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Studies on the Alkaloids of Menispermaceous Plants. CCXLII. Synthesis of Cycleanine. (3).[1] Synthesis of *dl*-Cycleanine[2]

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The cyclobisamide IV was synthesized by intramolecular condensation of an ω-amino acid XIII or its corresponding *p*-nitrophenyl ester.

Bischler–Napieralski cyclization of IV followed by $NaBH_4$ reduction and N-methylation gave a mixture of N-methyltetrahydroisoquinolines, from which *dl*-cycleanine (XIV), the diastereoisomer of cycleanine (XV), and a structural isomer of cycleanine (XVII) were isolated in crystalline state. The structural elucidations of the products were effected by IR, NMR, and mass spectral comparisons with the natural base. The structure of the isomeric product XVII was further proved by sodium–liquid ammonia cleavage reaction which afforded XVIII as the bisected product.

In previous papers of this series,[4] it has been stated that a synthesis of cycleanine (I) by Ullmann condensation of 8-bromoarmepavine (II) was unsuccessful. That is, the cycleanine type bases were not accessible even by the reaction catalysed by cupric oxide, but a product (III) which might be formed by incomplete Ullmann condensation between two molecules of the starting material was obtained. An attempted synthesis of III through

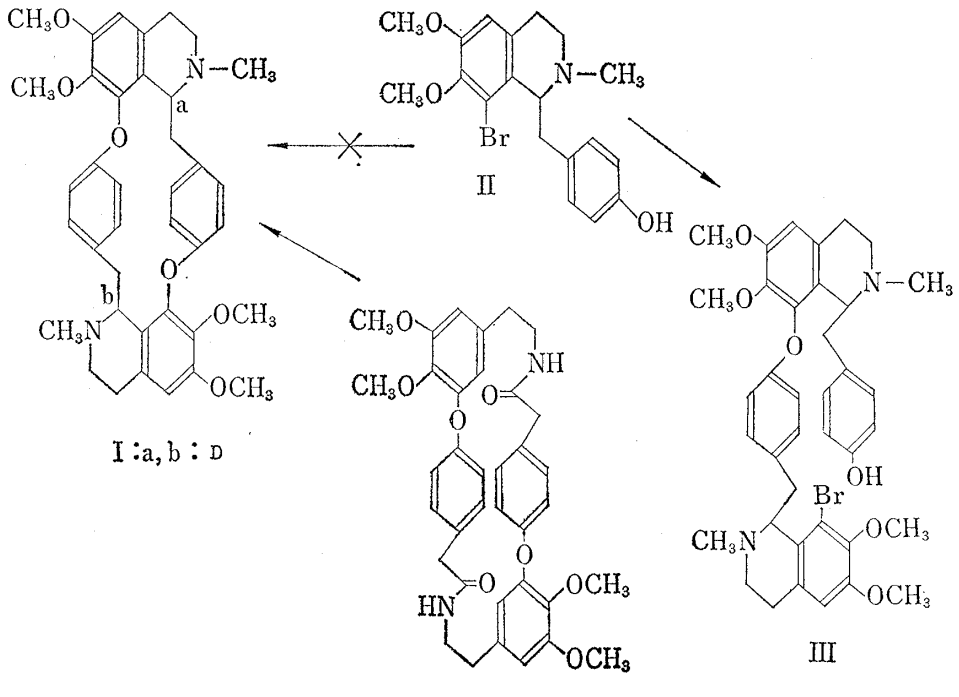


Chart 1

1) Part CCXLI, Part (2): *Chem. Pharm. Bull.* (Tokyo), **16**, 56 (1968).
2) This work was presented at the 10th Symposium on the Chemistry of Natural Products, Oct. 6, 1966, Tokyo. Symposium Papers, p. 31; preliminary communication appeared in *Tetrahedron Letters*, **No. 35**, 4243 (1966).
3) Location : *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
4) M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **15**, 1996 (1967); **16**, 57 (1968).

Bischler–Napieralski reaction also resulted in failure; and it was found that the isoquinoline ring-closure of N-acyl-3-(4-substituted-phenoxy)-*β*-phenethylamine occurred onto both *ortho* and *para* positions with respect to the phenoxyl group.

This paper deals with the first successful synthesis of *dl*-cycleanine which was achieved through Bischler–Napieralski reaction of a cyclobisamide (IV).

The key intermediate, cyclobisamide (IV), was synthesized through the following route.

Amino acid (VI), which was obtained by hydrogenation of nitrostyrene (V),[4] afforded N-protected amino acid (VII) on treatment with carbobenzoxy chloride (CBZo–Cl).

Alternately, Ullmann reaction catalysed by cupric oxide[5] between N-carbobenzoxy-3-bromo-4,5-dimethoxy-*β*-phenethylamine (VIII) prepared by N-carbobenzoxylation of the corresponding phenethylamine[4] and methyl *p*-hydroxyphenylacetate[6] yielded a mixture of diphenyl ether derivatives, from which the aimed compound (IX) was isolated by alumina chromatography. The structure of the by-product is uncertain; its formation might owe to the CBZo grouping which is known[7] to be unstable in some cases under alkaline condition.

