cis-trans ratio of the reduced products in the ether extract was determined as 85 to 15 by gaschromatography. The preparative separation of this mixture was carried out by alumina column chromatography, an eluting solvent being ether. The *cis* isomer was eluted first and then the *trans* one came out.

Catalytic Reduction of 1,3,5-Trimethylpyridinium Iodide

Hydrogenation of 1,3,5-trimethylpyridinium iodide was carried out in the same way as in case of 1,2,6-trimethyl derivative. The *cis-trans* ratio was determined as 80 to 20 by gaschromatography. Column chromatographic separation as in case of the 1,2,6-trimethyl derivative gave pure *cis* and *trans* isomers, the latter being eluted first with ether.

Derivatives of the Reduction Products

TABLE Ⅳ. Melting Points of Trimethylpiperidine Derivatives

	m.p. (°C)	
	picrate	methiodide
cis-1,2,6-trimethylpiperidine	225～227[a]	280～282 (decomp.)[b]
trans-1,2,6-trimethylpiperidine	244～245 (decomp.)	300～301 (〃)[b]
cis-1,3,5-trimethylpiperidine	147～148	275～276
trans-1,3,5-trimethylpiperidine	149～150	236～238

a) N. J. Leonard, F. D. Hauck, Jr.: J. Am. Chem. Soc., **79**, 5279 (1957).
b) R. Lukes, J. Jizba: Chem. Listy, **46**, 622 (1952); C. A., **47**, 9325 (1953).

NMR Spectra

The spectra were obtained by a JNM 3H-60 (Japan Electron Optics Laboratory Co., Ltd.) spectrometer operating at 60 Mc.p.s.

We are gratefully indebted to Dr. Waro Nakahara of Director of this Institute for his encouragement throughout this work.

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7. Tetsuji Kametani, Ryobun Yanase,*1 Shinzo Kano, and Kuniyoshi Sakurai*2: Bisbenzylisoquinoline Alkaloids and Related Compounds. Ⅺ.*3 Total Synthesis of Stereoisomeric Mixture of Magnoline.*4

(*Pharmaceutical Institute, Tohoku University School of Medicine*[*3] *and Tokyo College of Pharmacy*[*4])

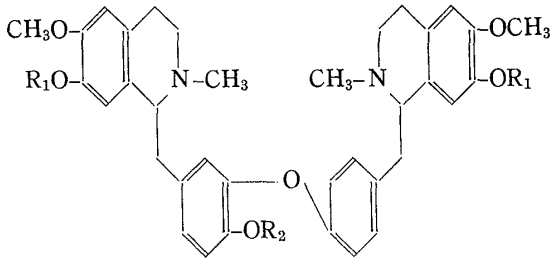
The diamide (Ⅸ) was prepared by Schotten-Baumann reaction of 2-(3-methoxy-4-hydroxyphenyl)ethylamine with the diacid chloride (Ⅴ), followed by ethoxycarbonylation. Cyclization gave the bisdihydroisoquinoline (Ⅺ), the dimethiodide of which, on reduction, gave a stereoisomeric mixture of magnoline or berbamunine (Ⅰ).

(Received March 7, 1966)

Magnoline, $C_{36}H_{40}O_6N_2$, m.p. 179°, occurs in the leaves of *Magnolia fuscata* ANDR., which grows on the Caucasian shores of the Black Sea. It is a yellow crystalline,

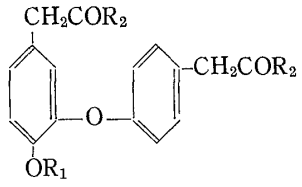
*1 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 柳瀬良文).
*2 No. 600, Kashiwagi-4-chome, Shinjuku-ku, Tokyo (加納慎蔵, 桜井邦好).
*3 Part Ⅹ: T. Kametani, *et al.*: J. Heterocyclic Chem., **3**, 239 (1966).
*4 This forms Part CLX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.

optically active substance forming vitreous salts with hydrogen halides.[1] The structure (I) of magnoline was established by Proskurnina and Orekhoff.[2] Furthermore, berbamunine, $C_{36}H_{40}O_6N_2$, m.p. 190~191° was isolated from *Berberis amunrensis* RUPR. var. *japonica* (Regel) REHD. *forma Bretschneideri* (Rehd.) OHWI by Tomita and Kugo[3] and the structure was also assigned as I by chemical methods.[4,5] Furthermore, it was clarified that berbamunine is a phenolic base belonging to the dauricine type and that O-methylberbamunine, O-methyldauricine, and O-methylmagnoline are optical isomers indicated by the same structural formula (II).

