Table III. Thin-layer Chromatography of the Metabolite from Dog Urine

| Compound | Solvent system | | |
|---|---|---|---|
| | I | V | VI |
| | | Rf | |
| Cyclohexylamine | 0.69 | 0.46 | 0.75 |
| Metabolite of CHS-Na | 0.68 | 0.46 | 0.76 |

The compounds were detected with quinhydrone reagent.

## Summary

The urinary metabolic product of CHS-Na in human, rabbit, and dog was studied. As a metabolite of CHS-Na, cyclohexylamine was found in the urine from human and dog which were received CHS-Na orally. From human urine, the metabolite was isolated as a benzoyl derivative and was quantitatively estimated. In rabbit, however, any metabolite of CHS-Na was not found in our experiment.

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# 133. Tetsuji Kametani, Haruhiko Yagi, and Shigeo Kaneda : Bisbenzylisoquinoline Alkaloids and Related Compounds. IX.*1 A Modified Total Synthesis of Stereoisomeric Mixture of Magnolamine.*2 (Studies on the Syntheses of Heterocyclic Compounds. CXLV.*3)

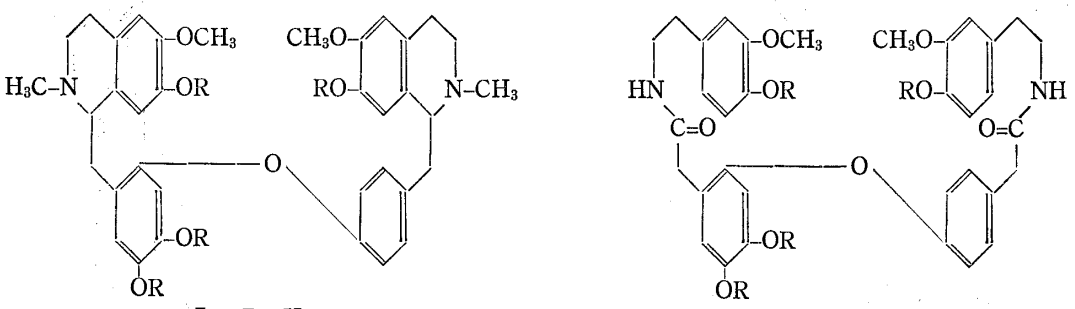
(*Pharmaceutical Institute, Tohoku University School of Medicine**4)

Magnolamine (I), $C_{36}H_{40}O_7N_2$, was isolated from the leaves of *Magnolia fuscata* which grows in Caucasian shores of the Black Sea by Proskurnina and Orekhoff.[1,2] Tomita and Ito[3] showed it to be a benzylisoquinoline alkaloid with the usual feature that two 1-benzylisoquinoline derivatives are joined, as in I.

In a previous paper[4] ring-closure of the diamide (II) by Bischler-Napieralski reaction, followed by reduction of its corresponding methiodide, gave a stereoisomeric mixture of magnolamine (I), but attempts to separate each diastereoisomers resulted in failure.

*1 Part VIII. T. Kametani, H. Yagi : Tetrahedron Letters, **1965**, 953.
*2 This study was presented at the Meeting of the Pharmaceutical Society of Japan (at Tokushima) in 1965.
*3 Part CXLI of this series [This Bulletin, **14**, 566 (1966)] should be corrected as Part CXLII; Part CXLIII : Yakugaku Zasshi, **83**, 838 (1963); and Part CXLIV : *Ibid.*, **83**, 851 (1963).
*4 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 八木治彦, 金田重夫).
1) N.F. Proskurnina, A.P. Orekhoff: J. Gen. Chem. U.R.S.S., **9**, 126 (1939); Chem. Zentr., **110**, I, 423 (1939).
2) *Idem* : J. Gen. Chem. U.R.S.S., **16**, 129 (1946); Chem. Abstr., **41**, 460 (1947).
3) M. Tomita, K. Ito : Yakugaku Zasshi, **78**, 103 (1958).
4) T. Kametani, H. Yagi : This Bulletin, **14**, 78 (1966).

The purpose of the present investigation was to study the Ullmann reaction of two 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives, namely, two components of biscoclaurine type alkaloids which were used as starting materials for total syntheses of tetrandrine[5] and liensinine[6] in order to obtain the corresponding O-tetrabenzylmagnolamine (XXI) as a possible intermediate for the synthesis of magnolamine; hydrolysis of XXI with ethanol-hydrochloric acid was also tried, leading eventually to a synthesis of stereoisomeric mixture of magnolamine that supports the structure (I).



I: R=H
XXI: R=$CH_2C_6H_5$

II: R=$CH_2C_6H_5$

Chart 1.