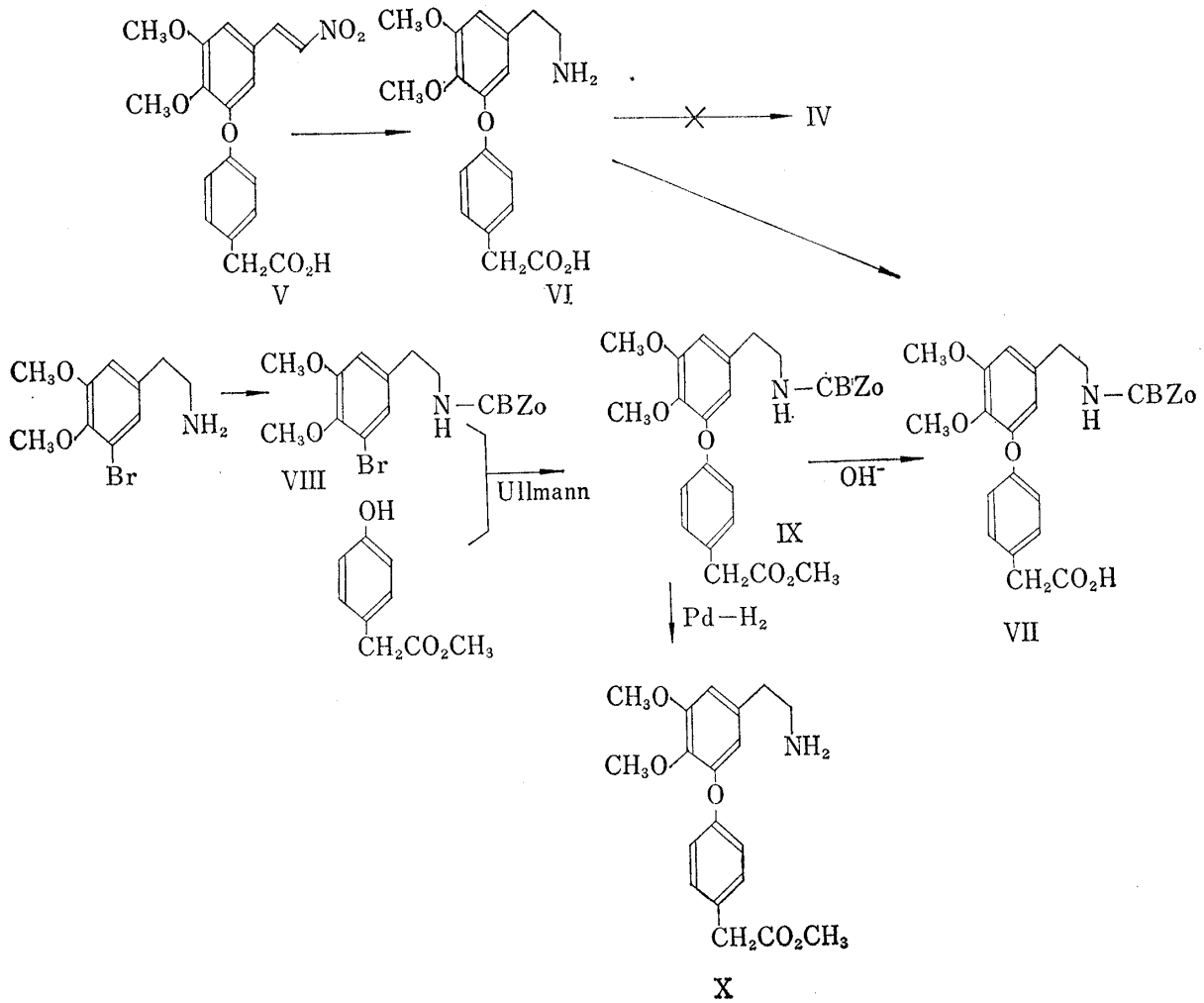


Chart 2

5) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1341 (1965).
6) H. Kondo and S. Uyeo, *Yakugaku Zasshi*, **53**, 557 (1933).
7) F. Wessely, K. Schlögl, and G. Korger, *Monatsh.*, **83**, 1156 (1952); K. Schlögl and H. Fabitschowitz, *Monatsh.*, **84**, 937 (1953); S.G. Waley, and J. Watson, *Biochem. J.*, **57**, 529 (1954); J.A. Maclaren, *Aust. J. Chem.*, **11**, 360 (1958).

Hydrolysis of the methyl ester of IX afforded the same N-CBZo-amino acid (VII) obtained from amino acid (VI). Alternatively, removal of the CBZo group by catalytic hydrogenolysis yielded amino ester (X).

Condensation between carboxylic acid (VII) and amine (X) with the aid of dicyclohexylcarbodiimide (DCC)[8] furnished an amide (XI), which was further converted to a carboxylic acid (XII) by potassium carbonate treatment.

