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Studies on the Alkaloids of Menispermaceous Plants. CCXLI.[1] Synthesis of Cycleanine. (2).[1] Bischler–Napieralski Reaction of N–Acyl–3,4–dimethoxy–5–(4–substituted–phenoxy)–β–phenethylamines[2]

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During the course of the studies for synthesis of II, the Ullmann reaction product of 8–bromoarmepavine, Bischler–Napieralski reaction of amide XI was carried out.

Characterization of the product was effected by metallic sodium–liquid ammonia fission reaction. It was found that the isoquinoline ring–closure of such an amide formulated as XVIII occurred onto both *o*– and *p*–positions to the phenoxyl grouping, that is, the direction of the ring–closure was unexpectedly affected by substituent borne on 4–position of the phenoxyl grouping.

In the preceding paper, the authors stated that the cupric oxide–catalysed Ullmann condensation of *dl*–8–bromoarmepavine (I) leads to a bisbenzylisoquinoline compound II, and that the reaction does not proceed to afford the expected cycleanine type bases (III).

The aims of the present work were to synthesize the Ullmann product (II) through different route and to examine if cycleanine type bases could be obtained by the further intramolecular Ullmann condensation of the product (II).

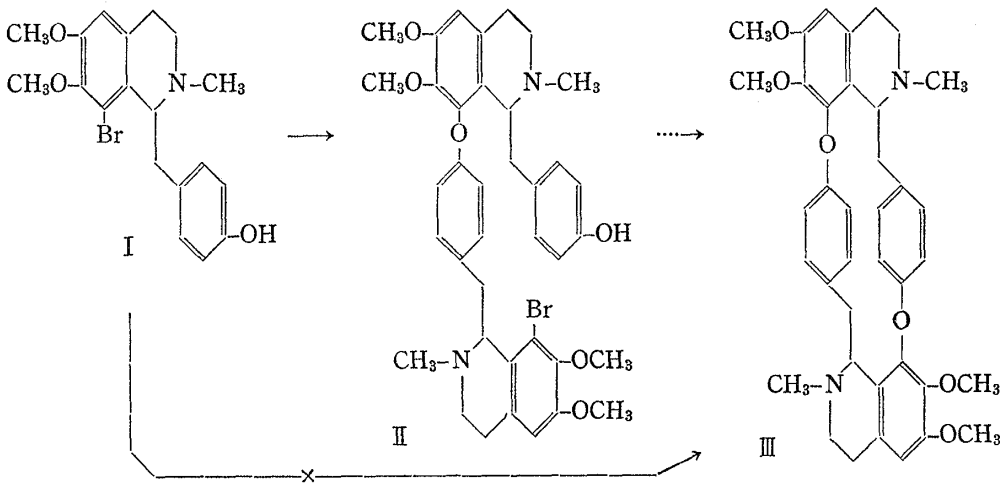

Chart 1

Though the initial aims were not attained, the authors wish to present here the results and informations obtained.

Synthesis of II was attempted by means of Bischler–Napieralski cyclization of the amide (XI), which was afforded through the following route.

1) Part CCXL, Part (1): *Chem. Pharm. Bull.* (Tokyo), **15**, 1996 (1967).
2) A part of this work was presented at the 10th Symposium on the Chemistry of Natural Products, Tokyo, Oct. 6, 1966, Symposium Paper, p. 31.
3) Location: *Yoshida–shimoadachi–cho, Sakyo–ku, Kyoto.*

