[Chem. Pharm. Bull. 18(5) 896—900 (1970)]

UDC 547.833.5.07 : 547.833.3.04 : 547.978.1.07

Syntheses of Aminoisoquinolines and Related Compounds. V.[1] The Direction of the Mannich Reaction on the Aminotetrahydroisoquinolines to the Aminoprotoberberines[2]

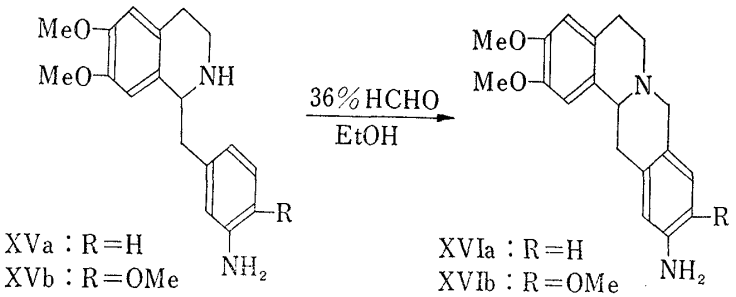
Saburo Ishiwata and Keiichi Itakura

Tokyo College of Pharmacy[3]

(Received November 19, 1969)

The Mannich reaction of 1-(3-aminobenzyl)tetrahydroisoquinolines (Va and Vb) with 36% formaldehyde solution in ethanol afforded the corresponding aminoprotoberberines (VIa and IXa, VIb and IXb), formed by the cyclization at the position *para* and *ortho* to the amino group and a modified synthesis of 9,10-disubstituted and 9,10,11-trisubstituted protoberberines was accomplished by the reduction or thermal decomposition of the diazonium salts of the aminoprotoberberines.

In the preceding paper,[2] the authors reported that an amino group like the hydroxyl group also promoted the Mannich reaction of the aminotetrahydroisoquinolines (XVa and XVb) without acid and that the cyclization occurres selectively at the position *para* to the amino group.



XVa : R=H
XVb : R=OMe

XVIa : R=H
XVIb : R=OMe

Chart 1

The aims of the present work were to be examined the direction of the Mannich reaction of tetrahydroisoquinolines (Va and Vb) having an amino group at 3-position of the benzene ring and to investigate the possibility for the synthesis of 9,10-disubstituted protoberberine.

The starting material (Va and Vb) in this reaction was synthesized by the same method as described in the preceding paper.

The Mannich reaction of Va and Vb with 36% formaldehyde solution in ethanol afforded respectively a mixture of VIa and IXa, and VIb and IXb, formed by the cyclization at the positions *para* and *ortho* to the amino group and these two mixture were found to give two spots each by thin-layer chromatography on silica gel. Accordingly, two mixture were chromatographed separately on silica gel and each separated into two components in 1:2 ratio.

These four components (VIa, VIb, IXa, and IXb) were subjected to deamination with sodium nitrite in 10% sulfuric acid solution followed by reduction of the resulting diazonium salts with 50% hypophosphorous acid solution to give the corresponding protoberberines (VIIa, VIIb, Xa, and Xb), which were identified with the authentic samples by the infrared (IR) and nuclear magnetic resonance (NMR)[4] spectral comparisons.

1) Part IV: S. Ishiwata and K. Itakura, *Chem. Pharm. Bull.* (Tokyo), 17, 628 (1970).
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) NMR spectra were measured by JNM-4H 100 Spectrophotometer at 100 Mc and tetramethylsilane was used as internal standard.

