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Masao Tomita, Yoshiaki Aoyagi, Yoshiro Sakatani, and Kazuyoshi Fujitani[*1] : Studies on the Alkaloids of Menispermaceous Plants. CCXL.[*2] Synthesis of Cycleanine. (1). Cupric Oxide Catalysed Ullmann Condensation of *dl*-8-Bromoarmepavine.[*3]

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Cycleanine (O,O-dimethylisochondodendrine) is an alkaloid first isolated from *Cyclea insularis* (MAKINO) DIELS and *Stephania cepharantha* HAYATA by H. Kondo, *et al.*1) in 1937, and was proved to have an exceptionally symmetric bisbenzylisoquinoline structure involving two diphenyl ether linkages in its molecule (formula I,1~3) a, b : D). Synthesis of this alkaloid, however, remained unsuccessful.

As one of the most hopeful routes for synthesis of this alkaloid, the Ullmann condensation of *dl*-8-bromoarmepavine (Ⅱ) catalysed by metallic copper was already attempted,4) though the course of the reaction was found to be discouraging. The products were shown to be only *dl*-armepavine (Ⅲa) and *dl*-N,O,O-trimethylcoclaurine (Ⅲb).

The present investigation was undertaken to re-examine the Ullmann condensation of *dl*-8-bromoarmepavine, substituting the metallic copper catalyst for cupric oxide which was recently shown5) to be more efficient than metallic copper or cuprous oxide,6) and to minimize the formation of by-products.

dl-8-Bromoarmepavine (Ⅱ) was prepared by a method similar to that described in the synthesis of *dl*-armepavine,7) and was submitted to Ullmann condensation in pyridine in the presence of potassium carbonate and cupric oxide. The product was worked out by usual manner and separated to phenolic and non-phenolic fractions. The phenolic fractions was found on thin-layer chromatographies to consist of the starting material and debrominated product, armepavine (Ⅲa). From the nonphenolic fractions, a species of base (Ⅳa) was obtained by chromatographic purification, though any spot corresponding to cycleanine was not found on thin-layer chromatogram. The IR spectrum of this product revealed the presence of phenolic hydroxyl group in the molecule.

O-Methylation of the product with diazomethane afforded the methyl ether (Ⅳb).

As both Ⅳa and Ⅳb showed positive Beilstein test, the quantitative analysis of bromine atom for Ⅳb was carried out, and the obtained results, 11.4% of bromine, suggested that the molecular weight of Ⅳb might be about 700. The NMR spectrum of Ⅳb showed two N-methyl and five O-methyl signals.

From the facts obtained above, the planar structure of the Ullmann condensation product and its methyl ether could be assigned as Ⅳa and Ⅳb, respectively. This con-

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[*2] Part CCXXXIX : T. Ibuka, M. Kitano : This Bulletin, **15**, 1944 (1967).

[*3] A part of this work was presented at the 10th Symposium on the Chemistry of Natural Products, Tokyo, Oct. 6, 1966 (Symposium Papers, p. 31).

1) H. Kondo, M. Tomita, S. Uyeo : Ber., **70**, 1890 (1937); Yakugaku Zasshi, **62**, 534 (1942).

2) E. Fujita, F. Murai : Yakugaku Zasshi, **71**, 1043 (1951).

3) M. Tomita, J. Kunitomo : *Ibid.*, **82**, 734 (1962).

4) K. Fujitani, T. Kishimoto, S. Niimura : *Ibid.*, **83**, 412 (1963).

5) M. Tomita, K. Fujitani, Y. Aoyagi : This Bulletin, **13**, 1341 (1965).

6) R.G.R. Bacon, H.A.O. Hill : J. Chem. Soc., **1964**, 1108.

7) K. Fujitani, Y. Aoyagi, Y. Masaki : Yakugaku Zasshi, **86**, 654 (1966).

clusion was further verified by sodium-liquid ammonia cleavage of Ⅳb, which afforded *dl*-armepavine (Ⅲa) and *dl*-N,O,O-trimethylcoclaurine (Ⅲb) as the bisected products.