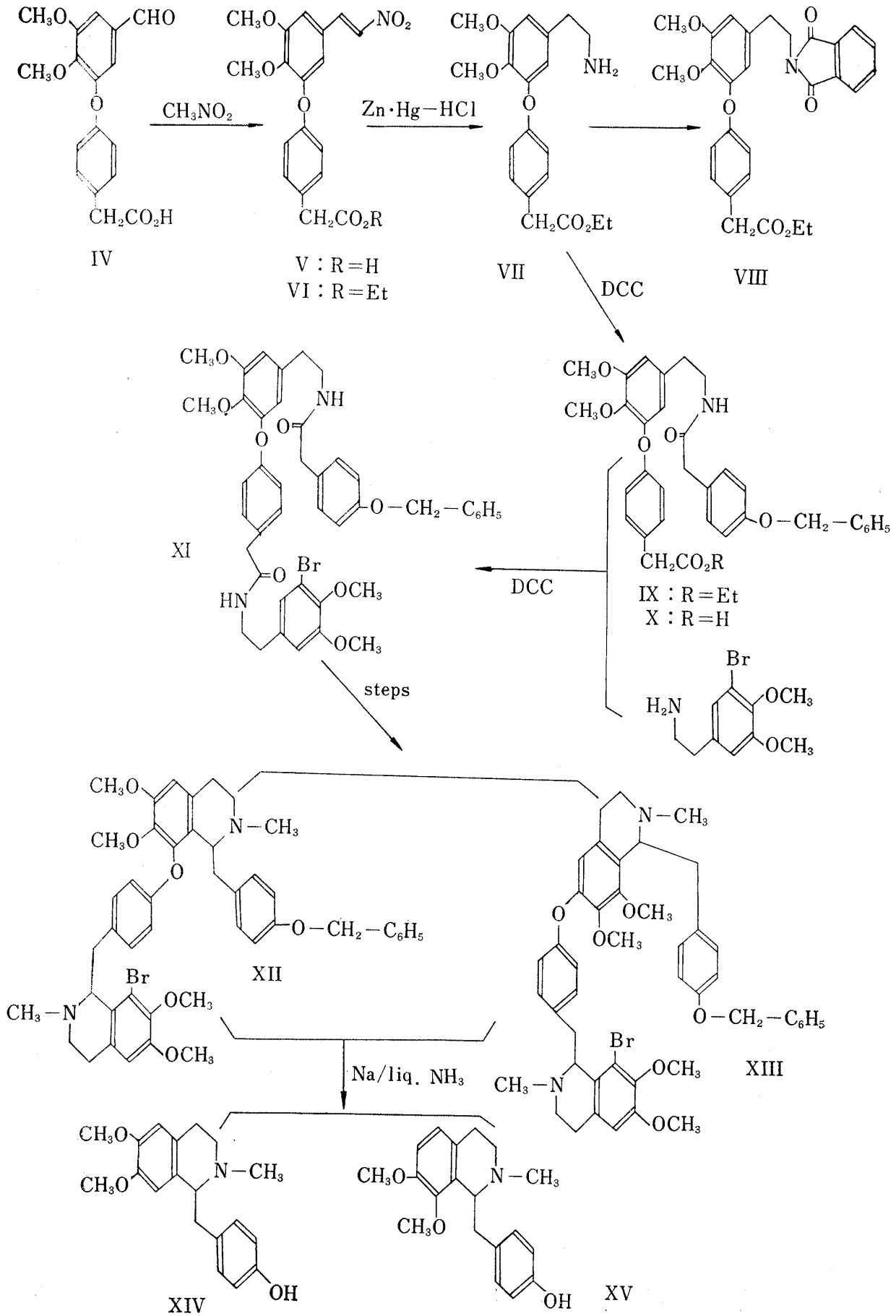

Chart 2

Phenoxybenzaldehyde (IV)[4] was condensed with nitromethane to give the nitrostyrene (V), which in turn was esterified, and the nitrovinyl-ester (VI) was reduced under Clemmensen condition to afford the corresponding phenethylamine (VII). The IR and NMR spectra of the phenethylamine and its N-phthaloyl derivative (VIII) were in full accord with the assigned structures. VII was treated with *p*-benzyloxyphenylacetic acid[5] in the presence of dicyclohexylcarbodiimide (DCC)[6] to give an amide (IX). The ethyl ester group of the amide was hydrolyzed in aqueous methanolic sodium hydroxide, and the resulted carboxylic acid (X) was again treated with DCC and 3-bromo-4,5-dimethoxy-*β*-phenethylamine.[7]

Bisamide (XI) obtained by the foregoing procedure was submitted to Bischler-Napieralski reaction in chloroform with the aid of phosphorus oxychloride; then the product was reduced with sodium borohydride, and N-methylated by formalin-borohydride method. The final product was purified on alumina column chromatography.

