Summary

A simple and sensitive method for extraction and detection of morphine in urine was described.

The continuous extraction method showed a virtually complete recovery of morphine and prevented the formation of emulsion unavoidable in the extraction by shaking.

The hydrolysis condition which led to liberation of most of morphine from the conjugates in urine was found to be that of heating for 30 minutes, in the 15% hydrochloric acid concentration. This procedure was simple, but afforded the comparable result to that of sealed tube hydrolysis in the 5% hydrochloric acid concentration.

Double thin-layer chromatographic method was successfully applied first to the separation of morphine from a large amount of impurtities in the urine extract using thicker plate (1 mm.) and then to the final detection of morphine using ordinary one (0.25 mm.).

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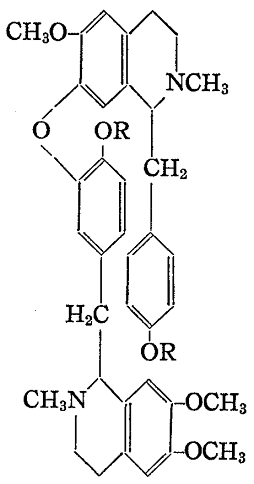
12. **Tetsuji Kametani, Seiichi Takano, Kazuko Masuko, and Fujinori Sasaki**: Bisbenzylisoquinoline Alkaloids and Related Compounds. V.[*1] A Total Synthesis of Diastereoisomeric Mixture of Liensinine.[*2,*3]

(*Pharmaceutical Institute, Tohoku University School of Medicine*[*4])

The isolation of a new alkaloid, liensinine, with the composition of $C_{37}H_{42}O_6N_2$, m.p. 95~99°, from the embryo loti of *Nelumbo nucifera* GAERTN. was described by Chao-yuan, *et al.*[1)] and it was then shown that liensinine possessed the structure (I), mainly based on the results of Hoffmann degradation and potassium permanganate oxidation.[2)]



I : R = H
I′: R = H
II : R = $CH_2C_6H_5$

The purpose of the present investigation was to study the Ullmann reaction between both tetrahydroisoquinoline derivatives, X and XVII, in order to obtain diastereoisomeric mixture of O,O-dibenzylliensinine (II) as a possible intermediate for the synthesis of I′, possessing the same planar structure as natural liensinine (I). Benzylation of 3-bromo-4-hydroxyphenylacetic acid[3)] (III) with benzyl chloride in the presence of sodium ethoxide in ethanol afforded 3-bromo-4-benzyloxyphenylacetic acid (IV), which was converted into the acid chloride (V).

[*1] Part IV. T. Kametani, K. Fukumoto: J. Chem. Soc., **1964**, 6141.

[*2] This forms Part CXXXII of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.

[*3] This work was reported at the Tohoku Branch Meeting of Pharmaceutical Society of Japan, February 20, 1965.

[*4] Kita-4-bancho, Sendai (亀谷哲治, 高野誠一, 増子和子, 佐々木藤紀).

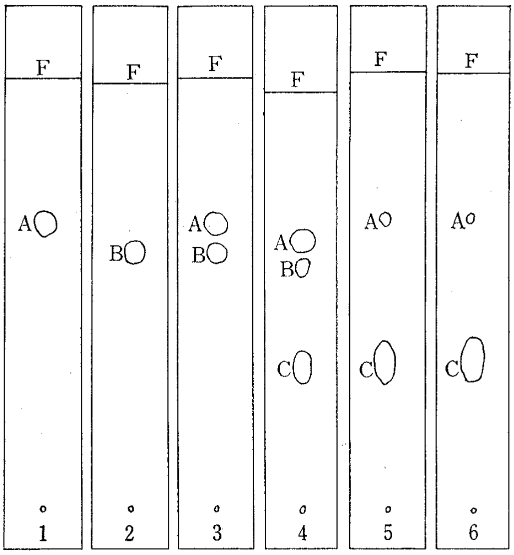
1) Chao Tse-yuan, Chou Yun-lee, Young Tao-tsin, Chou Tsan-quo: Scientia Sinica, **11**, 215 (1962).

