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Syntheses of Aminoisoquinolines and Related Compounds. III.[1] Influence of Substituents on the Direction of Ring-closure in the Bischler-Napieralski Reaction[2]

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The Bischler–Napieralski cyclization of phenethylamide (VII), having an ethoxycarbamido group in the 3-position of the benzene ring was found to take place in the positions *para* and *ortho* to the ethoxycarbamido group, and the two isoquinoline derivatives could be separated in the stage of N-methyl-1,2,3,4-tetrahydroisoquinolines (Xa and Xb) in 1:3.5 ratio (*para* to *ortho*).

Deamination of the 8-amino compound (XIb) gave a mixture of 6,7-dimethoxy derivative (XIb) and *dl*-nuciferin (XIIc), which were separated by chromatography on silica gel to give two components in 2:1 ratio.

The purpose of the present work was to examine the direction of the Bischler–Napieralski cyclization of a phenethylamide (VII) having an ethoxycarbamido group at the 3-position of the benzene ring and to investigate the possibility for the syntheses of 7,8-disubstituted isoquinoline.

For the synthesis of the phenethylamide, the nitroacetal (I) was used as the starting material in the same way as described in the previous paper.[1]

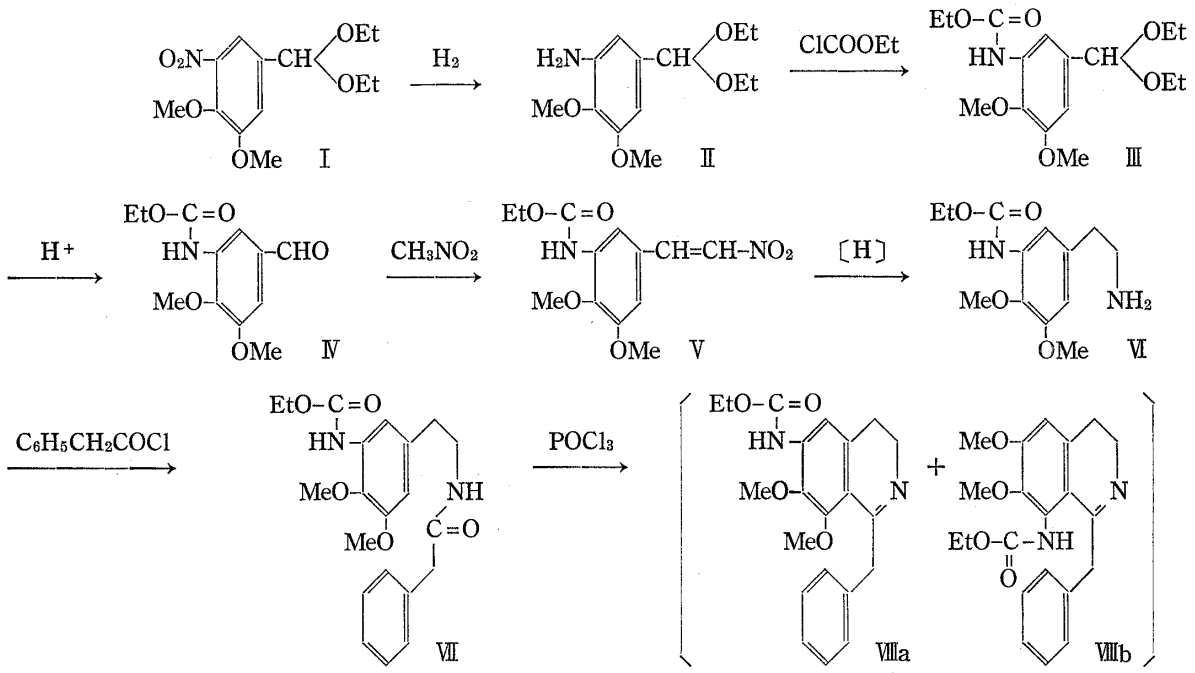

Chart 1

1) Part II: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **17**, 2256 (1969).
2) This work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1968.
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The Bischler–Napieralski cyclization of the amide (VII) with phosphoryl chloride in benzene gave a mixture of 3,4-dihydroisoquinolines (VIIIa and VIIIb) as a reddish brown syrup. Since 1-benzyl-3,4-dihydroisoquinolines are known to be readily oxidized by atmospheric oxygen to afford 1-benzoyl derivatives, their separation was not carried out. Reduction of the methiodides (IXa and IXb), prepared from the mixture of 3,4-dihydroisoquinolines with methyl iodide, with sodium borohydride in methanol afforded a mixture of N-methyl-1,2,3,4-tetrahydroisoquinolines (Xa and Xb) which was found to give two spots by thin-layer chromatography on silica gel. Accordingly, the mixture was chromatographed on silica gel and separated into two components in 1:3.5 ratio, showing *Rf* 0.34 and 0.29 (solvent, benzene: methanol =6:1). The former component of *Rf* 0.34 was hydrolyzed to the 6-amino derivative (XIa), which was subjected to deamination with sodium nitrite in 10% sulfuric acid solution and 50% hypophosphorous acid solution to give 7,8-dimethoxy compound (XIIa). This base was characterized as its picrate and, in the nuclear magnetic resonance (NMR) spectrum, the proton signal of N-methyl appeared at 7.66 τ as a singlet peak, that of O-methyl (C-7 and C-8) did at 6.10 τ and 6.13 τ as a singlet peak, respectively, and that of C (5) and C (6) also did at 3.19 τ as a singlet peak. These facts supported the structure of 7,8-dimethoxyisoquinoline.[4]