Cyclization of an ω-amino acid (XIII), which was obtained by catalytic hydrogenolysis of XII, by some appropriate ways was expected to furnish the aimed bisamide. Actually, on treatment with phosphorus oxychloride and triethylamine in chloroform[9] was obtained the cyclobisamide in 10% yield, and by DCC method also was afforded the amide, but only in 4% yield.

Then, *p*-nitrophenyl ester method, which has been widely applied[10] in the syntheses of cyclic peptides, was carried out to obtain the cyclobisamide starting from XII.

The carboxylic acid (XII) was esterified with *p*-nitrophenol by a method similar to that described by Bodanszky and du Vigneaud[11]; and resulted *p*-nitrophenyl ester was treated with hydrogen bromide-acetic acid to remove the CBZo group. The amine hydrobromide thus obtained was dissloved in dimethylformamide, then submitted to ring-closure by adding the solution dropwise into warm pyridine containing a small amount of triethylamine. By this procedure, the aimed bisamide was given in total yield of 17% from XII..

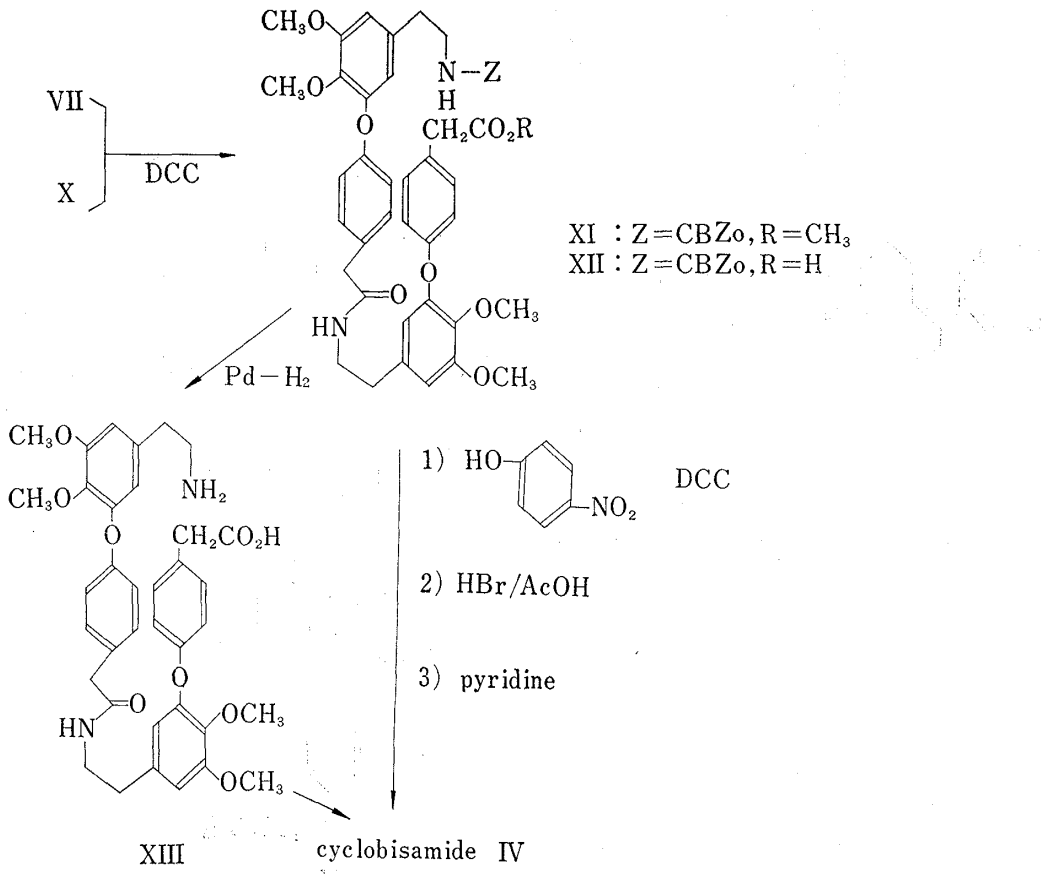


Chart 3

8) C.L. Stevens and M.E. Munk, *J. Am. Chem. Soc.*, **80**, 4065, 4069 (1958).
9) T. Wieland and B. Heinke, *Ann.*, **599**, 70 (1956).
10) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **40**, 624 (1957); M. Ohno and N. Izumiya, *Bull. Chem. Soc. Japan*, **38**, 1831 (1965); M. Ohno and N. Izumiya, *J. Am. Chem. Soc.*, **88**, 376 (1966); N. Izumiya, *Yuki Gosei Kagaku Kyokai Shi*, **23**, 1085 (1965).
11) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).

The cyclobisamide (IV) was obtained as crystalline adduct with equimolar amount of chloroform. The NMR spectra in dimethylsulfoxide-d_6 and in $CDCl_3$–pyridine and the analytical data agreed with the expected structure.

An ω-amino acid (VI), afforded by catalytic hydrogenation of nitrostyrene (V), was considered at first sight that it could be one of the most appropriate intermediates for the cyclobisamide. In practice, however, attempts of direct cyclo-dimerization of VI by several methods involving DCC,[8] phosphorus oxychloride–pydirine (or triethylamine),[9] or heating in decalin[12] methods were found all unsuccessful.