2) Pan Pei-chuan, Chou Yun-lee, Sun Tsun-tsi, Kao Yee-sheng: *Ibid.*, **11**, 321 (1962).

3) H. Kondo, S. Uyeo: Yakugaku Zasshi, **53**, 557 (1933).

Bischler-Napieralski cyclization of the amide (VII), which was obtained by Schotten-Baumann reaction of 3,4-dimethoxyphenethylamine (VI) with acid chloride (V) gave the 1-(3-bromo-4-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII) as an oil, which was characterized as the styphnate, m.p. 200∼200.5°. Reduction of the methiodide (IX) of the above dihydroisoquinoline derivative (VIII) with sodium borohydride in methanol gave one component (X) of the starting materials as a pale brown glass, which was characterized as the perchlorate, m.p. 180.5∼181.5°.

Schotten-Baumann reaction of 3-methoxy-4-tosyloxyphenethylamine[4,5] (XII) with 4-benzyloxyphenacetyl chloride[6] (XI) afforded the amide (XIII) as colorless needles, m.p. 100∼101°. Bischler-Napieralski reaction of the above amide (XIII) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (XIV), which was converted into the methiodide (XV). Reduction of the compound (XV) with sodium borohydride gave the tetrahydroisoquinoline derivative (XVI), whose detosylation yielded the substance (XVII) on being allowed to stand in ethanolic potassium hydroxide solution overnight.



A : (X) Rf=0.66∼0.64
B : (XVII) Rf=0.59∼0.60
C : O,O-Dibenzylliensinine (II) Rf=0.32∼0.34
F : The line of the liquid front
1 : Pure compd. (X)
2 : Pure compd. (XVII)
3 : Reaction time : 0 hr.
4 : 〃 : 10 hr.
5 : 〃 : 25 hr.
6 : 〃 : 48 hr.

Fig. 1. Thin-layer Chromatography of the Products during the Ullmann Reaction

Silica gel B. (Wako), activated at 120° for 2 hr. (0.25 mm.) and chloroform-methanol (5:4) as solvent were used at 17°: and the spots were detected by their fluorescence under UV light and by vapor of iodine.

Ullmann condensation between X and XVII was carried out in the presence of copper powder, potassium carbonate and a small amount of potassium iodide in pyridine.[7] During the reaction, the samples from the reaction mixture were taken up,

Table I. The Yield of Each Fraction (100 ml.) and Its Beilstein Test

Fraction No.	Yield (mg.)	Beilstein test
F_1 ⋮ F_{15}	trace	⧻
F_{16}	20	+
F_{17}	50	±
F_{18}	100	±
F_{19}	825	−
F_{20}	500	−
F_{21}	320	−
F_{22}	430	−
F_{23}	130	−

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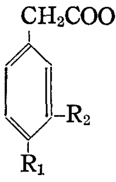
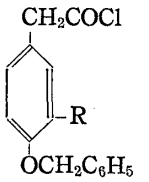
4) T. Kametani, S. Takano, E. Karibe: Yakugaku Zasshi, 83, 1035 (1963).
5) T. Kametani, S. Takano, K. Masuko, S. Kuribara: *Ibid.*, 85, 166 (1965).
6) D. A. A. Kidd, J. Walker: J. Chem. Soc., **1954**, 669.
7) M. Tomita, K. Fujitani, K. Kishimoto: Yakugaku Zasshi, 82, 1148 (1962).

and inspected by thin-layer chromatography, whose data were shown in Fig. 1. Only a new spot (C) was detected and attributed to that of diastereoisomeric mixture of O,O-dibenzylliensinine (II) by the results described in the experimental section. And then it was also revealed that the debrominated substance of X or the diphenyl derivative, which would be formed by bimolecular Ullmann reaction of X were not formed in this reaction.