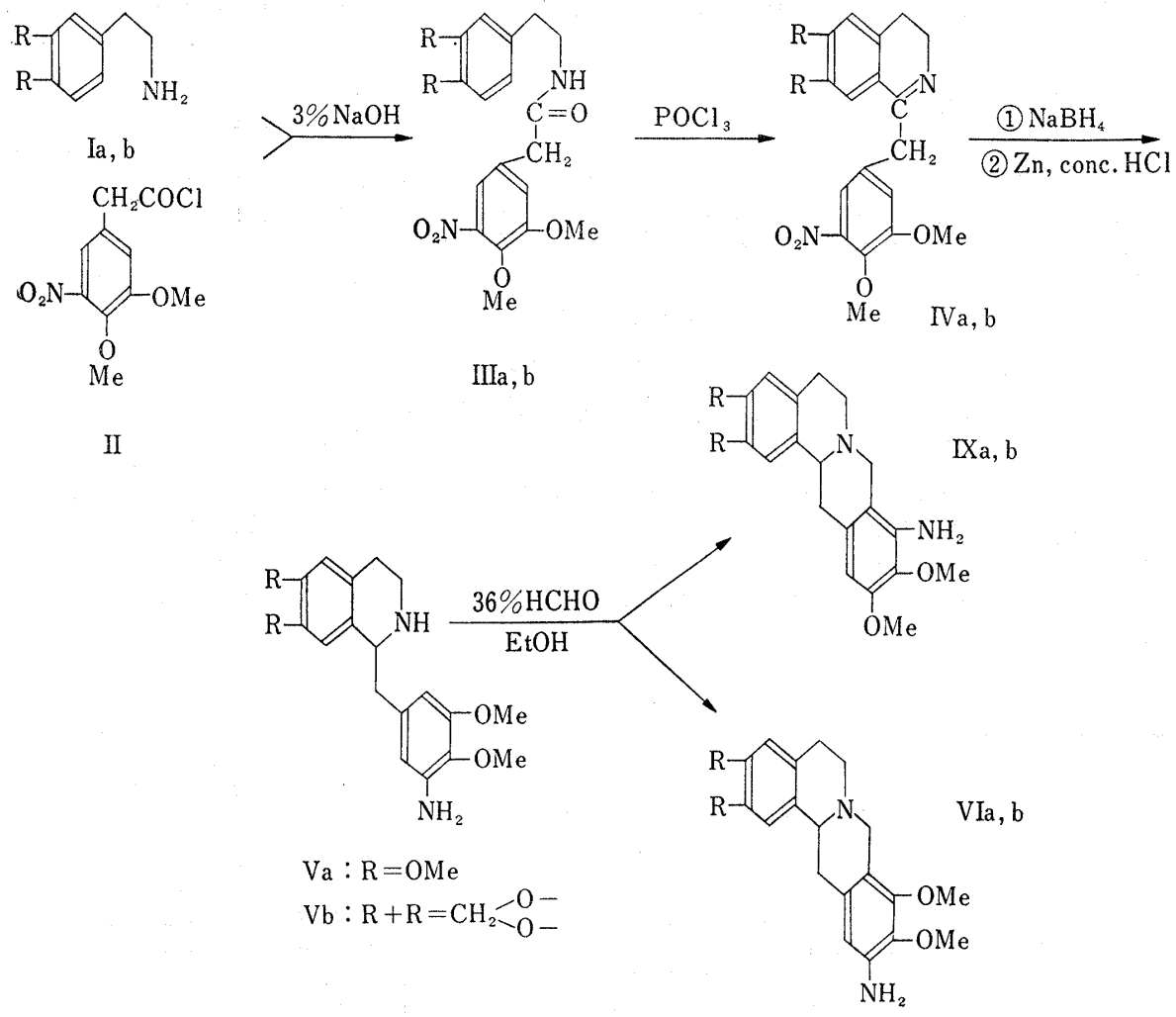


Chart 2

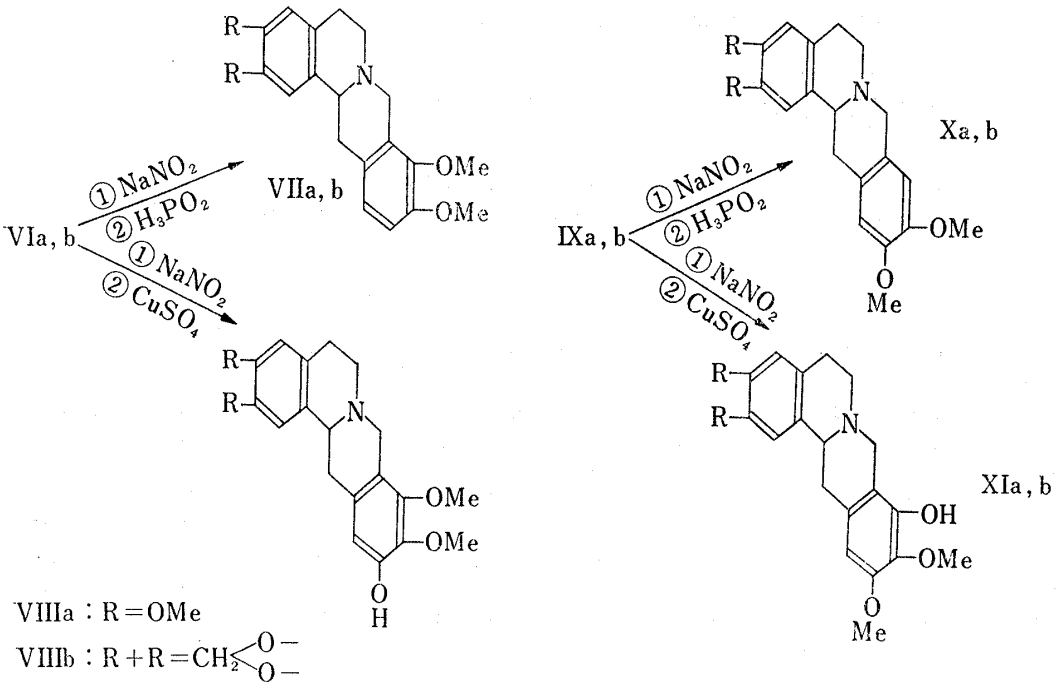


Chart 3

Table I. Nuclear Magnetic Resonance Spectra of Protoberberines in Deuteriochloroform