Bischler–Napieralski reaction of IV was carried out in anhydrous chloroform; and the product was immediately reduced to tetrahydroisoquinolines with sodium borohydride in methanol. Treatment of the product obtained above with formalin then with sodium borohydride yielded N-methyltetrahydroisoquinolines as a mixtrue which showed several spots on thin-layer chromatogram.

Isolation of *dl*-cycleanine from the above mixture was effected by column and preparative thin-layer chromatography and repeated recrystallizations. Additionally, two species of base were also isolated in crystalline state (Base A and B).

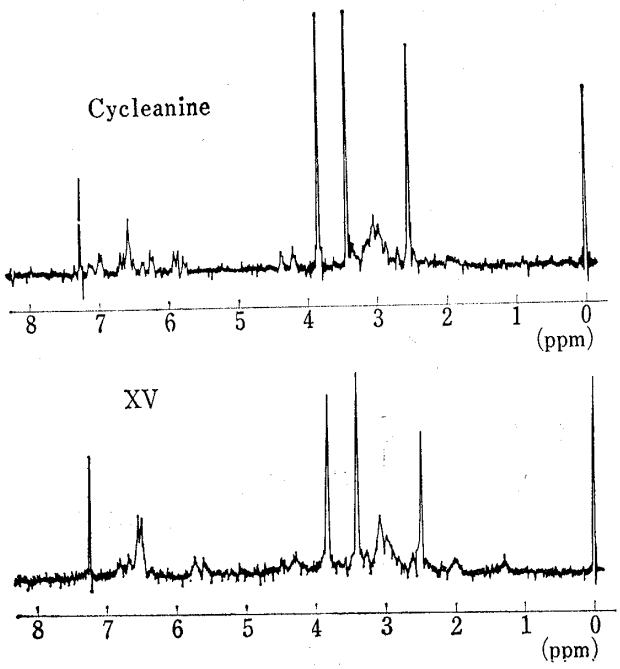


Fig. 1. NMR Spectra of Cycleanine and the Diastereoisomer (XV)

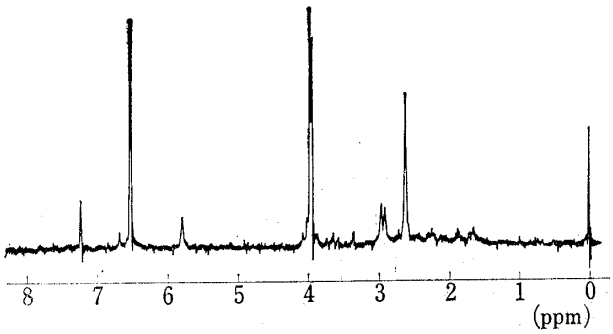


Fig. 2. NMR Spectrum of Base B (XVII)

dl-Cycleanine (XIV): The IR spectrum and thin-layer chromatograms were superimposable on those of natural cycleanine; and in the NMR spectrum, the chemical shifts for O–CH_3 and N–CH_3 groups were identical with those of the natural base, though the signals of the other remnant protons were not apparent enough owing to the small amount of the sample available. The mass spectrum showed the same parent ion peak at *m/e* 622 and essentially the same fragmentation pattern as natural cycleanine.[13]

Base A (XV): On thin-layer chromatography, this base was undistinguishable from natural cycleanine. However, the IR (KBr) spectrum of the base picrate, though very similar to that of authentic cycleanine picrate, has a slight but recognizable differences in finger print region. Further, the NMR spectrum (Fig. 1) shows a different pattern in aromatic region from that of the authentic sample; and the chemical shift for N–CH_3 groups (overlapped singlet) is found to appear higher by 2.5 cps than that of the natural base, though the overall spectral pattern is quite similar including the relative intensities of the

12) M. Dobrowsky, *Monatsh.*, **82**, 122 (1951); J.G. Beasely and A. Burger *J. Med. Chem.*, **7**, 686 (1964).
13) M. Tomita, T. Kikuchi, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Letters*, **No. 8**, 857 (1966).

signals. The mass spectrum of this base has the parent ion peak at *m/e* 622; and the fragmentation pattern is also similar to that of cycleanine. From these facts, it seemed most reasonable to conclude that Base A has the same planar structure with cycleanine but is diastereoisomeric with the configurations of the asymmetirc centers involved. Thus, formula XV was assigend for the structure of Base A.

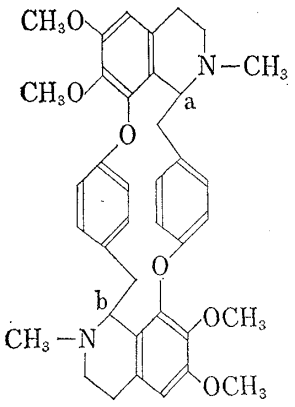
Base B (XVII): The mass spectral data of this product are in accord with the cycleanine formula except the disappearance of a peak at *m/e* 265.5 which is characteristic of the cycleanine type bases[13]; the NMR (Fig. 2) and IR spectral comparisons with natural cycleanine revealed that the product might be a structural isomer of cycleanine. From the NMR signal pattern which suggest the complete symmetry of the molecule, and from the fact[4] that Bischler-Napieralski ring-closure of such an amide as XVI occurred onto both *ortho* and *para* positions to phenoxyl grouping, the structure of Base B was assigned to the formula XVII.