Synthesis of 7-benzyloxy-1-(2-bromo-4,5-bisbenzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (III) as one component of starting materials in case of Ullmann reaction was examined as follows. Demethylation[7] of methyl 2-bromo-4,5-dimethoxyphenylacetate[8] (V) with hydrobromic acid in glacial acetic acid gave dihydroxycarboxylic acid (VI), which was converted into the ester (VII) in 8% yield by esterification. Benzylation of the ester (VII) with benzyl chloride in ethanol in the presence of potassium carbonate gave bisbenzyloxy-derivative (VIII), in whose NMR (nuclear magnetic resonance) spectrum the protons of methyl group of ethyl radical were shown at 8.80$\tau$ (J=8 c.p.s.) as a triplet and those of its methylene group were shown at 5.92$\tau$ (J=8 c.p.s.) as a quartet. Condensation of the compound (VIII) with 4-benzyloxy-3-methoxyphenethylamine (IX)[9] at 190° in an oil-bath for 5~6 hr. afforded the amide (X), m.p. 148~151°, which was cyclized with phosphoryl chloride in dry benzene to give the hydrochloride of 3,4-dihydroisoquinoline derivative (XI) as pale yellow scales, m.p. 194~196° (decomp.) in 85% yield. Reduction of XI in methanol with sodium borohydride gave the corresponding 1,2,3,4-tetrahydroisoquinoline derivative (XII), m.p. 89~90°. Eschweiler-Clarke reaction of XII with 100% formic acid and 37% formalin yielded our expected compound (III) as pale yellow prisms, m.p. 96~97°, whose NMR spectrum showed the protons of N-methyl group at 7.60$\tau$ as a singlet, those of O-methyl group at 6.32$\tau$, and those of the methylene group of benzyloxy radicals at 5.37, 5.17 and 5.09$\tau$. These facts support the structure of III.

Secondly, synthesis of 7-benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IV) was examined as follows. Condensation of methyl 4-hydroxyphenylacetate (XIII)[10] with amine (IX) at 195° in an oil-bath for 6 hr. gave the hydroxyamide derivative (XIV), which was converted into ethoxycarbonyloxy-derivative (XV) by ethoxycarbonylation with ethyl chlorocarbonate in 1*N* sodium hydroxide solution. This

5) M. Tomita, N. Fujitani, T. Kishimoto: Yakugaku Zasshi, **82**, 1148 (1961).
6) T. Kametani, S. Takano, K. Masuko, F. Sasaki: This Bulletin, **14**, 67 (1966).
7) S. Tamura, K. Ohkuma, T. Hayashi: J. Agr. Chem. Soc. Japan, **27**, 318 (1952).
8) T. Kametani, K. Fukumoto, T. Nakano: Yakugaku Zasshi, **82**, 1307 (1962); T. Kametani, K. Fukumoto: J. Chem. Soc., **1963**, 4289.
9) J. Finkelstein: J. Am. Chem. Soc., **73**, 550 (1951).
10) H. Salkowski: Ber., **22**, 2140 (1889).

