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Studies on the Syntheses of Heterocyclic Compounds. CCIX.[1] Total Syntheses of (±)-Isococlaurine and (—)-Lotusine

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Reductive dealkylation of 1-(4-benzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (I) with lithium and liquid ammonia gave mainly isococlaurine (II) together with coclaurine (IV) as by-product, which were characterized as their tribenzoate, respectively. Furthermore, reductive methylation of II with formalin and sodium borohydride, followed by methylation with methyl iodide, afforded (±)-lotusine iodide (VII).

Furthermore, synthesis and optical resolution of 6-acetoxy-1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (XII) was carried out to give our expected (+)-N-methylisococlaurine (VI), which was converted into the methiodide (VII), followed by treatment with sliver chloride, to give (—)-lotusine chloride (VIII).

The total syntheses of (±)-isococlaurine and (±)-/(—) lotusine halides have been accomplished.

Isococlaurine, $C_{17}H_{19}O_3N$, mp 216—217°, was isolated from *Radix pareirae* BRAVAE by King[3] in 1940, and its synthesis has already been described by Tomita and Yamaguchi,[4] but both specimens have not been compared. (—)-Lotusine, mp 213—215°, one of the alkaloids of a Formosan lotus embryo, was isolated as its chloride from *Nelumbo nucifera* GAERTN. by Furukawa, *et al.*[5] in 1965.

The purpose of the present investigation was to study the reductive dealkylation of 1-(4-benzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline[6] (I) in order to obtain the isococlaurine (II) as a possible intermediate for the synthesis of N-methylisococlaurine (VI). Twofold methylation of II eventually led to a synthesis of (±)-lotusine halide that supports the structures of VII and VIII. Furthermore, optical resolution of O-acetyl-O-benzyl-N-methylisococlaurine (XII), followed by methylation and hydrolysis, afforded (—)-lotusine iodide.

Reductive cleavage of I in tetrahydrofuran with metallic lithium in liquid ammonia according to Kametani's method[7] gave a mixture of two phenolic bases which were separated as its hydrochloride. An insoluble hydrochloride was separated from the filtrate (A). Recrystallization of an insoluble hydrochloride from ethanol gave (±)-coclaurine (IV) in a yield of 3.6% as colorless needles, mp 254—255°, identical with natural one on admixed melting point test and its infrared (IR) spectrum. Moreover, Schotten-Baumann reaction of IV with benzoyl chloride in the presence of 10% sodium hydroxide solution gave the tribenzoate (V), which was also identical with the tribenzoate[8] derived from natural coclaurine on admixed melting point test and IR spectrum.

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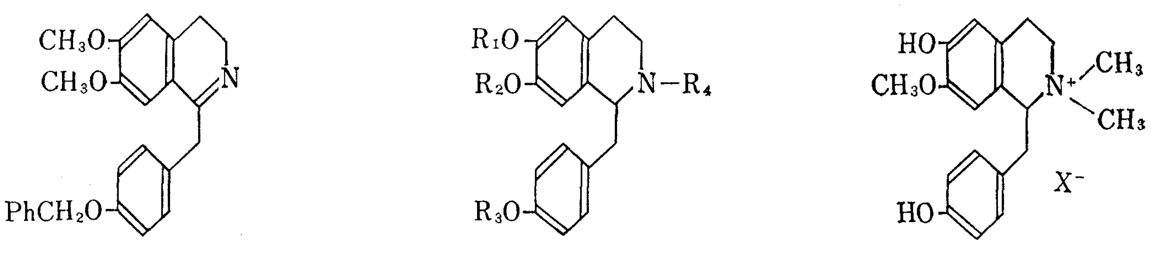
1) Part CCV: *J. Chem. Soc.* (C), **1967**, 2208; Part CCVI: *J. Chem Soc.* (C), **1967**, 2182; Part CCVII: *Chem. Comm.*, **1967**, 1103; Part CCVIII: *Chem. Comm.*, **1967**, 1212.
2) Location: *Kita-4-bancho, Sendai.*
3) H. King, *J. Chem. Soc.*, **1940**, 737.
4) M. Tomita and H. Yamaguchi, *Yakugaku Zasshi*, **72**, 1219 (1952).
5) H. Furukawa, T.H. Yang, and T.J. Lin, *Yakugaku Zasshi*, **85**, 472 (1965).
6) M. Tomita and H. Yamaguchi, *Pharm. Bull.* (Japan), **1**, 10 (1953).
7) T. Kametani, S. Takano, and F. Sasaki, *Yakugaku Zasshi*, **87**, 191 (1967).
8) M. Tomita, K. Nakaguchi, and S. Takagi, *Yakugaku Zasshi*, **71**, 1046 (1951).

