Studies on the Alkaloids of Menispermaceous Plants. CCXLIII.[1] Syntheses of Dauricine Type Bases. (3).[2] Synthesis of dl-Cuspidaline and dl-4'-O-Methylberbamunine

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A synthesis of dl-cuspidaline and dl-4'-O-methylberbamunine was carried out through Bischler–Napieralski reaction followed by separation of the diastereoisomers. The configuration of each racemic diastereoisomer was ascertained by NMR comparisons with the bases of known absolute configuration.

Cuspidaline (I) is one of the biscoclaurine alkaloids recently isolated from *Limacia cuspidata* (MIERS) HOOK. f. et THOM. collected in Borneo. The structure I for this base was given by spectrometric and degradative studies.[4]

The biogenetic role of cuspidaline (I) was discussed[4] as it might represent an intermediate to oxyacanthine–berbamine type alkaloids. Assuming intramolecular phenol oxidative coupling of cuspidaline type intermediates, such as cuspidaline (I), berbamunine (II), and magnoline, the biogenesis of oxyacanthine–berbamine series of biscoclaurine alkaloids could resaonably be explained.

This paper describes the sytnhesis of dl-form of these biogenetically important intermediates, dl-cuspidaline (XII) and its diastereoisomer, dl-4'-O-methylberbamunine (XIII). The products are to be regarded as key–intermediates in nonenzymatic biogenetic type syntheisis of biscoclaurine alkaloids.

Synthesis of the cuspidaline type bases was performed by a method essentially the same with that described by Kondo, *et al.*[5] in the synthesis of O–methyldauricine methine. 2–Methoxy–5,4'–biscarboxymethyldiphenyl ether (III) was condensed with β–3–methoxy–4–benzyloxyphenethylamine (IV), and the resulted bisamide (V) was submitted to Bischler–Napieralski cyclization with phosphorus oxychloride in chloroform, to give a bis–3,4–dihydro-isoquinoline (VI). VI was reduced with sodium borohydride to bis–1,2,3,4–tetrahydro-isoquinoline (VII), which in turn was N–methylated with formalin–sodium borohydride to afford a ditertiary bis–base (VIII). Benzyl protective groups for phenolic hydroxyl of VIII were eliminated by catalytic hydrogenolysis over palladised charcoal, and the cuspidaline type bases (IX) were obtained in an amorphous state.

The product (IX) and natural cuspidaline (I) behaved identically on thin–layer chromatography,[6] and their IR spectra were found to be superimposable. However, NMR spectrometric examination of IX suggested that it consisted of two species of bases diastereo-

