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Syntheses of Aminoisoquinoloines and Related Compounds. IV.[1] Syntheses of Aminoprotoberberines by the Mannich Reaction[2]

Saburo Ishiwata and Keiichi Itakura

Tokyo College of Pharmacy[3]

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The Mannich reaction of 1-(3-amino)- and (3-amino-4-methoxy)benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (Va and Vb) with 36% formaldehyde solution in ethanol without acid afforded aminoprotoberberines (VIa and VIb), formed by cyclization at the position *para* to the amino group.

It is known that intramolecular Mannich reaction of 1-benzyl-1,2,3,4-tetrahydroisoquinolines with formaldehyde solution in the presence of acid (the Pictet–Spengler reaction) is the most useful synthetic method for producing so-called berberine bridge and that the presence of an electron-releasing group such an alkoxyl and a hydroxyl group at the position *para* or *ortho* to the reaction site accelerates the reaction.[4]

Recently, Kametani and his co-workers reported that the hydroxyl group at the position *para* to the reaction site promoted the Mannich reaction without acid.[5]

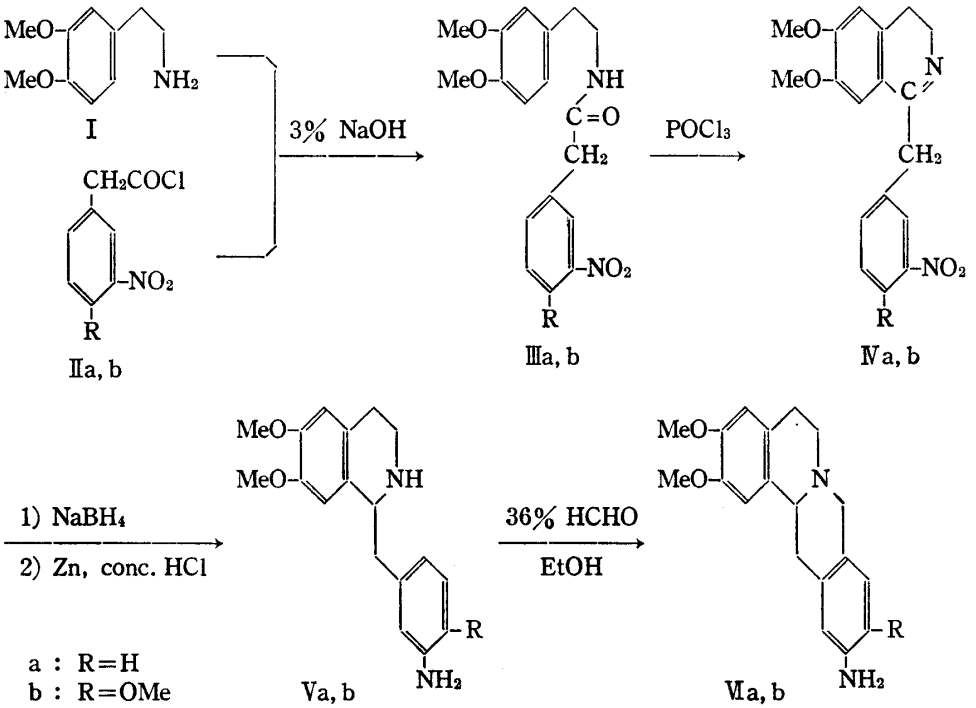

Chart 1

1) Part III: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), **17**, 2261 (1969).
2) This work was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *No. 600, Kashiwagi-4-chome, Shinjuku-ku, Tokyo.*
4) W.M. Whaley and T.R. Govindachari, *Org. Reactions*, **VI**, 151 (1951).
5) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (*C*), **1968**, 112.

The present work on the Mannich reaction of aminoisoquinolines for synthesizing aminoprotoberberines revealed that an amino group as well as the hydroxyl group also promoted the Mannich reaction without acid and that the cyclization occurred selectively at the position *para* to the amino group.