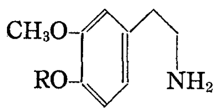
Alumina-chromatography of the product as above gave diastereoisomeric mixture of O,O-dibenzylliensinine (II) in a yield of 23%, which was characterized as the perchlorate. Finally, treatment of the above compound (II) with concentrated hydrochloric acid yielded the synthetic liensinine (I′), m.p. 95∼103°, with infrared and ultraviolet spectra superimposable on those of natural liensinine, which was extracted from the embryo loti of *Nelumbo nucifera* Gaertn. according to the procedure reported by Chao Tse-yuan, *et al.*[1] Both specimens behaved similarly on paper and thin-layer chromatography, but nuclear magnetic resonance spectra of synthetic and natural liensinine showed a marked difference in a signal of methoxyl radicals as described in experimental section. Since Fujitani, *et al.*[8] recently reported on the difference of nuclear magnetic resonance spectrum between natural product and the diastereoisomeric mixture in case of bisbenzylisoquinoline type alkaloid, which contains only one diphenyl ether group, I must be a diastereoisomeric mixture.



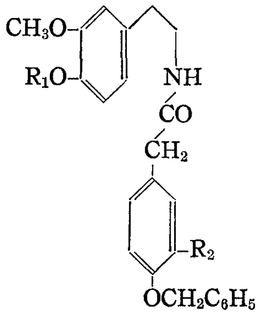
III : $R_1=OH$; $R_2=Br$
IV : $R_1=OCH_2C_6H_5$; $R_2=Br$



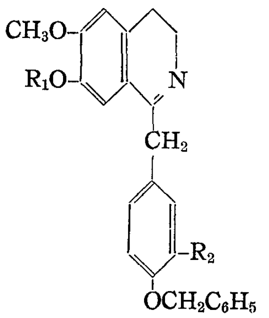
V : $R=Br$
XI : $R=H$



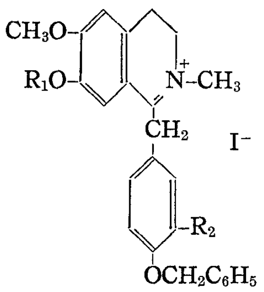
VI : $R=CH_3$
XII : $R=Ts$



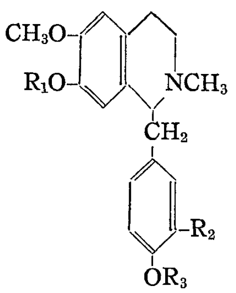
VII : $R_1=CH_3$; $R_2=Br$
XIII : $R_1=Ts$; $R_2=H$



VIII : $R_1=CH_3$; $R_2=Br$
XIV : $R_1=Ts$; $R_2=H$



IX : $R_1=CH_3$; $R_2=Br$
XV : $R_1=Ts$; $R_2=H$



X : $R_1=CH_3$; $R_2=Br$; $R_3=CH_2C_6H_5$
XVI : $R_1=Ts$; $R_2=H$; $R_3=CH_2C_6H_5$
XVII : $R_1=R_2=H$; $R_3=CH_2C_6H_5$

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[8] K. Fujitani, Y. Aoyagi, Y. Masaki: Yakugaku Zasshi, 84, 1234 (1964).

These facts reveal that the total synthesis of a mixture of stereoisomeric liensinine has been accomplished and the planar structure of natural liensinine (I) is correct.[*5]

Experimental[*6]