Although the product appeared homogenous on thin-layer chromatographic examinations, the nuclear magnetic resonance (NMR) spectrum revealed that the product consisted of almost equal amount of two substances with different planar structure.

Separation of each product was unsuccessful, though tried by various ways.

Characterization of this product mixture was effected by sodium-liquid ammonia cleavage reaction. Two kinds of bases were obtained in the ratio of 3 to 1 as the bisected products; one, the main, was proved to be *dl*-armepavine (XIV)[8] by the IR ($CHCl_3$) spectrum and mixed melting point, but the other was unknown.

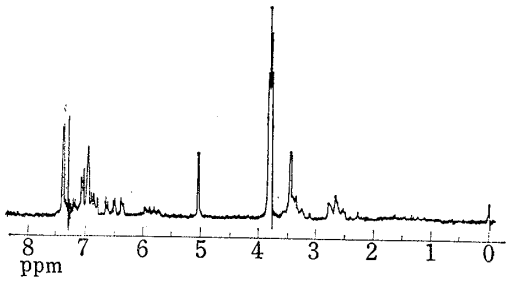

Fig. 1. NMR Spectrum of XI

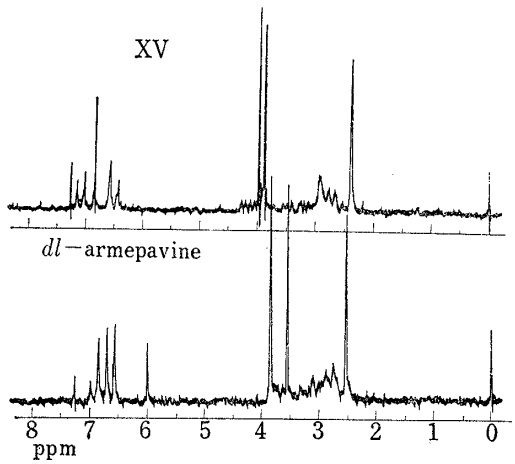

Fig. 2. NMR Spectra of *dl*-Armepavine and XV

The structure of this unknown base was eventually assigned to formula XV on the basis discussed below. The mass spectrum of the base has the same parent ion peak as *dl*-armepavine at *m/e* 313 and the fragmentation pattern is also identical. In comparison of the NMR spectrum (Fig. 2) with that of *dl*-armepavine, one of the O-methyl signals found in relatively higher field in the spectrum of armepavine is noticed to be shifted to ordinary region in that of this base. And, N-CH_3 signal of the unknown base is found in higher field than that of armepavine. Further, in aromatic region, a 1H singlet at 4.00 τ which could be assigned for the proton on 8-position of isoquinoline nucleus of armepavine is not found in that of the unknown base. Instead, a 2H singlet at 3.17 τ is found independently from A_2B_2 quartet of the benzylbenzene protons. These data show[9] that the base bears a substituent, which may be O-CH_3 group, on 8-position of the isoquinoline nucleus; thus the structure of this bisected base was proved to be XV.

4) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1341 (1965).
5) D.H.R. Barton and G.W. Kirby, *J. Chem. Soc.*, **1962**, 806.
6) C.L. Stevens and M.E. Munk, *J. Am. Chem. Soc.*, **80**, 4065, 4069 (1958).
7) M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **15**, 1996 (1997).
8) K. Fujitani, Y. Aoyagi, and Y. Masaki, *Yakugaku Zasshi*, **86**, 654 (1966).
9) M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 921 (1965).