The starting material (Va and Vb) in this reaction was synthesized as follows: 3,4-Dimethoxyphenethylamine (I) and 3-nitrophenylacetyl chlorides (IIa and IIb) were condensed by the Schotten–Baumann reaction to give amides (IIIa and IIIb), which were submitted dehydrative cyclization under the Bischler–Napieralski condition to afford 3,4-dihydroisoquinolines (IVa and IVb). Reduction of 3,4-dihydroisoquinolines with sodium borohydride in methanol and successively with zinc powder in methanolic hydrochloric acid solution gave amino compounds (Va and Vb).

The Mannich reaction of these bases with 36% formaldehyde solution in ethanol in the presence of nitrogen gas afforded aminoprotoberberines (VIa and VIb), formed by cyclization at the position *para* to the amino group in good yields.

These cyclization was proved by the following facts. Phenolic protoberberines (VIIa and VIIb), prepared from the amino compounds by the thermal decomposition of their diazonium salts in an aqueous solution, were identified by the infrared (IR) and nuclear magnetic resonance (NMR)[6] spectral comparisons with authentic samples[5,7] prepared from the phenolic isoquinolines (VIIIa and VIIIb) with 36% formaldehyde solution.

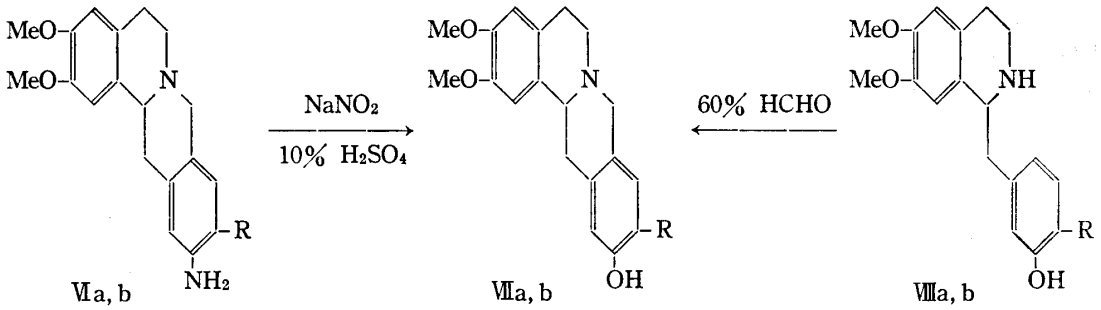

Chart 2

On the basis of these facts, it may be concluded that the Mannich reaction of 1-(3-amino)- and (3-amino-4-methoxy)benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (Va and Vb) with 36% formaldehyde solution took place at the position *para* to the amino group.

Experimental[8]

N-(3,4-Dimethoxyphenethyl)-2-(3-nitrophenyl)acetamide (IIIa)——A mixture of 1.5 g of 3-nitrophenylacetic acid, 3 ml of $SOCl_2$ and 10 ml of benzene was warmed at 60—70° for 40 min. The solvent and the reagent were removed under reduced pressure and the residue dissolved in dry benzene was added dropwise to a stirred mixture of 2 g of I in 200 ml of benzene and 150 ml of 3% aq. NaOH cooled in an ice bath. The reaction mixture was stirred for 1 hr and the benzene solution was washed with 5% aq. HCl and H_2O, dried over K_2CO_3 and evaporated. The residue was recrystallized from benzene to give 2.5 g of yellow plates, mp 133—135°. (lit.[9] 133°). *Anal.* Calcd. for $C_{18}H_{20}O_5N_2$: N, 8.14. Found: N, 8.14. IR cm^{-1} ($CHCl_3$): νC=O 1665, νNH 3400.

3,4-Dihydro-6,7-dimethoxy-1-(3-nitrobenzyl)isoquinoline (IVa)——A mixture of 2 g of the above amide and 4 ml of $POCl_3$ was refluxed in 30 ml of dry benzene for 1 hr. The solvent and an excess of $POCl_3$ were removed under reduced pressure and the resultant solid was washed with *n*-hexane for several times and recrystallized from EtOH to yield 1.8 g of yellow needles, mp 192—195° (decomp., *lit.*[9] 190°). *Anal.* Calcd. for $C_{18}H_{18}O_4N_2 \cdot HCl$; N, 7.72. Found: 7.41. IR cm^{-1} (KBr): νC=N 1650.

