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Syntheses of Benzimidazoles and Related Compounds. II.[1] Syntheses of 3*H*-Imidazo[4,5-*f*]- and 1*H*-Imidazo-[5,4-*g*]quinolines

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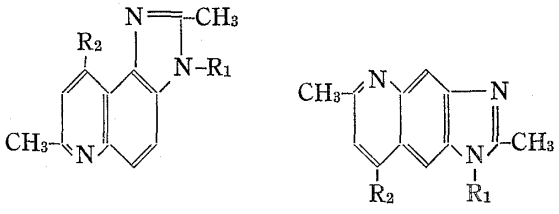
Reactions of 5-aminobenzimidazoles (I) with each crotonaldehyde and methyl propenyl ketonl selectively provided 3*H*-imidazo[4,5-*f*]quinoline derivatives (type-A), whereas reaction of I with ethyl acetoacetate gave a mixture of 3*H*-imidazo[4,5-*f*]- (type-A) and 1*H*-imidazo[5,4-*g*]quinoline derivative (type-B). This result was explained by the stability of σ complex of intermediate.

For synthesis of quinoline ring from 5(6)-aminobenzimidazole derivatives, Fries and co-workers[3] reported that the Skraup reaction of 2-phenyl-5(6)-aminobenzimidazole gave 2-phenyl-1(3)*H*-imidazo[4,5-*f*]quinoline (type-A) without giving 2-phenyl-1(3)*H*-imidazo[4,5-*g*]-quinoline (type-B) and that type-B was obtained from 2-phenyl-4(7)-bromo(or chloro)-5(6)-aminobenzimidazole blocked 4(7)-position of benzimidazole ring. In the preceding paper,[1] we reported that the Doebner–Miller reaction of 2-methyl-5(6)-aminobenzimidazole selectively provided 2,7-dimethyl-1(3)*H*-imidazo[4,5-*f*]quinoline (type-A).

It is well known that nitration of benzimidazole derivatives usually occurs at 5- or 6-position.[4] Also, the result calculated by Hückel molecular orbital theory of benzimidazole shows that electron density is higher at C_6-position than at C_4-position.[5] But, cyclization of 5(6)-aminobenzimidazole derivatives with the aldehyde selectively occurred at C_4-position as described above. The purpose of the present investigation was to study whether similarly selective cyclization occurred or not by reaction of the amines (I) with the ketone and ester. Crotonaldehyde and methyl propenyl ketone were respectively used as the aldehyde and ketone. As an alternative procedure for preparation of quinoline ring, the application of Conrad–Limpach reaction[6] was attempted. Here it might be supposed that cyclization of the amines (Ia and Ib) with each of crotonaldehyde, methyl propenyl ketone, and ethyl acetoacetate would give a mixture of two isomers of type-A and type-B in every reaction. This paper reports new informations in connection with the preparation and the ratio of isomers of type-A and type-B.



Type-A Type-B

Chart 1

In the Doebner–Miller reaction of the amines (Ia and Ib) with each of crotonaldehyde and methyl propenyl ketone in concentrated hydrochloric acid, only the corresponding 3*H*-imidazo

1) Part I: S. Ishiwata and Y. Shiokawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 1153 (1969).
2) Location: *No. 600, Kashiwagi-4-chōme, Shinjuku, Tokyo.*
3) K. Fries, E. Modrow, B. Raeke, and K. Weber, *Ann.*, **454**, 191 (1927).
4) J.B. Wright, *Chem. Rev.*, **48**, 397 (1951).
5) B. Pullman and A. Pullman, "Quantum Biochemistry," ed., John Wiley and Sons, Inc., New York, N.Y., 1963, p. 719.
6) R.C. Elderfield, "Heterocyclic Compound," Vol. 4, ed., John Wiley and Sons, Inc., New York, N.Y., pp. 33—35.