1) Part CCXLII: *Chem. Pharm. Bull.* (Tokyo), **16**, 62 (1968).
2) A part of this work was presented at the 16th Annual Meeting of the Kinki Branch, the Pharmaceutical Society of Japan. (Nov. 20, 1966. Fuse.) (Abstracts of Papers, p. 26. *cf. Yakugaku Kenkyu*, **37**, 339 (1966).) Part (2): K. Fujitani and Y. Masaki: *Yakugaku Zasshi*, **86**, 660 (1966).
3) Location : *Yoshida–Shimoadachi–cho, Sakyo–ku, Kyoto.*
4) M. Tomita, H. Furukawa, and K. Fukagawa, *Yakugaku Zasshi*, **87**, 793 (1967); M. Tomita and H. Furukawa, *Tetrahedron Letters*, 4293 (1966).
5) H. Kondo, Z. Narita, and S. Uyeo, *Yakugaku Zasshi*, **55**, 369 (1935); *Ber.*, **68**, 519 (1935).
6) Silica Gel G acc. to Stahl (E. Merck), solvent, MeOH–acetone (1:1); Aluminium Oxide G acc. to Stahl (E. Merck), solvent, CHCl₃–acetone (1:1) or CHCl₃.
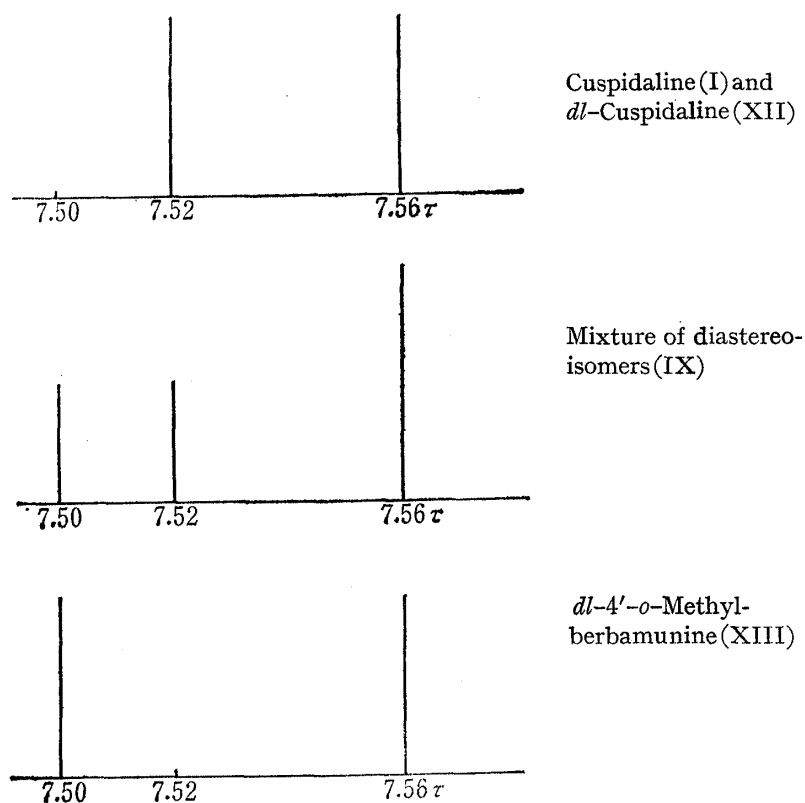
Fig. 1. NMR Spectra of N-CH₃ Signals

isomeric each to each. The signal pattern on the whole resembles to that of natural cuspidaline (I), but the signals for the N-methyl groups as shown in Fig. 1 appear in a distinctly different pattern. Confirmation of the character of IX was given by the fact that O,O-dimethyl ether (X) of IX gave an NMR spectrum entirely identical with the reported spectrum[7] of the diastereoisomeric mixture (1:1) of O-methyldauricine and O,O,O-trimethylberbamunine.

It was reported[7] on the spectrometry of dauricine type bases that the diastereoisomers are discriminated from each other by NMR measurements even when their IR spectra in solution are superimposable. The difference of the appearance of their methoxyl signals was noticed, but the assignment of methoxyl signals was left undetermined.

The NMR spectrum of the bistrideuteriomethyl ether (XI), prepared by the treatment of IX with deuteriodiazomethane, was examined to assign the chemical shift value for 7- and 7'-methoxyl groups. The spectrum was found to be superimposable with that of the dimethyl ether (X) except that it lacked signals for two methoxyl groups at 6.38 and 6.42τ.

Therefore, it was proved that 7- and 7'-methoxyl groups appear at higher field than the other methoxyls, as with the case of "monomeric" N-methylcoclaurine type bases,[8] and that the difference in appearance of methoxyl signal patterns of diastereoisomers of dauricine type is particularly due to their methoxyl groups with lower chemical shifts (near 6.20τ) attached at the other positions than C-7 and C-7' positions of the isoquinoline nuclei.

Synthetic cuspidaline base mixture (IX) crystallized after being left standing for several days, and was separated into two species by fractional recrystallization from methanol. Almost equal amounts of colorless prisms melting at 143—146° and colorless needles, mp 179—181° were obtained by the separation.