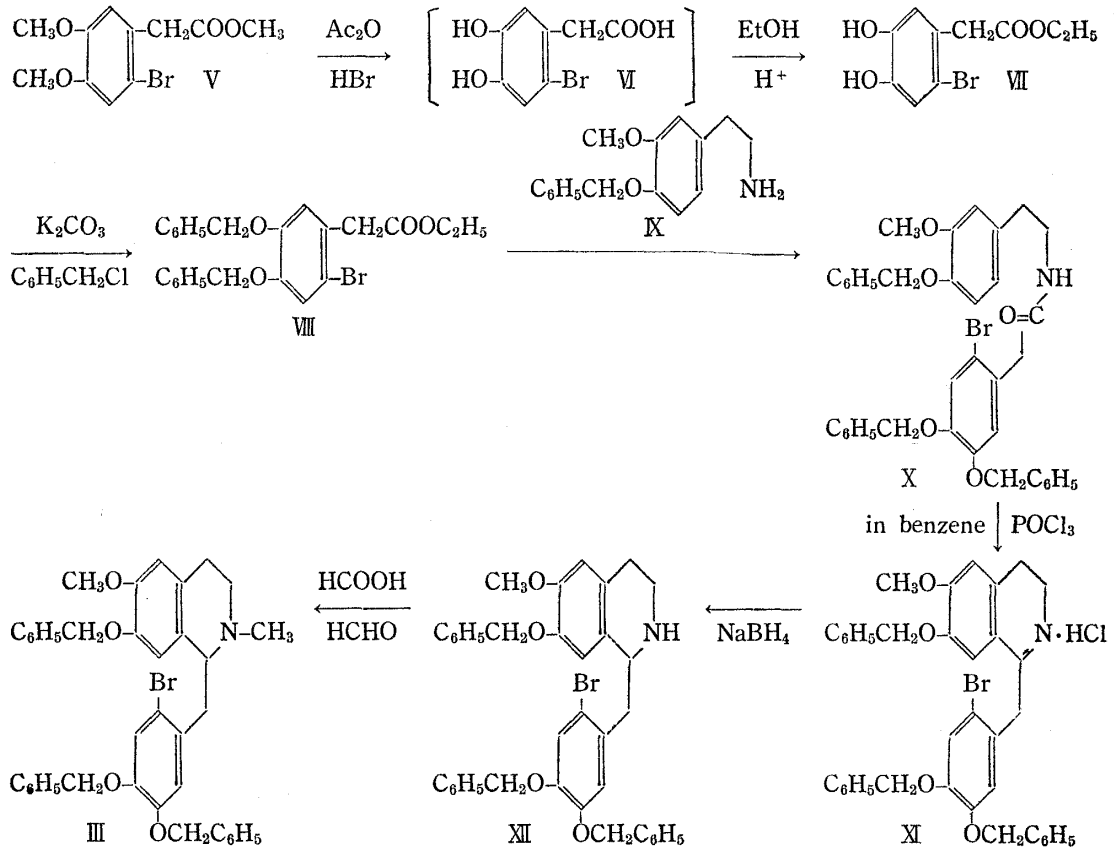


Chart 2.

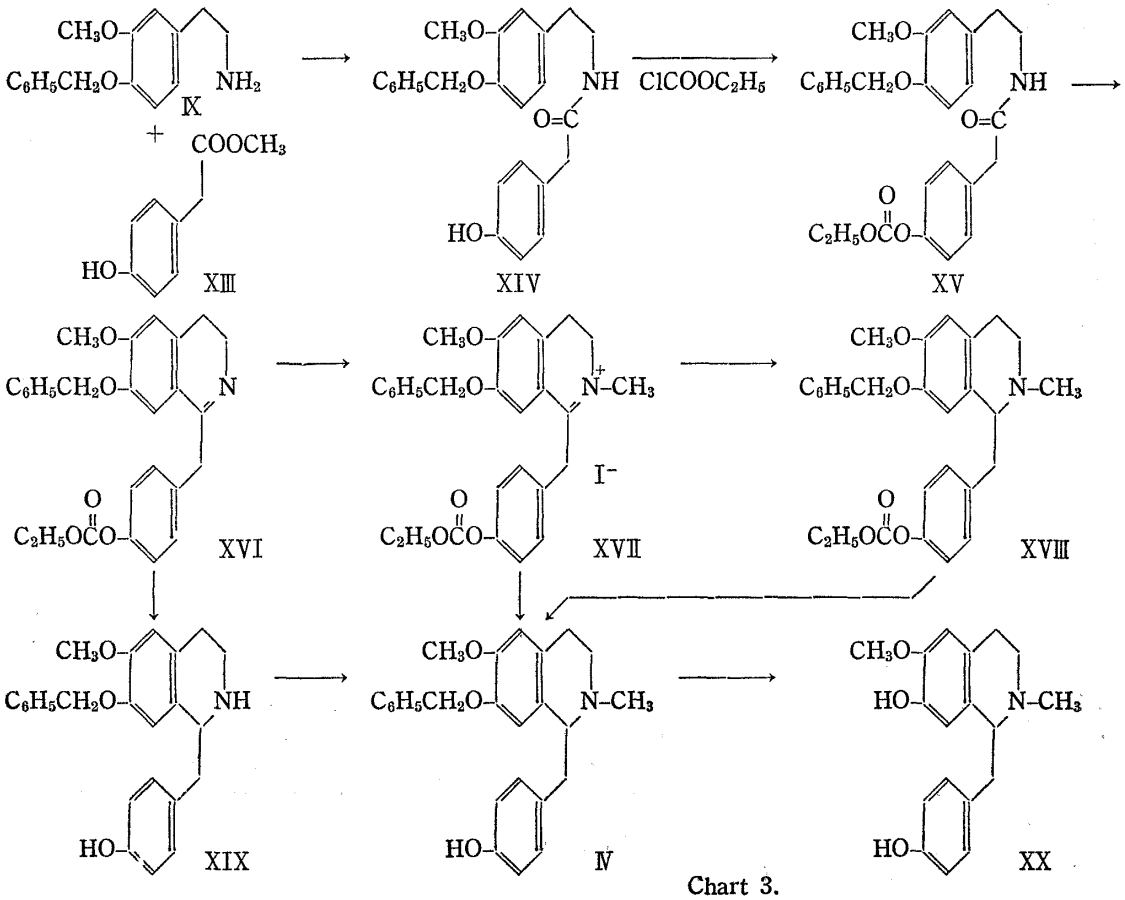


Chart 3.

compound was identical with an authentic sample.[9] Bischler-Napieralski reaction of the above amide (XIV) with phosphoryl chloride in dry toluene gave the hydrochloride of 3,4-dihydroisoquinoline derivative (XVI), whose methiodide (XVII) was reduced with sodium borohydride in chloroform-methanol to give 1,2,3,4-tetrahydroisoquinoline derivative (XVIII). This compound was characterized as its picrate and oxalate.

