 6.47 τ and the protons of the N-methyl groups at 7.46 and 7.48 τ. Dipicrate of IV was obtained as a yellow powder, mp 124—126°.

Debenzylation of the above O,O-dibenzyldaurinoline (IV) with ethanolic hydrochloric acid in a current of nitrogen gave a stereoisomeric mixture of daurinoline (II).

Since natural daurinoline (II) could not be available for comparison, our synthetic compound (II) was methylated with diazomethane to give a mixture of O,O-dimethyl ether (III), whose IR spectrum (in $CHCl_3$) was superimposable on those of O,O,O-trimethylmagnoline and O-methyldauricine.[6,7]

Furthermore, our synthetic O,O-dimethyldaurinoline (III) was characterized as its dipicrate, whose IR spectrum ($CHCl_3$) was also identical with that of O-methyldauricine dipicrate.[7]

Since it has been well established[6-8] that the infrared spectrum (in $CHCl_3$) of diastereoisomeric mixture of biscoclaurine type alkaloids which possess one biphenyl ether linkage in its moiety is superimposable on that of the corresponding optically active natural base, the synthesis of the stereoisomeric mixture of daurinoline has been acccomplished.

Experimental[9]

N-(3-Benzyloxy-4-methoxyphenethyl)-2-(4-ethoxycarbonyloxyphenyl)acetamide (IX)——A mixture of 13 g of methyl 4-hydroxyphenylacetate (VII) and 19 g of 3-benzyloxy-4-methoxyphenethylamine (VI) was heated in an oil-bath at 180° for 3 hr in a current of N_2 and the reaction mixture became a yellow solid after cooling, which was dissolved in $CHCl_3$. The extract was washed with 10% HCl aq. solution and water in order to remove the recovered amine, dried over Na_2SO_4, and evaporated to give 20 g of a yellow brown syrup. To a cooled solution of the above substance in 100 ml of 1 N NaOH aq. solution was added dropwise with stirring 12.5 g of ethyl chlorocarbonate, a viscous oil being precipitated.

The reaction mixture was extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a yellow brown syrup, which solidified on standing for a short time. Recrystallisation from benzene-hexane afforded 17 g of the amide as colorless needles, mp 101—102°. for *Anal.* Calcd: $C_{27}H_{29}O_6N$. C, 69.98; H, 6.26. Found: C, 70.27; H, 6.29.

6-Benzyloxy-1-(4-ethoxycarbonyloxybenzyl)-3,4-dihydro-7-methoxyisoquinoline (X) Hydrochloride——A mixture of 15 g of the above amide (IX), 100 ml of dry toluene, and 5 ml of $POCl_3$ was heated under reflux mildly in an oil-bath for 2 hr in a current of N_2, and, after cooling, the resultant mixture was poured into 1000 ml of hexane. A yellow precipitate (13.5 g) which separated was collected by filtration. Recrystallisation from EtOH afforded pale yellow needles, mp 208—209° (decomp.). *Anal.* Calcd. for $C_{27}H_{27}O_5N \cdot HCl$: C, 67.27; H, 5.88; N, 2.91. Found: C, 67.38; H, 5.92; N, 3.07.

6-Benzyloxy-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-7-methoxyisoquinoline (XI)——To a cooled mixture of 13 g of the above compound (X), 100 ml of $CHCl_3$, 250 ml of MeOH, and 2.5 ml of water was added portionwise 11 g of $NaBH_4$ with stirring, and the resultant mixture was stirred at room temperature for 1.5 hr. After the solvent had been distilled, the residue was dissolved in 100 ml of 2% NaOH aq. solution and the

6) T. Kametani, S. Takano, K. Masuko, and F. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **14**, 67 (1966).
7) T. Kametani, R. Yanase, S. Kano, and K. Sakurai, *Chem. Pharm. Bull.* (Tokyo), **15**, 56 (1967).
8) *a*) K. Fujitani, Y. Aoyagi, and Y. Masaki, *Yakugaku Zasshi*, **86**, 654 (1966); *b*) T. Kametani, S. Takano, R. Yanase, C. Kibayashi, H. Iida, and S. Kano, *Chem. Pharm. Bull.* (Tokyo), **14**, 73 (1966).
9) All melting points were not corrected.

solution was extracted with ether. To the resultant alkaline aq. solution was added an excess of crystalline NH_4Cl, and an ammoniacal solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over K_2CO_3, and evaporated to give 12 g of a pale brown powder, which was recrystallized from EtOH to give pale brown cubes, mp 178—180°. *Anal.* Calcd. for $C_{24}H_{25}O_3N$: C, 76.77; H, 6.71; N, 3.73. Found C, 76.54; H, 6.70; N, 3.99.