The base was bisected with metallic sodium in liquid ammonia, and the product was found to be solely XVIII,[4] the formula XVII for Base B was then confirmed.

It was shown by thin-layer chromatography that mother liquor of the crystalline products still contained several species of base other than isolated ones. These minor products resisted all attempts at further purifications.

The structure of all the isolated crystalline products were unequivocally assigned as stated above; thus a synthesis of *dl*-cycleanine was accomplished.

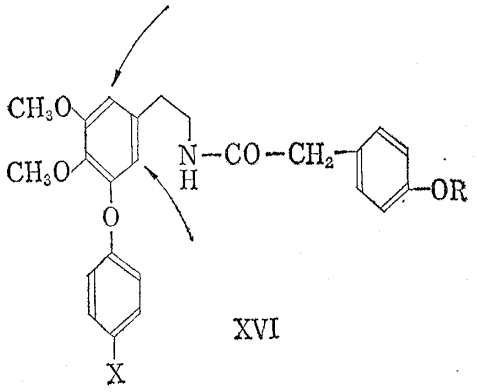
The fact that the diastereoisomer (XV) of cycleanine was produced in larger amount than *dl*-cycleanine, which was also noticed by NMR spectrometry of the mixture of *dl*-cycleanine and the diastereomer before separation of two species, seems to suggest the stereoselec-



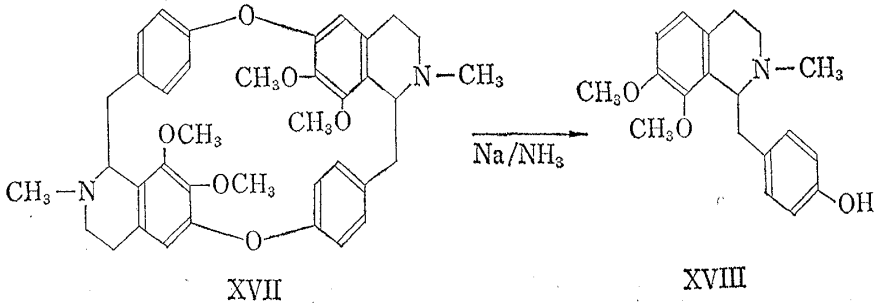
XIV : (a : D, b : D), (a : L, b : L)

dl-pair (*dl*-cycleanine)

XV : a : D, b : L (meso-form)



XVI



XVII XVIII

Chart 4

tivity of the sodium borohydride reduction of the bis-3,4-dihydroisoquinoline system. The stereospecific reduction of 3,4-dihydroisoquinolines involved in cyclic bisbenzylisoquinoline structure by methanolic sodium borohydride was recently discussed.[14] The results obtained by the present authors might offer an interesting datum for the stereochemical consideration on the reduction of these eighteen membered macroring systems.

Experimental[15]

3-(4-Carboxymethylphenoxy)-4,5-dimethoxy-β-phenethylamine (VI)——Nitrostyrene (V, 15 g) was dissolved in AcOH (200 ml), and hydrogenated over Adams PtO_2 catalyst (1.3 g) under atmospheric pressure at room temperature. After uptake ceased, the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*; then the residue was dissolved in AcOEt, and extracted thoroughly with water. The residue left after evaporation of water *in vacuo* was treated with a small amount of MeOH or tetrahydrofuran; the product (VI) was then afforded in crystalline state. Colorless microcrystals, mp 222—225°. Yield 7.0 g. *Anal.* Calcd. for $C_{18}H_{21}O_5N \cdot {}^1/_2H_2O$: C, 63.44; H, 6.50. Found: C, 63.68; H, 6.38. NMR signals (CF_3 COOH) τ: 5.95 and 5.97 (3H, s., O-CH_3).

N-Carbobenzoxy-3-(4-carboxymethylphenoxy)-4,5-dimethoxy-β-phenethylamine (VII)——To a solution of the foregoing amino-acid (VI, 550 mg) in 5% aq. KOH (100 ml), CBZo-Cl (1 ml) was added dropwise with stirring at room temperature. After the addition was completed, the reaction was further continued for 30 min at the same temperature. The resulted reaction mixture was washed with ether after warmed for 5 min on a water bath (60—70°); acidification of the mixture with conc. HCl and extraction with $CHCl_3$ afforded the product. Pale-yellow oily substance, yield 680 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH); 1715 (CO). NMR signals τ: 2.45 (1H, broad s., COOH); 2.70 (5H, s., benzyl benzene); 2.82, 3.12 (4,H A_2B_2 q., J=9 cps); 3.48 and 3.60 (1H, d., J=2 cps); 4.91 (2H, s., Ar-CH_2-O); 6.18 and 6.22 (3H, s., O-CH_3); 6.42 (2H, s., Ar-CH_2-CO).