Hydrolysis of the compound (XVIII) with 5% ethanolic sodium hydroxide solution gave our expected compound (IV) as colorless prisms, m.p. 139~141°, which was also obtained by reduction of the methiodide (XVII) with sodium borohydride, followed by hydrolysis of ethoxycarbonyl group in an alkaline media. The NMR spectrum of this compound (IV) showed the protons of N-methyl group at 7.60$\tau$ as a singlet, those of the methylene group in benzyloxy groups at 5.28$\tau$ as a singlet, those of O-methyl group at 6.28$\tau$, and one proton of hydroxy group at 4.75~5.17$\tau$ as a broad signal. Moreover, this compound (IV) was obtained by Eschweiler-Clarke reaction of O-benzylcoclaurine (XIX) which was prepared by reduction of the hydrochloride of 3,4-dihydroisoquinoline derivative (XVI) with sodium borohydride. Debenzylation of IV with 20% hydrochloric acid gave *dl*-N-methylcoclaurine (XX), which was identical with an authentic sample.[11] This fact proves that the structure of IV was correct.

After the resolution of both compounds (III) and (IV), Ullmann reaction between optically active compounds of both specimens would afford our expected O-benzylmagnolamine, but this paper describes the Ullmann reaction between both racemic compounds as a preliminary experiment.

Finally, condensation by heating both specimens (III) and (IV) at 150° in an oil-bath in the presence of pyridine, copper powder, potassium carbonate, and potassium iodide gave a stereoisomeric mixture of our expected O-benzylmagnolamine which was identical with an authentic sample.[4] During the above reaction, it was examined by thin-layer chromatography whether the spots of the compounds, (III) and (IV) have disappeared or not and whether the single spot having the same Rf value as an authentic sample (XXI) will be appeared or not. It took 48 hr. for only the latter spot to appear in thin-layer chromatography. Alumina chromatography of the reaction mixture afforded O-benzylmagnolamine (XXI) in 34% yield, whose diperchlorate was identical with that of an authentic sample (XXI).[4] In the previous paper[4] hydrolysis of XXI was examined to give our expected magnolamine (I). These facts reveal that modified total synthesis of the stereoisomeric mixture of magnolamine (I) has been accomplished.

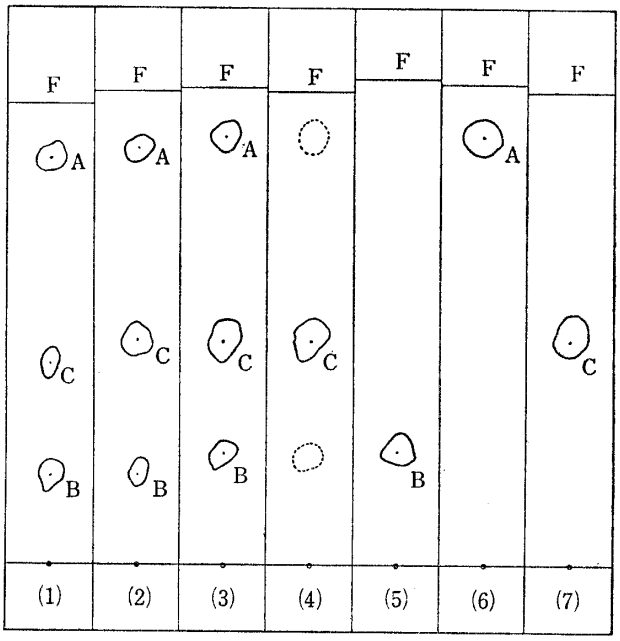



Fig. 1. Thin-layer Chromatography of the Product During the Ullmann Reaction.

Silica-gel B. (Wako) activated at 120° for 2 hr. (0.25 mm.) and benzene-methanol (10:2) as solvent were used at 25°, and the spots were detected by their fluorescence under UV light.

A: III, $R_f$=0.876~0.896. B: IV, $R_f$=0.190~0.231.
C: XXI, $R_f$=0.441~0.476. F: The line of the liquid front.
(1): Reaction time: 4 hr. (2): Reaction time: 10.5 hr.
(3): Reaction time: 21.5 hr.
(4): Reaction time: 48 hr. (5): Pure compd. (IV)
(6): Pure compd. (III) (7): Pure compd. (XXI)

11) D. A. A. Kidd, J. Walker: J. Chem. Soc., **1954**, 669.