The base which melts at 143—146° gave an NMR spectrum superimposable with that of natural cuspidaline (I) except a signal ascribable to methanol at 6.55τ. Elemental analysis

7) K. Fujitani, Y. Aoyagi, and Y. Masaki, *Yakugaku Zasshi*, **84**, 1234 (1964).
8) M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 921 (1965).
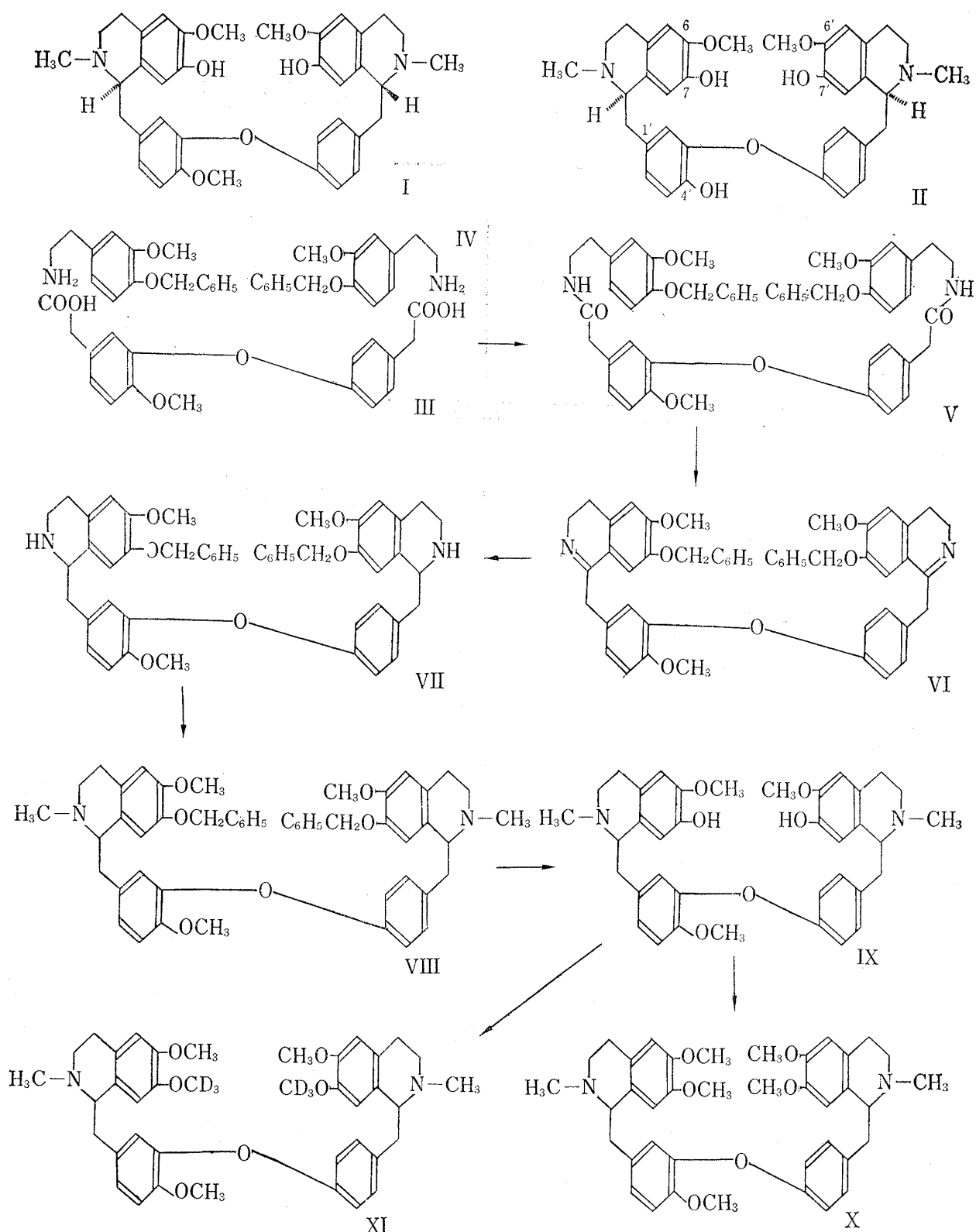
Chart 1

of the base agreed with $C_{37}H_{42}O_6N_2 \cdot CH_3OH$, and it was proved to be *dl*-cuspidaline methanol adduct. Further recrystallization of the base from ethanol gave colorless prisms, mp 167—168°, and the NMR spectrum and elemental analysis of this form completely agreed with *dl*-cuspidaline formula (XII).