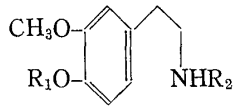


I : $R_1=R_2=H$ XV : $R_1=CH_2C_6H_5$; $R_2=H$
II : $R_1=R_2=CH_3$ XVI : $R_1=R_2=CO_2C_2H_5$
XIV : $R_1=CH_2C_6H_5$; $R_2=CO_2C_2H_5$

Chart 1.



III : $R_1=H$; $R_2=OH$
IV : $R_1=CO_2C_2H_5$; $R_2=OH$
V : $R_1=CO_2C_2H_5$; $R_2=Cl$



VI : $R_1=CH_2C_6H_5$; $R_2=H$
VII : $R_1=H$; $R_2=ZnCl$

Chart 2.

The purpose of the present investigation was to study the cyclization of the diamide (VIII and IX) in order to obtain the corresponding dihydroisoquinoline derivatives (X and XI) and its dimethiodides (XII and XIII) as possible intermediates for the synthesis of stereoisomeric mixture of magnoline or berbamunine (I).

Ethoxycarbonylation[6] of the dicarboxylic acid (III), which was used as a starting material in case of total synthesis of dauricine[7], gave the acid (IV), which was converted into the acid chloride (V) by chlorination with thionyl chloride in an excellent yield.

Schotten-Baumann reaction of 3-methoxy-4-benzyloxyphenethylamine (VI)[6] with the preceding acid chloride (V) afforded the diamide (VIII), whose infrared spectrum showed ethoxycarbonyl and amidocarbonyl band (C=O) at 1760 and 1660 cm^{-1}, respectively. Bischler-Napieralski reaction of the above diamide (VIII) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (X), which was converted into the dimethiodide (XII). Reduction of the compound (XII) with sodium borohydride in chloroform-methanol gave the tetrahydroisoquinoline derivative (XIV), whose de-ethoxycarbonylation yielded the substance (XV) on being refluxed with an ethanolic potassium hydroxide. Debenzylation of XV under various conditions for obtaining the objective compound (I) resulted in failure.

Secondly, Schotten-Baumann reaction of 3-methoxy-4-hydroxyphenethylamine, which was obtained by basification of the compound[8] (VII) with 1*N* sodium hydroxide solution, with a solution of the acid chloride (V) in chloroform afforded the diamide, which was converted into the diamide (IX) by ethoxycarbonylation. This diamide showed a maximum at 3400 cm^{-1} (NH) and both carbonyl bands at 1760 (ester) and

1) N. F. Proskurnina, A. P. Orekhoff : Bull. soc. chim. France, **5**, 1357 (1938); Chem. Abstr., **33**, 1439 (1939).
2) *Idem* : J. Gen. Chem. (U. S. S. R.), **10**, 707 (1940); Chem. Abstr., **35**, 2520 (1941).
3) M. Tomita, T. Kugo : Yakugaku Zasshi, **75**, 753 (1955).
4) *Idem* : *Ibid.*, **77**, 1075 (1957).
5) *Idem* : *Ibid.*, **77**, 1079 (1957).
6) J. Finkelstein : J. Am. Chem. Soc., **73**, 550 (1951).
7) T. Kametani, K. Fukumoto : Tetrahedron Letters, **1964**, 2771; J. Chem. Soc., **1964**, 6141.
8) T. Kametani, S. Takano, E. Karibe : Yakugaku Zasshi, **83**, 1035 (1963).

