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Synthesis of Benzimidazoles and Its Related Compounds. Synthesis of Benzimidazoles and 7-Substituted 1(3)H-Imidazo[4,5-*f*]quinolines

Saburo Ishiwata and Youichi Shiokawa

Tokyo College of Pharmacy[1]

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4 (7)- or 5 (6)-Substituted 2-methylbenzimidazole derivatives (III) were obtained by catalytic hydrogenation of the corresponding 2-chloro-2′-nitroacetanilide (II) in a good yield. Further, a mixture of 5 (6)-methoxy-2-methyl-6 (5)-nitrobenzimidazole (IVc) and its 4 (7)-nitro isomer was obtained by the reaction of 5 (6)-methoxy-2-methylbenzimidazole (IIIc) with fuming nitric acid. Similarly, nitration of 2,4 (7)-dimethylbenzimidazole (IIId) gave 2,4 (7)-dimethyl-5 (6)-nitrobenzimidazole (IVd). The title compounds were obtained by the reactions shown in Chart 1.

Synthesis of 1(3)*H*-imidazo[4,5-*f*]quinoline derivatives having a substituent in 7-position has not been reported, we attempted its synthesis by the route shown in Chart 1 and obtained the subject compounds. This paper reports new informations in connection with the preparation of benzimidazoles and 7-methyl-1(3)*H*-imidazo[4,5-*f*]quinolines.

Although synthesis of benzimidazole derivatives has been made by various methods, they can be divided into two classes by their starting materials; the one starting with *o*-phenylenediamine and the other with *o*-nitroacetanilide derivatives.

Catalytic hydrogenation of the latter over Raney nickel in ethanol under neutral condition gave N-acetyl-*o*-phenylenediamines, but the same reaction in the presence of hydrochloric acid afforded a small amount of 2-methylbenzimidazole (IIIa).

Recently, Schulenberg and Archer[2] reported that hydrogenation of 2-chloro-2′-nitro-*N*-phenylacetanilide over platinum oxide in ethanol gave 2-methyl-1-phenylbenzimidazole 3-oxide. Further, an acid was found to catalyze the cyclization of the intermediate hydroxylamine, which was converted into the *N*-oxide.

Benzimidazole 3-oxide and its derivatives were easily converted into the corresponding benzimidazoles with Raney nickel catalyst.[3]

Hydrogenation of 2-chloro-2′-nitroacetanilide (IIa) over Raney nickel instead of platinum oxide in ethanol directly gave 2-methylbenzimidazole (IIIa) in a good yield. Although 4′- or 6′-substituted compounds (IIb and IId) were similarly converted into the corresponding benzimidazole (IIIb and IIId), hydrogenation of 2–chloro-4′-methoxy-2′-nitro acetanilide (IIc) gave the corresponding acetyl-*o*-phenylenediamine instead of benzimidazole derivative under this condition.

When 2-methyl- (IIIa) or 2,5(6)-dimethylbenzimidazole (IIIb) was added gradually into fuming nitric acid (d=1.52), 2-methyl-5(6)-nitro-[4] (IVa) or 2,5 (6)-dimethyl-6(5)-nitrobenzimidazole[5] (IVb) was obtained, respectively. In the case of 5(6)-methoxy-2-methylbenzimidazole (IIIc), it gave a mixture which showed two spots on thin-layer chromatogrum in an approximate ratio of 1:1. This mixture was separated into each isomer by repeated silica gel chromatography. The isomers were identified with 5(6)-methoxy-2-methyl-6(5)-nitro-

1) Location: *No. 600, Kashiwagi-4-chome, Shinjuku, Tokyo.*
2) J.W. Schulenberg and S. Archer, *J. Org. Chem.*, **30**, 1279 (1965).
3) S. Takahashi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 1375 (1963).
4) O. Fischer and W. Hess, *Ber.*, **36**, 3970 (1903).
5) St. Niementowski, *Ber.*, **19**, 723 (1886).