Since the structure of amide (XI) is unambiguous, the structure of the compound which affords XIV and XV as bisected products on sodium-liquid ammonia cleavage might be drawn as formula XIII, because it is known[10] that the isoquinoline ring-closure of an amide such as XI under Bischler-Napieralski condition does not occur onto the *para*-position to the halogen substituent.

From the foregoing experiments, it was proved that the Bischler-Napieralaki cyclization of amide (XI) proceeds in two directions, that is, *ortho*- and *para*-positions with respect to the phenoxyl grouping, and eventually affords XII and XIII.

Furthermore, as an additional example of the cyclization of the amide having *p*-substituted phenoxyl grouping, Bischler-Napieralski reaction of a more readily accessible amide (IX) was carried out. The final products, N-methyltetrahydroisoquinolines, showed the same behaviors as that afforded from amide (XI) on thin-layer chromatography and NMR spectrometry. It was made clear from NMR spectrum that, in this case also, the ring-closure occurred in two directions, that is, two isomeric products (XVI) and (XVII) were afforded.

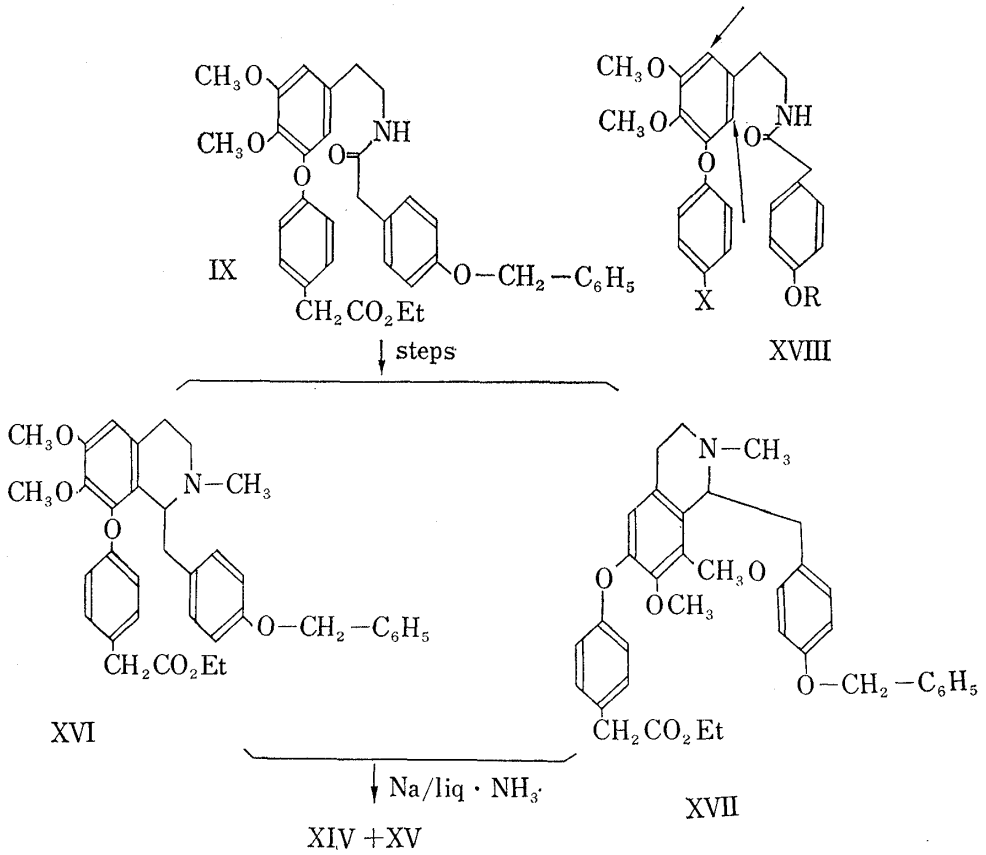

Chart 3

Metallic sodium-liquid ammonia cleavage of the product mixture also furnished almost equal amount of XIV and XV.