Another base, melting at 179—181°, gave an NMR spectrum very similar to that of *dl*-cuspidaline (XII) in relative intensities of signals, though slight but recognizable differences

in the signal patterns were noticed. Especially the appearance of N-methyl signals was clearly different from that of dl-cuspidaline (XII) as shown in Fig. 1. Elemental analysis agreed with $C_{37}H_{42}O_6N_2$. Thus, it was assumed that the base with higher melting point was the diastereoisomer (XIII) of dl-cuspidaline (XII). This was confirmed by the NMR comparison of the base methyl ether (XIV) with O,O,O-trimethylberbamunine (XIV′), derived from natural berbamine (XV), as they gave completely superimposable spectra.
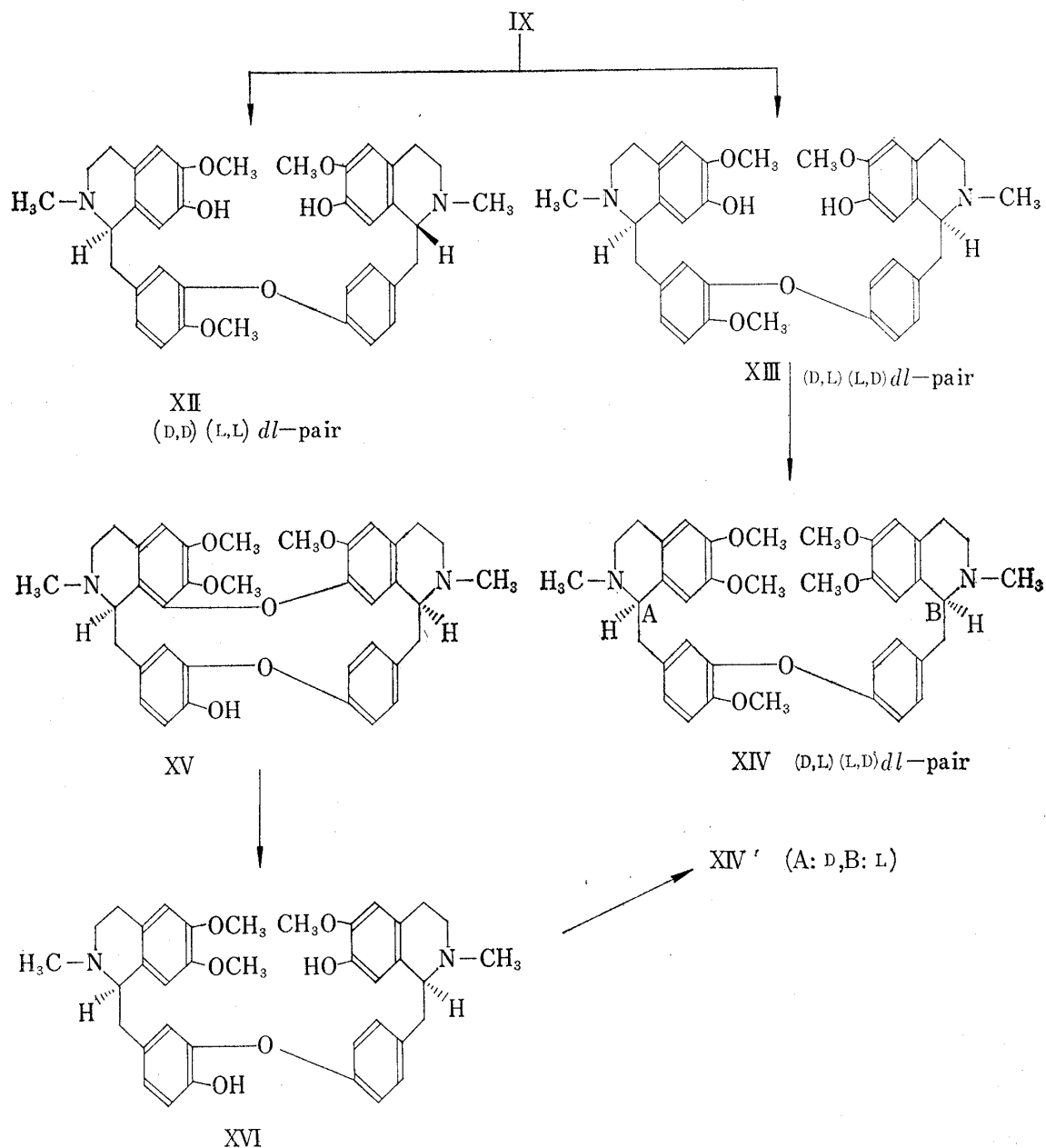

Chart 2

A dl-pair was represented by the formula of the one enantiomer.

