Estra-1,3,5(10)-trien-17α-ol(IXa)——Hydrolysis of IXb with 2.5% methanolic KOH and recrystallization of the hydrolyzate from acetone–hexane gave IXa as colorless needles. mp 158—161°. $[\alpha]_D^{20}$ +44.8° (c=0.17). *Anal.* Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.41; H, 9.38.

3-Benzyloxyestra-1,3,5 (10)-trien-17β-ol *p*-Toluenesulfonate (Xb)——To a solution of Xa (640 mg) in pyridine (18 ml) was added *p*-TsCl (1.94 g) and the reaction mixture was treated in the same manner as described in VIIIb. Recrystallization from ether gave Xb (578 mg) as colorless plates. mp 116—117°. $[\alpha]_D^{19}$+10.2° (c=0.78). *Anal.* Calcd. for $C_{32}H_{36}O_4S$: C, 74.39; H, 7.02. Found: C, 74.12; H, 7.10.

3-Benzyloxyestra-1,3,5(10)-trien-17α-ol Acetate (XIb)——A solution of Xb (300 mg) in N-methylpyrrolidone (5 ml) was heated at 160° with tetrabutylammonium acetate (1.5 g) for 7 hr. The reaction mixture was treated in the same manner as described in IXb. The crude product was submitted to preparative TLC using benzene as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.70) and recrystallization of the eluate from EtOH gave XIb (93 mg) as colorless leaflets. mp 99—100°. $[\alpha]_D^{18}$ +30.4° (c=0.39). *Anal.* Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.19; H, 7.87. Elution of the adsorbent corresponding to the spot (*Rf* 0.92) and recrystallization of the eluate from EtOH gave 3-benzyloxyestra-1,3,5(10),16-tetraene (27 mg) as colorless needles. mp 74—77°. $[\alpha]_D^{14}$ +57.1° (c=0.21). *Anal.* Calcd. for $C_{25}H_{28}O$: C, 87.16; H, 8.19. Found: C, 86.91; H, 7.97.

Estra-1,3,5(10)-triene-3,17α-diol 17-Acetate (XIa)——A solution of XIb (85 mg) in EtOH (30 ml) was shaken with 5% Pd/C (60 mg) under a stream of H_2 overnight. After removal of the catalyst by filtration the filtrate was concentrated to give the crystalline product. Recrystallization from aq. MeOH gave XIa (38 mg) as colorless prisms. mp 188.5—190°. $[\alpha]_D^{19}$ +38.5° (c=0.44). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.10; H, 8.27.

3-Benzyloxyestra-1,3,5(10)-trien-17α-ol (XIc)——Hydrolysis of XIb with 2.5% methanolic KOH and recrystallization of the hydrolyzate from acetone–hexane gave XIc as colorless prisms. mp 99—100°. $[\alpha]_D^{18.5}$ +33.3° (c=0.21). *Anal.* Calcd. for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 82.90; H, 8.30.

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Studies on the Syntheses of Heterocyclic Compounds. CCCXXI.[1] Synthesis of Isoquinoline Derivatives having Twenty-four Membered Ring System by Ullmann Reaction

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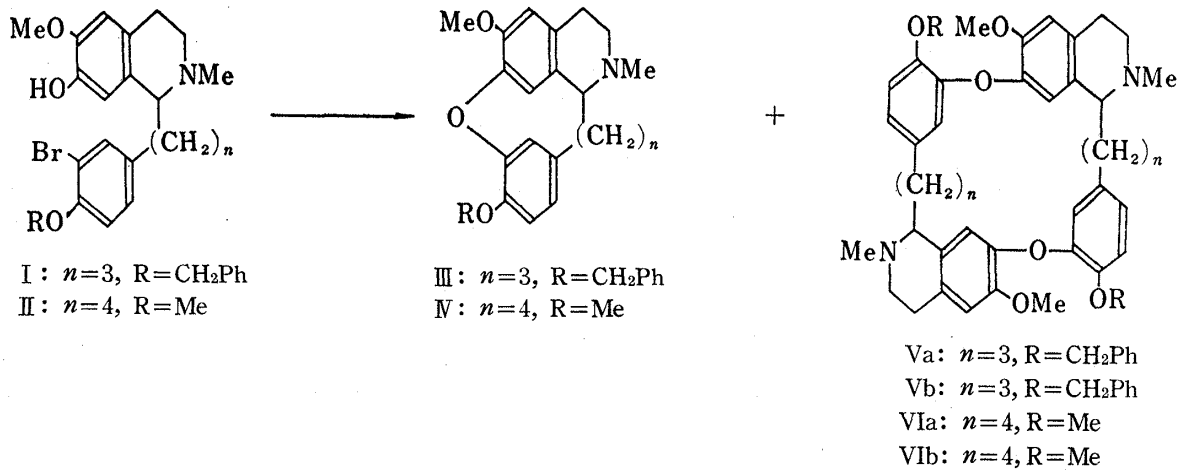
In a previous paper[3] we have reported that Ullmann reaction of 1-phenylpropylisoquinoline derivative (I) gave only twenty-two membered ring compounds (Va—b) as an intermolecular condensation product, but no intramolecular condensation product (III) was obtained. Therefore, Ullmann reaction of 1-[4-(3-bromo-4-methoxyphenyl)butyl]-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (II) having one more methylene group than the compound (I) was carried out, in order to examine whether both inter- and intramolecular