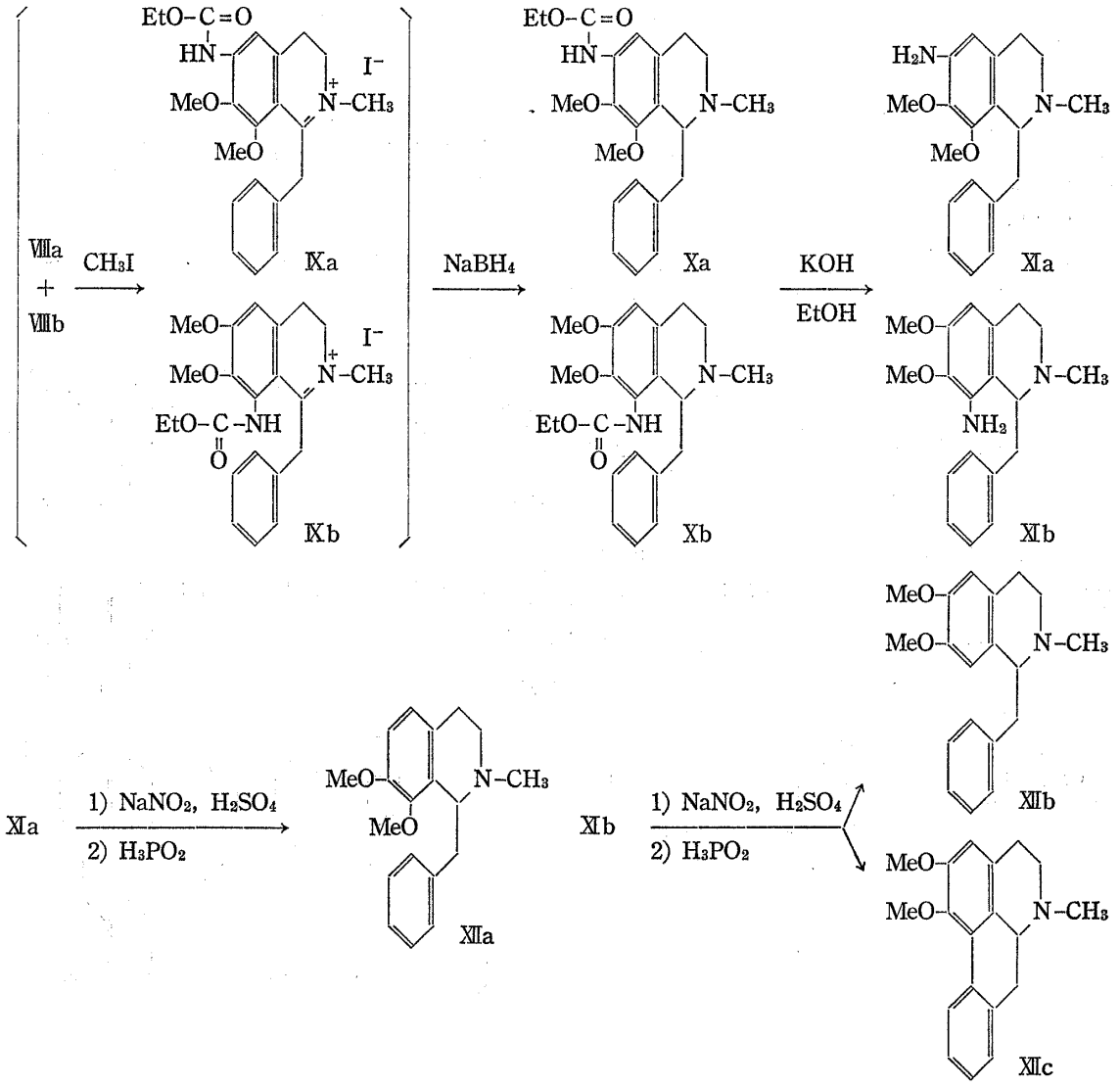

Chart 2

4) M. Tomita, Y. Aoyagi, Y. Sakata, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **16**, 56 (1968).

On the other hand, deamination of the 8-amino compound (XIb) prepared from the latter component of *Rf* 0.29, under the same conditions as described above, gave two products, which were separated by chromatography on silica gel into two components in 2:1 ratio.

Both specimens showed spots at *Rf* 0.22 and 0.29 (solvent, benzene:methanol=6:1) on thin-layer chromatogram of silica gel.

The former base (2 parts) was identified with the usual deamination product, 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XIIb)[1] by infrared (IR) and NMR spectral comparison. IR and NMR spectra of the latter base were superimposable on that of nuciferin,[5] an aporphine alkaloid, and the usual Pschorr reaction of XIb using copper powder as a catalyst gave also *dl*-nuciferin[6] in 30% yield.

From the forgoing experiments, it was proved that the Bischler-Napieralski cyclization of the amide (VII) having an ethoxycarbamido group in the 3-position of the benzene ring took place in the positions *para* and *ortho* to the ethoxycarbamido group, and eventually afforded Xa and Xb and that a modified synthesis of aporphine alkaloid was accomplished.

Experimental[7]