Therefore, the separation of diastereoisomers of dauricine type base was accomplished for the first time, and the configuration of the each product was clarified.

Further, examination of the separating diastereoisomers at the stage of bis–N–nor base (VII) was carried out. Bis–1,2,3,4,–tetrahydroisoquinoline (VII) oxalate was recrystallized from methanol, and the recrystallized material was treated in usual manner to afford IX. The obtained final product (IX) showed in NMR spectrometry that it consisted of larger amount of dl-cuspidaline (XII) and smaller amount of the diastereoisomer (XIII). The

mother liquor of the recrystallization was also submitted to N-methylation and debenzylation, and the product was found on NMR spectrometry to consist of smaller amount of *dl*-cuspidaline (XII) and larger amount of *dl*-4'-O-methylberbamunine (XIII).

These findings on NMR spectrometry suggested that the separation of diastereoisomers might also be applicable at the bis–N–nor stage (VII) of the synthetic reaction sequence.

Experimental[9]

N,N'-Bis(β-3-methoxy-4-benzyloxyphenethyl)-2-methoxydiphenyl Ether 5,4'-Diacetamide (V)——To a mixture of β-3-methoxy-4-benzyloxyphenethylamine (IV) (7.5 g) and 2-methoxy-5,4'-biscarboxymethyl-diphenyl ether (III) (5 g) was added 50 ml. of decalin and heated under reflux for 1 hr. After cooling, the decalin was decanted off, and the residue was washed with ether and dissolved in $CHCl_3$. The $CHCl_3$ solution was shaken successively with 5% HCl and 2% NaOH, then dried over anhyd. K_2CO_3. Evaporation of the solvent gave 12 g of crude crystalline product, which was recrystallized from methanol to give 8 g of colorless microcrystalline, mp 96° (lit.[10] mp 109—110°). $C_{49}H_{50}O_8N_2$. *Anal.* Calcd.: C, 74.03; H, 6.34. Found: C, 74.21; H, 6.58. IR ($CHCl_3$) cm^{-1}: $\nu_{C=O}$ 1660.

2-Methoxy-5,4'-bis(6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)diphenyl Ether (VII)——A mixture of 5 g of the bisamide (V), 10 g of $POCl_3$, and 75 ml of $CHCl_3$ was refluxed for 2 hr. The solvent and excess $POCl_3$ were evaporated off *in vacuo*, and the residue was treated with samll amount of dil. HCl, then washed with ether, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, and the solvent was evaporated to give crude 2-methoxy-5,4'-bis(6-methoxy-7-benzyloxy-3,4-dihydroisoquinolin-1-ylmethyl)diphenyl ether (VI) dihydrochloride as an oily substance (yield: 5 g). The obtained 3,4-dihydroisoquinoline (VI) dihydrochloride was dissolved in a mixture of 150 ml of MeOH and 20 ml of $CHCl_3$, and to this solution 2.5 g of $NaBH_4$ was added in portions with stirring at room temperature; the stirring was continued for 30 min after all the $NaBH_4$ was added, then the solvent mixture was evaporated to dryness. The residue was treated with dil. NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. K_2CO_3, then the solvent was evaporated to give crude 1,2,3,4-tetrahydro-isoquinoline (VII) as an oily residue (yield: 4 g). Oxalate: recrystallized from EtOH, mp 155°. $C_{49}H_{50}O_6N_2\cdot2C_2H_2O_4\cdot1^1/_2 H_2O$. *Anal.* Calcd.: C, 65.63; H, 5.82. Found: C, 65.81; H, 5.94.