Approach to the total synthesis of magnolamine by Ullmann reaction of optically active 1,2,3,4-tetrahydroisoquinolines (Ⅲ) and (Ⅳ) is under examination.

## Experimental*5

**Ethyl 2-Bromo-4,5-dihydroxyphenylacetate (VII)**——A mixture of 40 g. of methyl 2-bromo-4, 5-dimethoxyphenylacetate (V),[7] 200 ml. of 48% HBr aq. solution, and 100 ml. of $Ac_2O$ was heated under reflux at 140° in an oil-bath for 5 hr. After the reaction, removal of the excess of HBr and $Ac_2O$ gave the acid (Ⅵ) as a brownish-black viscous syrup, which was used in the following reaction.

To a solution of the preceding acid (Ⅵ) in 400 ml. of EtOH was added 8 ml. of conc. $H_2SO_4$ and the mixture was heated under reflux for 5 hr. After removal of the solvent, a suitable amount of EtOH was added to the residue and the solvent completely distilled off. The resultant residue was extracted with benzene. The benzene extract was washed with 5% $NaHCO_3$ aq. solution and water, dried on $Na_2SO_4$, and distilled to give the residue, which was again dissolved in hot $CHCl_3$. After cooling 3.4 g. of an amorphous powder was precipitated and collected by filtration. Recrystallization from ether-hexane gave the ester (Ⅶ) as colorless needles, m.p. 107~108°. *Anal.* Calcd. for $C_{10}H_{11}O_4Br$ : C, 43.67; H, 4.03. Found : C, 44.05; H, 4.10. IR $cm^{-1}$ (KBr) : $\nu_{OH}$ 3521 (unassociated OH); $\nu_{OH}$ 3322 (associated OH); $\nu_{C=O}$ 1709.

**Ethyl 2-Bromo-4,5-bisbenzyloxyphenylacetate (VIII)**——A mixture of 9 g. of the ester (Ⅶ), 100 ml. of EtOH, 9.2 g. of benzyl chloride, and 10 g. of $K_2CO_3$ was heated under reflux for 5 hr. After cooling the reaction mixture was filtered in order to remove an inorganic substance. After removal of the solvent the residue was dissolved in benzene the benzene, layer was washed with 10% NaOH aq. solution and water, and dried on $Na_2SO_4$. Removal of the solvent gave 10 g. of the crude ester (Ⅷ). Recrystallization from ether-hexane afforded col orlessneedles, m.p. 101~102°. *Anal.* Calcd. for $C_{24}H_{23}O_4Br$ : C, 63.35; H, 5.10. Found : C, 63.47; H, 5.04. IR $cm^{-1}$ (KBr) : $\nu_{C=O}$ 1733; $\delta_{CH}$ 754, 700 (monosubstituted benzene). NMR ($\tau$) (in $CCl_4$); 8.80 (3H, triplet, J=8 c.p.s., $C\underline{H}_3$ of Et group); 5.92 (2H, quartet, J=8 c.p.s., $C\underline{H}_2$ of Et group); 4.98 (4H, $2C\underline{H}_2$ of benzyl group); 6.42 (2H, $PhC\underline{H}_2O$-).

**N-(4-Benzyloxy-3-methoxyphenethyl)-2-(4,5-bisbenzyloxy-2-bromophenyl)acetamide (X)**——A mixture of 5.5 g. of Ⅷ and 3.8 g. of 4-benzyloxy-3-methoxyphenethylamine[9] was heated at 190° in an oil-bath for 5~6 hr. and the resultant reaction mixture was dissolved in $CHCl_3$. The solvent layer was washed with 10% HCl aq. solution and $H_2O$, dried on $Na_2SO_4$ and distilled, giving 5.5 g. of X. Recrystallization from benzene-EtOH gave a colorless powder, m.p. 148~151°. *Anal.* Calcd. for $C_{38}H_{36}O_5NBr$ : C, 68.47; H, 5.44; N, 2.10. Found : C, 68.35; H, 5.84; N, 2.06. IR $cm^{-1}$ (KBr) : $\nu_{NH}$ 3320 : $\nu_{C=O}$ 1645.

**7-Benzyloxy-1-(4,5-bisbenzyloxy-2-bromobenzyl)-3,4-dihydro-6-methoxyisoquinoline (XI)**——A mixture of 2.2 g. of the amide (X), 3.2 g. of $POCl_3$ and 20 ml. of dry benzene was heated under reflux on a water-bath for 2.5 hr. The reaction mixture was treated with an excess of hexane and an upper solvent layer was separated by decantation, giving the precipitate, which was dissolved in $CHCl_3$. The $CHCl_3$ extract was washed with $H_2O$, dried on $Na_2SO_4$ and distilled to give 2 g. of a pale brown syrup. Recrystallization from EtOH gave 3,4-dihydroisoquinoline derivative (Ⅺ) as pale, yellow scales, m.p. 194~196° (decomp.). *Anal.* Calcd. for $C_{33}H_{34}O_4NBr \cdot HCl \cdot \frac{1}{2}H_2O$*6 : C, 65.76; H, 5.23; N, 2.02. Found : C, 65.79; H, 5.48; N, 1.83. IR $cm^{-1}$ (KBr) : $\nu_{C=\overset{+}{N}H}$ 1647 (HCl salt of Ⅺ).