On the other hand, after the preceding insoluble hydrochloride of IV had been removed, the acidic filtrate (A) including other hydrochloride was made basic with ammonia and treated as usual, giving a phenolic base, whose tribenzoate (III), mp 203—204°, was obtained in a yield of 47.5%. This yield was calculated from the starting material (I). Recrystallization of this free base gave the racemic isococlaurine,[9] mp 216—217°, whose hydrochloride was characterized as pale brown plates, mp 156—157°, with correct analysis.

The natural (+)-isococlaurine (II)(lit.,[3] mp 216—217°) was not available for comparison. Accordingly, the difference between synthetic isococlaurine and natural coclaurine was investigated as the tribenzoate from the point of mixed melting point test and spectral measurement. The NMR spectrum of III showed the protons of the methyl of methoxyl group at 6.47τ and that of V showed the protons of 6-methoxyl group at 6.27τ. In the former case the signal of the methyl protons of methoxyl group is appreared in a higher field than the latter case perhaps due to the anisotropy of the benzene ring of 1-benzyl group. Therefore, the methoxyl group in case of III seems to be existed in the C_7-position. These facts reveal that reductive dealkylation of I mainly gave isococlaurine(II) together with coclaurine (IV) as by-product.

The reductive N-methylation of II with formalin and sodium borohydride gave N-methylisococlaurine[7] (VI), whose methylation with methyl iodide afforded a quarternary base (VII), namely, (±)-lotusine iodide, mp 205—207°. In this case the IR spectrum (in $CHCl_3$) of (±)-lotusine chloride (VIII), which was derived from the racemate (VII) by treatment with silver chloride, could not be compared with that of natural (—)-form (VIII) because of their insolubility in chloroform.



I

II : $R_1=R_3=R_4=H$, $R_2=CH_3$
III : $R_1=R_3=R_4=PhCO$, $R_2=CH_3$
IV : $R_1=CH_3$, $R_2=R_3=R_4=H$
V : $R_1=CH_3$, $R_2=R_3=R_4=PhCO$
VI : $R_1=R_3=H$, $R_2=R_4=CH_3$
IX : $R_1=R_3=Ac$, $R_2=R_4=CH_3$

VII : X=I
VIII : X=Cl

Chart 1

Accordingly, optical resolution of the oily O,O-diacetyl-N-methylisococlaurine (IX), which was obtained by acetylation of N-methylisococlaurine (VI), with (—)-dibenzoyltartaric acid was carried out, but our expected optically active (+)-N-methylisococlaurine (VI) could not be obtained. Therefore, synthesis and optical resolution of 6-acetoxy-1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydro-2-methylisoquinoline (XII) were attempted as follows.

Schotten-Baumann reaction of 3-hydroxy-4-methoxyphenethylamine with two molar equivalents of 4-benzyloxyphenylacetyl chloride gave the amide (X), but conversion of X into

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[9] According to the literature,[4] (+)-isococlaurine, $C_{17}H_{19}NO_3 \cdot H_2O$, was characterized as needles, mp 135—136°.

[10] M. Tomita, Sheng-Teh Lu, and San-Jyi Wang, *Yakugaku Zasshi*, **85**, 827 (1965).

XII as usual by way of the intermediates, 3,4-dihydroisoquinoline, methiodide, and 1,2,3,4-tetrahydroisoquinoline (XI), was not carried out in a good yield. Therefore, use of one mole of acid chloride with one mole of the above phenethylamine yielded the amide (XIII) in a good yield, which was acetylated to give the compound (XIV). Bischler–Napieralski reaction of the amide (XIV) gave 3,4-dihydroisoquinoline, which was methylated with methyl iodide and then reduced with sodium borohydride to give an expected acetyl-derivative (XII).

