[Chem. Pharm. Bull. 16(2) 217—226 (1968)]

UDC 581.19 : 547.94 : 582.675.4

Studies on the Alkaloids of Menispermaceous Plants. CCXLIV.[1] Synthesis of *dl*-Cepharanthine[2]

Masao Tomita, Kazuyoshi Fujitani, Yoshiaki Aoyagi, and Yasumichi Kajita

Faculty of Pharmaceutical Sciences, Kyoto University[3]

(Received March 16, 1967)

The first successful synthesis of *dl*-cepharanthine (XXXI) was described.

dl-Cepharanthine was isolated together with its diastereoisomer (XXX) and diastereoisomeric pair of the structural isomer (XXIX), which were anticipated to be formed by Bischler-Napieralski cyclization followed by reduction and N-methylation of the cyclobisamide (IVa) obtained *via* unambiguous route.

Cepharanthine is a biscoclaurine (bisbenzylisoquinoline) alkaloid having a unique structural feature with methylenedioxy group on its isoquinoline nucleus, which was isolated from Menispermaceous plants, *Stephania cepharantha* Hayata and *Stephania Sasakii* Hayata, by Kondo and his collaborators.[4]

The sturcture[5] and the absolute configuration[6] of the alkaloid were confirmed as shown in formula I.

Synthetic study of cepharanthine was initiated by Kondo, Kataoka, *et al.*[7]: A cyclobisamide (IVa or IVb) was synthesized by means of Schotten-Baumann reaction of diamine (II) and dicarboxylic acid chloride (III), and an attempted cyclization of the amide under Bischler-Napieralski condition was undertaken. On the other hand, Whaley and Robinson[8] projected a synthesis of this base according a scheme involving Ullmann condensation of coclaurine type intermediates at the last stage of the reaction sequence. Recently, a synthetic approach to this alkaloid through the route similar to that of Whaley was intended by Kametani, *et al.*[9] In spite of the attempts described above, synthesis of cepharanthine had remained ambiguous or unsuccessful.

This paper described the first successful synthesis of *dl*-cepharanthine, which was achieved through Bischler-Napieralski cyclization of cyclobisamide (IVa). The cyclobisamide was synthesized through the route on which the two amide bonds were formed stepwise to avoid the structural ambiguity.

5-Bromopiperonal (VI) obtained in relatively high yield (42—64%) from 5-bromoprotocatechuic aldehyde (V) through methylenation reaction catalysed by cupric oxide[10] was

1) Part CCXLIII: M. Tomita, K. Fujitani, Y. Masaki, and Y. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 70 (1968).
2) Part of this work was presented at the monthly meeting of the Kinki Branch, the Pharmaceutical Society of Japan. Jan. 21, 1967, *Tetrahedron Letters*, No. 13, 1201 (1967).
3) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
4) H. Kondo, Y. Yamamoto, and I. Keimatsu, *Yakugaku Zasshi*, **54**, 620 (1934); H. Kondo, M. Tomita, M. Satomi, and T. Ikeda, *ibid.*, **58**, 920 (1938); H. Kondo and M. Tomita, *ibid.*, **59**, 542 (1939).
5) H. Kondo and I. Keimatsu, *Yakugaku Zasshi*, **55**, 121, 894 (1935); **58**, 906 (1938); *Ber.*, **71**, 2553 (1938). M. Tomita, Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **1**, 105 (1953); **2**, 89, 375 (1954); **3**, 178, 250 (1955).
6) J. Kunitomo, *Yakugaku Zasshi*, **82**, 981 (1962).
7) H. Kondo, H. Kataoka, *et al.*, *Ann. Rep. ITSUU Lab.*, **1**, 15 (1950); **2**, 7, 11, 13 (1951); **3**, 10, 15 (1952); **4**, 20 (1953); **5**, 5 (1954); **6**, 9 (1955).
8) W.M. Whaley and C.N. Robinson, *J. Org. Chem.*, **19**, 1029 (1954).
9) A paper read at the monthly meeting of the Tohoku Branch, the Pharmaceutical Society of Japan, July 16, 1966. *cf. Yakugaku Kenkyu*, **37**(9), 281 (1966).
10) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), in press.