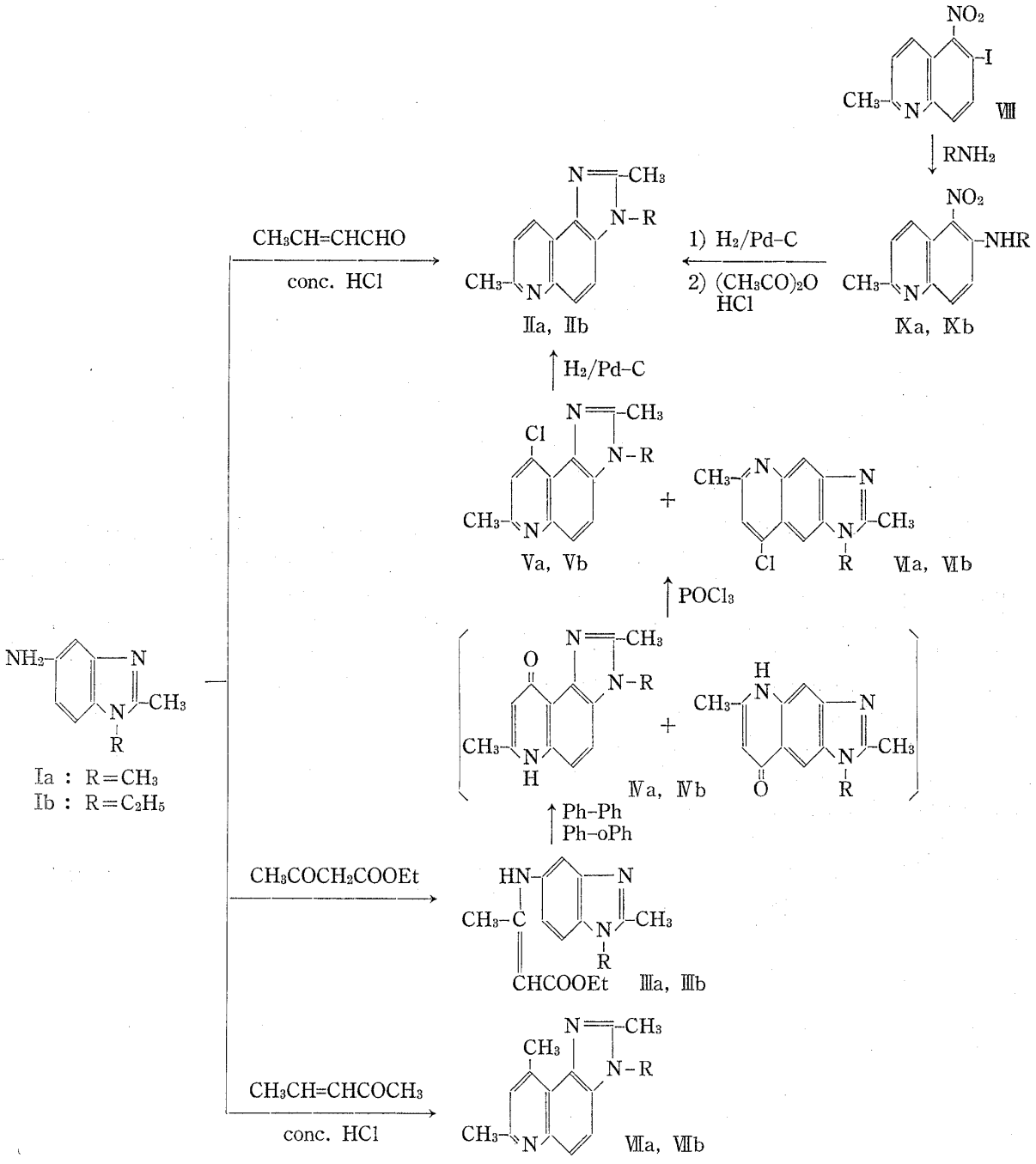


Chart 2

[4,5-*f*]quinoline derivatives (IIa, IIb, VIIa, and VIIb) (type-A) were obtained in 75—87% yield (Chart 2). The structures of the so obtained compounds (IIa, IIb, VIIa, and VIIb) were assigned on the basis of nuclear magnetic resonance (NMR) spectra which showed the coupling constant of 9 cps due to aromatic protons at C_4-H and C_5-H (Table I) and ultraviolet (UV) absorption spectra showed the characteristic absorption of type-A at the wavelength of 255 (shoulder), 258, and 310—320 mμ in ethanol. Moreover, IIa and IIb were respectively identified with 2,3,7-trimethyl- and 2,7-dimethyl-3-ethyl-3*H*-imidazo[4,5-*f*]quinoline, which were derived from 5-nitro-6-methylamino- (IXa) and 5-nitro-6-ethylaminoquinaldine (IXb), by mixed melting point determination and by infrared (IR) and NMR spectral comparison. From the result described above, the Doebner–Miller reaction of the amines (Ia and Ib) selectively gave compounds of type-A in spite of the difference of reactivity between the aldehyde and ketone.

Next, the reaction of the amines (Ia and Ib) with ethyl acetoacetate provided the crotonates (IIIa and IIIb) in a good yield and NMR spectrum of the crotonate (IIIa) was shown in Fig. 1.