**7-Benzyloxy-1-(4,5-bisbenzyloxy-2-bromobenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (XII)**——To a solution of 1.8 g. of HCl salt of Ⅺ in 360 ml. of MeOH was gradually added 1.8 g. of $NaBH_4$ with stirring. The color of the reaction mixture changed from yellow to colorless. Furthermore, the mixture was stirred at room temperature for an additional 30 min. Removal of the solvent gave the residue, which was extracted with benzene. The benzene extract was washed with $H_2O$, dried on $K_2CO_3$ and distilled to give 1.2 g. of a pale yellow syrup. Recrystallization from MeOH afforded 1,2,3,4-tetrahydroisoquinoline (Ⅻ) as a colorless powder, m.p. 89~90°. *Anal.* Calcd. for $C_{38}H_{36}O_4NBr$ : C, 70.21; H, 5.53; N, 2.16. Found : C, 70.51; H, 5.46; N, 2.08. IR $cm^{-1}$ (KBr) : $\nu_{NH}$ 3413.

**7-Benzyloxy-1-(4,5-bisbenzyloxy-2-bromobenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (III)**——A mixture of 5 g. of Ⅻ, 80 ml. of 100% $HCO_2H$, and 80 ml. of 37% formalin was heated on a water-bath for 4 hr. After cooling, the reaction mixture was basified with 10% $NH_4OH$ aq. solution, a yellowish-brown viscous substance being separated and extracted with benzene. The benzene extract was washed with $H_2O$, dried on $K_2CO_3$ and distilled, yielding 4.5 g. of a pale yellow syrup, which was recrystallized from MeOH to give the compound (Ⅲ) as pale, yellow prisms, m.p. 96~97°. *Anal.* Calcd. for $C_{39}H_{38}O_4NBr$ : C, 70.43; H, 5.76; N, 2.11. Found : C. 70.21; H, 5.99; N, 1.99. IR $cm^{-1}$ (KBr) : $\nu_{N-Me}$ 2770. NMR ($\tau$) (in $CDCl_3$) : 7.60 (3H, singlet, $N-C\underline{H}_3$); 6.32 (3H, singlet $O-C\underline{H}_3$); 5.37, 5.17, 5.09 (6H, 3 $PhC\underline{H}_2O$-).

*5 All melting points were not corrected.

*6 This was dried over $P_2O_5$ at 100° (5 mm.) for 2.5 hr.

**N-(4-Benzyloxy-3-methoxyphenethyl)-4-hydroxyphenylacetamide (XIV)**——A mixture of 18 g. (1.2 moles) of β-(4-benzyloxy-3-methoxy)phenethylamine (IX)[9] and 9.6 g. (1 mole) of methyl 4-hydroxyphenylacetate was heated at 195° in an oil-bath for 6 hr. During this reaction, the reaction mixture colored red and a reflux of MeOH was observed. After the reaction mixture had been dissolved in $CHCl_3$, the solvent layer was in turn washed with 10% HCl aq. solution, $H_2O$, saturated $NaHCO_3$ aq. solution, and $H_2O$, dried on $Na_2SO_4$, and distilled to give 21 g. (98%) of XIV as a reddish viscous syrup, which was used in the following reaction without purification.

**N-(4-Benzyloxy-3-methoxyphenethyl)-4-ethoxycarbonyloxyphenylacetamide (XV)**——To a stirred solution of 22.7 g. of the preceding amide (XIV) in 100 ml. of 1*N* NaOH aq. solution was drop by drop added 7 g. of $ClCO_2C_2H_5$ at 0~5° within 30 min., and the mixture was allowed to stand at the same temperature as above for 1 hr., the crystals being separated and extracted with benzene. The benzene extract was washed with $H_2O$, 10% HCl aq. solution, dried on $Na_2SO_4$ and distilled to give 23 g. (80%) of colorless crystals. Recrystallization from benzene-hexane gave the amide (XV) as colorless needles, m.p. 105.5~106° (lit.,[9] m.p. 101~102°). *Anal.* Calcd. for $C_{27}H_{29}O_6N$: C, 69.95; H, 6.31; N, 3.02. Found: C, 69.88; H, 6.81; N, 2.89.