Formerly, it was reported[11] that the Bischler-Napieralski cyclization of an amide such as XVIII (X=H) occurred only to the *ortho*-position to the phenoxyl group. On consideration of the above fact and the result now obtained, it could be said that the direction of isoquinoline ring-closure of an amide such as XVIII under Bischler-Napieralski condition was unexpectedly affected by a substituent X borne on 4-position of the phenoxyl grouping.

10) M. Tomita and H. Watanabe, *Yakugaku Zasshi*, **58**, 783 (1938); K. Fujitani, T. Kishimoto, and S. Niimura, *Yakugaku Zasshi*, **83**, 412 (1963).
11) K. Fujitani, N. Matsumoto, K. Yoshioka, I. Yoshida, and Y. Inubushi, *Yakugaku Zasshi*, **84**, 333 (1964).

Experimental[12]

3-(4-Carboxymethylphenoxy)-4,5-dimethoxy-β-nitrostyrene (V)——3-(4-Carboxymethylphenoxy)-4,5-dimethoxybenzaldehyde (IV, 4.5 g) was dissolved in EtOH (100 ml) containing nitromethane (4.0 g). The solution was cooled on an ice bath, and 5% aq. KOH solution (40 ml) was added dropwise into the above solution with stirring. After 1 hr, the resulted mixture was poured into ice water (500 ml) containing 50 ml of conc. HCl. The precipitated crude nitrostyrene (V, yellow crystalline solid) was recrystallized from benzene. Yellow cubes, mp 131°. Yield 5.0 g. *Anal.* Calcd. for $C_{18}H_{17}O_7N$: C, 60.16; H, 4.77; N, 3.90. Found: C, 59.95; H, 4.57; N, 3.69.

3,4-Dimethoxy-5-(4-ethoxycarbonylmethylphenoxy)-β-nitrostyrene (VI)——The foregoing nitrostyrene (V) (10 g) was dissolved in 30 ml of anhyd. EtOH, and the solution was refluxed with conc. H_2SO_4 (0.5 ml) for 30 min. On cooling the solution, the product precipitated. Recrystallization from EtOH afforded yellow plates, mp 74—75°. Yield, 9.2 g. *Anal.* Calcd. for $C_{20}H_{21}O_7N$: C, 62.01; H, 5.46; N, 3.63. Found: C, 61.74; H, 5.25; N, 3.33.

Clemmensen Reduction of VI——The nitrostyrene (VI, 300 mg) and amalgamated zinc prepared from zinc powder (2.5 g) and $HgCl_2$ (300 mg) were stirred in EtOH (10 ml). Concentrated HCl was added dropwise into the above mixture until yellow coloring of the reaction mixture disappeared. The temperature of the mixture was kept below 50° during the reaction. EtOH was evaporated *in vacuo* after separation of excess Zn–Hg. The residue was washed with ether, made alkaline with conc. NH_4OH, and the product was extracted with AcOEt. 3,4-Dimethoxy-5-(4-ethoxycarbonylmethylphenoxy)-β-phenethylamine: Colorless oily substance, yield 180 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722 (ester carbonyl). NMR signals τ: 2.80, 3.08 (4H, A_2B_2 q., $J=9$ cps); 3.40 (1H, d., $J=2$ cps); 3.53 (1H, d., $J=2$ cps); 5.75, 5.93 (2H, q., $J=7.5$ cps, O–CH_2–Me); 6.14 and 6.22 (3H, s., O–CH_3); 6.43 (2H, s., Ar–CH_2–CO); 8.25 (2H, broad s., NH_2); 8.78 (3H, t., $J=7.5$ cps, CH_3 of ethyl group). The foregoing phenethylamine (VII, 200 mg) and phthalic anhydride (250 mg) were heated to reflux in xylene for 2.5 hr. The residue left after evaporation of xylene was fractionated by alumina chromatography in $CHCl_3$. From the appropriate fractions, the N-phthaloyl derivative (VIII) was isolated as colorless oily substance. Yield, 60 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 and 1715 (phthaloyl and ester carbonyls). NMR signals τ: 2.20 (4H, multiplet, phthaloyl benzene); 2.81, 3.13 (4H, A_2B_2 q., $J=9$ cps); 5.72, 5.92 (2H, q., $J=7.5$ cps, CH_2–Me); 6.18 and 6.23 (3H, s., O–CH_3); 6.43 (2H, s., Ar–CH_2–CO), 8.74 (3H, t., $J=7.5$ cps, CH_3 of ethyl group).