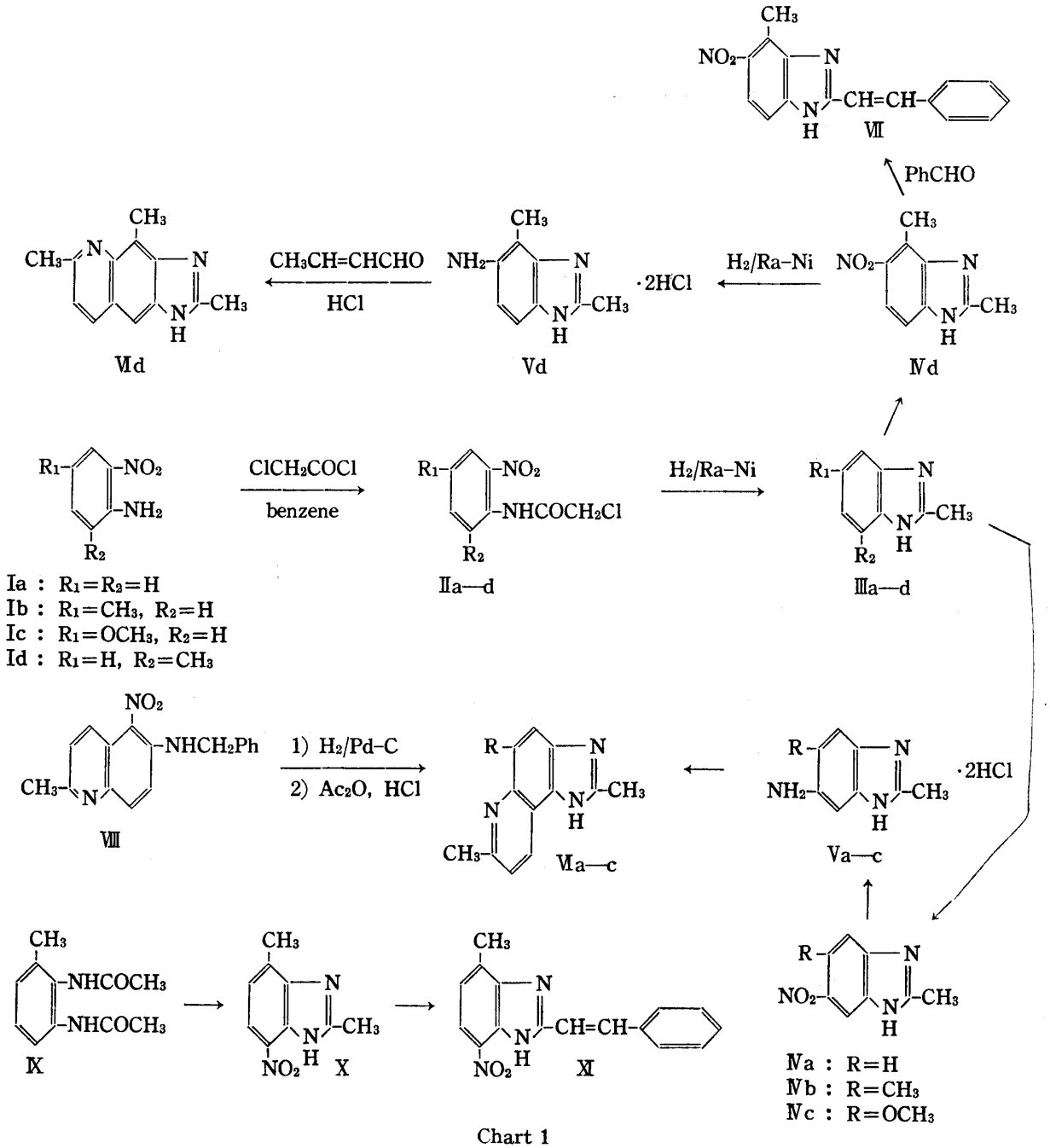


Chart 1

benzimidazole[6] (IVc) and its 4(7)-nitro isomer[6] by mixed melting point determination and infrared (IR) spectral comparison.