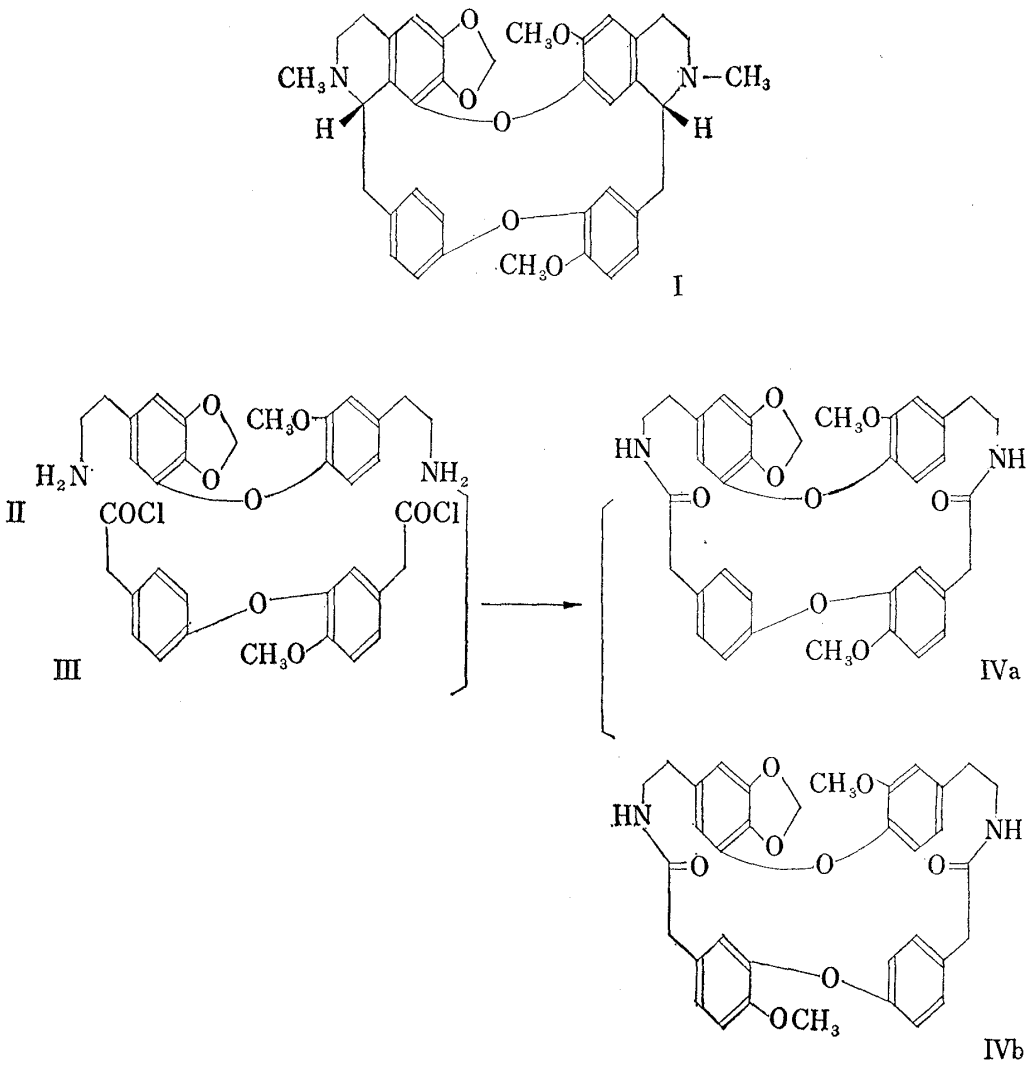


Chart 1

condensed with nitromethane in the presence of ammonium acetate in acetic acid to afford a nitrostyrene (VII), which was reduced to a phenethylamine (VIII) under Clemmensen condition. Preparation of VIII starting with 5-bromoprotocatechuic aldehyde was already reported by Erne and Ramirez,[11] but the modification adopted by the present authors raised the yield in every step of the reaction sequence.

N-Formylation of the foregoing phenethylamine with formic acid in decalin afforded N-formyl derivative (IX).

On the one hand, 3-methoxy-4-hydroxy-β-nitrostyrene (X)[12] was treated with ethyl chloroformate in pyridine and the resulted O-carbethoxy derivative (XI) was reduced under Clemmensen condition to give a phenethylamine (XII). The O-carbethoxy-amine (XII) was treated with carbobenzoxy chloride to protect the amino function; then the protective group for the phenolic hydroxyl was removed selectively by treatment with aqueous sodium bicarbonate. N-Carbobenzoxyhomovanillylamine (XIII) was thus obtained.

Ullmann condensation reaction catalysed by cupric oxide[13] between IX and XIII followed by removal of the formyl group by hydrochloric acid treatment in methanol afforded the diphenyl ether derivative (XIV), one of the key intermediates for the aimed cyclobisamide.

11) M. Erne and F. Ramirez, *Helv. Chim. Acta*, 33, 912 (1950).
12) G. Hahn and K. Stiehl, *Ber.*, 71, 2154 (1938).
13) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), 13, 1341 (1965).