3-Bromo-4-benzyloxyphenylacetic Acid (IV)——To a solution of 2.4 g. of EtONa in 58 ml. of ethanol, 30 g. of 3-bromo-4-hydroxyphenylacetic acid (Ⅲ) was added, giving a red clear solution to which 33 g. of benzyl chloride was added, and the mixture was heated on a water-bath. After 7 hours' refluxing a red color disappeared and NaCl separated. The mixture was distilled off, admixed with 180 ml. of H_2O, and extracted with benzene. The extract was washed with H_2O, dried on Na_2SO_4, and distilled to give an oil, which was heated under reflux with a mixture of 4.4 g. of KOH, 4.4 ml. of water and 44 ml. of EtOH in a current of N_2 for 16 hr., in order to complete the hydrolysis of benzyl 3-bromo-4-benzyloxyphenylactate formed as by-product. The residue obtained by removal of the solvent was dissolved in 12 ml. of H_2O, and the mixture was extracted with ether. The aqueous layer was acidified with AcOH to give the colorless precipitate, which was again extracted with ether. Removal of the solvent gave the residue, which was recrystallized from benzene-ligroin to yield 36 g. of 3-bromo-4-benzyloxyphenylacetic acid (Ⅳ) as colorless needles, m.p. 115~115.5°. *Anal.* Calcd. for $C_{15}H_{13}O_3Br$: C, 56.12; H, 4.02. Found : C, 55.92; H, 4.31.

N-(3,4-Dimethoxyphenethyl)-3-bromo-4-benzyloxyphenylacetamide (VII)——To a suspension of 1.7 g. of the preceding acid (Ⅳ) in 24 ml. of ligroin was added 0.76 g. of thionyl chloride, and the mixture was heated at 62° on a water-bath for 2 hr. Removal of an excess of thionyl chloride *in vacuo* gave 3-bromo-4-benzyloxyphenacetyl chloride (Ⅴ) as a crystalline solid, which was extracted with 10 ml. of $CHCl_3$.

A solution of 2.4 g. of 3,4-dimethoxyphenethylamine (Ⅵ) in 10 ml. of $CHCl_3$ was dropwise added to a cooled and stirred $CHCl_3$ solution of Ⅴ as above. After the addition, the mixture was allowed to stand for 1 hr., washed with 3% HCl, saturated aq. $NaHCO_3$, and H_2O, and dried on K_2CO_3. Removal of the solvent gave a viscous syrup, which was recrystallized from MeOH to give the amide (Ⅶ) as colorless long needles (2.3 g., 87.5%), m.p. 129.5~130.5°. *Anal.* Calcd. for $C_{25}H_{26}O_4NBr$: C, 61.98; H, 5.41; N, 2.89. Found : C, 61.95; H, 5.36; N, 2.92.

1-(3-Bromo-4-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII)——A mixture of 3 g. of the above amide (Ⅶ), 25 ml. of dry benzene, and 2.5 ml. of $POCl_3$ was refluxed for 20 min. until a gas of HCl no longer evolved. An excess of 250 ml. of ligroin was added to the reaction mixture and an upper layer was removed by decantation. The residue was repeatedly washed with ligroin and dissolved in $CHCl_3$. The resultant $CHCl_3$ solution was poured into an excess of cooled and stirred ammonium hydroxide solution. The solvent was separated, washed with H_2O, dried on K_2CO_3, and distilled, to give 2.8 g. of the dihydroisoquinoline (Ⅷ) as a pale yellow viscous syrup. Recrystallization of the picrolonate from EtOH yielded yellow needles, m.p. 200~200.5° (decomp.). *Anal.* Calcd. for $C_{25}H_{24}O_3NBr \cdot C_{10}H_8O_5N_4 \cdot H_2O$[*7] : C, 56.15; H, 4.57; N, 9.36. Found : C, 56.50; H, 4.17; N, 9.55. The perchlorate of Ⅷ was characterized by recrystallization from MeOH as colorless feathers, m.p. 179~180.5°. *Anal.* Calcd. for $C_{25}H_{24}O_3NBr \cdot HClO_4 \cdot \frac{1}{2}H_2O$: C, 52.14; H, 4.50; N, 2.43. Found : C, 51.91; H, 4.56; N, 2.14. IR ν_{max}^{KBr} cm^{-1} : 3450 (OH) (water of crystallization).