2-Methoxy-5,4'-bis(2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)diphenyl Ether (VIII)——To a solution of 3.7 g of (VII) in a mixture of 80 ml of MeOH and 25 ml of $CHCl_3$, 1.2 g of 37% formalin was added dropwise with stirring at room temperature, and the stirring was continued for 30 min, then 1 g of $NaBH_4$ was added in small portions to the solution with stirring. After additional stirring for 30 min, the solvents were evaporated *in vacuo*, and the residue was treated with dil. NaOH, then extracted with ether. Ethereal solution was dried over anhyd. K_2CO_3 and the solvent was evaporated to give 3.5 g of N–methylated base (VIII) as an oily substance.

2-Methoxy-5,4'-bis(2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)diphenyl Ether (IX) (Diastereoisomeric Mixture of *dl*-Cuspidaline (XII) and *dl*-4'-O-Methylberbamunine (XIII)——Four grams of VIII was dissolved in 200 ml of EtOH, and 16 ml of 1% $PdCl_2$ and 1.6 g of active charcoal (Darco G 60) were added, then stirred under the stream of hydrogen under atmospheric pressure at room temperature. After the consumption of hydrogen ceased, the catalyst was filtered off, and the filtrate was condensed to dryness, then dissolved in dil. HCl. Acidic solution was washed with ether to remove the unchanged material, then made ammoniacal alkaline with the addition of NH_4Cl, and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3, and the solvent was distilled off to give 2.86 g of amorphous powder. The residue behaved identically in color and spots on thin–layer chromatography with natural cuspidaline (I). The IR ($CHCl_3$) spectrum was superimposable with that of natural cuspidaline (I).

Fractional Recrystallization of IX into *dl*-Cuspidaline (XII) and *dl*-4'-O-Methylberbamunine (XIII)—— The base mixture (IX) (700 mg) was repeatedly recrystallized from MeOH. Prismatic crystals were obtained first from the crystalline fractions of the recrystallization, then needles came from the mother liquor portions, and finally 100 mg of colorless prisms, mp 143—146°, and 100 mg of colorless needles, mp 179—181° were obtained.

The NMR spectrum of prisms with lower melting point was identical with that of natural cuspidaline (I) except a signal at 6.55 τ (singlet, 3H) due to the methyl group of the solvent. $C_{37}H_{42}O_6N_2\cdot CH_3OH$. *Anal.* Calcd.: C, 71.00; H, 7.21. Found: C, 70.70; H, 7.39. The prisms from MeOH were further recrys-

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9) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a Varian A–60 spectrometer at 60 Mc in $CDCl_3$ with Me_4Si as an internal standard.

10) I.N. Gorbacheva, L.P. Varnakova, E.M. Kleiner, I.I. Chernova, and N.A. Preobrazhenskii, *Zh. Obshch. Kh.*, **28**, 167 (1958).

tallized from EtOH to give colorless prisms melting at 167—168°. The NMR spectrum of the prisms from EtOH was identical with natural cuspidaline (I) in every respect. $C_{37}H_{42}O_6N_2$. *Anal.* Calcd.: C, 72.76; H, 6.93. Found: C, 72.55; H, 7.22.

The needles from MeOH with mp 179—181°, gave superimposable IR (CHCl₃) spectrum with that of natural cuspidaline (I), and behaved identically on TLC. Thd NMR spectrum has its N–methyl signals at τ: 7.56, 7.50 (singlets, 2×3H); and methoxyl signals at τ: 6.18 (overlapped singlets, 3×3H) (natural cuspidaline: 7.56, 7.52 τ (6H, 2×NCH₃), 6.18 τ (9H, 3×OCH₃)). $C_{37}H_{42}O_6N_2$. *Anal.* Calcd.: C, 72.76; H, 6.93. Found: C, 72.75; H, 7.16.

2-Methoxy-5,4′-bis(2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)diphenyl Ether (X)————The amorphous mixture (IX) (260 mg) was dissolved in a mixture of 4 ml of MeOH and 10 ml of ether, and the excess CH₂N₂–Et₂O was added. After standing overnight, the reaction mixture was treated by usual procedure, and an oily non–phenolic base (X) (250 mg) was obtained. The NMR spectrum was identical with that[7] of equimolecular mixture of O–methyldauricine (D,D) and O,O,O–trimethylberbamunine (D,L).