5-Nitroveratrumaldehyde Diethylacetal (I)——A mixture of 50 g of 5-nitroveratrumaldehyde,[8] 45 g of $(EtO)_3CH$, 60 ml of EtOH and 1 g of NH_4Cl was refluxed for 3 hr and the mixture was evaporated under reduced pressure. The residue was dissloved in ether and ethereal solution was washed with water, dried over K_2CO_3 and evaporated. The product was purified by distillation under reduced pressure, as yellow oil, bp 169—171° (3 mmHg). Yield: 50 g.

3-Ethoxycarbamido-4,5-dimethoxybenzaldehyde (IV)——The nitroacetal dissolved in EtOH was reduced to aminoacetal (II) in the presence of Raney Ni. The aminoacetal was used for the next step without purification. To a stirred solution of the aminoacetal (from 30 g of I) dissolved in 40 ml of pyridine was added 12 ml of ethyl chloroformate in an ice bath. After the addition, the reaction mixture was heated on a water bath for half an hour and diluted with water (40 ml). This mixture was added dropwise to 200 ml of 15% HCl with stirring and stirring was continued for 1 hr to give pale yellow precipitates. The precipitates were extracted with $CHCl_3$ and the extract was washed with water, dried over K_2CO_3 and evaporated to give a solid, which was recrystallized from benzene to yield 15 g of colorless plates, mp 105—106°. *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.61; H, 5.90; N, 5.72.