1-(3-Bromo-4-benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X)——To the preceding dihydroisoquinoline (Ⅷ) was added an excess of methyl iodide, which was enough for dissolving the compound (Ⅷ). The mixture was allowed to stand at room temperature for a brief period during which time crystals separated. Evaporation of an excess of methyl iodide, with a quantitative yield, gave the methiodide (Ⅸ), m.p. 200~201° (decomp.), which was too easy to become resinous, and, therefore, used without recrystallization in the following reaction. Only one recrystallization from methanol gave the crude methiodide (Ⅸ) as yellow plates. *Anal.* Calcd. for $C_{26}H_{27}O_3NBrI$: C, 50.59; H, 4.41; N, 2.27. Found : C, 51.21; H, 4.56; N, 2.33.

Sodium borohydride (4 g.) was added in small portions with shaking to a cooled suspension of 4.1 g. of the above crude methiodide (Ⅸ) in 30 ml. of $CHCl_3$ and 100 ml. of EtOH, the yellow solution becoming

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[*5] Recently a total synthesis of liensinine has been reported independently by Hsich, *et al.*[9)]

[*6] Infrared and ultraviolet spectra were measured on a Type EPI-2 Hitachi infrared spectrophotometer and Type ETS-3 Hitachi recording spectrophotometer, respectively. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference. Melting points were determined on a Kofler block and uncorrected.

[*7] This was dried over P_2O_5 at room temperature (3 mm. Hg) for 36 hr.

9) Y. Y. Hsich, P. C. Pan, W. C. Chen, Y. S. Kao : Scientia Sinica, **13**, 2020 (1964).

colorless. After the reaction the solvent was distilled off *in vacuo,* the residue was treated with a small amount of 1% NaOH and H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried on K_2CO_3, and evaporated, leaving 2.8 g. of the tetrahydroisoquinoline derivative (X) as a colorless viscous syrup. Recrystallization of the perchlorate of X from EtOH afforded colorless scales, m.p. 180~181°. *Anal.* Calcd. for $C_{26}H_{28}O_3NBr \cdot HClO_4$: C, 53.56; H, 5.01; N, 2.40. Found : C, 53.07; H, 5.33; N, 2.34.

N-(3-Methoxy-4-tosyloxyphenethyl)-2-(4-benzyloxyphenyl)acetamide(XIII)——A solution of 3.81 g. of 3-methoxy-4-tosyloxyphenethylamine[7] (XII) in 50 ml. of $CHCl_3$ was added to a cooled solution of 2.5 ml. of triethylamine in 25 ml. of $CHCl_3$. To the above mixture was dropwise added a solution of 2.94 g. of 4-benzyloxyphenylacetyl chloride[8] (XI) in 25 ml. of $CHCl_3$. After being allowed to stand at room temperature overnight, the solvent was distilled off at <50°, and the residue was crystallized on being triturated with a small amount of MeOH. Recrystallization from MeOH gave 3.5 g. of the amide (XIII) as colorless scales, m.p. 108~109°. *Anal.* Calcd. for $C_{31}H_{31}O_6NS$: C, 68.23; H, 5.73; N, 2.57. Found : C, 67.93; H, 5.76; N, 2.67. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3400 (NH), 1655 (C:O), 1370 and 1148 ($-SO_2-O-$).

1-(4-Benzyloxybenzyl)-2-methyl-6-methoxy-7-tosyloxy-1,2,3,4-tetrahydroisoquinoline (XVI)——A mixture of 0.5 g. of the above amide (XIII), 3 ml. of dry benzene, and 2 ml. of $POCl_3$ was heated at 73~75° for 30 min. and then at 80° for 45 min. After the mixture had been cooled, 100 ml. of ligroin was added to it and an upper layer was removed by decantation. The residual oil was dissolved in 30 ml. of $CHCl_3$ and decomposed with an excess of saturated $NaHCO_3$. The solvent was separated, washed with H_2O, dried on Na_2SO_4, and distilled off, to give 0.4 g. of 1-(4-benzyloxybenzyl)-6-methoxy-7-tosyloxy-3,4-dihydroisoquinoline (XIV) as a reddish-brown syrup, which could not be characterized as crystals.