1) Part CCCXX: T. Kametani, K. Ohkubo, and S. Takano, *Yakugaku Zasshi*, **89**, 1048 (1969).
2) Location: *a*) *Aobayama, Sendai*; *b*) *No. 600, Kashiwagi, Shinjuku, Tokyo.*
3) T. Kametani, H. Iida, and S. Tanaka, *Yakugaku Zasshi*, **89**, 230 (1969).

reactions would be occured or not, and the formation of the compound (IV) besides two macro ring compounds (VIa—b) was confirmed. Hereby we wish to report these results.



I: n=3, R=CH_2Ph
II: n=4, R=Me

III: n=3, R=CH_2Ph
IV: n=4, R=Me

Va: n=3, R=CH_2Ph
Vb: n=3, R=CH_2Ph
VIa: n=4, R=Me
VIb: n=4, R=Me

Chart 1

The bromide (VIII), which was obtained by bromination of 5-(4-methoxyphenyl)valeric acid[4] (VII) with bromine in acetic acid, was fused with 4-benzyloxy-3-methoxyphenethylamine[5] by heating at 180° for 1.5 hr to give the amide (X) in good yield. Bischler–Napieralski reaction of the above amide (X) gave the corresponding 3,4-dihydroisoquinoline (XI), which was characterized as its hydrochloride. Reaction of the methiodide (XII) with sodium borohydride gave 1-[4-(3-bromo-4-methoxyphenyl)butyl]-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XIV) as a pale yellow syrup, which was also obtained by reduction of the hydrochloride of XI with sodium borohydride, followed by N-methylation of the 1,2,3,4-tetrahydroisoquinoline (XIII). Further debenzylation of XIV with conc. hydrochloric acid–ethanol (1:1) afforded a phenolic base (II), whose infrared (IR) spectrum showed an absorption band due to a hydroxy group at 3500 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) revealed five aromatic proton resonances at 2.68—3.47 τ, a phenolic proton resonance at 4.2—5.5 τ, two O-methyl resonances at 6.17 τ and N-methyl protons at 7.59 τ.

Secondly, Ullmann reaction of II in the presence of copper powder and potassium carbonate in pyridine at 170—175° for 48 hr was carried out, to give three kinds of products, namely the base (A), the base (B), and IV, which were separated by repeated chromatography on silica gel and alumina.

Regarding the base A and B, the fragmentation pattern of the mass spectra of both compounds was identical. The molecular ion peaks (M^+) of both compounds were shown at m/e 706 and the $(M\text{-}2)^{2+}$ ion peaks were shown at m/e 352 as the base peak. The NMR spectrum of the base (A) revealed ten aromatic proton signals at 2.05—3.50 τ, four O-methyl proton signals at 6.16 and 6.17 τ, and two N-methyl proton signals at 7.59 τ, whereas ten aromatic proton signals were observed at 2.05—3.70 τ, four O-methyl proton signals at 6.17 and 6.21, and two N-methyl proton signals at 7.59 τ in case of the base (B). On the other hand, both IR spectra of the bases (A and B) in chloroform were identical each other, but there appeared a distinct difference in the thin-layer chromatogram. These facts reveal that both bases A and B are in relation to the diastereoisomers (VIa and VIb) each other, but, the relative configuration of both asymmetric centers remains unclear.