The nuclear magnetic resonance (NMR) spectra of the products (IVd and X) which were obtained by nitration of 2,4(7)-dimethylbenzimidazole (IIId) and 3-acetamido-*o*-acetotoluidide (IX), were shown in Fig. 1. From the fact that the signals due to methyl proton of each compound (IVd and X) at 6.85 and 6.87 τ had disappeared in the spectra of these 2-benzylidene compounds (VII and XI), the remaining signals at 7.02 and 7.16 τ seem to be the base on methyl proton of 4(7)-position, and it may be said that the chemical shift of 4(7)-methyl proton of 5(6)-nitro compound (IVd) lies at a lower magnetic field than that of 4(7)-methyl proton of its 7(4)-nitro isomer (X) by inductive effect due to the *ortho*-nitro group. Further, it seems that the large coupling constant of aromatic protons indicates an *ortho*-coupling. According to the report of Black,[7] coupling constant of 4(7)- and 5(6)-proton is larger than that of 5(6)- and 6(5)- proton of benzimidazole ring. On the basis of these considerations,

the two compounds (IVd and X) were respectively assigned to 2,4(7)-dimethyl-5(6)-nitrobenzimidazole (IVd) and its 7(4)-nitro isomer (X).

Reaction of 5(6)-amino-2-methylbenzimidazole hydrochloride (Va), which was obtained by catalytic hydrogenation of 5(6)-nitro-2-methylbenzimidazole (IVa), with crotonaldehyde in the presence of concentrated hydrochloric acid selectively gave 2,7-dimethyl-1(3)*H*-imidazo[4,5-*f*]quinoline (VIa). Position of the cyclization was determined by the way in Chart 1; (VIa) was identified with 2,7-dimethyl-1(3)*H*-imidazo[4,5-*f*]quinoline, which was derived from 5-nitro-6-benzylaminoquinaldine *via* 5-nitro-6-iodoquinaldine obtained by Petrow's procedure,[8] by mixed melting point determination and IR and NMR spectral comparison.

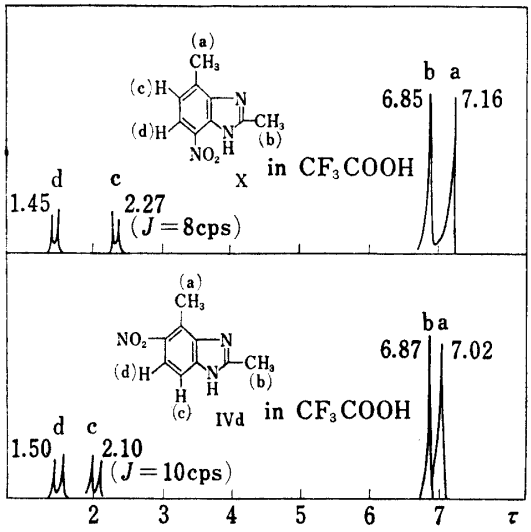
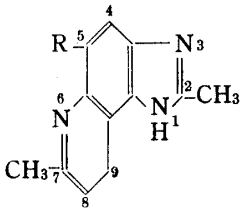


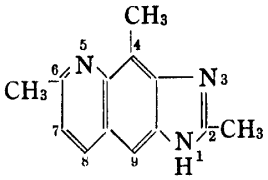
Fig. 1. The NMR Spectra of IVd and X

The fact that this cyclization occurred at 4(7)-position of benzimidazole ring agreed with the result that 2-phenyl-1(3)*H*-imidazo[4,5-*f*]quinoline[9] was obtained by the Skraup

Table I. Chemical Shifts (τ) in CF_3COOH



R		C(4)–H	C(5)–R	C(8)–H	C(9)–H	C–CH_3	C–CH_3
H	VIa	1.55 (1.52)	1.52 (1.55)	1.79 (d) J=9 cps	0.41 (d) J=9 cps	6.75	6.79
CH_3	VIb	1.65	6.94	1.78 (d) J=9 cps	0.40 (d) J=9 cps	6.75	6.86
OCH_3	VIc	2.16	5.69	1.78 (d) J=10 cps	0.48 (d) J=10 cps	6.78	6.90



C(7)–H	C(8)–H	C(9)–H	C–CH_3	C–CH_3	C–CH_3
1.97 (d) J=9 cps	0.75 (d) J=9 cps	1.40	6.75	6.81	6.81

6) H.B. Gillespie, M. Engelman, F. Spano and S. Graff, *J. Am. Chem. Soc.*, **79**, 2245 (1957).
7) P.J. Black and M.L. Heffernan, *Australian J. Chem.*, **15**, 862 (1962).
8) V. Petrow and B. Sturgeon, *J. Chem. Soc.*, **1954**, 570.
9) E. Modrow, B. Raeke, K. Weber and K. Fries, *Ann.*, **454**, 121 (1927).