N-Carbobenzoxy-3-bromo-4,5-dimethoxy-β-phenethylamine (VIII)——To a solution of 3-bromo-4,5-dimethoxy-β-phenethylamine (20 g and triethylamine (25 ml) in $CHCl_3$ (150 ml)), CBZo-Cl (90%, 18 ml) was added dropwise on an ice bath with stirring. After the addition, reaction mixture was further stirred at room temperature for 30 min, and washed successively with 2% HCl, 2% aq. NaOH, and water. Evaporation of $CHCl_3$ yielded a crystalline solid from which, on recrystallization from MeOH, the product (VIII) was obtained in pure state. Colorless cubes, mp 110—111°. Yield 22 g. *Anal.* Calcd. for $C_{18}H_{20}O_4NBr$: C, 54.83; H, 5.12. Found: C, 54.91; H, 5.20.

Ullmann Reaction between VIII and Methyl *p*-Hydroxyphenylacetate——Finely powdered anhyd. K_2CO_3 (7 g) and freshly prepared CuO (3.0 g) were added into a solution of VIII (53 g) and methyl *p*-hydroxyphenylacetate (35 g) in absoluted pyridine (30 ml) with stirring, and the resulted mixture was heated on an oil bath (145—150°) under nitrogen atmosphere with continuous stirring. After 4 hr, the mixture was poured into ether (1 liter), and washed successively with 5% aq. NaOH, 2% HCl, 5% aq. NaOH, and water. Ether was evaporated; the residue (light-brown oily substance, yield 47 g) was dissolved in MeOH (200 ml), and refluxed for 1 hr with aq. K_2CO_3 (15 g in 30 ml water) to hydrolyze the ester grouping. MeOH was evaporated *in vacuo*; and the residue was diluted with water (200 ml), washed with ether, made acidic with conc. HCl, and extracted with $CHCl_3$. Evaporation of $CHCl_3$ afforded the acidic product, which showed two spots on thin-layer chromatogram. Pale-yellow oily substance, yield 28 g.

The foregoing mixture was treated in MeOH (100ml) with ethereal diazomethane prepared from 35 g of nitrosomethylurea overnight; the residue left after evaporation of the solvent was dissolved in a mixture of ether and AcOEt (1 to 1), and washed with 5% aq. NaOH and water. Evaporation of the solvent afforded oily methyl esters (22 g) which showed distinct two spots on thin-layer chromatogram. Separation of the two esters was effected by alumina chromatography; and characterization of the product was achieved by NMR spectrometry. N-Carbobenzoxy-3,4-dimethoxy-5-(4-methoxycarbonylmethylphenoxy)-β-phenethylamine (IX): Colorless oily substance, yield 15.1 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH); 1725 and 1715 (CO). NMR signals τ: 2.72 (5H, s., benzylbenzene); 2.83, 3.11 (4H, A_2B_2 q., J=9 cps); 3.47 and 3.58 (1H,

14) H. Furukawa, *Yakugaku Zasshi*, **86**, 253 (1966); Y. Watanabe, H. Furukawa, and M. Kurita, *Yakugaku Zasshi*, **86**, 257 (1966).

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

d., J=2 cps); 4.93 (2H, s., Ar–CH_2–O); 6.19 and 6.23 (3H, s., O–CH_3); 6.34 (3H, s., CO–O–CH_3); 6.45 (2H, s., Ar–CH_2–CO).

Hydrolysis of IX (Preparation of VII)——A methanolic solution of IX (2.5 g in 50 ml) was refluxed with 2% aq. NaOH (30 ml) for 15 min. After evaporation of MeOH *in vacuo*, the residue was treated by usual manner, and acidic product was extracted with CH_2Cl_2. The product, a colorless oily substance, was identified by the IR ($CHCl_3$) spectrum with the authentic sample (VII) obtained from amino-acid (VI). Yield 2.3 g.

3,4-Dimethoxy-5-(4-methoxycarbonylmethylphenoxy)-β-phenethylamine (X)——The foregoing methyl ester (IX, 12.5 g) was shaken in MeOH (200 ml) with hydrogen and 5% palladised charcoal (1.0 g). Catalyst was filtered off and MeOH was evaporated *in vacuo*. The residue was treated by usual manner for extraction of basic substance with $CHCl_3$. Evaporation of $CHCl_3$ gave the product as colorless oil. Yield 8.4 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (ester carbonyl). NMR signals τ: 2.82, 3.10 (4H, A_2B_2 q., J=9 cps); 3.40 and 3.57 (1H, d., J=2 cps); 6.15 and 6.23 (3H, s., O–CH_3); 6.35 (3H, s., CO–O–CH_3); 6.43 (2H, s., Ar–CH_2–CO); 7.71 (2H, broad s., NH_2).