Finally, optical resolution of O-acetyl-O-benzyl-N-methylisococlaurine (XII) with (−)-dibenzoyltartaric acid gave the tartrate, which was converted into optically active compound (XI) by basification. Hydrolysis of XI with zinc powder and hydrocholric acid afforded (+)-N-methylisococlaurine (VI). Methylation of VI with methyl iodide, followed by treatment with silver chloride, gave (−)-lotusine chloride (VIII), whose IR spectrum (in KBr) was superimposable on that of natural (−)-lotusine chloride kindly donated by Prof. Tomita and Dr. Furukawa.

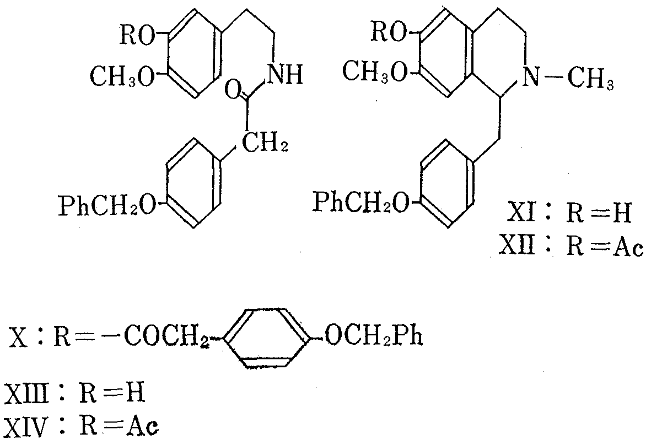

Chart 2

These facts reveal that the total syntheses of (±)-isococlaurine and (±)-/(−)-lotusine halides have been accomplished.

Experimental[11]

(±)-Isococlaurine (II) and (±)-Coclaurine (IV)——To a stirred solution of 540 mg of Li in 300 ml of liq. NH_3 was added dropwise a solution of 2 g of 1-(4-benzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (I)[6] in 50 ml of tetrahydrofuran, and then stirring was continued for further 8 hr. Absolute MeOH (100 ml) was added slowly to destroy the excess of Li. After the filtration, removal of the solvent from the filtrate *in vacuo* gave the residue which was dissolved in a small amount of water and filtered. The above filtrate was acidified with conc. HCl aq. solution until the solution showed the pH 8.0. After the precipitate had been collected by filtration, it was again admixed with 10% HCl aq. solution, from which an insoluble hydrochloride was separated from an acidic solution (A). Recrystallization of the former insoluble substance from EtOH gave 53 mg (3.6%) of (±)-coclaurine (IV) hydrochloride as colorless needles, mp 254—255, whose IR spectrum and Rf value on TLC[12] were identical with those of natural coclaurine hydrochloride. Both specimens showed no depression on admixed melting point. *Anal.* Calcd. for $C_{18}H_{19}ON \cdot HCl \cdot H_2O$: C, 60.08; H, 6.53; N, 4.12. Found: C, 60.38; H, 6.76; N, 4.28.

Schotten–Baumann reaction of IV with benzoyl chloride as usual gave N,O,O-tribenzoate (V). Recrystallization from benzene–ether afforded colorless cubes, mp 214—215°, which showed no depression on admixed melting point test with N,O,O-tribenzoate (V) derived from natural coclaurine. The IR spectra (in $CHCl_3$ and KBr) and TLC[13] of both specimens were also identical. NMR ($CDCl_3$)(τ): 6.27 (3H, singlet, 6-OCH_3).

The preceding acidic solution (A) was made basic with conc. ammonia and extracted with 50 ml of $CHCl_3$ for six times. The extract was washed with water, dried on Na_2SO_4, and distilled to give 1 g of a pale brown caramel-like substance. Schotten–Baumann reaction of the above base (VI) with benzoyl chloride in the presence of an excess of 10% NaOH aq. solution gave the tribenzoate. Recrystallization from benzene–ether gave 1.47 g (47.5%) of the tribenzoate (III) as colorless cubes, mp 203—204°, which showed depression on admixed melitng point test with that of (±)-coclaurine. *Anal.* Calcd. for $C_{38}H_{31}O_6N$: C, 76.36; H, 5.23; N, 2.34. Found: C, 76.35; H, 5.32; N, 2.73. NMR ($CDCl_3$)(τ): 6.47 (3H, singlet, 7-$OC\underline{H}_3$).