On the one hand, catalytic hydrogenolysis of Ⅳb gave the debrominated product (Ⅴ), of which structure was further ascertained as follows: Ullmann condensation between *dl*-8-bromo-N,O,O-trimethylcoclaurine (Ⅵ)8) and *dl*-armepavine (Ⅲa) proceeded to give the diphenyl ether compound in 32% yield. Identity of the above mentioned debrominated product (Ⅴ) and the Ullmann product was proved by thin-layer chromatographies and IR and NMR spectral comparisons.

Further, sodium-liquid ammonia cleavage of Ⅴ afforded *dl*-armepavine (Ⅲa) and *dl*-N,O,O-trimethylcoclaurine (Ⅲb) as the bisected bases.

From the above experiments, it has been found that the Ullmann condensation of 8-bromoarmepavine is first effected by means of cupric oxide catalyst to afford a bisbenzylisoquinoline system, though simultaneous formation of two diphenyl ether bonds was not achieved, and the synthetic approach to cycleanine through this route was found unsuccessful.

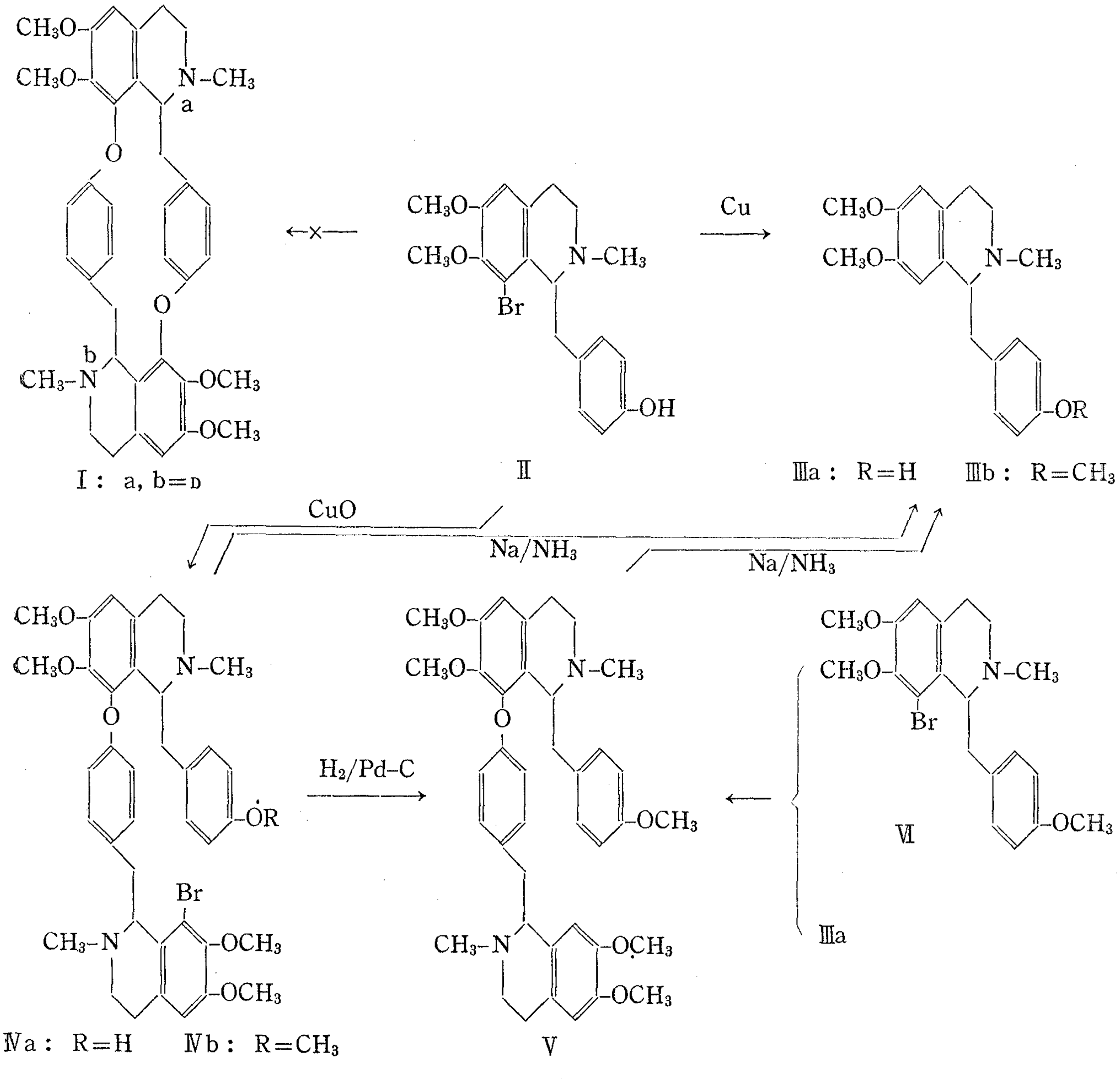

Chart 1.

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8) M. Tomita, K. Fujitani, Y. Masaki, Y. Sakatani: This Bulletin, in press.

Experimental[*4]

N-(2-(3-Bromo-4,5-dimethoxyphenyl)ethyl)-2-(4-acetoxyphenyl)acetamide——3-Bromo-4,5-dimethoxy-β-nitrostyrene[4] (110 g.) was suspended on a mixture of MeOH (1.5 L.) and conc. HCl (700 ml.). Amalgamated zinc prepared from zinc powder (150 g.) and 5% aq. $HgCl_2$ (300 ml.) was added portionwise into the above mixture with stirring. The temperature of the reaction mixture was kept below 60°. The stirring was continued for 1 hr. after disappearance of the yellow coloring of the reaction mixture. MeOH was evaporated *in vacuo*. The residue was poured into water (1 L.), washed with ether, and made alkaline with conc. NH_4OH; the basic product was then extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave a light-brown oily substance which was proved to be the phenethylamine by comparison of the oxalate with authentic sample.[4] 3-Bromo-4,5-dimethoxy-β-phenethylamine : Light-brown oily substance, yield, 92 g. Oxalate : Recrystallized from EtOH, colorless microcrystals, m.p. and mixed m.p. 205~211°.