N-(2-(3,4-Dimethoxy-5-(4-methoxycarbonylmethylphenoxy)phenyl)ethyl)-2-(4-(2,3-dimethoxy-5-(N-carbobenzoxy-2-aminoethyl)phenoxy)phenyl)acetamide (XI)——A mixture of amine (X, 2.5 g) and carboxylic acid (VII, 3.1 g) in CH_2Cl_2 (30 ml) was treated with DCC (1.37 g) under stirring at room temperature for 2 hr. A crystalline material (N,N'-dicyclohexylurea) was separated by filtration. The filtrate was diluted with CH_2Cl_2 (50 ml), and washed successively with 2% HCl, 5% aq. NaOH, and water. Evaporation of CH_2Cl_2 gave the crude product as light-brown oily substance. Yield 5.4 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (amide NH); 1720 (broad, CO); 1662 (amide CO). This crude product was utilized for the next step without further purification.

N-(2-(3-(4-Carboxymethylphenoxy)-4,5-dimethoxyphenyl)ethyl)-2-(4-(2,3-dimethoxy-5-(N-carbobenzoxy-2-aminoethyl)phenoxy)phenyl)acetamide (XII)——The foregoing product (5.4 g) was dissolved in MeOH (100 ml), and refluxed with aq. K_2CO_3 (5 g in 20 ml water) for 1 hr. MeOH was evaporated; and the residue was poured into ether (500 ml), and extracted thoroughly with 1% aq. NaOH solution. The acidic product was then extracted with $CHCl_3$ after the above extract was made acidic with conc. HCl. Evaporation of $CHCl_3$ gave XI as an pale-yellow oily substance. Yield 5.1 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (amide NH); 1715 (CO); 1662 (amide CO). NMR singals τ: 2.70 (5H, s., benzylbenzene); 4.91 (2H, s., Ar–CH_2–O); 6.19 and 6.22 (6H, overlapped s., 2×O–CH_3); 6.44 and 6.54 (2H, s., Ar–CH_2–CO).

N-(2-(3-(4-Carboxymethylphenoxy)-4,5-dimethoxyphenyl)ethyl)-2-(4-(2,3-dimethoxy-5-(2-aminoethyl)phenoxy)phenyl)acetamide (XIII)——The CBZo group of the foregoing amido-carboxylic acid (XI, 500 mg) was removed by hydrogenolysis over Pd catalyst (200 mg) in EtOH (30 ml). Evaporation of the solvent after separation of the catalyst afforded the product (XIII) as a colorless powder. Yield 450 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1663 (amide CO). NMR signals τ: 6.16 and 6.25 (6H, overlapped s., 2×O–CH_3).

Cyclization of XIII by DCC Method (Formation of IV)——A solution of XIII (260 mg) in CH_2Cl_2 (200 ml) was treated overnight with DCC (100 mg) at room temperature. The reaction mixture was washed successively with 2% HCl, 5% aq. NaOH, and water. The residue left after evaporation of the solvent was fractionated by silica gel chromatography in $CHCl_3$–acetone. From the appropriate fractions was isolated the aimed compound, cyclobisamide (IV), as a crystalline adduct with equimolar amount of $CHCl_3$. Cyclo-N,N'-bis(2-(4-(2,3-dimethoxy-5-(2-aminoethyl)phenoxy)phenyl)acetyl) (IV): Colorless microcrystals, mp 280—285° (decomp.). Yield 12 mg. This was hardly soluble in common organic solvents except dimethylformamide. IR ν_{max}^{KBr} cm^{-1}: 3320 (amide NH); 1658 (amide CO). NMR signals in $CDCl_3$–pyridine τ: 6.19 and 6.22 (overlapped s., 2×O–CH_3); in dimethylsulfoxide-d_6 τ: 1.70 (s., $CHCl_3$). *Anal.* Calcd. for $C_{36}H_{38}O_8N_2 \cdot CHCl_3$: C, 59.57; H, 5.28; N, 3.76. Found: C, 59.92; H, 5.69; N, 3.46.

Cyclization of XIII by $POCl_3$-Triethylamine Method——Into a solution of XIII (400 mg) in anhyd. $CHCl_3$ (100 ml) containing triethylamine (1 ml), $POCl_3$ (0.2 ml) was added with stirring on an ice bath. The solvent was evaporated after 30 min; the residue was dissolved in AcOEt, washed successively with 2% HCl, 5% aq. NaOH, and water. The crude product resulted by evaporation of the solvent was purified on silica gel chromatography. The cyclobisamide IV: Yield 45 mg.

Preparation of the Cyclobisamide by *p*-Nitrophenyl Ester Method——XII (5.9 g) and *p*-nitrophenol (1.21 g) was treated with DCC (1.44 g) in CH_2Cl_2 (50 ml) for 1 hr at room temperature with stirring. The solvent was evaporated after removal of crystalline material. The residue was dissolved in AcOH (10 ml), then poured into 2N HBr/AcOH (20 ml) with stirring. After stirring at room temperature for 1 hr, the mixture was warmed with stirring on a water bath (50—60°) for 5 min, and poured into ether (300 ml); the ether was then separated by decantation from a precipitated oily material. The foregoing product was dissolved in DMF (50 ml), and added dropwise into anhyd. pyridine (400 ml) containing triethylamine (10 ml) with stirring on a water bath (60—70°). After the addition was completed, the reaction mixture was further stirred on the bath for 5 hr, and left overnight at room temperature. The residue left after evaporation of pyridine was dissolved in AcOEt, and washed successively with 3% HCl, 5% NaOH, and water. The solvent was evaporated; the residual semi-crystalline substance was triturated with a mixture of $CHCl_3$–AcOEt (1 to 1); the cyclobisamide IV was then afforded in crystalline state. Yield 970 mg.