A mixture of 0.4 g. of the above dihydroisoquinoline (XIV) and 1 ml. of methyl iodide was allowed to stand at room temperature overnight, and removal of an excess of methyl iodide at <30° *in vacuo* gave the methiodide (XV) as a reddish-brown caramel-like solid.

To a solution of the above methiodide (XV) in 30 ml. of MeOH was added 0.5 g. of sodium borohydride in small portions with shaking. After the reaction, the solvent was distilled off, the residue treated with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed wtih H_2O, dried on Na_2SO_4, and evaporated, leaving a pale green viscous syrup, which was again extracted with ether. Removal of the solvent gave 0.31 g. of the tetrahydroisoquinoline derivative (XVI) as an oily syrup. Recrystallization of the styphnate from MeOH gave yellow scales, m.p. 92~93°. *Anal.* Calcd. for $C_{32}H_{33}O_5NS \cdot C_6H_3O_8N_3$: C, 57.86; H, 4.60; N, 7.10. Found : C, 58.19; H, 4.69; N, 6.71.

1-(4-Benzyloxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (XVII)——A solution of 0.9 g. of the preceding tetrahydroisoquinoline (XVI) in 3 ml. of tetrahydrofuran was admixed with 2.3 ml. of 5% ethanolic KOH solution. After being allowed to stand at room temperature overnight, the mixture was distilled off at <40°, and 20 ml. of H_2O was added. This was treated with crystalline NH_4Cl until the solution showed pH 8.8, and the yellow precipitate formed was extracted with benzene. The benzene extract was washed with saturated NaCl solution, dried on Na_2SO_4, and distilled off, to give 0.5 g. of the tetrahydroisoquinoline derivative (XVII) as a pale yellow viscous syrup, which was recrystallized from MeOH to afford colorless plates, m.p. 138~139°. *Anal.* Calcd. for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found : C, 77.06; H, 6.99; N, 3.44. The picrate was crystallized from MeOH to afford yellow scales, m.p. 80~81°. *Anal.* Calcd. for $C_{25}H_{27}O_3N \cdot C_6H_3O_7N_3$: C, 60.18; H, 4.89. Found : C, 59.91; H, 5.00. The chloroplatinate of XVII was characterized by recrystallization from EtOH as a colorless powder, m.p. 160~170°. *Anal.* Calcd. for $C_{25}H_{27}O_3N \cdot \frac{1}{2}H_2PtCl_6 \cdot H_2O$: C, 49.03; H, 5.43; N, 2.29. Found : C, 48.60; H, 5.05; N, 2.75.

Diastereoisomeric Mixture of O,O-Dibenzylliensinine (II)——A mixture of 2.5 g. of 1-(4-benzyloxy-3-bromobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X), 2 g. of 1-(4-benzyloxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (XVIII), 295 mg. of Cu powder, 1.07 g. of K_2CO_3, 100 mg. of KI, and 9.5 ml. of dry pyridine was gradually heated, with stirring, in an oil-bath in a current of N_2 until the temperature of the mixture reached 150~151° (bath), at which temperature the mixture was kept for 48 hr. The mixture was cooled and admixed with 20 ml. of benzene. Filtration and evaporation of the solvent gave the residue which was thrice extracted with benzene. The extract was washed with H_2O and dried on Na_2SO_4. Removal of the solvent gave the residue, which was chromatographed on alumina column (20 × 3.5 cm.).