The foregoing phenethylamine (5.0 g.) and *p*-hydroxyphenylacetic acid (2.9 g.) was dissolved in decalin (30 ml.) and the resulted solution was refluxed for 1 hr. The reaction mixture was poured into AcOEt (200 ml.) and phenolic substance was extracted with 5% aq. NaOH. The aqueous layer was treated by usual manner for extraction of phenolic substance with $CHCl_3$. The residue left after evaporation of $CHCl_3$ was dissolved in pyridine (20 ml.), and treated with Ac_2O (10 ml.) at room temperature overnight. The reaction mixture was poured into ice-water (200 ml.) and extracted with $CHCl_3$; the organic layer was washed successively with 2% aq. NaOH, 2% HCl, and water. Evaporation of $CHCl_3$ afforded light-brown crystalline solid, from which, by column chromatography on alumina with $CHCl_3$ and recrystallization from CCl_4, the title compound was isolated. Colorless microcrystals, m.p. 117~118°. Yield, 2.1 g. *Anal.* Calcd. for $C_{20}H_{22}O_5NBr$: C, 55.05; H, 5.09. Found : C, 54.78; H, 5.21.

1-(4-Hydroxybenzyl)-6,7-dimethoxy-8-bromo-1,2,3,4-tetrahydroisoquinoline——The above amide (2.0 g.) was dissolved in anhyd. toluene (10 ml.) and refluxed for 45 min. in the presence of $POCl_3$ (1 ml.). The residue left after evaporation of the reagent and solvent was dissolved in MeOH (30 ml.) and treated with $NaBH_4$ (2.5 g.) under stirring for 30 min. MeOH was evaporated off; the residue was treated by usual manner, and the basic product was extracted with ether. Recrystallization of the residue left after evaporation of the solvent from acetone gave the pure product. Colorless pillars, m.p. 180.5~182°. Yield, 490 mg. *Anal.* Calcd. for $C_{18}H_{20}O_3NBr$: C, 57.14; H, 5.33. Found : C, 57.04; H, 5.55.