Separation of (±)-Isococlaurine——After 1.3 g of Li had been added to 350 ml of liquid NH_3 in small portions within 20 min, a solution of 4 g of 3,4-dihydroisoquinoline (I) in 100 ml of dry tetrahydrofuran

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[11] IR and NMR spectra were measured on a Type EPI-3 Hitachi recording spectrophotometer and a Varian A-60 spectrophotometer with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mps were not corrected.

[12] Wakogel B-5; thickness, 250 μ; solvent, MeOH.

[13] Wakogel B-5; thickness, 250 μ; solvent, $CHCl_3$: acetone (9:1).

was added dropwise to the above mixture, and then stirring was continued for further 5 hr. After the reaction, the resultant mixture was extracted with 300 ml of *n*–BuOH. The extract was wsahed with 100 ml of saturated NH_4Cl aq. solution, and the solvent was evaporated to a volume of 150 ml. After the solvent had been dried on Na_2SO_4 and filtered, an ethereal solution saturated with an excess of dry HCl gas was added to the above filtrate, and *n*–hexane was then added to separate HCl salt of II. Collection by filtration and repeated recrystallization from water gave 0.7 g of pale brown plates, mp 156—157°(lit.,[4] mp 215°). *Anal.* Calcd. for $C_{17}H_{19}O_3N \cdot HCl \cdot H_2O$: C, 60.08; H, 6.53; N, 4.12. Found: C, 59.13; H, 6.36; N, 3.88.

A solution of 0.5 g of the above HCl salt of II in water was made basic with saturated Na_2CO_3 aq. solution and extracted with a mixture of EtOH–$CHCl_3$ (1:9). The solvent layer was separated, dried on K_2CO_3, and distilled to give 0.18 g of isococlaurine (II), whose recrystallization from acetone afforded colorless plates, mp 216—217°(lit.,[4] mp 135—136°).[14]

(±)–N–Methylisococlaurine (VI)——A mixture of 380 mg of isococlaurine (II), 40 ml of MeOH, and 1.8 ml of 37% formalin was heated under reflux for 30 min, and 2 g of $NaBH_4$ was then added portionwise to the above mixture. After the addition, the resultant mixture was refluxed for additional 30 min, to which 30 ml of ice–water was added. Removal of the solvent gave an aqueous solution, which was acidified with 10% HCl aq. solution and filtered. The filtrate was made alkaline with ammonia, and extracted with 50 ml of $CHCl_3$ for five times. The extract was washed with water, dried on Na_2SO_4, and distilled to give 320 mg of a caramel–like substance, which solidified on being triturated with MeOH–ether–*n*–hexane. Recrystallization from acetone gave 140 mg of N–methylisococlaurine (VI) as colorless prisms, mp 225—226° (decomp.)(lit.,[10] mp 218—219°), whose Gibbs reaction showed green color. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 2860 (N–Me), δ875 (tetra–substituted benzene), 830, 793 (di–substituted benzene). *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot \frac{1}{2}H_2O$: C, 70.11; H, 7.19; N, 4.54. Found: C, 70.51; H, 7.15; N, 4.05.

(±)–Lotusine iodide (VII)——A mixture of 50 mg of the above compound (VI) and excess of MeI in 10 ml of tetrahydrofuran was heated for 10 min. The excess of the reagent and solvent were removed by distillation. Recrystallization of the residue from EtOH gave (±)–lotusine iodide (VII) as colorless prisms, mp 205—207°. *Anal.* Calcd. for $C_{19}H_{24}O_3NI$: C, 51.70; H, 5.48; N, 3.17. Found: C, 52.06; H, 5.80; N, 3.16

O,O–Diacetyl–N–methylisococlaurine (IX)——A mixture of 0.5 g of N–methylisococlaurine, 20 ml of tetrahydrofuran, 1 ml of Ac_2O, and 1.4 g of K_2CO_3 was shaken severely at room temperature for 2.5 hr. After the reaction, removal of the solvent gave a colorless solid, which was dissolved in water and extracted with 150 ml of $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and distilled to give 522 mg of a yellow syrup. IR ν_{max} cm^{-1}: 1765 (acetyl C=O).