1665 (amide) cm^{-1}. Bischler-Napieralski reaction of the diamide (IX) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (XI), which was converted into the dimethiodide (XIII) on being allowed to stand in methyl iodide in the presence of nitrogen. Reduction of the compound (XIII) with sodium borohydride in methanol-chloroform gave the tetrahydroisoquinoline derivative (XVI). Removal of the ethoxycarbonyl radical by hydrolysis with an ethanolic sodium hydroxide solution afforded the compound (I) as a yellow powder, whose infrared spectrum showed a maximum at 3500 cm^{-1} (OH) and N-methyl radical at 2880 and 2850 cm^{-1} (in $CHCl_3$). Recrystallization of the picrate of the above compound (I) from methanol-ether gave a yellow powder, m.p. 140~145°, with the correct analysis.

The natural magnoline and berbamunine were not available for comparison. Accordingly, methylation of the stereoisomeric mixture of synthetic magnoline with diazomethane gave O-methylmagnoline, namely, O-methyldauricine (II), whose infrared spectrum was superimposable on that of natural O-methyldauricine (II) in chloroform. The latter natural product was obtained by methylation of natural dauricine donated by Dr. R. H. F. Manske. The infrared spectra of the picrate of both specimens were also identical completely. Since magnoline and berbamunine are optical isomers each other, these facts reveal that a total synthesis of the stereoisomeric mixture (I) of magnoline or berbamunine has been accomplished.

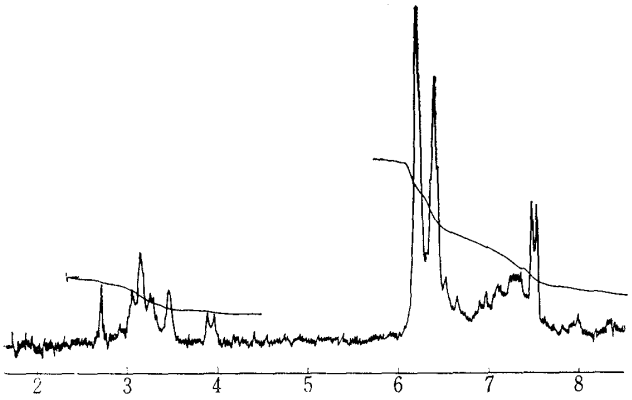


Fig. 1. Nuclear Magnetic Resonance Spectrum of O,O,O,-Trimethylmagnoline in $CDCl_3$

In this case all the attempts to separate one of the two diastereoisomers in a crystalline state under a variety of procedure, for instance, alumina-, paper-, cellulose-, and thin-layer-chromatography, and preparative gas chromatography, were examined, but resulted in failure.

Furthermore, the patterns of nuclear magnetic resonance (NMR) spectrum of the diastereoisomeric mixture of O-methylmagnoline (II) were similar to those of synthetic O,O,O-trimethylberbamunine which was reported by