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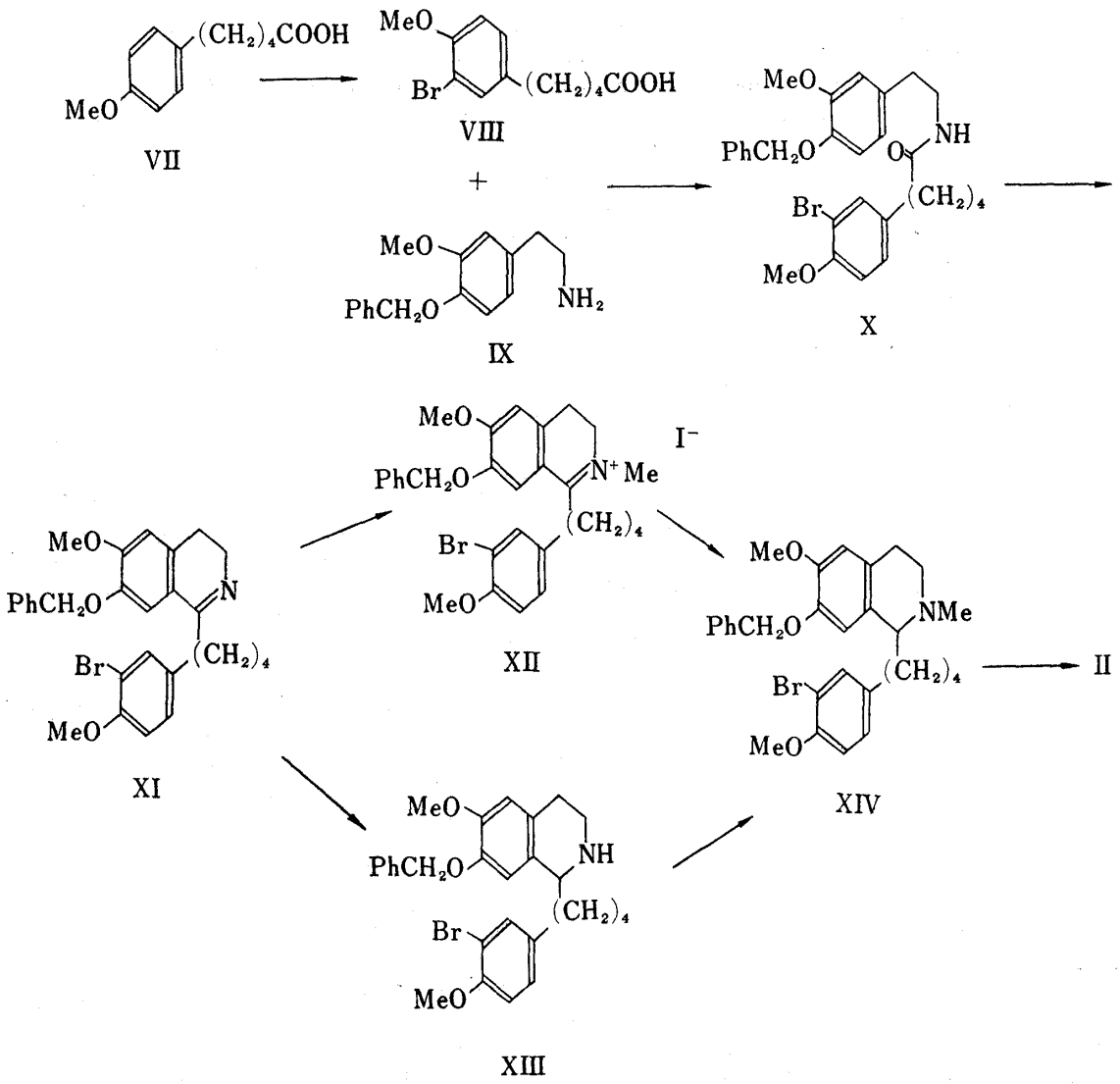

Chart 2

The mass spectrum of IV showed molecular ion peak (M^+) due to $C_{22}H_{27}O_3N$ at *m/e* 353 and its NMR spectrum showed five aromatic proton signals at 3.10—3.52 τ, two O-methyl proton signals at 6.13 τ, and one N-methyl proton signal at 7.65 τ. Furthermore, no hydroxy absorption band was observed in its IR spectrum and microanalysis of the perchlorate also supported the structure of IV. These results revealed that one of three products was assigned to the intramolecular condensation product (IV). Thus, it is interesting that both intra- and intermolecular cyclization have occurred in case of Ullmann reaction of II.