2-Methoxy-5,4′-bis(2-methyl-6-methoxy-7-trideuteriomethoxy-1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)-diphenyl Ether (XI)————One hundred milligrams of the amorphous base mixture (IX) was dissolved in a mixture of 4 ml of dioxane and 0.5 ml of deuterium oxide, and to this solution CD₂N₂–dioxane[11] was added with stirring at room temperature. After standing overnight, dil. HCl was added to destroy excess CD₂N₂, and the solvent was removed. The residue was treated in usual manner, to give an oily non–phenolic base (XI) (70 mg) NMR spectrum was superimposable with that of the O–methyl ether (X) except that it lacked the signals at 6.38, 6.42 τ (2×OCH₃) of X.

dl-O,O,O-Trimethylberbamunine (XIV)————Fifteen milligrams of *dl*-4′-O–methylberbamunine (XIII) (mp 179—181°) was dissolved in a mixture of 2 ml of MeOH, 0.5 ml of CHCl₃, and 20 ml of ether, and then excess CH₂N₂–Et₂O was added to the solution. Treatment in usual manner after standing overnight, gave 13 mg of non–phenolic product (XIV). The NMR spectrum was superimposable with that of O,O,O–trimethylberbamunine (D,L) (XIV′) derived from natural berbamine (XV).

Preparation of O,O,O-Trimethylberbamunine (XIV′) from Berbamine (XV)————A modification of the described method[12] was employed, and the diphenolic intermediate (XVI) was isolated and characterized.

To a mixture of *ca.* 300 ml of liquid ammonia and 100 ml of anhyd. ether, metallic sodium and a solution of 1.0 g of berbamine (XV) benzene adduct (in 30 ml of anhyd. toluene diluted to 100 ml with anhyd. ether) were added alternately each in small portions; the reaction temperature was being kept —50 to —55° by means of Dry Ice–acetone bath. After consuming 0.7 g of metallic sodium, the reaction was ceased by adding NH₄Cl, and the product was worked up in a usual manner, to give a phenolic base (XVI) (0.98 g). The product (XVI) crystallized on trituration with CH₂Cl₂–hexane, and was recrystallized from the same solvent mixture. Colorless needles, mp 161—164°. $[\alpha]_D^{17}$ +61.1° (c=1.44 CHCl₃). *Anal.* Calcd.: $C_{37}H_{42}O_6N_2$. *Anal.* Calcd.: C, 72.76; H, 6.93; N, 4.59. Found: C, 73.01; H, 7.16; N, 4.35.

XVI (100 mg) was dissolved in small volume of CH₂Cl₂, and excess CH₂N₂–Et₂O was added. After standing for 4 days, the solvent was removed. The residue was taken into dil. HCl, then the solution was basified with NaOH and extracted with ether. Ethereal solution was washed with dil. NaOH and water, dried over anhyd. K₂CO₃. Removal of the solvent gave 99 mg of light brown oil, which was purified by column chromatography (Al₂O₃–benzene) to give 88 mg of colorless oil (XVI). IR (CHCl₃): identical with the spectrum of O–methyldauricine.[13] $[\alpha]_D^{17}$ +31.84° (c=0.314, Me₂CO) (lit.[14] $[\alpha]_D^{19}$ +52.6°, c=0.3042, Me₂CO) $[\alpha]_D^{17}$ +21.69° (c=2.58, CHCl₃).

XVI dimethiodide: pale yellow needles, mp 183—185°. Mixed mp with authentic O,O,O–trimethylberbamunine dimethiodide[14] did not depress. IR (Nujol) was identical with that of authentic specimen.

11) K.J. van der Merwe, P.S. Steyn, and S.H. Eggers, *Tetrahedron Letters*, 3925 (1965).
12) Y. Inubushi, *Yakugaku Zasshi*, **72**, 220 (1952).
13) M. Tomita and Y. Okamoto, *Yakugaku Zasshi*, **84**, 1030 (1964).
14) M. Tomita and T. Kugo, *Yakugaku Zasshi*, **77**, 1079 (1957).