Protoberberines	Substituents						Lit.
	O-CH_3	O-CH_2O	Aromatic H				
Xylopine(Xa)	6.12—6.14(×4)	—	3.26	3.34	3.38	3.43	(*a*)
Tetrahydropseudoberberine(Xb)	6.26(×2)	4.10	3.27	3.36	3.42(2H)		(*b*)
Tetrahydropalmatine(VIIa)	6.12—6.14(×4)	—	3.10[d]	3.24[d]	3.28	3.39	(*c*)
Canadine(VIIb)	6.27(×2)	4.10	3.12[d]	3.25[d]	3.28	3.42	(*d*)
	τ-values d, doublet						

a) T. Kametani and M. Ihara, *Yakugaku Zasshi*, **87**, 174 (1967)
b) R.D. Haworth, W.H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1686 (1924)
c) M. Tomita, M. Kozuka, and S. Uyeo, *Yakugaku Zasshi*, **86**, 460 (1966)
d) R. Mirza, *J. Chem. Soc.*, **1957**, 4400

Further, these four aminoprotoberberines were converted into the corresponding hydroxyl compounds (VIIIa, VIIIb, XIa, and XIb) by the decomposition of their diazonium salts with cupric sulfate in an aqueous solution, in yields of 3—7%. One of these hydroxyprotoberberines, VIIIa, was identified by the IR and NMR spectral comparisons with the natural stepharotine.[5]

Table II

Compd.	mp (°C)	Solvent	appearance	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
VIa	173—174	MeOH	needles	$C_{21}H_{26}O_4N_2$	68.09	7.07	7.56	67.52	7.10	7.99
VIb	185—187	MeOH	plates	$C_{20}H_{22}O_4N_2$	67.78	6.26	7.91	67.36	6.35	7.99
IXa	143—145	MeOH	needles	$C_{21}H_{26}O_4N_2 \cdot H_2O$	64.39	7.27	7.21	64.20	7.47	7.65
IXb	135—137	MeOH	prisms	$C_{20}H_{22}O_4N_2 \cdot \frac{1}{2}H_2O$	66.10	6.38	7.71	66.39	6.21	8.21
VIIIa	228—230[a]	EtOH	powder	$C_{21}H_{25}O_5N \cdot HBr$	55.76	5.79	3.10	55.65	6.08	3.13
VIIIb	225—227	EtOH	powder	$C_{20}H_{21}O_5N \cdot HBr$	55.05	5.08	3.21	54.84	5.16	3.12
XIa	227—229[c]	EtOH	powder	$C_{21}H_{25}O_5N \cdot HBr$	55.76	5.79	3.10	55.46	5.82	3.00
XIb	212—214	EtOH	powder	$C_{20}H_{21}O_5N \cdot HBr \cdot 2H_2O$	50.85	5.55	2.97	51.24	5.28	3.15

a) mp 227—229° in lit.[b]
b) T. Kametani, H. Iida, and T. Kikuchi, *Yakugaku Zasshi*, **88**, 1185 (1968)
c) mp 227—229° in lit.[b]

Table III. Infrared (in Chloroform) and Nuclear Magnetic Resonance (in Deuteriochloroform) Spectra of Amino and Hydroxyl Protoberberines

Compd.	NMR (τ)					IR (cm^{-1})	
	C_1- and C_4-H		C_{12}–H	O–CH_3	O–CH_2–O	Bohlmann bands	NH_2 or OH
VIa	3.31	3.40	3.68	6.14—6.19(×4)	—	2750	3350, 3440
VIb	3.31	3.42	3.70	6.14—6.19(×2)	4.11	2750	3350, 3430
IXa	3.29	3.40	3.80	6.13—6.22(×4)	—	2760	3350, 3440
IXb	3.29	3.41	3.81	6.18—6.20(×2)	4.10	2760	3350, 3450
VIIIa	3.30	3.41	3.50	6.13—6.18(×4)	—	2760	3520
VIIIb	3.27	3.40	3.52	6.17—6.18(×2)	4.09	2760	3540
XIa	3.28	3.38	3.70	6.13—6.19(×4)	—	2760	3530
XIb	3.28	3.40	3.71	6.17—6.19(×2)	4.09	2750	3540

5) M. Tomita, M. Kozuka, and S. Uyeo, *Yakugaku Zasshi*, **86**, 460 (1966).