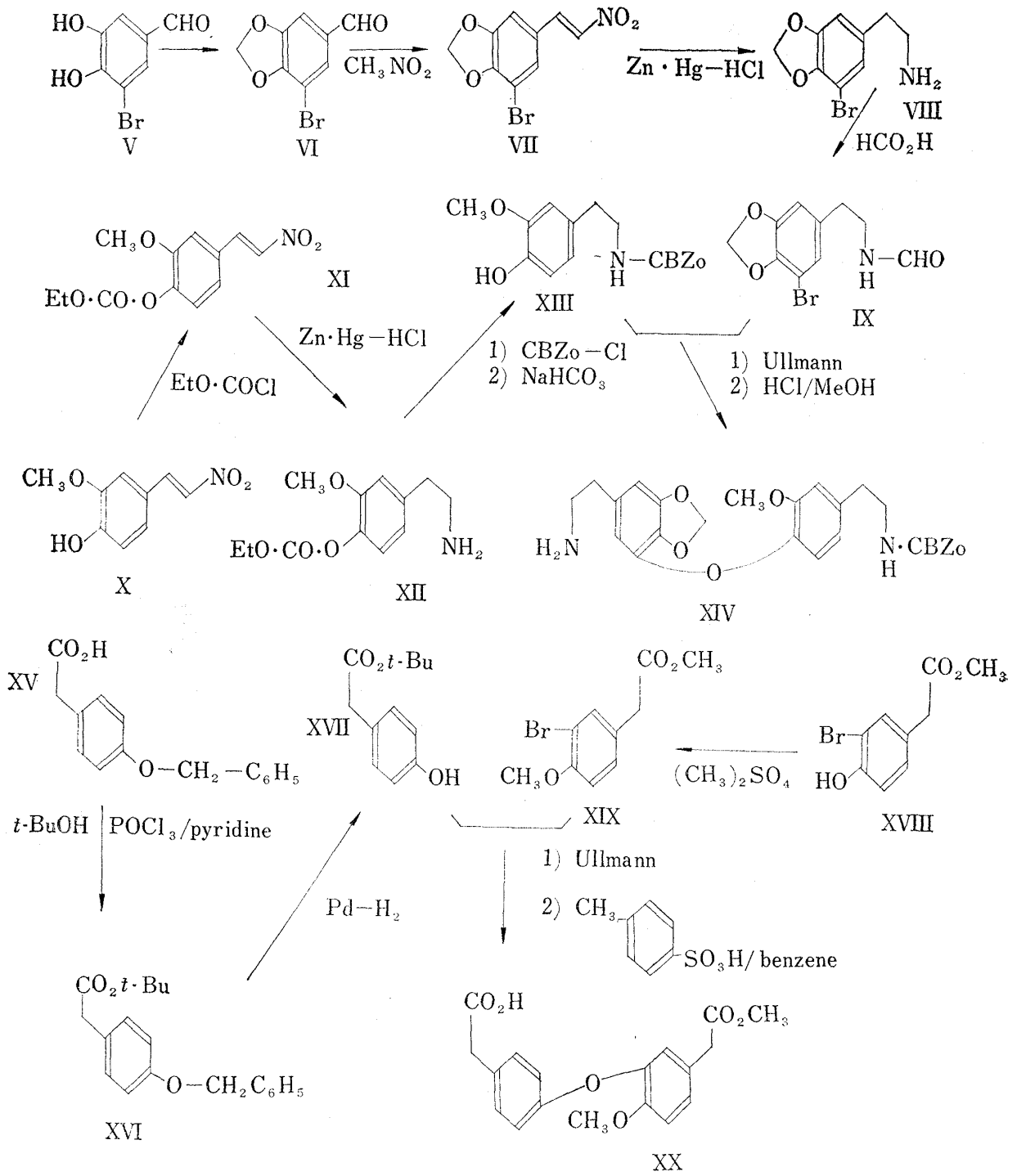


Chart 2

Another intermediate for the synthesis of cyclobisamide, diphenyl ether diacetic acid mono-ester (XX) was prepared by the following scheme.

tert-Butyl ester was employed for a selectively removable protective group for the carboxylic acid function.

Preparation of *tert*-butyl *p*-hydroxyphenylacetate (XVI) from the corresponding carboxylic acid (XV)[14] was effected by phosphorus oxychloride-pyridine method[15]; and

14) D.H.R. Barton and G.W. Kirby, *J. Chem. Soc.*, **1962**, 806.

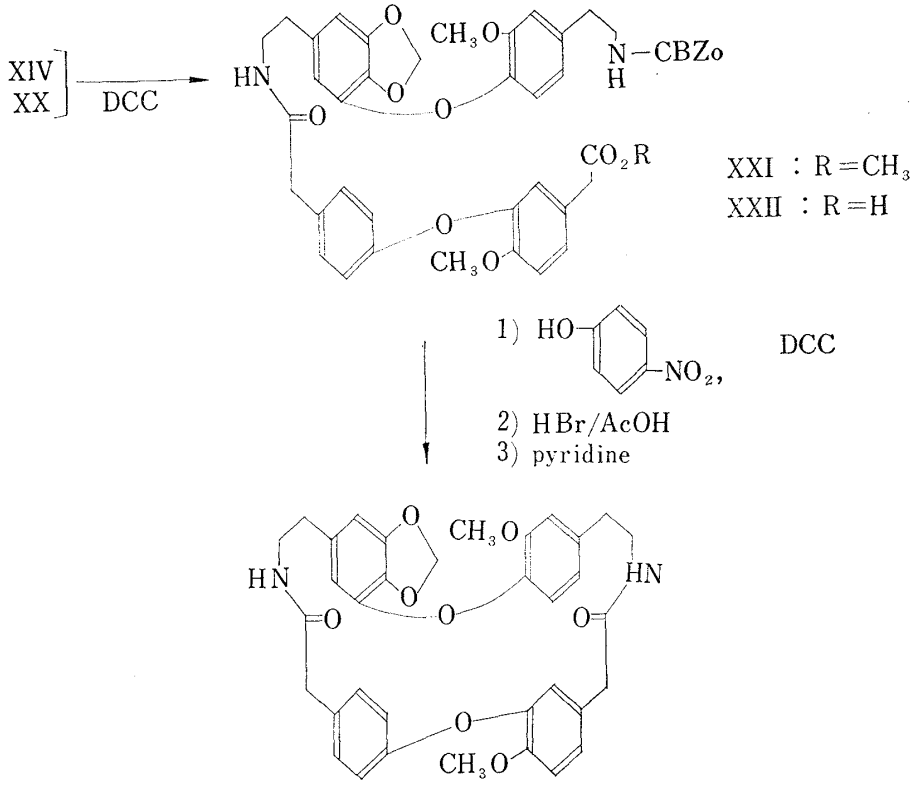
the resulted ester was in turn debenzylated by hydrogenolysis over palladised charcoal to give the hydroxy ester (XVII).

Methyl 3-bromo-4-methoxyphenylacetate (XIX)[16] was prepared by methylation of the corresponding phenolic methyl ester (XVIII)[16] with dimethyl sulfate in dimethylformamide.

Cupric oxide-catalysed Ullamnn condensation between the hydroxy ester (XVII) and bromo ester (XIX) followed by the selective removal of *tert*-butyl group by treatment with *p*-toluenesulfonic acid in benzene yielded the half ester (XX).

Condensation of the amine (XIV) and the above carboxylic acid (XX) with the aid of dicyclohexylcarbodiimide in methylene chloride gave an amide (XXI); and hydrolysis of the ester group of the resulted amide by aqueous potassium carbonate afforded the corresponding carboxylic acid (XXII).

The cyclization of XXII to the cyclobisamide was effected by *p*-nitrophenyl ester method similar to that adopted by the present authors in the synthesis of *dl*-cycleanine.[17] The cyclobisamide (IVa) was obtained as colorless needles of mp 232—234°. IR and NMR spectral data and elemental analysis were in full accord with the structure (IVa).



IVa

Chart 3

Bischler-Napieralski cyclization of the amide (IVa) with the aid of phosphorus oxychloride in chloroform was carried out. It was reported[18] previously by the present authors that the cyclization of such an amide having a structure as XXIII under Bischler-Napieralski condition occurred on both *ortho* and *para* positions to the phenoxyl grouping.

15) E. Taschner, J. Biernat, B. Rzeszotarska, and C. Wasielewski, *Ann.*, **646**, 123 (1961).
16) H. Kondo and S. Uyeo, *Yakugaku Zasshi*, **53**, 557 (1933).
17) M. Tomita, K. Fujitani, and Y. Aoyagi, *Tetrahedron Letters*, No. 35, 4243 (1966); *Chem. Pharm. Bull.* (Tokyo), **16**, 62 (1968).
18) M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **16**, 56 (1968).