Bischler-Napieralski Reaction of the Cyclobisamide (IV)——The cyclobisamide (IV, 1.5 g) was suspended on anhyd. $CHCl_3$ (40 ml), and the mixture was refluxed with $POCl_3$ (10 ml) for 3 hr. The reaction mixture became gradually clear and colored yellowish-brown. The solvent and reagent was evaporated *in vacuo* after an addition of toluene (20 ml); the residue was immediately dissolved in MeOH (100 ml) and treated with $NaBH_4$ (2.0 g) for 30 min with stirring. MeOH was evaporated *in vacuo*; the residue was treated by usual manner, and the basic substance was extracted with $CHCl_3$. Removal of $CHCl_3$ by distillation yielded the product (tetrahydroisoquinolines) as a mixture which shows several spots on thin-layer chromotogram. Yield 1.01 g.

The foregoing product (1.01 g) was treated with formalin (1.5 ml) in MeOH (50 ml) for 30 min with stirring, then reduced for 30 min by $NaBH_4$ (2.0 g) added. The residue left on evaporating the solvent was treated by usual manner, and the basic material were extracted with ether. Removal of ether by distillation afforded a mixture of N-methyltetrahydroisoquinolines as a colorless glassy substance. Yield 700 mg.

The product (700 mg) was fractionated to 20 parts by alumina (Aluminium Oxide standardized acc. to Brockmann, Grade II—III, Merck) chromatography in $CHCl_3$. From fraction 1 and 2, a product (Base B, XVII) was isolated as a crystalline solid, which, on recrystallization from MeOH, afforded a colorless pillars, mp 210—212°. Yield 29 mg.

The fraction 3 and 4 was found to contain several (about 10) basic substances which shows overlapped indistinct spots on thin-layer chromatogram. Isolation of a product in pure state from these fractions, though tried by various ways, was unsuccessful.

In the product mixture obtained from fraction 5—12, a distinct spot could be assigned to cycleanine was found on thin-layer chromatograms. Preparative thin-layer chromatography of the above mixture (220 mg) was carried out on alumina (Aluminium oxide G acc. to Stahl, Merck) using $CHCl_3$–AcOEt (10 to 1) as developper. On treatment of the alumina powder scraped together with 1% aq. HCl–MeOH followed by extraction of basic material by usual method, crude cycleanine type bases was obtained, of which NMR spectrum showed two N–CH_3 signals with relative intensity of 1 to 2 (at 7.47 and 7.51 τ), which could be assigned to that of *dl*-cycleanine and the diastereoisomer XV, respectively. The product mixture was treated with picric acid in acetone. Base A picrate: Yellow prisms, mp 180—205° (decomp.). Yield 7 mg. The free base obtained from the above picrate (6 mg) by usual method was recrystallized from acetone. Base A: Colorless pillars, mp 230—233° (decomp.). Yield 3.5 mg.

The mother liquor of Base A picrate was treated by usual manner for extraction of bases with $CHCl_3$. The residue (12 mg) left after evaporation of $CHCl_3$ was purified by preparative thin-layer chromatography on silica gel (Silica gel G acc. to Stahl, Merck) using MeOH as developper. The scraped silica gel powder was treated by usual manner; and the basic product was extracted into $CHCl_3$. Evaporation of $CHCl_3$ afforded a crystalline solid, from which, by repeated recrystallization from acetone, *dl*-cycleanine XIV was isolated in pure state. *dl*-Cycleanine (XIV): Colorless pillars, mp 222—225°. Yield 1 mg. NMR signals τ: 6.17 and 6.60 (O–CH_3); 7.47 (N–CH_3).

Metallic Sodium-Liquid Ammonia Fission of Base B (XVII)——Metallic sodium was added to liquid ammonia (20 ml) with stirring on an dry ice-acetone bath (−71°) until the mixture showed a blue color. A solution of Base B (20 mg) in dioxane (2 ml) was added to the above mixture with continuous stirring. An additional amount of metallic sodium was added so that the reaction mixture kept always the coloring. After 30 min, the reaction was ceased by adding NH_4Cl until the coloring disappeared; ammonia was evaporated at room temperature, and the residue was treated by usual method for extraction of basic substance with ether. The product resulted by evaporation of ether was triturated with acetone; the bisected base was then afforded in crystalline state. Yield 16 mg. Colorless pillars, mp and mixed mp 165—167°. The IR ($CHCl_3$) and NMR spectra were superimposable on those of 1-(4-hydroxybenzyl)-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVIII).

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