**7-Benzyloxy-1-(4-ethoxycarbonyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline( XVI)**——A mixture of 35 g. of XV, 12.5 g. of $POCl_3$ and 240 ml. of dry toluene was heated under reflux in an oil-bath for 1.5 hr. After an excess of hexane had been added to the reaction mixture, the crystals separated were collected by filtration to give 27.3 g. of XVI as pale, yellow scales, m.p. 195~196° (lit.,[9] m.p. 195~196°). Recrystallization of the picrate from EtOH gave yellow scales, m.p. 165°. *Anal.* Calcd. for $C_{27}H_{27}O_5N \cdot C_6H_3O_7N_3$: C, 58.76; H, 4.49; N, 8.30. Found: C, 58.90; H, 4.42; N, 8.29. IR $cm^{-1}$ (KBr): $\nu_{C=O}$ 1767.

**7-Benzyloxy-1-(4-ethoxycarbonyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Methiodide (XVII)**——After a solution of 5 g. of XVI in 100 ml. of $CHCl_3$ had been fully shaken with saturated $NaHCO_3$ aq. solution on cooling in the presence of $N_2$, the solvent layer was separated, washed with $H_2O$, dried on $K_2CO_3$, and distilled in a current of $N_2$, giving 4.2 g. of a yellow syrup, to which was added 25 ml. of $CH_3I$. The mixture was warmed at 25~30° for 4 hr. in the presence of $N_2$, yellow precipitate being separated, collected by filtration, and washed with ether, to give 5.0 g. (82%) of a yellow powder. Recrystallization from acetone-ether gave yellow needles, m.p. 181.5° (decomp.) (lit.,[9] m.p. 168~169°). *Anal.* Calcd. for $C_{23}H_{30}O_5NI$: C, 57.23; H, 5.15; N, 2.38. Found: C, 57.58; H, 5.15; N, 2.40. IR $cm^{-1}$ (KBr): $\nu_{C=O}$ 1764; $\nu_{C=\overset{+}{N}H-}$ 163.1

**7-Benzyloxy-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-6-methoxyisoquinoline (XIX)**——To a mixture of 2.5 g. of XVI, 20 ml. of $CHCl_3$, 50 ml. of MeOH and 2 ml. of $H_2O$ was in small portions added 1g. of $NaBH_4$ at room temperature with stirring within 30 min., and the mixture was heated under reflux on a water-bath for 30 min. After the removal of the solvent the resultant residue was treated with 100 ml. of $H_2O$ and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried on $Na_2SO_4$ and distilled, giving 2.0 g. of a colorless syrup. Recrystallization from benzene gave the compound (XIX) as colorless prisms, m.p. 153~154°. *Anal.* Calcd. for $C_{24}H_{25}O_3N$: C, 76.77; H, 6.71; N, 3.73. Found: C, 77.07; H, 7.06; N, 3.73. IR $cm^{-1}$ (KBr): $\nu_{OH}$ 3550 (unassociated OH); $\nu_{OH}$ 3350 (associated OH).

**7-Benzyloxy-1-(4-ethoxycarbonyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XVIII)**——To a solution of 13 g. of the preceding methiodide (XVII) in 50 ml. of $CHCl_3$ and 150 ml. of MeOH containing 2 ml. of $H_2O$ was in small portions added 4 g. of $NaBH_4$ at 0~5° with stirring, and the mixture was allowed to stand for 1 hr. After the reaction mixture had been acidified with glacial AcOH, the solvent was distilled under reduced pressure, the residue was then basified with saturated $NaHCO_3$ aq. solution and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried on $K_2CO_3$ and distilled to give 10 g. of XVIII as a yellow viscous syrup.

Recrystallization of the picrate from EtOH gave yellow needles, m.p. 160~160.5° (decomp.). *Anal.* Calcd. for $C_{28}H_{31}O_5N \cdot C_6H_3O_7N_3$: C, 59.12; H, 4.96; N, 8.12. Found: C, 59.54; H, 4.96; N, 8.26. IR $cm^{-1}$ (KBr): $\nu_{C=O}$ 1764.

Recrystallization of the oxalate from EtOH gave colorless prisms, m.p. 174~175° (decomp.). *Anal.* Calcd. for $C_{28}H_{31}O_5N \cdot C_2H_2O_4$: C, 65.32; H, 6.03; N, 2.54. Found: C, 65.54; H, 6.16; N, 2.42. IR $cm^{-1}$ (KBr): $\nu_{C=O}$ 1767.