Another examples of the occurrence of the undesired direction of Bischler–Napieralski cyclization was given by the present authors[17]; the cyclization of cyclobisamide (XXVI) eventually leads to cycleanine type bases (XXVIIa and b), together with the undesired product (XXVIII). Accordingly, the Bischler–Napieralski reaction of the bisamide (IVa) was expected to afford two isomeric cyclization products as XXIV and XXV.

Although 1–benzyl–3,4–dihydroisoquinolines are known to be readily oxidized by atmospheric oxygen to afford 1–benzoyl derivatives, the occurrence of bisbenzyl–3,4–dihydroisoquinoline type alkaloid as stebisimine was reported recently.[19] On the basis of this fact, isolation of the Bischler–Napieralski products of IVa was attempted.

The basic product extracted from the reaction mixture was found at first to show distinct two spots on thin–layer chromatography. But, the isolation of each product at this stage was eventually not accomplished; the procudts were found to have an unstable character under oxygenous atmosphere even at room temperature.

Thus, the Bischler–Napieralski product was immediately hydrogenated to avoid the ready oxidation, and the mixture of tetrahydroisoquinolines yielded was N–methylated and submitted to the further experimentations.

Differences in the composition of the final product mixture depending on the reducing agents were noticed in this step. The finding would be consistent with the recent discussions on the stereoselectivity of reduction involving bis–3,4–dihydroisoquinoline system with eighteen membered macroring such as dehydroepistephanine iodide.[20]

The following three methods were employed for the reduction of bis–3,4–dihydroisoquinolines; sodium borohydride reduction, zinc–sulfuric acid method, and catalytic hydrogenation over platinum, and the composition differences were examined on thin–layer chromatography.

The final products were found to show distinct four spots on thin–layer chromatograms (Base A, B, C, and D in order of decreasing *Rf* values). Zinc–sulfuric acid method gave no substantial difference with catalytic hydrogenation, but sodium borohydride reduction was found to show a detectable difference in relative ratios of the spots in density. Base B and C showed smaller spots on thin–layer chromatogram compared with Base A and D respectively. This might be understood as ascribable to the stereoselectivity of the reducing agent, and it was assumed that Base A and B possess the same planar structure and are diastereoisomeric each to each, and that Base C and D also stand in the similar relation.

The *Rf* value of Base C was found to be identical with that of natural cepharanthine.

The reaction products by the above three different method were combined, and isolation of the four bases were performed utilizing preparative thin–layer chromatography.

The behaviors of Base C on thin–layer chromatograms were found to be identical with those of natural cepharanthine, and the base gave superimposable spectra with the natural base on IR ($CHCl_3$) and NMR measurements. Thus, Base C was proved to be *dl*–cepharanthine (XXXI).

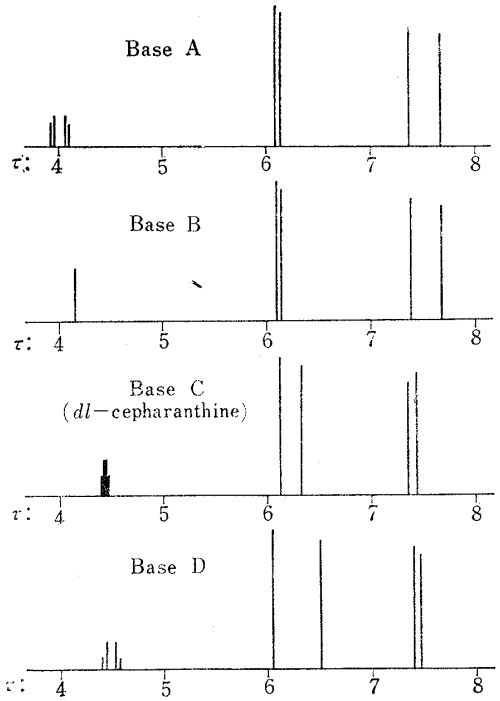
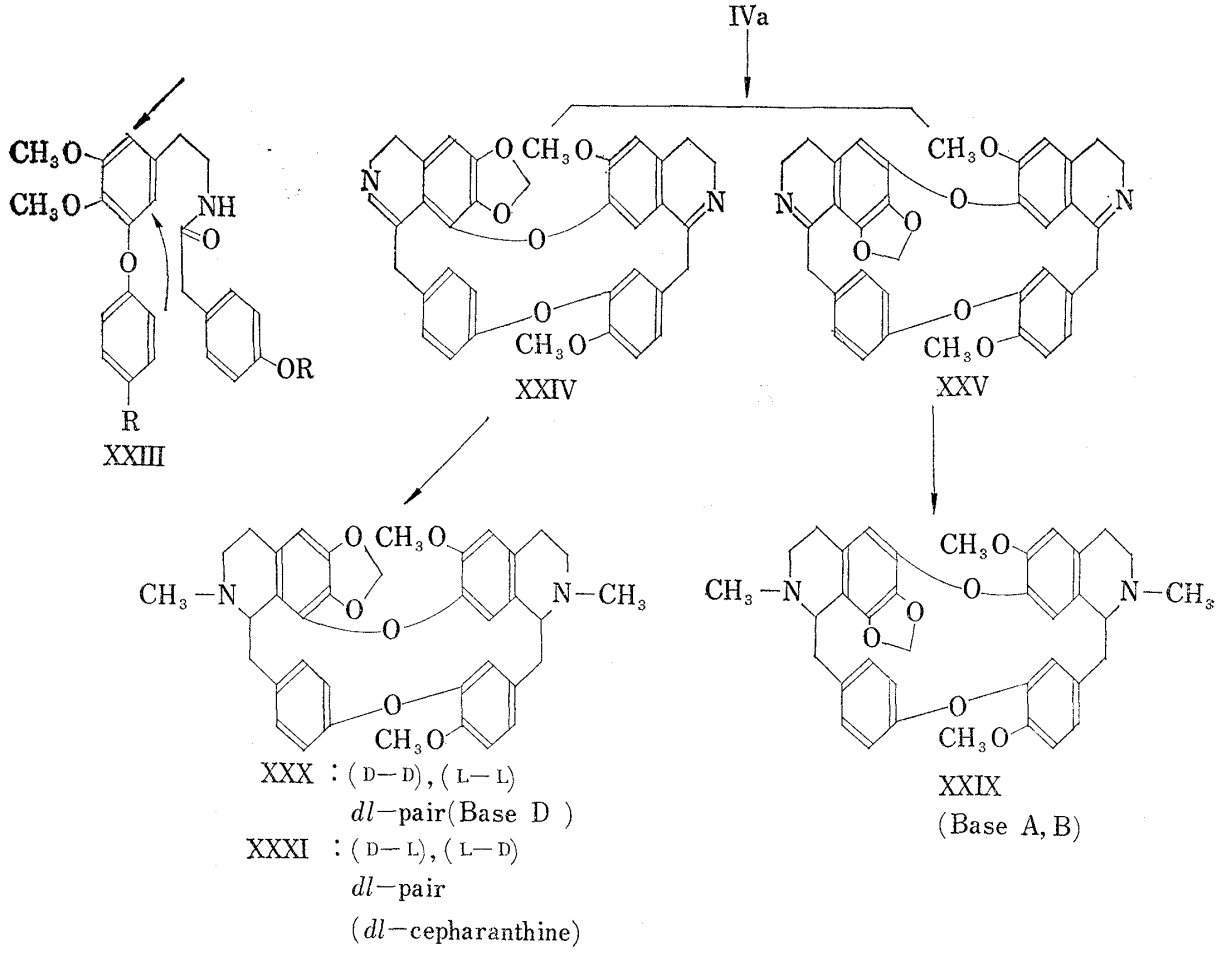