Elution with benzene (3200 ml.), benzene-$CHCl_3$ (2:1; 1300 ml.), benzene-$CHCl_3$ (1:1; 1600 ml.) and benzene-$CHCl_3$ (1:2; 2600 ml.) successively and evaporation of each solvent gave a viscous oily base, showing a positive Beilstein test. This substance was identical with the starting material (X) in IR spectrum and mixed melting point test of their perchlorates. Successive elution with benzene-$CHCl_3$ (1:3, 23 × 100 ml.) fractions gave the results shown in Table I. The eluate F_{19}~F_{21} gave a diastereoisomeric mixture of O,O-dibenzylliensinine as a pale yellow glass. Nuclear magnetic resonance spectrum of this compound in $CDCl_3$ showed two signals of methylene proton in benzyloxy group at 5.00 τ and 5.12 τ independently, excluding symmetrical structure such as biphenyl-derivatives which would be formed by bimolecular condensation of X. Recrystallization of the perchlorate from EtOH gave a colorless powder, m.p. 113～117°. *Anal.* Calcd. for $C_{51}H_{54}O_6N_2 \cdot 2HClO_4 \cdot H_2O$: C, 60.65; H, 5.79; N, 2.77. Found : C, 60.83; H, 5.60; N, 2.84. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 3500 (OH) (water of crystallization).

Diastereoisomeric Mixture of Liensinine (I′)——A solution of 0.5 g. of the above compound (II) in 20 ml. of benzene was shaken with 50 ml. of conc. HCl for 30 min. After being allowed to stand at room temperature overnight, the mixture was heated under reflux in a current of N_2 at 100° for 6 hr. After cooling, the reaction mixture was diluted with an excess of H_2O, and then, H_2O was removed by distillation *in vacuo*. After an additional mixture of EtOH and benzene had been added to the above residue, evaporation of the solvent gave the crude HCl salt as a caramel-like substance, which was dissolved in H_2O and extracted with benzene. The aqueous layer was basified with 10% NaOH and extracted with $CHCl_3$. The above alkaline solution was filtered, and crystalline NH_4Cl was added to the filtrate, giving a pale yellow precipitate, which was thrice extracted with 100 ml. of $CHCl_3$. The solvent was washed with saturated NaCl solution, dried on Na_2SO_4, and distilled off, to give a caramel-like substance (266 mg.). Recrystallization from ether gave diastereoisomeric mixture of liensinine (I′) as colorless plates, m.p. 95～103°. *Anal.* Calcd. for $C_{37}H_{42}O_6N_2 \cdot \frac{1}{2}H_2O$: C, 71.71; H, 6.99; N, 4.52. Found : C, 71.39; H, 6.83; N, 4.07. IR $\nu_{\max}^{KBr}$ cm^{-1}: 3430 (broad) (OH) (water of crystallization and phenolic OH), 2845 (N-Me). UV $\lambda_{\max}^{95\%\ EtOH}$ mμ (log ε) : (synthetic) 285 mμ (log ε 4.06), (natural) 285 mμ (log ε 4.03), Rf (paper chromatography) (synthetic) 0.555, (natural) 0.558 [BuOH-AcOH-H_2O (5:1:4) as solvent; the spots were detected by their fluorescence under UV light (short wave 2536 Å, cycle 50)]. NMR (τ) (in $CDCl_3$) spectra : (synthetic), 6.18, 6.25, 6.42, 6.50, 6.57 (9H, 3OMe), and 7.48 (6H, 2NMe); (natural), 6.14 (3H, OMe), 6.20 (3H, OMe), 6.59 (3H, OMe) and 7.48 (6H, 2NMe).

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Summary

Diastereoisomeric mixture of O,O-dibenzyl-liensinine (II) was successfully obtained by the modified Ullmann reaction of *dl*-1-(4-benzyloxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (XVII) with *dl*-1-(3-bromo-4-benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X) which has a large substituent such as benzyloxy-group at the ortho position of bromobenzene nucleus, without any detectable side reaction on the thin-layer chromatography. Removal of benzyl group by treating II with hydrochloric acid gave diastereoisomeric mixture of liensinine (I′), whose infrared and ultraviolet spectra were identical with those of natural product.

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