3-Ethoxycarbamido-4,5-dimethoxy-β-nitrostyrene (V)——A solution of 3 g KOH dissolved in each 10 ml of water and EtOH was added dropwise to a mixture of 10 g of the aldehyde (IV), 3 g of CH_3NO_2 and 140 ml of EtOH with stirring at 0—5°. After stirring further for 1 hr, the reaction mixture was added dropwise to 500 ml of 10% HCl to give yellow precipitates. Recrystallization of the nitrostyrene from EtOH gave 7 g of yellow needles, mp 128—129°. *Anal.* Calcd. for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.61; H, 5.46; N, 9.57.

3-Ethoxycarbamido-4,5-dimethyoxy-β-phenethylamine (VI)——Eletrolytic reduction of 5 g of the nitrostyrene gave a reddish brown oily base, which was converted into hydrochloride.

Recrystallization of the hydrochloride from EtOH gave 2 g of colorless needles, mp 175—178° (decomp.). *Anal.* Calcd. for $C_{13}H_{20}O_4N_2 \cdot HCl$: C, 51.23; H, 6.95; N, 9.19. Found: C, 50.80; H, 7.03; N, 9.37.

N-(3-Ethoxycarbamido-4,5-dimethoxyphenethyl)phenylacetamide (VII)——To a stirred mixture of the above amine (liberated from 1.5 g of the hydrochloride) in 100 ml of ether and 50 ml of 3% NaOH cooled in an ice bath was added dropwise phenylacetyl chloride (prepared from 1 g of phenylacetic acid and 3 ml of $SOCl_2$ in the usual manner).

After the addition, the reaction mixture was further stirred for 1 hr, and the ethereal layer was separated, with successively with water, 5% HCl and water, and dried over K_2CO_3. Evaporation of the solvent gave a colorless solid, which was recrystallized from benzene to yield 1.7 g of the amide as colorless plates, mp 125—126°. NMR (τ) (100 Mc): 8.68 (3H, triplet, J=7 cps, O-$CH_2\underline{CH_3}$), 6.15, 6.19 (6H, 2×O-$\underline{CH_3}$), 5.75 (2H, quartet, J=7 cps, O-$\underline{CH_2}CH_3$), 3.60 (1H, doublet, J=2 cps, C_1-$\underline{H}$), 2.70 (5H, broad, $C_6\underline{H_5}$), 2.44 (1H, doublet,

5) M. Tomita, Y. Watanabe, M. Tomita and H. Furukawa, *Yakugaku Zasshi*, **81**, 469 (1961). H.R. Arthur and H. Tcheung, *J. Chem. Soc.*, **1959**, 2306.

6) J.M. Gulland and R.P. Harworth, *J. Chem. Soc.*, **1928**, 581.

7) All melting points were uncorrected. NMR spectra were measured by HITACHI H-6013 (60 Mc) spectrophotometer and JNM 4H-100 (100 Mc) spectrophotometer in $CDCl_3$ and tetramethylsilane was used as internal reference.

8) K.H. Slotta and G. Szyszka, *Ber.*, **68**, 184 (1935).

J=2 cps, C_5–H). *Anal.* Calcd. for $C_{21}H_{26}O_5N_2$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.19; H, 6.62; N, 7.21.