Fig. 1. NMR Spectra of the Products

19) D.H.R. Barton, G.W. Kirby, and A. Wiechers, *J. Chem. Soc.*, **1966**, 2313.
20) Y. Watanabe, H. Furukawa, and M. Kurita, *Yakugaku Zasshi*, **86**, 257 (1966).

The structure of the remnant Base A, B, and D were concluded as follows: The IR ($CHCl_3$) spectra of Base A and B were found to be closely similar to each other, except slight but recognizable differences in finger print regions. Further, as shown in Fig, 1, the similarities in the pattern of $O-CH_3$ and $N-CH_3$ signals were observed in NMR spectra of Base A and B.

Base C (*dl*-cepharanthine) and Base D also showed a similar relationship to each other as in Base A and B, upon spectrometric comparisons.



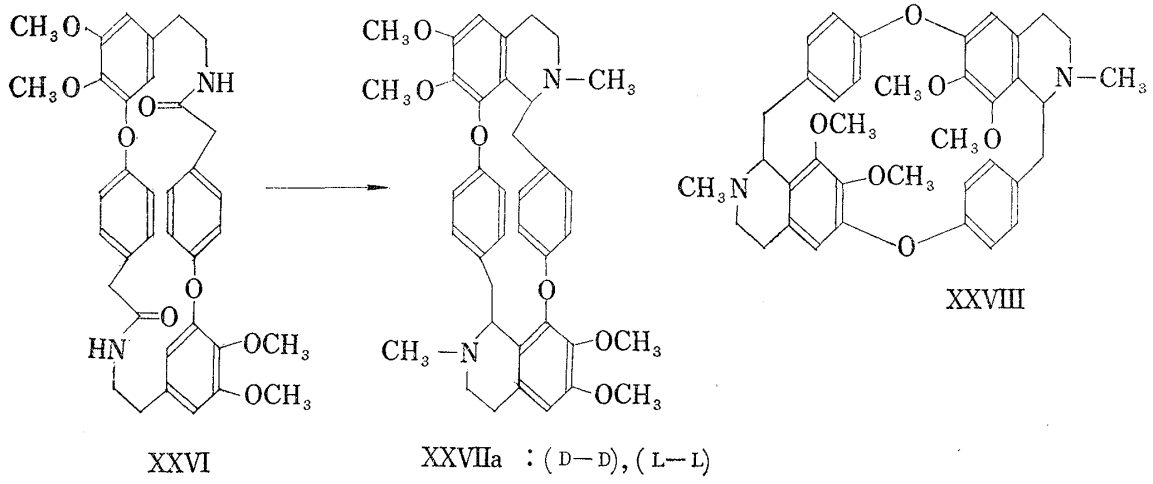


Chart 4

From these data combined with the above mentioned stereoselectivity observed on the thin-layer chromatograms of the borohydride reduction product, it seemed undisputed to conclude that the finally obtained four species of bases are two diastereoisomeric pairs of structural isomers.

The mass spectrometry of the bases revealed that their spectra were almost identical and that they have the same or similar structure with cepharanthine. The formation of a structural isomer with the undesired direction of Bischler–Napieralski ring-closure was anticipated as stated before. The similarity of the mass spectra of isomers of this type was exemplified by the present authors[17] in the synthesis of *dl*-cycleanine.

On the basis of these data, and the spectrometric comparisons of the bases, one might conclude that Base A and B were the two diastereoisomers derived from the bis-3,4-dihydroisoquinoline (XXV) with the same planar structure not other than XXIX, and that Base D was the diastereoisomer (XXX) of *dl*-cepharanthine (XXXI).

The products which were expected to be afforded from the cyclobisamide (IVa) were all isolated and characterized as stated above, and thus a synthesis of *dl*-cepharanthine was accomplished.

Experimental[21]

3-Bromo-4,5-methylenedioxy-β-nitrostyrene (VII)——The solution of 5-bromopiperonal (64 g), nitromethane (65 g), and NH_4OAc (30 g) in AcOH (400 ml) was heated to reflux for 2 hr. After cooling, the mixture was poured into water (1 liter); a precipitated crystalline solid was collected by filtration. Recrystallization of the above crystalline substance from 50% (by vol.) $CHCl_3$–EtOH afforded the product. Yield 55 g. Yellow needles, mp 160—162° (lit.[11] mp 160—161°).