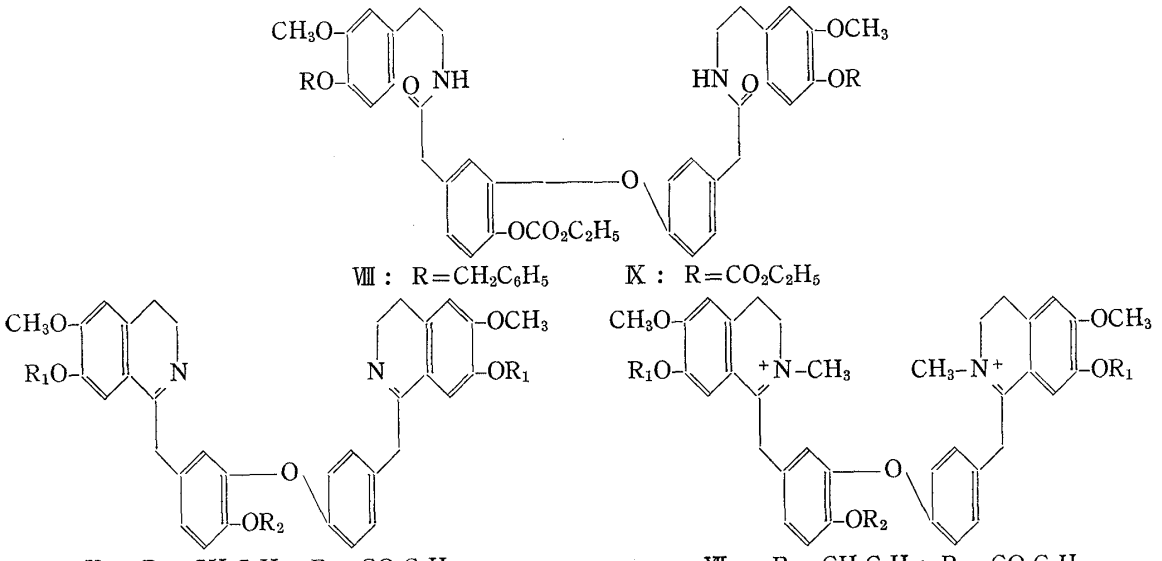


Chart 3.

Fujitani, *et al*[9]. as is shown in Fig. 1. They also have described that the infrared spectrum of diastereoisomeric mixture of synthetic dauricine was completely identical with that of natural dauricine in chloroform. Moreover, it is well known that the infrared spectrum of synthetic compound is identical with that of natural product having the same plane formula and a different configuration in case of bisbenzylisoquinoline derivatives containing one diphenyl ether linkage.[7,10~12]

Experimental*5

2-Ethoxycarbonyloxy-4′,5-dihydroxycarbonylmethyldiphenyl Ether (IV)——To a solution of 5.0 g. of the acid[7] (III) in 10 ml. of 1*N* NaOH solution was added 4.0 g. of ethyl chlorocarbonate and the mixture was shaken for 10 min. After the reaction mixture had been acidified with 10% HCl aq. solution and extracted with ether, the solvent layer was separated, washed with water, and dried on Na_2SO_4. Removal of the solvent gave 4.8 g. of the compound (IV) as a pale yellow oil, which solidified on being allowed to stand. Recrystallization from ether gave colorless needles, m.p. 127~129°. *Anal.* Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.72; H, 4.74.

2-Ethoxycarbonyloxy-4′,5-di-(3-methoxy-4-benzyloxyphenethylaminocarbonylmethyl)diphenyl Ether (VIII)——The acid (IV) (2.0 g.) was refluxed on a water-bath for 1 hr. with 10 ml. of $SOCl_2$, and then the excess of $SOCl_2$ was removed by distillation. The crude acid chloride (V) as above was dissolved in 50 ml. of abs. $CHCl_3$, to which solution was added a mixture of 6.0 g. of HCl salt. of amine (VI) and 7.0 g. of Et_3N in 100 ml. of $CHCl_3$. The mixture was allowed to stand at room temperature for 2 hr. and then washed with 10% HCl aq. solution and then $NaHCO_3$ aq. solution. The solvent was dried on Na_2SO_4 and distilled off, to give 5.6 g. of VIII as a brown viscous syrup, whose recrystallization was so difficult that it was used in the following reaction without purification.

2-Hydroxy-4′,5-(2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)diphenyl Ether (XV)——A mixture of 2.0 g. of the diamide (VIII), 30 ml. of dry benzene, and 5.0 g. of $POCl_3$ was refluxed on a water-bath for 2 hr. An excess of *n*-hexane was added to the reaction mixture and the upper layer was removed by decantation. The reddish residue was repeatedly washed with *n*-hexane and then dissolved in $CHCl_3$. The $CHCl_3$ solution was basified with 10% NH_4OH aq. solution, washed with H_2O, and dried on Na_2SO_4. Evaporation of the solvent in a current of N_2 afforded 1.8 g. of the bisdihydroisoquinoline derivative (X) as a reddish oil.

A mixture of 1.8 g. of the above compound (X) and 10 ml. of MeI was allowed to stand at room temperature overnight in the presence of N_2. Removal of the solvent by distillation in a current of N_2 gave 2.0 g. of the dimethiodide (XII) as a yellow amorphous powder.