A mixture of 0.5 g of the preceding compound, 0.54 g of (+)–dibenzoyltartaric acid, and 8 ml of acetone was allowed to stand in a refrigerator for 3 days, and its tartrate was precipitated. Filtration and recrystallization from acetone–*n*–hexane afforded 0.23 g of pale yellow plates, mp 116°. *Anal.* Calcd. for $C_{42}H_{39}O_{13}N \cdot 2H_2O$: C, 61.77; H, 5.57. Found: C, 61.78; H, 5.84.

N–[3–(4–Benzyloxy)phenacyloxy–4–methoxyphenethyl]–4–benzyloxyphenylacetamide (X)——A solution of 2.1 g of NaOH in 80 ml of water and a solution of 10.3 g of 4–benzyloxyphenylacetyl chloride in 80 ml. of dry $CHCl_3$ were concurrently added to a stirred solution of 3.6 g of 3–hydroxy–4–methoxyphenethylamine hydrochloride in 50 ml of water. Dropwise addition of two former solutions took 30 min, and the mixture was stirred for further 30 min. After the reaction, the solvent layer was separated, and the resultant aqueous layer was extracted with 30 ml of $CHCl_3$ for three times. The $CHCl_3$ solvent as above was combined,washed with water, dried on Na_2SO_4, and distilled to give 10.4 g of a pale yellow solid, whose recrystallization from benzene–*n*–hexane afforded colorless plates, mp 110°. IR ν_{max}^{KBr} cm^{-1}: 3920 (NH), 1765 (ester C=O), 1640 (amide C=O). *Anal.* Calcd. for $C_{39}H_{37}O_6N$: C, 74.89; H, 6.13. Found: C, 74.65; H, 6.40.

6–Acetoxy–1–(4–benzyloxybenzyl)–7–methoxy–1,2,3,4–tetrahydro–2–methylisoquinoline (XII)——A mixture of 2 g of the preceding amide, 50 ml of dry toluene, and 4.5 ml of $POCl_3$ was heated under reflux in an oil–bath at 100—110° for 1 hr in a current of N_2, and then the reaction mixture was pured into 200 ml of *n*–hexane. A brown viscous syrup thus precipitated as HCl salt was collected by decantation, washed with an excess of *n*–hexane fully, and extracted with $CHCl_3$. The solvent layer was poured into a cooled and stirred conc. NH_4OH aq. solution in the presence of N_2. After stirring for 20 min, the solvent layer was separated, washed with water, dried on Na_2SO_4, and distilled to give 1.6 g of a pale brown syrup, which was used directly in the following reaction because of difficult purification.

Secondly, a mixture of 1.6 g of the above isoquinoline, 30 ml of MeOH, and 6 g of MeI was heated on a water–bath at 65—70° for 50 min, and removal of the solvent gave 1.75 g of the crude methiodide, which was used in the following reaction without purification in order to avoid oxydation of 1–benzyl group. $NaBH_4$ (6 g) was added in small portions with shaking to a solution of 1.75 g of the preceding methiodide in 100 ml of MeOH within 40 min. The mixture was stirred and refluxed for an additional 1 hr and then the solvent was distilled off. The pale yellow residue was treated with water and extracted with $CHCl_3$. The solvent was washed with water, dried on K_2CO_3, and distilled to afford 1.08 g of a yellow syrup, whose column–chromatography on 30 g of silicic acid using $CHCl_3$ as solvent gave 351 mg of 1,2,3,4–tetrahydroisoquinoline

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[14] According to the literature,[1] natural isococlaurine showed mp 216—217°.

derivative as a yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3525 (OH), 2810 (N–Me). Since the compound (XI) could not be obtained in a crystalline state, it was also used in the following reaction without recrystallization.