***dl*-6-Benzyloxy-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-2-methylisoquinoline (XII)**——To a solution of 11 g of the above compound (XI) in 50 ml of MeOH and 20 ml of $CHCl_3$ was added 8 ml of 37% HCHO, and the mixture was stirred at room temperature for 3.5 hr. To the resultant mixture was added portionwise 20 g of $NaBH_4$ with stirring and, after addition, the mixture was stirred at room temperature for 2 hr. After the solvent had been distilled, the excess $NaBH_4$ was decomposed with dil. AcOH aq. solution, and the mixture was made basic with 200 ml of 2% NaOH aq. solution. To the preceding solution was added an excess of NH_4Cl, and the mixture was extracted with ether. The extract was washed with water, dried over K_2CO_3, and evaporated to give 9 g of a yellow syrup. Recrystallisation of the oxalate from MeOH afforded colorless prisms, mp 189—190° (decomp.). *Anal.* Calcd. for $C_{25}H_{27}O_3N \cdot C_2H_2O_4$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.41; H, 6.15; N, 2.88.

Stereoisomeric Mixture of O,O-Dibenzyldaurinoline (IV)——A mixture of 3 g of *dl*-XII, 3.5 g of *dl*-XIII,[6] 13 ml of pyridine, 1.2 g of K_2CO_3, 0.4 g of Cu powder, and 0.13 g of KI was heated with stirring at 150—155° in an oil-bath for 45 hr in a current of N_2. After cooling, the reaction mixture was extracted with $CHCl_3$, and the resultant extract was filtered. Removal of the solvent gave a brown syrup, which was again extracted with benzene. The extract was washed with 5% NaOH aq. solution and water, dried over K_2CO_3, and evaporated to give 3.5 g of a brown syrup, which was chromatographed on Al_2O_3 (length, 20 cm; diameter, 3.5 cm).

Evaporation of the first benzene eluate (4.7 liters) afforded the starting material (XIII) as a syrup, whose thin-layer chromatography (TLC)[10] showed the same *Rf* value as that of XIII. Furthermore, Beilstein test was positive.

Evaporation of 2 liters of the second $CHCl_3$ eluate gave 1.2 g of a yellowish brown syrup, which was chromatographed on silicic acid (length, 15 cm; diameter, 1.6 cm) to give our expected compound (IV). Evaporation of the first $CHCl_3$ eluate (600 ml) afforded a syrup, whose TLC[10] showed the same *Rf* value as that of XIII. After 500 ml of the second eluate ($CHCl_3$—MeOH=50:1) had been separated, the third eluate (840 ml) was evaporated to give 500 mg of IV. NMR (τ) ($CDCl_3$): 7.48 (3H, singlet, N-CH_3), 7.46 (3H, singlet, N-CH_3), 6.47, 6.43, 6.20 (9H, three singlets, O-CH_3), 4.93 (4H, singlet, OCH_2Ph). Purification of the dipicrate by reprecipitation from benzene—hexane afforded a yellow powder, mp 124—126°. *Anal.* Calcd. for $C_{51}H_{54}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 60.56; H, 4.84; N, 8.97. Found: C, 60.06; H, 5.12; N, 8.97.

Stereoisomeric Mixture of Daurinoline (II)——A mixture of 200 mg of the above substance (IV), 15 ml of EtOH, and 15 ml of conc. HCl solution was refluxed mildly for 2 hr in a current of N_2, and the solvent was then distilled. The resultant residue was made basic with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and evaporated to give 150 mg of a yellow syrup, which solidified on standing.

Purification from hexane—$CHCl_3$ afforded a pale yellow powder, mp 103—107° (sinters at 101°). *Anal.* Calcd. for $C_{37}H_{42}O_6N_2 \cdot H_2O$.[11]: C, 70.68; H, 7.05; N, 4.46. Found: C, 70.64; H, 6.90; N, 4.45. NMR (τ) ($CDCl_3$): 7.52, 7.48 (6H, two singlets, 2NCH_3), 6.48, 6.40, 6.20 (9H, three singlets, 3OCH_3).

Stereoisomeric Mixture of O,O-Dimethyldaurinoline[O-Methyldauricine (III)]——To a solution of 20 mg of IV in 50 ml of EtOH was added 50 ml of ether containing an excess of CH_2N_2, and the mixture was allowed to stand in a refrigerator for 2 days. The reaction mixture was evaporated to give 20 mg of a pale yellow syrup, whose dipicrate was purified by reprecipitation from $CHCl_3$—hexane to give a yellow powder, mp 143—145° (decomp.). The IR spectrum (in $CHCl_3$) of this dipicrate of III was identical with that of natural O-methyldauricine dipicrate, which was obtained by methylation of natural dauricine.[6,7]

Acknowledgement We are grateful to the Analytical Centers of Pharmaceutical Institute, Tohoku University School of Medicine for microanalyses and NMR determination. We also thank President Dr. M. Terasaka and Dr. S. Nagase of Tokyo College of Pharmacy for their grateful assistance.

10) In this case silica gel B-5 (WAKO) was used and MeOH—acetone (5:4) was used as solvent.
11) This sample was dried on P_2O_5 at 50°/2 mm for 72 hr.