A Mixture of 6-Ethoxycarbamido-7,8-dimethoxy-(VIIIa) and 8-Ethoxycarbamido-6,7-dimethoxy-1-benzyl-3,4-dihydroisoquinoline (VIIIb)——A mixture of 1.5 g of the amide, 3 ml of $POCl_3$ and 30 ml of benzene was refluxed for 1 hr on a water bath, and the mixture was evaporated under reduced pressure. The resultant residue was washed with *n*-hexane for several times. This mixed base was characterized as picrolonate. Picrolonate: Recrystallized from EtOH, yellow needles, mp 171—175° (decomp.). *Anal.* Calcd. for $C_{21}H_{24}O_4N_2 \cdot C_{10}H_8O_5N_4$: C, 58.85; H, 5.10; N, 13.29. Found: C, 58.50; H, 5.19; N, 13.27.

6-Ethoxycarbamido-7,8-dimethoxy-(Xa) and 8-Ethoxycarbamido-6,7-dimethoxy-1-benzyl-1,2,3,4-tetrahydro-2-methylisoquinoline (Xb)——The preceding residue was dissolved in $CHCl_3$ and the solution was shaken with 10% NH_4OH and water, dried over Na_2SO_4 and evaporated under reduced pressure in the presence of N_2. The oily viscous residue was dissolved in 10 ml of CH_3I, and the reaction mixture was stood for a day at room temperature. Removal of the reagent gave a reddish brown glassy mass, which was washed with ether. To a solution of the above methiodide (IXa and IXb) in 30 ml of MeOH was added 1.5 g of $NaBH_4$ with stirring in small portions, and the reaction mixture was stirred for 1 hr at room temperature. The mixture was poured into ether (200 ml) and the basic product was extracted with 3% HCl. The aqueous extract was made alkaline with conc. NH_4OH and the product was extracted with ether. The extract was washed with water, dried over K_2CO_3 and evaporated to give 0.95 g of syrup which showed two spots having *Rf* 0.34 and *Rf* 0.29 on thin-layer chromatogram of silica gel (solvent, benzene: MeOH=6:1). Accordingly, the mixture was chromatographed on silica gel and separated into two components in 1:3.5 ratio. The former component (Xa) (*Rf* 0.34, 170 mg) was characterized as picrolonate. Recrystallization of the picrolonate from EtOH gave yellow plates, mp 123—124° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_4N_2 \cdot C_{10}H_8O_5N_4 \cdot H_2O$[9]: C, 58.48; H, 5.68; N, 12.77. Found: C, 58.73; H, 6.00; N, 12.25.

The latter component (Xb) (*Rf* 0.29, 600 mg) was characterized as picrate. Recrystallization of the picrate from EtOH gave yellow plates, mp 175—177° (decomp.). *Anal.* Calcd. for $C_{22}H_{28}O_4N_2 \cdot C_6H_3O_7N_3$: C, 54.81; H, 5.10; H, 11.42. Found: C, 54.77; H, 4.95; H, 11.24.

6-Amino-1-benzyl-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (XIa)——A mixture of 200 mg of Xa and 15 ml of 10% KOH–EtOH solution was refluxed for 2 hr in the presence of N_2. The solvent was evaporated and the residue was acidified with conc. HCl.

The acidic solution was basified with conc. NH_4OH and the product was taken up in ether. The extract was dried over K_2CO_3 and evaporated to give 140 mg of a yellow syrup. Picrolonate: Recrystallized from EtOH, yellow needles, mp 173—175° (decomp.). *Anal.* Calcd. for $C_{19}H_{24}O_2N_2 \cdot C_6H_3O_7N_3$: C, 60.41; H, 5.59; N, 14.58. Found: C, 60.30; H, 5.74; N, 14.40. NMR (τ) (60 Mc): 7.63 (3H, N–C$\underline{H}_3$), 6.10, 6.17 (6H, 2×O–C$\underline{H}_3$), 3.74 (1H, C_5–$\underline{H}$), 2.72 (5H, $C_6\underline{H}_5$).