1-(4-Hydroxybenzyl)-2-methyl-6,7-dimethoxy-8-bromo-1,2,3,4-tetrahydroisoquinoline(*dl*-8-bromoarmepavine) (II)——The above product (490 mg.) was dissolved in MeOH (50 ml.) and treated with formalin (0.5 ml.) for 30 min. with stirring at room temperature; then $NaBH_4$ (1.0 g.) was added, and the reaction mixture was further stirred for 30 min. MeOH was evaporated *in vacuo*; the residue was treated by usual manner for extraction of basic substance with ether. Solvent was evaporated and the residual crystalline solid was recrystallized from MeOH. Colorless cubes, m.p. and mixed m.p. 163~166°. Yield, 350 mg.

Ullmann Reaction of *dl*-8-Bromoarmepavine (II)——Finely powdered anhyd. K_2CO_3 (1.5 g.) was added into the solution of *dl*-8-bromoarmepavine (2.6 g.) in *ca.* 6 ml. of anhyd. pyridine; then the mixture was heated on an oil bath with stirring under nitrogen atmosphere. When the temperature of the bath was raised to 140°, cupric oxide (700 mg.) was added; and the reaction was continued for 4.5 hr. The temperature of the bath was kept at 145~150° during the reaction. After the reaction ended, the basic product were extracted with ether, and separated to phenolic and nonphenolic bases by shaking the ether solution with 5% aq. NaOH. Phenolic part : Pale-yellow viscous oily substance. Yield, 950 mg. It afforded colorless microcrystals from MeOH, m.p. 163~165°. This substance was identified with the starting material (II) by IR ($CHCl_3$) spectrum and mixed m.p. Although a small amount of the debrominated product, armepavine (IIIa), was detected on thin-layer chromatogram, the mother liquor of II was not further examined. Non-phenolic part : Pale-yellow oily substance. Yield, 800 mg. Two kinds of bases, one is crystalline and another oily, were isolated from the crude bases by column chromatography on silica gel. Crystalline : Colorles microcrystals, m.p. 164~166°. Yield, 120 mg. The NMR spectrum and mixed m.p. showed that the substance was the starting material (II). Oily (IVa) : Colorless viscous oily substance. Yield, 190 mg. It resisted all attempts at crystallizations. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3550 (phenolic OH). NMR : (see Fig. 1.).

O-Methylation of IVa——IVa (40 mg.) was dissolved in MeOH (5 ml.). Ethereal diazomethane prepared from nitrosomethylurea (3.0 g.) was added into the above solution. The resulted mixture was left at room temperature overnight. The reaction mixture was added into ether (100 ml.); then the basic substance was extracted with 3% HCl. The product was extracted with ether after basification of the above extract with conc. NH_4OH. Evaporation of the solvent gave a pale-yellow oily substance, yield, 40 mg., from which, on purification by alumina column chromatography, the pure product (IVb) was afforded, yield, 30 mg. NMR :

[*4] 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. NMR spectra were taken on Varian A-60 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Solutions of basic or neutral substances were dried over anhyd. K_2CO_3 and of acidic substances over anhyd. $MgSO_4$.

(see Fig. 1.). *Anal.* Calcd. for $C_{39}H_{45}O_6N_2Br$: Br, 11.13. Found : Br, 11.4.