reaction of 5(6)-amino-2-phenylbenzimidazole. Similarly, 5(6)-substituted compounds (Vb and Vc) were converted into the corresponding 1(3)*H*-imidazo[4,5-*f*]quinoline (VIb and VIc) in 50–55% yield and 2,4,6-trimethyl-1(3)*H*-imidazo[4,5-*g*]quinoline (VId) was derived from 2,4(7)-dimethyl-5(6)-aminobenzimidazole hydrochloride (Vd).

The structure of the obtained compounds (VIb, VIc and VId) was supported by IR (KBr), ultraviolet (UV) absorption (in EtOH) and NMR (in CF_3COOH) spectra (Table I).

Experimental[10]

General Procedure for Hydrogenation of 2'-Nitro-2-chloroacetanilides (II)——The anilide (II) (4 g) was hydrogenated over Raney Ni (4 g) in EtOH (150 ml) under atmospheric pressure at room temperature. After the consumption of 4 mole of H_2, the reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in a small amount of 10% HCl solution, the solution was made alkaline with conc. NH_4OH and extracted with ether. The extract was washed with water, dried over K_2CO_3, evaporated *in vacuo* and the residue was recrystallized from water or dil. EtOH to give following colorless product (III).

IIIa (2.0 g or 81.2% yield), mp 175—176°. *Anal.* Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.41; H, 6.27; N, 20.92.

IIIb (2.0 g or 78.3% yield), mp 202—203°. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.34; H, 6.64; N, 19.17.

IIId (2.22 g or 86.8% yield), mp 168.5—169.5°. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.72; H, 6.95; N, 19.05.

5(6)-Methoxy-2-methylbenzimidazole (IIIc)——After the treatment as described above, the alkaline solution was extracted with *n*-BuOH, the extract was washed with water and dried over K_2CO_3. The solvent was evaporated under reduced pressure to give a solid. To a solution of the obtained solid in AcOH (10 ml) was added 15% HCl solution (10 ml) and then refluxed for 1 hr. After cooling, the solution was made alkaline with conc. NH_4OH. The precipitated crystals were collected by filtration and washed with water. The product was recrystallized from water to give 1 g (37.7%) of colorless needles, mp 142—143°. *Anal.* Calcd. for $C_9H_{10}ON_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.78; H, 6.35; N, 17.19.

5(6)-Methoxy-2-methyl-6(5)-nitrobenzimidazole (IVc) and Its 4(7)-Nitro Isomer——IIIc (1 g) was added in a small portions to fuming nitric acid (3 ml, $d=1.52$) at 15—20° under stirring. After the addition was completed, the solution was further stirred for 0.5 hr, poured into ice water and made alkaline with conc. NH_4OH. The precipitate was collected by filtration and washed with water. The product was dissolved in benzene–MeOH and the solution was chromatographed on a silica gel (30 g) column with benzene and benzene–MeOH (100:1). The eluate was fractionated and the residue obtained by concentrating each fraction was checked by means of thin-layer chromatography. At first, 0.51 g of the yellow crystal was obtained and identified with 5(6)-methoxy-2-methyl-4(7)-nitrobenzimidazole[6] by IR spectrum and mixed melting point measurement, mp 203—204° (dil. EtOH). *Anal.* Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.64; H, 4.78; N, 20.05. IR cm^{-1} (KBr): $\nu_{NH\cdots N}$ 2800—3600.

Next, 0.68 g of IVc was obtained and identified with 5(6)-methoxy-2-methyl-6 (5)-nitrobenzimidazole[6] by IR spectrum and mixed melting point measurement, mp 172—173° (dil. EtOH). *Anal.* Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.28; H, 4.78; N, 19.98. IR cm^{-1} (KBr): $\nu_{NH\cdots N}$ 2600—3600.

2,4(7)-Dimethyl-5(6)-nitrobenzimidazole (IVd)——IVd was prepared from IIId (4 g) by the procedure described for the preparation of IVc and recrystallized from dil. EtOH to give 4.8 g (91.7%) of crystal, mp 161—162°. *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.30; H, 4.87; N, 21.83. IR cm^{-1} (KBr): $\nu_{NH\cdots N}$ 2600—3600.