Experimental

NMR spectra were measured on JNM-4H 100 Mc spectrometer using tetramethylsilane as an internal standard. Melting points were measured on a Yanagimoto micro-melting point apparatus and were not corrected. Mass spectra were taken on a Hitachi RMU-6D mass spectrometer.

5-(3-Bromo-4-methoxyphenyl)valeric Acid (VIII)——To a solution of 10.4 g of 5-(4-methoxyphenyl)-valeric acid[4] (VII) in 50 ml of AcOH was added dropwise 8 g of Br_2 in AcOH with stirring. After the reaction mixture had been poured into 100 ml of ice-water, the precipitate was collected by filtration. Recrystallization from benzene gave 11 g (78%) of the acid (VIII) as colorless prisms, mp 115—116°. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd. for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.27. Found: C, 50.46; H, 5.16.

N-(4-Benzyloxy-3-methoxyphenethyl)-3-bromo-4-methoxyphenethylvaleramide (X)——A mixture of 9 g of the above acid (VIII) with 8 g of the amine[5] (IX) was heated at 180° for 1.5 hr and the reaction mixture was then recrystallized from AcOEt to give 13.7 g (84 %)of the amide (X) as colorless needles, mp 126—127°.

IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1645 (C=O); δ_{max}^{KBr} 750, 700 (mono-substituted benzene). *Anal.* Calcd. for $C_{28}H_{32}O_4NBr$: C, 63.88; H, 6.13; N, 2.66. Found: C, 63.77; H, 6.03; N, 2.52.

7-Benzyloxy-1-[4-(3-bromo-4-methoxyphenyl)butyl]-3,4-dihydro-6-methoxyisoquinoline (XI) Hydrochloride——A mixture of 13 g of X, 10 g of $POCl_3$, and 130 ml of dry benzene was refluxed on a water-bath for 4 hr, and an excess of hexane was added to the above reaction mixture. After standing in a refrigerator overnight, the precipitate was collected and washed with ether. Recrystallization from MeOH–ether gave 12.8 g (95%) of HCl salt of XI as colorless prisms, mp 115—117°. IR ν_{max}^{KBr} cm^{-1}: 1655 (=C=$\overset{+}{N}$H–). *Anal.* Calcd. for $C_{28}H_{31}O_3NBrCl\cdot H_2O$[6]: C, 59.74; H, 5.91; N, 2.45. Found: C, 59.29; H, 5.88; N, 2.42.

7-Benzyloxy-1-[4-(3-bromo-4-methoxyphenyl)butyl]-3,4-dihydro-6-methoxyisoquinoline Methiodide (XII)——After 12.8 g of the HCl salt of XI had been treated with 10% aq. K_2CO_3 solution and extracted with $CHCl_3$, the extract was dried over K_2CO_3 and evaporated to give 12 g of XI as a pale yellow syrup. IR ν_{max}^{KBr} cm^{-1}: 1625 (=C=N–). NMR τ ($CDCl_3$): 2.4—3.4 (10H, aromatic protons), 4.87 (2H, singlet, $PhC\underline{H}_2O$), 6.08, 6.17 (6H, two singlets, $2\times OC\underline{H}_3$).

A mixture of 12 g of the above compound (XI) and 25 g of MeI was allowed to stand at room temperature for 1 hr and the excess of MeI was removed by distillation to give the solid, whose recrystallization, after repeated washing with ether, from acetone-ether gave 15 g of XII as pale yellow prisms, mp 99—100°. *Anal.* Calcd. for $C_{29}H_{33}O_3NBrI\cdot H_2O$[6]: C, 52.11; H, 5.28; N, 2.09. Found: C, 51.86; H, 5.19; N, 1.94.