1-Benzyl-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (XIIa)——To a solution of 100 mg of XIa in 2 ml of 10% aq. H_2SO_4 was added 20 mg of $NaNO_2$ dissolved in 0.5 ml of water at 0°, and the reaction mixture was stirred for 30 min. Then 2 g of 50% $H_3PO_2 \cdot H_2O$ was added over period of 5 min and the mixture was kept in an ice box overnight. After the mixture had been basified with conc. NH_4OH, the product was extracted with ether and the extract was dried over K_2CO_3 and evaporated to give 60 mg of a reddish brown oil, which was converted into the picrate. Recrystallization of the picrate from EtOH gave yellow rhombic plates, mp 146—148° (decomp.). NMR (τ) (60 Mc): 7.66 (3H, N–C$\underline{H}_3$), 6.10, 6.13 (6H, 2×O–C$\underline{H}_3$), 3.19 (2H, C_5, C_6–$\underline{H}$), 2.69 (5H, $C_6\underline{H}_5$). *Anal.* Calcd. for $C_{19}H_{23}O_2N \cdot C_6H_3O_7N_3$: C, 57.03; H, 5.98; N, 10.64. Found: C, 57.25; H, 5.06; N, 10.52.

8-Amino-1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (XIb)——Prepared from Xb (200 mg) in the same method as described for Xa. Yield: 140 mg. Recrystallization of the picrate from EtOH gave yellow needles, mp 174—176° (decomp.). NMR (τ) (60 Mc): 7.51 (3H, N–C$\underline{H}_3$), 6.14, 6.20 (6H, 2×O–C$\underline{H}_3$), 3.83 (1H, C_5–$\underline{H}$), 2.73 (5H, $C_6\underline{H}_5$). *Anal.* Calcd. for $C_{19}H_{24}O_2N_2 \cdot C_6H_3O_7N_3$: C, 54.91; H, 5.25. Found: C, 55.45; H, 5.03.

Deamination of the 8-Amino Compound——To a stirred solution of 300 mg of XIb in 4 ml of 10% aq. H_2SO_4 was added 60 mg of $NaNO_2$ dissolved in 1 ml of water at 0°, and the mixture was stirred for 30 min at 0—5°. Then 6 g of 50% $H_3PO_2 \cdot H_2O$ was added over period of 10 min, and the reaction mixture was kept in an ice box overnight.

After basification of the mixture with conc. NH_4OH, the alkaline solution was extracted with benzene and the extract was dried over K_2CO_3. Evaporation of the solvent gave 250 mg of a brown syrup, which was separated by chromatography on silica gel into two components. Yield: 130 mg of 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolines (XIIb) as a pale yellow oil. 60 mg of *dl*-nuciferin (XIIc) as a colorless solid. IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of both specimens were completely identical with authentic samples.

The Pschorr Cyclization Reaction of the 8-Amino Compound——To a solution of 200 mg of XIb in 3 ml of 10% aq. H_2SO_4 and 6 ml of MeOH was added 40 mg of $NaNO_2$ dissolved in 1 ml of H_2O at 0°. The reaction

9) This was dried over P_2O_5 at 90—100° (3 mmHg) for 24 hr.

mixture was kept at 0—5° for 2 hr after which it was boiled under refluxed with 1 g of copper powder for 30 min. After filtration, MeOH was evaporated to give a reddish brown solution and the solution was basified with conc. NH_4OH and the product was extracted with ether. The extract was dried over K_2CO_3 and evaporated to give 150 mg of a brown syrupy mass, which was chromatographed on alumina (3 g).

Eluation with benzene gave 60 mg of a solid, which was characterized as its picrate. Recrystallization of the picrate from EtOH gave yellow needles mp 178—180° (decomp.). *Anal.* Calcd. for $C_{19}H_{21}O_2N \cdot C_6H_3O_7$: C, 57.63; H, 4.65; N, 10.65. Found: C, 57.25; H, 4.65; N, 10.68.

This product was completely identical with the authentic sample mentioned above by IR ($CHCl_3$) spectrum.

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