**7-Benzyloxy-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (IV)**——(a) A mixture of 3.3 g. of XVIII and 20 ml. of 5% EtOH-NaOH solution was heated at 60~70° for 30 min. in the presence of $N_2$. After the reaction, the solvent was removed by distillation and 20 ml. of $H_2O$ was added to the resultant residue. The above alkaline aqueous solution was made to be pH 9~10 by adding an excess of crystalline $NH_4Cl$, colorless crystals being precipitated. Filtration and washing with water gave 2.8 g. of the compound (IV). Recrystallization from benzene-hexane gave colorless prisms, m.p. 139~141°. *Anal.* Calcd. for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.72; H, 7.17; N, 3.59. IR $cm^{-1}$ ($CHCl_3$): $\nu_{OH}$ 3580 (unassociated OH); $\nu_{OH}$ 3300 (associated OH); $\nu_{N-M_3}$ 2800. IR $cm^{-1}$ (KBr): $\delta_{CH}$ 735.3 and 697 (monosubstituted benzene). NMR (τ) (in $CDCl_3$): 7.60 (3H, singlet, N-$C\underline{H}_3$); 6.28 (3H, singlet, O-$C\underline{H}_3$); 5.28 (2H, singlet, Ph-$C\underline{H}_2$-O-); 4.75~5.17 (1H, broad, O$\underline{H}$).

(b) To a mixture of 2.7 g. of XVII, 15 ml. of $CHCl_3$, 50 ml. of MeOH, and 1 ml. of $H_2O$ was in small portions 1.2 g. of $NaBH_4$ at room temperature with stirring within 30 min. and, after the reaction mixture had been allowed to stand at room temperature for 30 min., it was heated under reflux on a water-bath for

1 hr. After the reaction, the solvent was removed, and 100 ml. of $H_2O$ was added to the resultant residue, giving a viscous syrup, which was extracted with $CHCl_3$. The extract was washed with $H_2O$, dried on $Na_2SO_4$, and distilled to give 2 g. of Ⅳ.

(c) A mixture of 1.2 g. of XIX, 15 ml. of 100% $HCO_2H$, and 15 ml. of 37% formalin was heated at 130° in an oil-bath for 6 hr. After the reaction the mixture was basified with 10% $NH_4OH$ aq. solution, 1.0 g. of colorless crystals being collected by filtration. Yield of Ⅳ; 1.0 g.

***dl*-N-Methylcoclaurine (XX)**——A mixture of 200 mg. of Ⅳ and 20% HCl aq. solution was heated at 90~100° on a water-bath for 6 hr. and, after cooling, was basified with $NH_4OH$ aq. solution, colorless precipitates being collected by filtration. Recrystallization from toluene-petroleum ether and then from toluene gave 92 mg. of XIX as colorless prisms, m.p. 161~162°, which were identical with an authentic sample prepared according to the literature[11] by mixed melting point test and IR spectrum.

**Synthesis of Diastereoisomeric Mixture of O-Benzylmagnolamine (XXI) by Ullmann Reaction**——A mixture of 500 mg. of Ⅲ, 310 mg. of Ⅳ, 42 mg. of Cu powder, 150 mg. of $K_2CO_3$, 14 mg. of KI, and 2.5 ml. of pyridine was heated, with stirring, at 150° in an oil-bath for 48 hr. The color of the reaction mixture changed from pale yellow to dark reddish-purple. During the reaction, the samples from the reaction mixture were taken up, and the formation of O-benzylmagnolamine was inspected by thin-layer chromatography, whose data are shown in Fig. 1.

A new spot (C) which formed was identical with that of an authentic sample[4] on thin-layer chromatography (Fig. 1) using benzene-MeOH (10:2) as elution solvent, and it revealed that the debrominated substance of Ⅲ and diphenyl derivative which would be formed by bimolecular Ullmann reaction of Ⅲ were not detected. After 48 hours' heating two spots of starting materials (B) and (C) disappeared completely.

After the reaction, the mixture was cooled and extracted with 100 ml. of benzene. Filtration and evaporation of the solvent gave the residue. This procedure was thrice repeated in order to remove pyridine. Finally, the resultant residue was dissolved in benzene. The benzene extract was washed with 10% NaOH and saturated NaCl aq. solution, dried on $K_2CO_3$ and distilled to give 0.5 g. of XXI as a brownish-violet viscous substance, which was chromatographed on alumina (10 g.). Elution with benzene and evaporation of the solvent gave 250 mg. of a pale brown glassy substance. Recrystallization of the diperchlorate from $CHCl_3$-ether afforded a colorless powder, m.p. 115~118°, which was identical with that of an authentic sample[4] by mixed melting point test and IR spectrum.

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## Summary

O-Benzylmagnolamine (XXI) was successfully obtained by the modified Ullmann reaction of *dl*-7-benzyloxy-1-(4,5-bisbenzyloxy-2-bromobenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (Ⅲ) with 7-benzyloxy-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (Ⅳ) without any detectable side reaction in thin-layer chromatography. Since removal of benzyl group by hydrolysis had already afforded magnolamine (I), a modified total synthesis of stereoisomeric mixture of magnolamine has been accomplished.

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