3-Bromo-4,5-methylenedioxy-β-phenethylamine (VIII)——The foregoing nitrostyrene (VII, 53 g) and amalgamated zinc prepared from zinc powder (200 g) and $HgCl_2$ (20 g) were suspended on EtOH (2 liter). Under vigorous stirring, conc. HCl was added portionwise into the above mixture until the yellow coloring of the reaction mixture disappeared. After the decolorization was completed, the reaction mixture was further stirred for 30 min. An excess Zn–Hg was filtered off; EtOH was evaporated *in vacuo*, and the residue was poured into water (1 liter). The aqueous solution was made alkaline with conc. NH_4OH after washed with ether; then the basic product was extracted into $CHCl_3$, and the washed $CHCl_3$ extracts were evaporated to give the product. Light-brown viscous oily substance, yield 32 g. NMR signals τ: 3.19 and 3.39 (1H, d., $J=1.5$ cps); 4.00 (2H, s., methylenedioxy); 8.60 (2H, broad s., NH_2). Hydrochloride: Recrystallized from EtOH–acetone, colorless platelets, mp 238—240° (dec.) (lit.[11] mp 250—251°). *Anal.* Calcd. for $C_9H_{10}O_2NBr \cdot HCl$: C, 38.53; H, 3.95. Found: C, 38.75; H, 4.22.

N-Formyl-3-bromo-4,5-methylenedioxy-β-phenethylamine (VIII)——The solution of the above phenethylamine (4.5 g) and 98% formic acid (2 ml) in decalin (20 ml) was heated to reflux for 1 hr. After cooling, decalin was removed by decantation, and the remained crystalline material was recrystallized from EtOH. Pale-yellow pillars, mp 126—127°. Yield 4.0 g. *Anal.* Calcd. for $C_{10}H_{10}O_3NBr$: C, 44.13; H, 3.71. Found: C, 43.92; H, 3.89.

3-Methoxy-4-O-carbethoxy-β-nitrostyrene (XI)——To a solution of 3-methoxy-4-hydroxy-β-nitrostyrene (15 g) in pyridine (100 ml), ethyl chloroformate (15 ml) was added dropwise with stirring on an ice bath. After the addition was completed, the mixture was futher stirred for 3 hr at room temperature, then poured into water (1 liter). The precipitated crystals were collected by filtration, then washed with water and MeOH. Yellow needles, mp 125—126°. Yield 20 g. *Anal.* Calcd. for $C_{12}H_{13}O_6N$: C, 53.90; H, 4.90. Found: C, 53.63; H, 4.95.

3-Methoxy-4-O-carbethoxy-β-phenethylamine (XII)——Amalgamated zinc prepared from zinc powder (50 g) and $HgCl_2$ (5 g) was agitated with MeOH (100 ml) on an ice bath. To the above mixture, conc. HCl and a solution of the foregoing nitrostyrene (19 g) in tetrahydrofuran (200 ml) were added alternately. The temperature of the reaction mixture was kept below 50° during the reaction. After the addition of the

21) All melting points were measured on Yanagimoto's Micro Melting Point Apparatus and not corrected. Unless specified to the contrary, chromatography was carried out on Alumina Activated (Nakarai Chemicals) or silica gel (Merck) with control by thin-layer chromatography, and solutions of basic or neutral substances were dried over anhyd. K_2CO_3 and of acidic substances over anhyd. $MgSO_4$. The 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.

nitrostyrene solution was completed and the yellow coloring of the reaction mixture disappeared, an excess Zn–Hg was filtered off, and MeOH and tetrahydrofuran were removed by distillation *in vacuo*; then the residue was poured into water(500 ml), washed with ether, and the basic product was extracted into $CHCl_3$ after basification with conc. NH_4OH. Evaporation of the solvent gave the product as a pale-yellow oily material. Yield 9.5 g. Oxalate: Recrystallized from EtOH; colorless microcrystals, mp 185—191° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}O_4N \cdot \frac{1}{2}C_2H_2O_4$: C, 54.92; H, 6.39. Found: C, 55.19; H, 6.57.

N-Carbobenzoxy-3-methoxy-4-hydroxy-β-phenethylamine (N-carbobenzoxyhomovanillylamine, XIII)——Carbobenzoxy chloride (5 ml) was added dropwise into the mixture of the foregoing phenethylamine (6.5 g) and anhyd. K_2CO_3 (10 g) in dimethylformamide (50 ml) on an ice bath, and the resulted reaction mixture was stirred for 1 hr. Water (300 ml) was added into the above mixture and the organic substances were extracted into ether after the aqueous mixture had been acidified with conc. HCl. The residue left after evaporation of the solvent was dissolved in MeOH (100 ml), and the solution was refluxed for 1 hr with 15% aq. $NaHCO_3$ solution (20 ml). MeOH was evaporated *in vacuo*; the residue was treated by usual manner for extraction of phenolic substance into ether. The residue left by evaporating the solvent was fractionated on silica gel chromatography, and recrystallized from *n*-hexane–ether. Colorless needles, mp 73—74°. Yield 4.0 g. *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36. Found: C, 67.82; H, 6.55.

Ullmann Reaction between IX and XIII——IX (9.0 g) and XIII (10 g) were dissolved in pyridine (*ca.* 10 ml); to the solution, finely powdered anhyd. K_2CO_3 (3.0 g) and cupric oxide (700 mg) were added with stirring. The resulted mixture was heated on an oil bath (150±5°) under nitrogen with continuous stirring. After 4 hr, the reaction mixture was poured into ether (300 ml), washed successively with 5% aq. NaOH, 3% citric acid, 5% NaOH, and water; then ether was removed by distillation. The remained oily substance (8.4 g) was treated with conc. HCl (3 ml) in MeOH (100 ml) for 1 hr under reflux. MeOH was evaporated *in vacuo*, the residue was poured into 2% HCl (200 ml) and washed with ether, then the acidic water layer was thoroughly extracted with $CHCl_3$. The $CHCl_3$ layer was washed twice with 2% HCl; then $CHCl_3$ was removed by distillation after washed with 2% NH_4OH and water. The product was obtained as a pale-yellow oil. N–Carbobenzoxy–3–methoxy–4–(2,3–methylenedioxy–5–(2–aminoethyl)phenoxy)–β–phenethylamine (XIV): Yield 3.8 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH); 1715 (CO). NMR signals τ: 2.69 (5H, s., benzylbenzene); 3.53 and 3.72 (1H, d., J=1.5 cps); 4.09 (2H, s., methylenedioxy); 4.90 (2H, s., Ar–CH_2–O–); 6.20 (3H, s., O–CH_3); 8.67 (2H, s., NH_2).