6) NMR spectra were measured by JNM-4H 100 Spectrophotometer at 100 Mc and tetramethylsilane was used as internal standard.
7) M. Tomita and J. Niimi, *Yakugaku Zasshi*, **79**, 1019 (1959).
8) All melting points were not corrected.
9) T.R. Govindachari and K. Nagarajan, *Chem. Abstr.*, **50**, 7804 g (1956).

1-(3-Aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Va)——To a stirred mixture of 0.7 g of the above hydrochloride in 20 ml of MeOH, 0.5 g of $NaBH_4$ was added portionwise and the reaction mixture was stirred further for 40 min. To this mixture was added 3 g of Zn powder and 20 ml of conc. HCl, and the reaction mixture was refluxed for 1 hr and the solvent was evaporated. The residue was taken up in $CHCl_3$ by the treatment of conc. NH_4OH and the extract was dried over K_2CO_3 and evaporated to give a pale yellow solid. Recrystallization of the solid from benzene gave 0.45 g of colorless plates, mp 144—146°. *Anal.* Calcd. for $C_{18}H_{22}O_2N_2$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.61; H, 7.45; N, 9.14. NMR (τ, $CDCl_3$): 2.90—3.50 (6H, multiplet, aromatic H), 6.18 and 6.21 (6H, s., $2\times$O–CH_3). (CF_3COOH): 2.45—2.70 (4H, multiplet, aromatic H), 3.13 and 3.47 (2H, s., aromatic H), 6.05 and 6.22 (6H, s., $2\times$O–CH_3).

11-Amino-2,3-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIa)——A mixture of 400 mg of Va, 120 mg of 36% HCHO, and 30 ml of EtOH was refluxed for 1 hr in the presence of N_2. The residue left after evaporation of the solvent was dissolved in $CHCl_3$ and the extract was washed with H_2O, dried over K_2CO_3 and evaporated to give a viscous oil (340 mg), which was characterized as its picrate. Recrystallization of the picrate from EtOH gave yellow plates, mp 263—266° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_3N_2\cdot C_6H_3O_7N_3$: C, 55.65; H, 4.67; N, 12.98. Found: C, 55.28; H, 4.18; N, 13.35. IR cm^{-1} ($CHCl_3$): νNH_2 3450, 3350, *trans*-quinolizine band 2760. NMR (τ, $CDCl_3$): 3.15 (1H, multiplet), 3.31 and 3.43 (2H, s.), 3.55 (2H, multiplet): aromatic H, 6.16 and 6.18 (6H, s., $2\times$O–CH_3). (CF_3COOH): 2.50 (3H, multiplet), 3.01 and 3.10 (2H, s.): aromatic H, 6.00 and 6.03 (6H, s., $2\times$O–CH_3).

Diazotization of the Amino Compound (VIa)——To a stirred mixture of 0.3 g of VIa and 6 ml of 10% aq. H_2SO_4, a solution of 70 mg of $NaNO_2$ in 1 ml of H_2O was added at 0—5° and the reaction mixture was stirred further for 0.5 hr. After decomposition of excess HNO_2 with urea, the mixture was refluxed for 5 min and the resultant phenolic base extracted with ether by the usual manner. The extract was dried over Na_2SO_4 and evaporated to yield 130 mg of VIIa as a colorless solid, which was recrystallized from EtOH gave colorless needles, mp 264—267°(lit.[7] 263°). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.73; N, 4.50. Found: C, 72.86; H, 6.73; N, 4.43. IR cm^{-1} (KBr): νOH 3400, *trans*-quinolizine band 2750, NMR (τ, CF_3COOH): 3.01 (5H, multiplet, aromatic H), 5.98 and 6.00 (6H, s., $2\times$O–CH_3).