N-(2-(3,4-Dimethoxy-5-(4-ethoxycarbonylmethylphenoxy)phenyl)ethyl)-2-(4-benzyloxyphenyl)acetamide (IX)——*p*-Benzyloxyphenylacetic acid (560 mg), phenethylamine (VIII, 880 mg), and DCC (500 mg) were dissolved in CH_2Cl_2(30 ml), and the resulted solution was stirred at room temperature for 30 min. After the reaction ended, precipitated colorless crystals (N,N′-dicyclohexylurea) were separated off by filtration, and the CH_2Cl_2 solution was washed successively with 1% HCl, 2% NaOH, and water. Evaporation of the solvent afforded pale-yellow oil, from which an amide IX was isolated by chromatography on silica gel. Pale-yellow oily substance, yield, 1.3 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400: (amide NH); 1725 (ester carbonyl); 1663 (amide carbonyl).

N-(2-(3-(4-Carboxymethylphenoxy)-4,5-dimethoxyphenyl)ethyl)-2-(4-benzyloxyphenyl)acetamide (X)——The foregoing amide (3.0 g) was dissolved in MeOH (50 ml), and the solution was refluxed with 2N NaOH (20 ml) for 20 min. MeOH was evaporated *in vacuo*, the residual aqueous solution was extracted with $CHCl_3$ after washed with ether and acidified with conc. HCl. The obtained crude material was purified on silica gel column chromatography. Pale-yellow oily substance, yield, 2.4 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (amide NH); 1710 (COOH); 1660 (amide CO). NMR signals τ: 2.61 (5H, s., benzylbenzene); 4.98 (2H, s., Ar–CH_2–O); 6.19 and 6.21 (3H, s., O–CH_3); 6.42 and 6.54 (2H, s., Ar–CH_2–CO).

N-(2-(3-(4-(2-(3-Bromo-4,5-dimethoxyphenyl)ethylcarbamoylmethyl)phenoxy)-4,5-dimethoxyphenyl)ethyl)-(4-benzyloxyphenyl)acetamide (XI)——The foregoing amide-carboxylic acid (X) (2.3 g) and 3-bromo-4,5-dimethoxy-β-phenethylamine (1.1 g) was dissolved in CH_2Cl_2 (15 ml); then DCC (900 mg) was added with stirring. After 30 min, the crystalline ureas were separated off by filtration. The CH_2Cl_2 solution was washed successively with 1% HCl, 2% aq. NaOH, and water. Evaporation of the solvent gave an oil, which, on silica gel chromatography, afforded amide (XI). Pale-yellow viscous oily substance, yield 1.1 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1661 (amide CO). NMR (see Fig. 1).

Bischler–Napieralski Reaction of Amide (XI)——The amide (XI, 1.1 g) was dissolved in anhyd. $CHCl_3$ (30 ml) and the mixture was refluxed for 3 hr with $POCl_3$ (2 ml). The residue left after evaporation of the

12) Chromatography was carried out on activated alumina (Nakarai Chemicals) or on silica gel (Merck) with control by thin-layer chromatography. All melting points were measured on Yanagimoto Micro Melting Point Apparatus and not corrected. The NMR spectra were taken on Varian A-60 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard, and the mass spectra on Hitachi Mass Spectrometer Model RMU-6D equipped with direct inlet system Model MG-150. Solutions of basic or neutral substances were dried over anhyd. K_2CO_3 and of acidic substances over anhyd. $MgSO_4$.

reagent and solvent was dissolved in MeOH (20 ml) and treated with $NaBH_4$ (2.0 g) under stirring at room temperature for 30 min. MeOH was evaporated *in vacuo*; the residue was treated by usual manner, and the basic product was extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave pale-yellow oily substance, which was used for the next step without purification.