7-Benzyloxy-1-[4-(3-bromo-4-methoxyphenyl)butyl]-1,2,3,4-tetrahydro-6-methoxyisoquinoline (XIII)——To a mixture of 5 g of X, 50 ml of MeOH, and 1 ml of water was added in small portions 2 g of $NaBH_4$, and, after standing for 1 hr, the solvent was distilled off, to give the residue, which was extracted with benzene. After drying over K_2CO_3, the benzene was distilled off, to give 4.7 g of XIII as a pale yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH). NMR τ ($CDCl_3$): 2.50—3.95 (10, aromatic protons), 4.91 (2H, singlet, $OC\underline{H}_2Ph$), 6.18 (6H, singlet, $2\times OC\underline{H}_3$). Recrystallization of the oxalate of XIII from EtOH gave colorless needles, mp 146—147°. *Anal.* Calcd. for $C_{28}H_{32}O_3N\cdot H_2C_2O_4$: C, 60.00; H, 5.71; N, 2.33. Found: C, 60.44; H, 6.08; N, 2.20.

7-Benzyloxy-1-[4-(3-bromo-4-methoxyphenyl)butyl]-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (XIV)——a) To a mixture of 16.3 g of XII, 80 ml of $CHCl_3$, 80 ml of MeOH, and 5 ml of H_2O was added in small portions 5 g of $NaBH_4$, and, after standing for 1 hr, the solvent was evaporated and the residue was extracted with benzene. The extract was dried over K_2CO_3 and evaporated to give 10 g of XIV as a pale yellow syrup, whose IR and NMR spectra were identical with those of an authentic sample described below.

b) A mixture of 4.7 g of XIII, 40 ml of MeOH, and 30 ml of 37% CH_2O was stirred at room temperature for 0.5 hr. To the above mixture was added in small portions 3 g of $NaBH_4$ and then the solvent was distilled off. The resultant syrup was extracted with benzene. The extract was dried over K_2CO_3 and evaporated to give 4 g of XIV as a pale yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2780 (N-Me). NMR τ ($CDCl_3$): 2.50—3.50 (10H, aromatic protons), 4.91 (2H, singlet, $OC\underline{H}_2Ph$), 6.17, 6.18 (6H, two singlets, $2\times OC\underline{H}_3$), 7.61 (3H, singlet, $NC\underline{H}_3$). Recrystallization of the oxalate of XIV from EtOH–ether gave colorless needles, mp 98—100°. *Anal.* Calcd. for $C_{29}H_{34}O_3NBr\cdot H_2C_2O_4\cdot 1/2H_2O$[6]: C, 59.71; H, 5.98; N, 2.25. Found: C, 59.81; H, 6.18; N, 2.15.

1-[4-(3-Bromo-4-methoxyphenyl)butyl]-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline(II)——A solution of 13 g of XIV in 130 ml of EtOH–conc. HCl solution (1:1) was heated at 110° for 1 hr and the solvent was then distilled off. The residue was basified with 10% aq. NH_4OH solution and extracted with ether. The extract was dried over K_2CO_3 and evaporated to give 10 g of II as a pale yellow syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 2780 (NMe). NMR τ ($CDCl_3$): 2.68—3.24 (3H, aromatic protons), 3.38 (1H, singlet, C_5–H), 3.47 (1H, singlet, C_8–H), 4.2—5.5 (1H, broad signal, O$\underline{H}$), 6.17 (6H, two singlets, $2\times OC\underline{H}_3$), 7.59 (3H, singlet, $NC\underline{H}_3$).

Ullmann Reaction of II——A mixture of 3.2 g of II, 2.5 ml of pyridine, 1 g of Cu powder, and 3 g of K_2CO_3 was heated with stirring at 170—175° for 48 hr. An excess of $CHCl_3$ was added to the reaction mixture and the precipitated inorganic substances were filtered off. Concentration of the filtrate gave the residue, which was extracted with ether. Evaporation of ether gave a syrup which was chromatographed on 30 g of SiO_2. Elution with MeOH–$CHCl_3$ (1:20) gave a pale brownish syrup which showed three spots on its thin-layer chromatography (TLC).[7] This syrup was again chromatographed on 30 g of Al_2O_3 and the first elution with benzene gave a syrup, which was extracted with ether–hexane (1:1). Evaporation of the extract gave 350 mg of IV, whose TLC[7] showed one spot. NMR τ ($CDCl_3$): 3.10—3.52 (5H, aromatic protons), 6.13 (3H, singlets, $OC\underline{H}_3$), 7.65 (3H, singlet, $NC\underline{H}_3$). Mass (*m/e*): 353 (75%), 339 (15%), 338 (35%), 325 (40%), 324 (100%), 311 (28%), 310 (36%), 296 (26%), 282 (36%), 190 (17%). Recrystallization of the perchlorate of IV from acetone–ether afforded colorless needles, mp 272—274°. *Anal.* Calcd .for $C_{22}H_{27}O_3N\cdot HClO_4$: C, 58.21; H, 6.22; N, 3.01. Found: C, 58.31; H, 6.18; N, 3.01. IR, NMR, and Mass spectra of the free base (IV), which was obtained by the usual method from the perchlorate of IV, were superimposable on those of the original syrupy base but could not be crystallized.