In the NMR spectra of eight protoberberine-type compounds, it was observed that the proton signal in 12-position of protoberberine, at the position *para* to the amino or hydroxyl group, was appeared at a higher magnetic field than that of the *ortho* position.[6]

From the foregoing experimental results, it was found that the Mannich reaction of aminotetrahydroisoquinolines (Va and Vb) having an amino group at 3-position of the benzene ring take place in the position *para* or *ortho* to the amino group and that a modified synthesis of 9,10-disubstituted and 9,10,11-trisubstituted protoberberines can be effected by the reduction or decomposition of the diazonium salts of the corresponding amino group.

Experimental[7]

N-(3,4-Dimethoxyphenethyl)-2-(3,4-dimethoxy-5-nitrophenyl)acetamide (IIIa)——A mixture of 2 g of 3,4-dimethoxy-5-nitrophenylacetic acid, 4 ml of $SOCl_2$ and 15 ml of benzene was warmed at 60—65° for 40 min. The solvent and an excess of $SOCl_2$ were removed under reduced pressure and the residue dissolved in 15 ml of dry benzene was added dropwise to a stirred mixture of 2 g of Ia in 200 ml of benzene and 150 ml of 3% aq. NaOH cooled in an ice bath. The reaction mixture was stirred further 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 pale yellow needles, mp 122—124°. *Anal.* Calcd. for $C_{20}H_{26}O_7N_2$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.81; H, 6.33; N, 7.10. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1660.

N-(3,4-Methylendioxyphenethyl)-2-(3,4-dimethoxy-5-nitrophenyl)acetamide (IIIb)——Prepared from Ib (2 g) and II (1.5 g) in the same method as described for IIIa. Recrystallization from benzene gave 2.4 g of yellow needles, mp 113—115°. *Anal.* Calcd. for $C_{19}H_{20}O_7N_2$: C, 58.76; H, 5.19; N, 7.21. Found: C, 59.01; H, 5.13; N, 7.45. IR cm^{-1} ($CHCl_3$): ν_{NH} 3400, $\nu_{C=O}$ 1660.

3,4-Dihydro-6,7-dimethoxy-1-(3,4-dimethoxy-5-nitrobenzyl)isoquinoline (IVa)——A mixture of 2 g of the amide (IIIa), 4 ml of $POCl_3$, and 30 ml of benzene was refluxed for 1 hr. Evaporation of the solvent and an excess of $POCl_3$ gave a yellow viscous oil (2 g), which was characterized as its picrate. Recrystallization of the picrate from EtOH gave yellow needles, mp 195—197° (decomp.). *Anal.* Calcd. for $C_{20}H_{24}O_6N_2 \cdot C_6H_3O_7N_3$: C, 50.47; H, 4.41; N, 11.34. Found: C, 50.64; H, 4.06; N, 11.18. IR cm^{-1} ($CHCl_3$): $\nu_{C=N^+H}$ 2450—2750, $\nu_{C=N}$ 1643 (crude hydrochloride).

3,4-Dihydro-1-(3,4-dimethoxy-5-nitrobenzyl)-6,7-methylendioxyisoquinoline (IVb)——Prepared from 2 g of the amide (IIIb) in the same method as described for IVa. Recrystallization of the hydrochloride from EtOH gave 1.8 g of yellow needles, mp 185—188° (decomp.). *Anal.* Calcd. for $C_{19}H_{18}O_6N_2 \cdot HCl$: C, 56.09; H, 4.46; N, 6.89. Found: C, 55.81; H, 4.78; N, 6.63. IR cm^{-1} (KBr): $\nu_{C=N}$ 1654.