***tert*-Butyl *p*-benzyloxyphenylacetate (XVI)**——*p*–Benzyloxyphenylacetic acid (XV, 30 g) was dissolved in pyridine (160 ml) and *tert*–butanol (250 ml); and the solution was cooled to −10°. Into the above solution, phosphorus oxychloride (14 ml) was added dropwise with vigorous stirring. The reaction mixture was kept for 30 min at −10° with stirring, then for 2 hr at room temperature. The residue left on evaporation of the reagent and solvent was poured into ether (1 liter) and washed successively with water, 2% citric acid, 2% NH_4OH, and water. Evaporation of the solvent gave yellowish oily substance which was proved to be XVI by NMR spectrometry. Yield 30.0 g. NMR signals τ: 2.75 (5H, s., benzylbenzene); 2.93, 3.22 (4H, A_2B_2 q., J=9 cps); 5.07 (2H, s., Ar–CH_2–O); 6.67 (2H, s., Ar–CH_2–CO); 8.62 (9H, s., $C(CH_3)_3$).

***tert*-Butyl *p*-hydroxyphenylacetate (XVII)**——The solution of the foregoing ester (9.8 g) in 99% EtOH (150 ml) was shaken with 10% palladised charcoal (1.0 g) and hydrogen unitl uptake ceased. The catalyst was filtered off, then the solvent was removed by evaporation *in vacuo*. The resdiue was dissolved in ether (300 ml); evaporation of the solvent after washing with 3% NH_4OH and water gave pale-yellow crystalline mass, from which, by recrystallization from cyclohexane, the pure proudct was obtained. Yield 6.5 g. Colorless pillars, mp 96—97°. *Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.93.

Methyl 3-bromo-4-methoxyphenylacetate (XIX)——Methyl 3–bromo–4–hydroxyphenylacetate (15 g) was dissolved in dimethylformamide (150 ml); then anhyd. K_2CO_3 (20 g) and dimethyl sulfate (15 ml) were added into the above solution. The resulted mixture was heated at 90—100° with stirring for 1.5 hr. After cooling, the reaction mixture was poured into water (500 ml); then the organic substances were extracted into ether, and washed successively with 2% aq. NaOH, 2% HCl, and water. Evaporation of ether followed by chromatographic purification on silica gel afforded the product as a colorless oily substance. Yield 14 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester carbonyl). NMR signals τ: 6.17 and 6.34 (3H, s., O–CH_3); 6.46 (2H, s., Ar–CH_2–CO).

Ullmann Reaction between XVII and XIX——The solution of XVII (7.0 g) and XIX (8.7 g) in pyridine (10 ml) was heated on an oil bath (145—150°) with stirring under nitrogen atmosphere in the presence of CuO (400 mg) and anhyd. K_2CO_3 (1.5 g). After 4 hr, the reaction mixture was poured into ether (300 ml), and the resulted ethereal solution was washed successively with 2% aq. NaOH, 1% HCl, and water. The residue (dark-brown oil, 6.3 g) left after evaporation of ether was dissolved in benzene (100 ml) containing *p*–toluene sulfonic acid (1 g); and the solution was refluxed for 1 hr. After cooling, the reaction mixture was poured into ether (200 ml); then the acidic product was extracted into 2% aq. NH_4OH. The alkaline aquoeus layer was extracted with ether after acidification with conc. HCl. Evaporation of the solvent gave brown oil (2.1 g), from which the pure product was isolated by silica gel chromatography and recrystallization from *n*–hexane–ether. Methyl 3–(4–carboxymethylphenoxy)–4–methoxyphenylacetate: Colorless needles, mp 114—116°. Yield 1.3 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 and 1730. NMR signals τ: 1.75 (1H, broad s.,

COOH); 6.19 and 6.32 (3H, s., O–CH_3); 6.39 and 6.46 (2H, s., Ar–CH_2–CO). *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.43; H, 5.75.

N-2-(3,4-Methylenedioxy-5-(2-methoxy-4-(2-benzyloxycarbonylaminoethyl)phenoxy)phenyl)ethyl-2-(4-(2-methoxy-5-methoxycarbonylmethylphenoxy)phenyl)acetamide (XXI)——The foregoing phenethylamine (XIV, 1.7 g) and carboxylic acid (XX, 1.2 g) were dissolved in CH_2Cl_2 (20 ml) together with dicyclohexylcarbodiimide (750 mg), and the mixture was stood at room temperature with stirring. After 45 min, precipitated crystals were separated by filtration, the filtrate was washed successively with 3% aq. citric acid, 2% NH_4OH and water. Evaporation of the solvent gave yellowish brown oil of which purification by chromatography on silica gel afforded the product. Pale-yellow oily substance. Yield 2.0 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (NH); 1710 (CO); 1660 (amide CO).

N-2-(3,4-Methylenedioxy-5-(2-methoxy-4-(2-benzyloxycarbonylaminoethyl)phenoxy)phenyl)ethyl-2-(4-(2-methoxy-5-carboxymethylphenoxy)phenyl)acetamide (XXII)——The solution of the foregoing amide (2.0 g) in MeOH (50 ml) containing 25% aq. K_2CO_3 (8 ml) was refluxed for 30 min. The residue left on evaporation of MeOH *in vacuo* was poured into ether (200 ml). The acidic substance was extracted into 1% aq. NaOH from the above ethereal solution. Acidification of the aqueous extract with conc. HCl followed by extraction with CH_2Cl_2 and removal of the solvent gave the product as pale-yellow oil. Yield 1.8 g. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH); 1715 (CO); 1660 (amide CO). NMR signals τ: 1.72 (1H, broad s., COOH); 2.70 (5H, s., benzyl benzene); 4.14 (2H, s., methylenedioxy); 4.91 (2H, s., Ar–CH_2–O); 6.23 (6H, s., 2×O–CH_3); 6.49 and 6.58 (2H, s., Ar–CH_2–CO).