$NaBH_4$ (2.0 g.) was added in small portions with shaking to a solution of 2.0 g. of the dimethiodide (XII) dissolved in 40 ml. of $CHCl_3$–MeOH (1:1). The mixture was stirred for 1.5 hr. and then the solvent was distilled off in a current of N_2. The yellow residue was treated with a small amount of H_2O and extracted with $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and evaporated to leave 1.4 g. of bistetrahydroisoquinoline derivative (XIV) as a yellow glass.

A solution of 1.0 g. of the above compound (XIV) in 50 ml. of MeOH– 1*N* NaOH (4:1) was refluxed for 1 hr. in a current of N_2 and then the solvent was distilled off, to give yellow residue which was dissolved in $CHCl_3$. The solvent was washed with H_2O, dried on Na_2SO_4, and distilled off, to give 0.5 g. of XV as a yellow powder. Recrystallization from EtOH–H_2O gave a colorless powder, m.p. 100~110°. *Anal.* Calcd. for $C_{50}H_{52}O_6N_2 \cdot 1\frac{1}{2}H_2O$*6: C, 74.69; H, 7.27; N, 3.47. Found: C, 74.52; H, 6.86; N, 3.38.

2-Ethoxycarbonyloxy-4′,5-di-(3-methyl-4-ethoxycarbonyloxyphenethylaminocarbonylmethyl)diphenyl Ether (IX)——The acid chloride (V), prepared from 2.0 g. of the acid (IV) and an excess of $SOCl_2$, in 50 ml. of abs. $CHCl_3$ was added at a time to a solution of 4.5 g. of zinc chloride (VII) in 25 ml. of 1*N* NaOH aq. solution. The mixture was stirred vigorously for 10 min. and then admixed with a solution of 5.3 g. of ethyl chlorocarbonate in 50 ml. of abs. $CHCl_3$. The mixture was again stirred for 10 min. and the solvent layer was separated, washed with 10% HCl aq. solution, saturated $NaHCO_3$ aq. solution and H_2O, and dried on K_2CO_3. Removal of the solvent gave 5.95 g. of IX as a pale yellow viscous syrup. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400; ν_{CO} 1760; ν_{CO} 1665.

2-Hydroxy-4′,5-bis-(2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)diphenyl Ether (I)——A mixture of 1.8 g. of the diamide (IX), 50 ml. of dry benzene, and 6 ml. of $POCl_3$ was

*5 All melting points were not corrected.

*6 This was dried on P_2O_5 at 50° for 2 days.

9) K. Fujitani, Y. Aoyagi, Y. Masaki: Yakugaku Zasshi, **84**, 1234 (1964).
10) T. Kametani, S. Takano, K. Masuko, F. Sasaki: This Bulletin, **14**, 67 (1966).
11) T. Kametani, H. Yagi: Tetrahedron Letters, No. 15, 953 (1965); *Idem*: This Bulletin, **14**, 78 (1966).
12) T. Kametani, S. Takano, R. Yanase, C. Kibayashi, H. Iida, S. Kano, K. Sakurai: *Ibid.*, **14**, 73 (1966).

refluxed on a water-bath for 6 hr. An excess of *n*-hexane was added to the reaction mixture, and it was allowed to stand overnight. The upper layer was then removed by decantation. The residue was repeatedly washed with *n*-hexane and then dissolved in $CHCl_3$, whose organic solvent layer was washed with saturated $NaHCO_3$ solution and H_2O, and dried on K_2CO_3. Removal of the solvent gave 1.2 g. of the 3,4-dihydroisoquinoline derivative (XI) as an orange caramel-like glass, m.p. 93~98°, which could not be purified and used in the following reaction without purification.

A mixture of 0.9 g. of the above compound (XI) and 8 ml. of MeI was allowed to stand in the presence of N_2 at room temperature for 2 hr., and then yellow precipitates were separated from the excess of MeI by decantation. $NaBH_4$ (1.5 g.) was added in small portions with shaking to a solution of the above dried dimethiodide (XIII) in 100 ml. of $CHCl_3$–MeOH (3:2). The mixture was stirred for 2 hr. and then the solvent was removed by distillation, a pale yellow residue being treated with a small amount of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried on K_2CO_3, and distilled off, to give 0.5 g. of the tetrahydroisoquinoline derivative (XVI) as an orange powder, which was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): ν_{N-Me} 2800, 2850; $\nu_{C=O}$ 1760.