1-(3-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (Va)——To a stirred mixture of the crude hydrochloride (IVa) in 30 ml of MeOH was added portionwise 0.7 g of $NaBH_4$ and the reaction mixture was stirred further for 40 min. After addition of 5 g Zn powder and 35 ml of conc. HCl to this mixture, the reaction mixture was refluxed for 1 hr and filtrated. Evaporation of the solvent gave a yellow residue, which was extracted with $CHCl_3$ by the treatment of conc. NH_4OH, and the extract was dried over K_2CO_3 and evaporated to give a yellow oil. The product was purified on alumina chromatography to yield 0.6 g of Va and characterized as its picrolonate. Recrystallization of the picrolonate from EtOH gave yellow plates, mp 157—159° (decomp.). *Anal.* Calcd. for $C_{20}H_{26}O_4N_2 \cdot C_{10}H_8O_5N_4$: C, 57.87; H, 5.50. Found: C, 57.85; H, 5.74. IR cm^{-1} ($CHCl_3$): ν_{NH_2} 3450, 3350. NMR (τ, $CDCl_3$): 3.36 and 3.42 (2H, s, aromatic H), 3.70 and 3.79 (2H, d, $J=2$ cps, aromatic H), 6.15—6.18 (12H, $4\times$O–C$\underline{H}_3$).

A Mixture of 11-Amino-2,3,9,10-tetramethoxy (VIa)- and 9-Amino-2,3,10,11-tetramethoxy(IXa)-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine——A mixture of 0.8 g of Va, 190 mg of 36% HCHO and 50 ml of EtOH was refluxed for 1 hr in the presence of N_2. Evaporation of the solvent gave a reddish brown residue, which was dissolved in $CHCl_3$ and the extract was washed with H_2O, dried over K_2CO_3 and evaporated to give a reddish brown oily product (0.75 g). The product was chromatographed on silica gel (30 g) eluted with $CHCl_3$–MeOH (100:1) to be separated into two components in 1:2 ratio. The first eluted component (0.21 g) was VIa, formed by the cyclization at the position *para* to the amino group and the second was IXa (0.40 g), formed by the cyclization at the *ortho* position (see Table II and III).

1-(3-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-methylendioxyisoquinoline (Vb)——Prepared from IVb (1 g) in the same method as described for Va. Yield: 0.55 g. IR cm^{-1} ($CHCl_3$): ν_{NH_2} 3450, 3370. NMR (τ, $CDCl_3$): 3.30 and 3.44 (2H, s, aromatic H), 3.70 and 3.78 (2H, d, $J=2$ cps, aromatic H), 6.21 (6H, $2\times$O–C$\underline{H}_3$). Picrolonate: Recrystallized from EtOH, as yellow needles, mp 221—223° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}O_4N_2 \cdot C_{10}H_8O_5N_4$: C, 57.42; H, 4.99; N, 13.86. Found: C, 57.25; H, 4.96; N, 13.75. The

6) *cf.* T. Kametani, K. Fukumoto, H. Iida, and T. Kikuchi, *Yakugaku Zasshi*, **88**, 1482 (1968).
7) All melting points were not corrected.

Mannich reaction of this compound (0.8 g) under the same conditions as described for Va gave a similar result. Yield: VIb 220 mg, IXb 400 mg.

General Procedure for the Deamination of the Amino Compounds——To a stirred mixture of 0.2 g of aminoprotoberberine and 5 ml of 10% aq. H_2SO_4 was added a slight excess of $NaNO_2$ in 1 ml of H_2O at 0—5° and the reaction mixture was stirred further for 0.5 hr. To this mixture, 3 g of 50% $H_3PO_2 \cdot H_2O$ was added dropwise and the mixture was kept in an ice box overnight. The mixture was basified with conc. NH_4OH and the product was extracted with $CHCl_3$, and the extract was dried over K_2CO_3 and evaporated to give the corresponding protoberberine. Yield: 0.10—0.12 g. The IR and NMR spectra of these compounds were superimposable with those of authentic samples (see Table I).

General Procedure for the Convertion of the Amino Compounds into the Hydroxyl Compounds——To a stirred mixture of 0.3 g of an aminoprotoberberine and 7 ml of 10% aq. H_2SO_4 was added a slight excess of $NaNO_2$ in 1 ml of water at 0—5° and the reaction mixture was stirred further for 0.5 hr. After decomposition of excess HNO_2 with urea, the reaction mixture was added to 30 ml of boiling water contained 3 g of $CuSO_4$ and the boiling was continued for 2 hr. On cooling, the reaction mixture was basified with conc. NH_4OH and the crude base was taken up in $CHCl_3$, and the phenolic base was extracted with 3% aq. NaOH from the $CHCl_3$ solution. 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 K_2CO_3. Evaporation of the solvent afforded an oily product, which was purified on silica gel chromatography. Yields: 10—20 mg (see Table II and III).

Acknowledgement The author wish to thank to Dr. M. Tomita for the identification of *dl*-stepharotine and to D.U. Mizoguchi for many suggestions to manuscripts. Thanks are also due to Tokyo Research Laboratory, Kowa. Co., Ltd. and members of Microanlyses Laboratory of this college for elemental analyses and to T. Ono for measurements of NMR spectra.