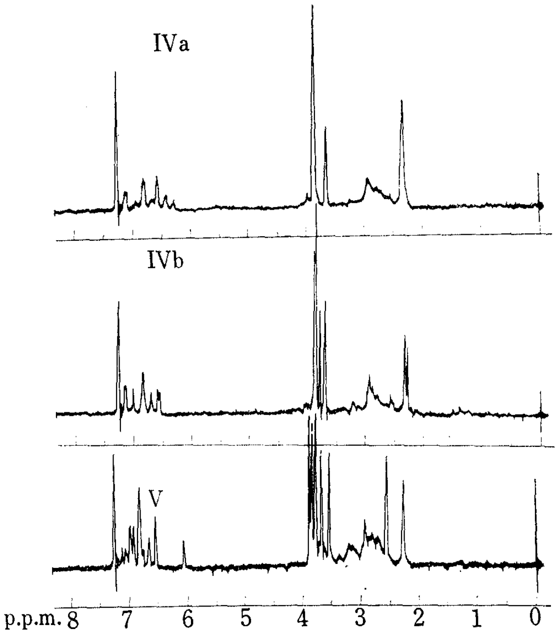

Fig. 1. NMR Spectra of IVa, IVb, and V

Metallic Sodium-Liquid Ammonia Fission of IVb——On a dry ice-acetone bath (−65°), metallic sodium was added to a mixture of liq. NH_3 (10 ml.) and ether (10 ml.) with stirring until the mixture showed a blue color. A solution of IVb (50 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 the coloring for 30 min. After the reaction was completed, NH_4Cl was added to the mixture until the color disappeared. Ammonia was evaporated at room temperature, and the residue was treated by usual manner for isolation of phenolic and non-phenolic bases. Phenolic : Colorless microcrystals from acetone, m.p. 163~167°. Yield, 18 mg. This base was proved to be *dl*-armepavine (IIIa)[7] by IR ($CHCl_3$) and mixed m.p. Non-phenolic : Colorless oily substance, yield, 18 mg. The IR ($CHCl_3$) spectrum of this base was completely identical with that of D-N,O,O-trimethylcoclaurine.[9]

Hydrogenolysis of IVb——IVb (30 mg.) was dissolved in MeOH (20 ml.) and hydrogenated over 5% palladised charcoal until uptake ceased. Catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was treated by usual manner, and basic substance was extracted with ether. Evaporation of the solvent gave pale-yellow oil, from which, by silica gel column chromatography, the pure product (V) was isolated as colorless oil. Yield, 11 mg. NMR : (see Fig. 1.).

Ullmann Reaction between *dl*-8-Bromo-N,O,O-trimethylcoclaurine (VI) and *dl*-Armepavine (IIIa)——Finely powdered anhyd. K_2CO_3 (800 mg.) and cupric oxide (500 mg.) were added to a solution of VI (810 mg.) and IIIa (630 mg.) in anhyd. pyridine (5 ml.) with stirring. The resulted mixture was heated on an oil bath (140~150°) for 6 hr. with continuous stirring under nitrogen atmosphere. After the reaction ended, the reaction mixture was taken up into a small amount of MeOH, and the solvent and pyridine were distilled off *in vacuo*. The residue was treated by usual method, and the non-phenolic bases were purified on silica gel column chromatography. The product, pale-yellow oily substance, was isolated in 32% yield. The IR ($CHCl_3$) and NMR spectra and thin-layer chromatograms of the product were superimposable on those of the above debrominated product (V). This substance involving the salts and metho-iodide was hardly crystallized.

Metallic Sodium-Liquid Ammonia Cleavage of V——On a dry ice-acetone bath (−69°), metallic sodium was added to liquid NH_3 (20 ml.) with stirring until the mixture showed a blue color. A solution of V (100 mg.) in dioxane (3 ml.) was added to the above mixture with continuous stirring, and an additional amount of metallic sodium was added portionwise so that the coloring was kept for 30 min. After the reaction ended, crystalline NH_4Cl was added to the mixture until blue color disappeared. The residue left after evaporation of NH_3 was treated by usual manner, and separated to phenolic and non-phenolic bases. Phenolic base : Colorless pillars from acetone, m.p. 163~165°. Yield, 21 mg. This base was identified with *dl*-armepavine (IIIa) by IR ($CHCl_3$) spectral comparison, thin-layer chromatographies, and mixed m.p. Non-phenolic base : Colorless oily substance. Yield, 39 mg. This product was identified with *dl*-N,O,O-trimethylcoclaurine (IIIb) by IR ($CHCl_3$) spectrum and thin-layer chromatographies.

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[9] M. Tomita, E. Fujita, F. Murai : Yakugaku Zasshi, **71**, 226 (1951).