Finally, to a solution of 351 mg of the preceding compound (XI) in 70 ml of tetrahydrofuran was added a mixture of 1.4 g of crystalline K_2CO_3 and 1 ml of Ac_2O, and the mixture was severely shaken at room temperature for 2 hr. After the reaction, removal of the solvent gave the residue, to which an excess of water was added to precipitate an oil. The oily substance was extracted with ether. The extract was washed with water, dried on Na_2SO_4, and distilled to give 303 mg of a pale yellow syrup, whose recrystallization from ether–petroleum ether afforded colorless prisms, mp 198—198.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2810 (N–Me), 1755 (C=O). *Anal.* Calcd. for $C_{27}H_{29}O_4N$: C, 75.10; H, 6.77; N, 3.24. Found: C, 74.92; H, 6.53; N, 3.52.

(+)–N–Methylisococlaurine (VI)——A solution of 220 mg of (−)–dibenzoyltartaric acid in acetone was added to a solution of 256 mg of(±)–XII in acetone. After a small amount of *n*–hexane had been added to the above mixture, a tubid mixture was allowed to stand in a refrigerator for 72 hr. The crude tartrate was precipitated and collected by filtration to give colorless crystals, whose recrystallization from MeOH afforded 150.3 mg of colorless prisms, mp 124—125°.

To a solution of 150.3 mg of the above tartrate in 30 ml of $CHCl_3$ was added 50 ml of saturated $NaHCO_3$ aq. solution and the mixture was shaken for 2 hr. The $CHCl_3$ layer was separated and dried on Na_2SO_4. Removal of the solvent gave 52.4 mg of a yellow syrup, which could not be crystallized and therefore used without purification in the following reaction. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 2810 (N–Me).

A mixture of 50 mg of the preceding compound, 10 ml of EtOH, 10 ml of conc. HCl solution, and 1 g of Zn was heated on a water–bath at 80—90° with stirring for 1 hr, and then 1 g of more Zn dust and 10ml of conc. HCl solution were added, and the heating and stirring were continued for further 1 hr to give a colorless clear solution. The excess of Zn was filtered off, and the bulk of the solvent was removed by distillation. The residual solution was made basic (pH 8.6) with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on K_2CO_3, and removed by distillation. The residual solution was made basic (pH 8.6) with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on K_2CO_3 and distilled to give 21.2 mg of a yellow syrp. Recrystallization from tetrahydrofuran gave (+)–N–methylisococlaline (VI) as pale yellow prsms, mp 214—215° [lit.,[15] mp 216—218°(decomp.)]. $[\alpha]_2^D$ +42.4°(c=0.1, acetone; $[\alpha]_D^5$ +70.9°(c=0.1, MeOH).[16]

(−)–Lotusine Chloride (VIII)——A mixture of 30 mg of the above 1,2,3,4–tetrahydroisoquinoline (+)–(VI), 20 ml of tetrahydrofuran, and an excess of MeI was refluxed on a water–bath for 30 min. Removal of the solvent and reagent gave 32 mg of a pale yellowish–brown syrup.

To a solution of 26 mg of the preceding methiodide in 30 ml of EtOH was added AgCl which was freshly prepared from 0.72 g of $AgNO_3$ and 0.26 g of NaCl. The above mixture was refluxed on a water–bath for 3 hr, and the excess of AgCl was filtered off. Removal of the solvent from the filtrate gave a pale yellow syrup, whose recrystallization from EtOH afforded 8 mg of colorless prisms, mp 213.5—214°, IR ν_{max}^{KBr} cm^{-1}: 3620 (OH). $[\alpha]_D^8$ −15.0°(c=0.53, MeOH). *Anal.* Calcd. for $C_{19}H_{24}O_3NCl \cdot 2H_2O$[17]: C, 59.45; H, 6.92. Found: C, 60.03; H, 6.90. Further desication on P_2O_5 at 80° for 48 hr was held, by the result of which almost the same crystals as above, mp 214—214.5° were obtained. *Anal.* Calcd. for $C_{19}H_{24}O_3NCl \cdot 2H_2O$: C, 59.45; H, 6.92. Found: C, 59.35; H, 6.60. The IR spectrum (in KBr) of synthetic (−)–lotusine chloride was superimposable on that of natural one, and admixed melting point test showed no depression.

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[15] M. Tomita, T. Sakai, and S. Matsumura, *Yakugaku Zasshi*, **79**, 1120 (1959).
[16] According to Tomita, *et al.*[9], $[\alpha]_D^5$ showed +6.41°(c=0.313, acetone).
[17] This compound was dried on P_2O_5 at 50° for 24 hr.