N-(3,4-Dimethoxyphenethyl)-2-(4-methoxy-3-nitrophenyl)acetamide (IIIb)——Prepared from 2 g of I and 1.5 g of 4-methoxy-3-nitrophenylacetic acid in the same method as described for IIIa. Recrystallization from benzene gave 2.7 g of pale yellow needles, mp 113—115°(lit.[10] 113°). *Anal.* Calcd. for $C_{19}H_{22}O_6N_2$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.47; H, 6.90; N, 7.36. IR cm^{-1} ($CHCl_3$): νNH 3400, νC=O 1665.

3,4-Dihydro-6,7-dimethoxy-1-(4-methoxy-3-nitrobenzyl)isoquinoline (IVb)——Prepared from 2 g of the above amide in the same method as described for IVa. Recrystallization of the crude base from EtOH gave 1.8 g of yellow needles, mp 221—223° (decomp., lit.[10] 220°). *Anal.* Calcd. for $C_{19}H_{20}O_5N_2\cdot HCl$: C, 58.09; H, 5.13; N, 7.13. Found: C, 58.46; H, 5.49; N, 7.22.

1-(3-Amino-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Vb)——Prepared from 1 g of IVb in the same method as described for Va. The crude product was purified on alumina chromatography to afford 0.65 g of colorless oil. IR cm^{-1} ($CHCl_3$): νNH_2 3350, 3450. NMR (τ, $CDCl_3$): 3.40 (5H, multiplet, aromatic H), 6.15, 6.17, and 6.19 (9H, s., $3\times$O–CH_3).

11-Amino-2,3,10-trimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (VIb)——Prepared from Vb (600 mg), 36% HCHO (180 mg), and EtOH (50 ml) in the same method as described for VIa. Recrystallization of the crude product from EtOH gave colorless plates, mp 225—228°. *Anal.* Calcd. for $C_{20}H_{24}O_3N_2$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.25; H, 7.14; N, 8.60. IR cm^{-1} ($CHCl_3$): νNH_2 3400, *trans*-quinolizine band 2750. NMR (τ, $CDCl_3$): 3.28, 3.40, 3.49, and 3.52 (4H, s., aromatic H), 6.12, 6.14, and 6.18 (9H, s., $3\times$O–CH_3). (CF_3COOH): 2.47, 2.99, 3.04, and 3.11 (4H, s., aromatic H), 5.97, 6.00, and 6.01 (9H, s., $3\times$O–CH_3).

Diazotization of the Amino Compound (VIb)——To a stirred mixture of 0.5 g of VIb and 10 ml of 10% aq. H_2SO_4 was added a solution of 100 mg of $NaNO_2$ in 1 ml of H_2O at 0—5° and the reaction mixture was stirred further for 0.5 hr. After decomposition of excess HNO_3 with urea, the mixture was added dropwsie to 30 ml of H_2O contained 3 g of $CuSO_4$ on refluxing and the refluxing was continued for 2 hr. On cooling, the reaction mixture was basified with conc. NH_4OH and precipitates were extracted with $CHCl_3$, and phenolic base was taken up in 3% aq. NaOH from the extract. To this alkaline solution was added an excess of NH_4Cl and the product was extracted with $CHCl_3$, and the extract was dried over Na_2SO_4 and evaporated to give 150 mg of the crude base, which was purified on silica gel (3 g) chromatography. Recrystallization from $CHCl_3$–EtOH gave 50 mg of colorless prisms, mp 239—242° (*lit.*[5] 238°). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.06; H, 6.72; N, 4.02. IR cm^{-1} ($CHCl_3$): νOH 3550, *trans*-quinolizine band 2750. NMR (τ, CF_3COOH): 3.04 (2H, s.), 3.12 and 3.22 (2H, s.): aromatic H, 6.03 (9H, s., $3\times$O–CH_3).

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10) C. Ferrari and V. Deulofeu, *Tetrahedron*, **18**, 419 (1962).