6) These samples were dried on P_2O_5 at 60° for 2 days under reduced pressure.

7) TLC was carried out as follow: alumina, ether–benzene (1:1); detection by Dragendorf reagent.

Secondly, elution with benzene–$CHCl_3$ (5:1) gave a syrup, which was triturated with acetone to give crystals. Recrystallization from $CHCl_3$–ether afforded 250 mg of the base (A), namely, VIa as colorless needles, mp 253—255°. NMR τ ($CDCl_3$): 2.05—3.50 (10H, aromatic protons), 6.16, 6.17 (12H, two singlets, $4\times OC\underline{H}_3$), 7.57 (6H, singlet, $2\times NC\underline{H}_3$). *Anal.* Calcd. for $C_{44}H_{54}O_6N_2\cdot 1/2H_2O$[6]: C, 73.82; H, 7.74; N, 3.91. Found: C, 73.93; 73.67; H, 7.94; 7.75; N, 3.64. Mass (*m/e*): 706 (M^+) (40%), 691 (M^+–15) (42%), 676 (M^+–30) (37%), 661 (M^+-45) (17%), 646 (M^+-60) (6%), 352 (M-2)$^{++}$ (100%), 338 (M^+-140) (12%), 324 (M^+-372) (47%), 310 (M^+-396) (26%), 296 (M^+-410) (28%). The filtrate, from which the base (A) was removed by filtration, was chromatographed on 20 g of Al_2O_3 and removal of the benzene–$CHCl_3$ (10:1) gave 200 mg of the base (B), namely, VIb, as a pale yellow syrup. NMR τ ($CDCl_3$): 2.05—3.70 (10H, aromatic protons), 6.17, 6.12 (12H, two singlets, $4\times OC\underline{H}_3$), 7.59 (6H, singlets, $2\times NC\underline{H}_3$). Recrystallization of the perchlorate of VIb from acetone–ether afforded colorless needles, mp 280—282°. *Anal.* Calcd. for $C_{44}H_{54}O_6N_2\cdot 2HClO_4\cdot 2H_2O$[6]: C, 55.99; H, 6.41. Found: C, 56.08; H, 6.51. The fragmentation patterns in the mass spectrum of Vb was identical with that of Va.

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Studies on Ergot Alkaloids and Related Compounds. XVI.[1] On the So-called Bohlmann Absorption of 2,4-Disubstituted Octahydrobenzo[*f*]quinoline Derivatives[2]

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Previously, we have prepared a series of 2,4-disubstituted octahydrobenzo[*f*]quinoline derivatives, structurally related to lysergic acid and established their stereochemistries and conformations of their stereoisomers on the basis of chemical and physical evidences.[2,4]

Recently, Edwards and his coworkers[5] have suggested from study on the lupine alkaloids that in a given conformation of a heterocyclic system, at least one hydrogen antiparallel to the lone pair of nitrogen is on carbon atom attached to nitrogen, the shape and intensity of Bohlmann *trans* band[6] being proportional to the number of *trans* diaxial hydrogen. This report pushed us to write this paper based on data obtained from our compounds (I—VIII), which exhibited strong and characteristic absorptions in the Bohlmann band region, although they are not of the quinolizidine type compounds.

Infrated spectra of the previously described compounds (I—VIII, measured in chloroform) were exemplified by four typical examples as shown in Fig. 1, to which all eight compounds could be classified by the shape of their Bohlmann bands.

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