A mixture of 0.5 g. of the above compound (XVII), 1 g. of NaOH and 40 ml. of EtOH was heated under reflux for 2 hr. in the presence of N_2. After the reaction, the solvent was removed by distillation *in vacuo* and the residue was dissolved in small amount of water. An ammoniacal solution, which was obtained by the addition of crystalline NH_4Cl to the above aqueous solution, was repeatedly extracted with CH_2Cl_2. The solvent layer was separated, washed with saturated NaCl aq. solution, dried on Na_2SO_4, and distilled off, to give 0.25 g. of I as an orange syrup, which chromatographed on Al_2O_3–silica gel (2:1) using a solution of $CHCl_3$–MeOH (2:1) as solvent to give a pale orange powder, m.p. ca. 90°. After the sample had been dried on P_2O_5 at 50°/3 mm. for 3 days, it melted at 145° (sinters at 135°). IR cm^{-1} ($CHCl_3$): ν_{OH} 3500; ν_{N-Me} 2800 and 2850. Recrystallization of the picrate from MeOH–ether gave a yellow powder, m.p. 140~145°. *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 54.65; H, 4.40; N, 10.62. Found: C, 55.00; H, 4.63; N, 10.58.

O-Methyldauricine (II)——To a solution of 0.2 g. of natural dauricine which was purified according to Manske's procedure[13] in 10 ml. of EtOH was added a solution of an excess of CH_2N_2 in ether, and the mixture was allowed to stand in a refrigerator for 4 days. After a pale brown precipitate formed had been removed by filtration, the filtrate was distilled *in vacuo* to give 0.2 g. of a pale brown oil. Recrystallization of the dipicrate from $CHCl_3$–hexane gave a yellow powder, m.p. 145° (sinters at 130°). *Anal.* Calcd. for $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_7N_3 \cdot 4H_2O$*7: C, 52.39; H, 5.21; N, 5.99. Found: C, 51.98; H, 5.26; N, 5.96.

Stereoisomeric Mixture of O,O,O-Trimethylmagnoline (O-Methyldauricine, O,O,O-Trimethylberbamunine)——The same treatment of 0.2 g. of synthetic magnoline mentioned above with CH_2N_2 gave 0.15 g. of a pale brown syrup, whose dipicrate was recrystallized from $CHCl_3$–hexane to afford O,O,O-trimethylmagnoline (O-methyldauricine or O,O,O-trimethylberbamunine) as a yellow powder, m.p. 145° (sinters at 125°). The infrared spectrum of this synthetic picrate was superimposable on that of the sample obtained by desication of the above natural O-methyldauricine picrate. *Anal.* Calcd. for $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 55.84; H, 4.78; N, 10.22. Found: C, 56.32; H, 4.72; N, 10.19.

Furthermore, the infrared spectrum of natural O-methyldauricine was also identical with that of synthetic magnoline as above. NMR (τ) ($CDCl_3$) (synthetic): 7.53 (3H, singlet, N-CH_3); 7.48 (3H, singlet; N-CH_3); 6.40~6.20 (15H, 5-OCH_3); 3.96 (1H, C_8-H); 3.89 (1H, $C_{8'}$-H); 3.46~3.06 (9H, aromatic protons) (Fig. 1).

We thank Dr. R. H. F. Manske, Dominion Rubber Company Ltd., Research Laboratories, Guelph, Ontario, Canada, for gift of natural dauricine. We are also grateful to Mrs. F. Seto, Miss N. Nanjo, and Miss R. Kobayashi, for microanalyses and to Miss T. Oikawa for infrared spectra.

*7 This was dried on P_2O_5 at 50° for 2 days, but it seems to be hygroscopic.

13) R. H. F. Manske, M. Tomita, K. Fujitani, Y. Okamoto: This Bulletin, **13**, 1476 (1965).