The product obtained above was dissolved in a mixture of MeOH (20 ml) and $CHCl_3$ (10 ml), then formalin (2.0 ml) was added with stirring. After keeping the mixture overnight at room temperature, $NaBH_4$ (2.0 g) was added with stirring, and the reaction was continued for further 30 min. The solvent was evaporated off *in vacuo*; the residue was treated by usual manner for extraction of basic product with ether. Evaporation of the solvent gave an oily substance from which the product, a mixture of XII and XIII, was isolated by alumina chromatography. Colorless oily substance, yield 680 mg.

Metallic Sodium–Liquid Ammonia Fission of the Mixture of XII and XIII——On a dry ice–acetone bath (−73°), metallic sodium was added with stirring to liquid ammonia (*ca.* 30 ml) until the mixture showed a blue color. The mixture of XII and XIII (250 mg) was dissolved in ether (20 ml), and the solution was added into the above mixture. Additional amounts of metallic sodium were added so that the reaction mixture kept the blue coloring for 30 min. After the reaction ended, NH_4Cl was added until the coloring disappeared. Ammonia was evaporated at room temperature, and the residue was treated by usual manner for extraction of basic substance with ether. Chromatographic purification of the products on silica gel furnished two crystalline bisected bases, *dl*-armepavine (XIV) and 1-(4-hydroxybenzyl)-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XV). *dl*-Armepavine: Colorless pillars from acetone, mp and mixed mp 162—165°. Yield, 50 mg. The IR ($CHCl_3$) spectrum of this base was superimposable on that of the authentic sample. XV: Colorless pillars from acetone, mp 164—166°. Yield 18 mg. The IR, NMR, and mass spectral data of this base were in full accord with the assigned structure (XV).

Bischler–Napieralski Reaction of Amide (IX)——Amide (IX, 1.2 g) was dissolved in anhyd. toluene (30 ml); and the solution was refluxed for 1 hr with $POCl_3$ (2 ml). The residue left after evaporation of the reagent and solvent was treated with $NaBH_4$ (2.0 g) on an ice bath in MeOH (30 ml) for 30 min. MeOH was evaporated *in vacuo*; the residue was dissolved in ether, and extracted thoroughly with 2% HCl. The extract was made alkaline with conc. NH_4OH, and the basic product was extracted with ether . Evaporation of the solvent gave an oily product.

The foregoing product was dissolved in MeOH (20 ml) and treated with formalin (0.5 ml), then with $NaBH_4$ (1.0 g) on an ice bath. The product isolated by a usual manner for extraction of basic material was an oily substance. The purification of the product was effected by washing the solution of the above product in AcOEt (100 ml) with pH 2.5 McIlvaine's buffer solution (five times with each 25 ml of the buffer solution). AcOEt was evaporated; and the residue was purified on silica gel chromatography. Mixture of XVI and XVII: Pale-yellow oily substance, yield 300 mg.

Metallic Sodium–liquid Ammonia Cleavage of the Mixture of XVI and XVII——The above mixture (90 mg) was submitted to the reaction in liquid ammonia (50 ml) by the same work up procedures described before. *dl*-Amepavine (XIV) and XV were isolated from the reaction mixture in the same yield (18 mg). Both were identified with the authentic samples by IR ($CHCl_3$) spectra and mixed mp.

Acknowledgement The authors are indebted to Dr. T. Shingu of this Faculty for the measurement of NMR spectra, and to Dr. T. Ibuka for mass spectra. Thanks are also due to the members of the Microanalytical Center of this University for elemental analyses. Part of the expenses for this work were furnished by the Scientific Research Funds provided by the Ministry of Education, for which the authors wish to express the profound gratitude.