2,4(7)-Dimethyl-7(4)-nitrobenzimidazole (X)——To a solution of IX (2 g), which was obtained from the reaction of 2,3-diaminotoluen[11] with acetic anhydride, in AcOH (15 ml) and acetic anhydride (4 ml), fuming nitric acid (1.5 ml, $d=1.52$) was added dropwise at 17—23° under stirring. After the addition was completed, the solution was further stirred for 0.5 hr, then poured into ice water and made alkaline with conc. NH_4OH. The precipitate was collected by filtration and washed with water. The product was recrystallized from dil. EtOH to give 1.75 g (94%) of crystal, mp 197—198° (decomp.). *Anal.* Calcd. for $C_9H_9O_2N_3 \cdot 1/2H_2O$: C, 53.99; H, 5.04; N, 20.99. Found: C, 53.97; H, 4.54; N, 21.51. IR cm^{-1} (KBr): $\nu_{NH\cdots N}$ 2800—3600.

4(7)-Methyl-5(6)-nitro-2-styrylbenzimidazole (VII)——A mixture of IVd (0.5 g) and benzaldehyde (1.5 g) was heated in a sealed tube at 190—200° for 2 hr, poured into ice water, the precipitate was filtered, washed with ether and recrystallized from dil. EtOH to give 0.41 g (56.1%) of yellow crystal, mp 215—216°.

10) All melting points were uncorrected.

11) L. Bradford, T.J. Elliott and F.M. Rowe, *J. Chem. Soc.*, **1947**, 437.

Anal. Calcd. for $C_{16}H_{13}O_2N_3$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.66; H, 5.01; N, 14.97. IR cm^{-1} (KBr): $\nu_{C=C}$ 1645.

4(7)-Methyl-7(4)-nitro-2-styrylbenzimidazole (XI)——Prepared from X (0.3 g) and benzaldehyde (0.9 g) as described for VII. Recrystallization from dil. EtOH gave 0.31 g (70.7%) of yellow crystal, mp 220°. *Anal.* Calcd. for $C_{16}H_{13}O_2N_3 \cdot 1/4H_2O$: C, 67.72; H, 4.76; N, 14.81. Found: C, 67.34; H, 4.68; N, 14.83.

General Procedure for Hydrogenation of Nitrobenzimidazoles (IV)——The nitro compound (IV) (4 g) was hydrogenated over Raney Ni (4 g) in anhyd. EtOH (100 ml) under atmospheric pressure at room temperature. After the consumption of 3 mole of H_2, the catalyst was removed by suction in a nitrogen atmosphere and the filtrate was saturated with hydrogen chloride. The precipitate was filtered and washed with anhyd. EtOH to give following colorless product (V).

Va (4.05 g or 83% yield), mp>300°. *Anal.* Calcd. for $C_8H_9N_3 \cdot 2HCl$: C, 43.66; H, 5.04; N, 19.09. Found: C, 43.69; H, 5.14; N, 18.86.

Vb (3.90 g or 81% yield), mp>300°. *Anal.* Calcd. for $C_9H_{11}N_3 \cdot 2HCl$: C, 46.17; H, 5.60; N, 17.95. Found: C, 46.41; H, 5.64; N, 17.69.

Vc (3.90 g or 80.7% yield), mp 244° (decomp.). *Anal.* Calcd. for $C_9H_{11}ON_3 \cdot 2HCl$: C, 43.22; H, 5.24; N, 16.80. Found: C, 42.90; H, 5.25; N, 17.07.

Vd (3.60 g or 73% yield), mp 272—274° (decomp.). *Anal.* Calcd. for $C_9H_{11}N_3 \cdot 2HCl \cdot 1/2H_2O$: C, 44.45; H, 5.82. Found: C, 44.57; H, 6.17.