Cyclo-N-(4-(2-methoxy-5-(2-(3-methoxy-4-(2,3-methylenedioxy-5-(2-aminoethyl)phenoxy)phenyl)ethylcarbamoylmethyl)phenoxy)phenylacetyl) (IVa)——The foregoing carboxylic acid (1.5 g) and *p*-nitrophenol (350 mg) was treated with dicyclohexylcarbodiimide (450 mg) in CH_2Cl_2 (30 ml) at room temperature with stirring. After 45 min precipitated crystals were separated off by filtration; and the solvent was removed by evaporation. The residue was dissolved in AcOH (5 ml), then treated with 2N HBr/AcOH (5 ml) under stirring at room temperature. After 1 hr, the reaction mixture was poured into ether (300 ml); then the ether was separated from the precipitated oily substance by decantation. The separated oily substance was dissolved in dimethylformamide (10 ml) and washed with ether by the same manner that described above. The oily substance thus obtained was again dissolved in dimethylformamide (50 ml), and the resulted solution was added dropwise into warm pyridine (300 ml) during 1 hr with stirring on a water bath (65—75°). After the addition was completed, the reaction mixture was further stirred on the bath for 5 hr. The solvent was evaporated *in vacuo*, the residue was poured into AcOEt (300 ml) and washed with 5% NaOH, 2% HCl, and water. Evaporation of the solvent afforded the crude product as a yellowish amorphous powder (900 mg), from which, on silica gel chromatography and trituration with acetone, the pure product was given in crystalline state. Colorless microcrystals, mp 232—234° (decomp.). Yield 520 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375 (amide NH); 1660 (amide CO). NMR signals τ: 4.08 (2H, s., methylenedioxy); 6.14 and 6.18 (3H, s., O–CH_3); 6.57 and 6.62 (2H, s., Ar–CH_2–CO). *Anal.* Calcd. for $C_{35}H_{34}O_8N_2 \cdot \frac{1}{2}H_2O$: C, 67.84; H, 5.69; N, 4.52. Found: C, 67.89; H, 5.87; N, 4.16.

Bischler-Napieralski Reaction of the Cyclobisamide (IVa)——The bisamide (100 mg) was heated to reflux in $CHCl_3$ (10 ml) with phosphorus oxychloride (0.7 ml) for 2.5 hr. The residue left on evaporation of the reagent and solvent was dissolved in MeOH (20 ml), and treated with $NaBH_4$ (500 mg) with stirring for 30 min at room temperature. The reaction mixture was poured into ether (200 ml) and the basic product was extracted into 1% HCl.

The aqueous extract was made alkaline with conc. NH_4OH, and the product was extracted into ether. Evaporation of the solvent gave a mixture of tetrahydroisoquinolines as a colorless glassy mass, which was used for the next step without purification. The above products mixture was treated in MeOH (10 ml) with formalin (0.5 ml) with stirring at room temperature. After 30 min, $NaBH_4$ (500 mg) was added, and the reaction mixture was poured into ether after stirring for further 30 min. Extraction with 1% HCl, basification with conc. NH_4OH and extraction with ether followed by removal of the solvent afforded product, a mixture of N-methyltetrahydroisoquinolines, as a colorless glassy mass (60 mg).

On the other hand, Bischler-Napieralski product obtained from 100 mg of the amide was dissolved in MeOH (30 ml), and the solution was heated to reflux with zinc powder (10 g) and 20% H_2SO_4 (30 ml) under stirring. After 2 hr, an additional amount of 20% H_2SO_4 (10 ml) was added and the reaction was continued for a total of 4 hr. After cooling, excess zinc powder was filtered off and the filtrate was poured into ether (300 ml). The basic product was isolated from the above ethereal solution by usual manner. Colorless glassy substance, yield 80 mg. This was N-methylated by the same work up procedure that described above, and afforded a mixture of N-methyltetrahydroisoquinolines (51 mg).

The Bischler-Napieralski product started with 500 mg of the bisamide was shaken in MeOH (30 ml) with hydrogen and PtO_2 (200 mg) until uptake ceased. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in ether (200 ml) and treated by usual manner to give basic substance. N-methylation of the product by the same work up method gave a mixture of N-methyltetrahydroisoquinolines (290 mg).

The above three final products were combined and submitted to preparative thin-layer chromatography on silica gel (Silica gel G acc. to Stahl, Merck) using MeOH as developer. The four zones corresponding to Base A, B, C, and D were scraped, and treated for 1 hr with MeOH containing a small amount of 10% NH_4OH. The silica gel was filtered off and the filtrate was evaporated *in vacuo* to dryness. The residue was treated by usual manner, and Base A, B, C, and D were isolated in crude state. Yield for Base A, B, C, and D was 46, 70, 23, and 15 mg, respectively.

Base A——The above crude product was purified on silica gel (15 g) column chromatography using 3% methanolic $CHCl_3$ (by vol.) as eluant. Colorless amorphous powder, yield 25 mg.

Base B——Silica gel (20 g) column chromatography of the above crude product using the same eluant as above gave pure Base B. Colorless amorphous powder, yield 36 mg.

Base C (*dl*-cepharanthine)——The above crude product was fractionated on alumina (20 g) in 50% (by vol.) benzene–$CHCl_3$. From the appropriate fractions was isolated the pure product. Colorless amorphous powder. Yield 3.5 mg.

Base D——The crude Base D was purified by preparative thin-layer chromatography on alumina (Aluminium Oxide G acc. to Stahl) using 20% (by vol.)AcOEt–$CHCl_3$ as developer. Colorless amorphous powder, yield 3 mg.

Acknowledgement The authors express thier gratitude to Dr. T. Shingu of this Faculty for measurements of NMR spectra and helpful discussions on the 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 anlyses. 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 their profound gratitude.