6-Benzylamino-5-nitroquinaldine (VIII)——A mixture of 6-iodo-5-nitroquinaldine[8] (0.3 g) and benzylamine (3 g) was heated on a water bath for 3 hr, poured into ice water, the precipitate was collected by filtration and washed with water. Recrystallization from dil. EtOH gave 0.18 g (64%) of yellow crystal, mp 162.5—163.5°. *Anal.* Calcd. for $C_{17}H_{15}O_2N_3$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.62; H, 4.96; N, 14.80. IR cm^{-1} (KBr): ν_{NH} 3290.

2,7-Dimethyl-1(3)H-imidazo[4,5-*f*]quinoline (VIa)——From Va: A solution of Va (1 g) and crotonaldehyde (1 ml) in conc. HCl solution (30 ml) was heated under reflux for 2 hr, filtered, the filtrate was made alkaline with conc. NH_4OH and kept in a refrigerator overnight. The precipitate was collected by filtration, washed with water and recrystallized from water to give 0.5 g (56%) of colorless needles, mp 103—105°. *Anal.* Calcd. for $C_{12}H_{11}N_3 \cdot 3H_2O$: C, 57.35; H, 6.83; N, 16.72. Found: C, 57.07; H, 6.57; N, 17.11.

The picrate, prepared in the customary manner, crystallized from EtOH as yellow crystal, mp 230° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}N_3 \cdot 2C_6H_3O_7N_3$: C, 43.97; H, 2.62; N, 19.24. Found: C, 44.17; H, 2.38; N, 19.57.

From VIII: VIII (0.5 g) in AcOH (50 ml) was hydrogenated over 1% Pd–C (0.5 g) under atmospheric pressure at room temperature. After the consumption of 4 mole of H_2, the catalyst was removed by filtration. To the filtrate was added acetic anhydride (5 ml), the solution was heated on a water bath for 0.5 hr and evaporated *in vacuo*. The residue was dissolved in 15% HCl solution (20 ml) and the solution was heated under reflux for 0.5 hr. After cooling, the solution was made alkaline with conc. NH_4OH and kept in a refrigerator overnight. The precipitate was collected by filtration, washed with water and recrystallized from water to give 0.17 g (50.6%) of colorless needles, mp 103—105°.

This product was identified with VIa, prepared from Va, by mixed melting point determination, IR and NMR spectral comparison.

2,5,7-Trimethyl-1(3)H-imidazo[4,5-*f*]quinoline (VIb)——Prepared from Vb (1 g) and crotonaldehyde as described for VIa. Recrystallization from dil. EtOH gave 0.46 g (51%) of colorless needles, mp 95°. *Anal.* Calcd. for $C_{13}H_{13}N_3 \cdot 2H_2O$: C, 63.13; H, 6.94; N, 16.99. Found: C, 63.01; H, 6.81; N, 17.03.

The picrate was recrystallized from EtOH as yellow crystal, mp 240° (decomp.). *Anal.* Calcd. for $C_{13}H_{13}N_3 \cdot 2C_6H_3O_7N_3$: C, 44.84; H, 2.87; N, 18.83. Found: C, 44.76; H, 3.28; N, 18.56.

2,7-Dimethyl-5-methoxy-1(3)H-imidazo[4,5-*f*]quinoline (VIc)——After the treatment as described for VIa, the alkaline solution was extracted with $CHCl_3$, the extract was washed with water, dried over K_2CO_3 and evaporated *in vacuo*. The oily residue was dissolved in $CHCl_3$ and the solution was chromatographed on a silica gel (10 g) column with $CHCl_3$. The eluate was evaporated *in vacuo* to give 0.44 g (48.5%) of crystalline residue,[12] mp 115—117°. *Anal.* Calcd. for $C_{13}H_{13}ON_3 \cdot 1\frac{1}{2}H_2O$: C, 61.39; H, 6.35; N, 16.53. Found: C, 61.37; H, 6.42; N, 16.24.

2,4,6-Trimethyl-1(3)H-imidazo[4,5-*g*]quinoline (VId)——Prepared from Vd (1 g) and crotonaldehyde (1 ml) as described for VIa. Recrystallization from dil. EtOH gave 0.35 g (38.8%) of colorless crystal, mp 275°. *Anal.* Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 74.03; H, 6.02; N, 19.84. IR cm^{-1} (KBr): $\nu_{NH\cdots N}$ 2250—3280.

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12) Recrystallization from various organic solvents gave viscous oil.