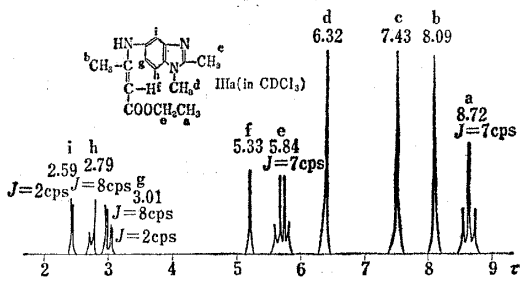
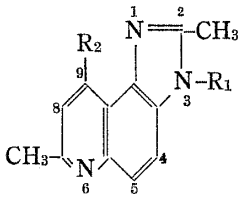
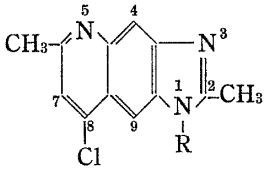


Fig. 1. The NMR Spectrum of IIIa

Cyclization of the crotonates (IIIa and IIIb) was carried out in diphenyl–diphenyl ether mixture by a usual method[7] and the products (IVa and IVb) were respectively converted by treatment with phosphoryl chloride into the mixtures of the chloro compounds (Va and VIa; Vb and VIb) which showed two spots on thin-layer chromatogram. The mixture of Va and VIa was obtained in 41% over-all yield from the amine (Ia) in three steps. From the amine (Ib), similarly, the mixture of Vb and VIb was obtained in 45.8% over-all yield. These mixtures were respectively separated into each isomer (Va and VIa; Vb and VIb) by silica gel chromatography. From NMR (Table I) and UV spectra of each compound (Va, Vb, VIa, and VIb), it was presumed that the first eluated compound (V) was 3*H*-imidazo[4,5-*f*]quinoline derivative (type-A) and the second (VI) was 1*H*-imidazo[5,4-*g*]quinoline derivative (type-B), that is, V possessed the characteristic absorption of type-A in the UV spectra at the wavelength of 256 (shoulder), 260, and 320 mμ in ethanol and doublet bands (J=9 cps) of aromatic protons at 2.11 and 2.34 τ in the NMR spectra in deuteriochloroform, whereas the UV and NMR spectra of VI respectively showed the characteristic absorption of type-B at 247.5 and 332 mμ and two singlet bands due to aromatic protons at 1.68 and 2.13 τ. The estimated proportion of type-A (V) to type-B (VI) is about 5.7:1 and 6.1:1 in the case of N-methyl- (Ia) and N-ethyl compound

Table I. Chemical Shifts (τ) in $CDCl_3$





(d=doublet J=9 cps)

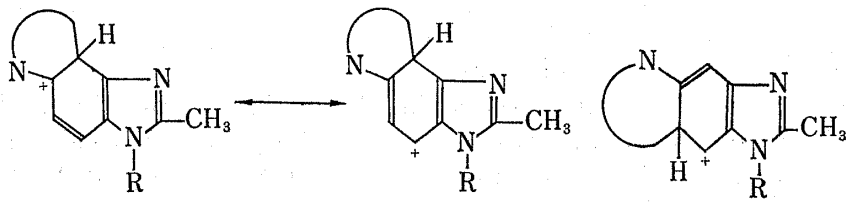
	Type A	2-CH_3	7-CH_3	3-R_1	9-R_2	8-H	4-H	5-H
IIa	R_1=CH_3 R_2=H	7.37	7.25	6.28	1.22 (d)	2.64 (d)	2.44 (d)	2.15 (d)
IIb	R_1=C_2H_5 R_2=H	7.32	7.24	CH_2 5.78 CH_3 8.56	1.18 (d)	2.62 (d)	2.38 (d)	2.12 (d)
Va	R_1=CH_3 R_2=Cl	7.32	7.29	6.25	—	2.58	2.42 (d)	2.14 (d)
Vb	R_1=C_2H_5 R_2=Cl	7.27	7.27	CH_2 5.75 CH_3 8.56	—	2.56	2.34 (d)	2.11 (d)
VIIa	R_1=R_2=CH_3	7.41	7.32	6.32	6.86	2.86	2.49 (d)	2.14 (d)
VIIb	R_1=C_2H_5 R_2=CH_3	7.36	7.31	CH_2 5.83 CH_3 8.59	6.84	2.86	2.44 (d)	2.14 (d)

Type B		1-R	2-CH_3	6-CH_3	4-H	7-H	9-H
VIa	R=CH_3	6.27	7.38	7.29	1.71	2.70	2.22
VIb	R=C_2H_5	CH_2 5.78 CH_3 8.56	7.37	7.31	1.68	2.70	2.13

7) C.R. Hauser and G.A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).

(Ib), respectively. Further, the compounds which were obtained by dehalogenation of Va and Vb over Pd–C in ethanol were respectively identified with IIa and IIb by mixed melting point determination and by IR and NMR spectral comparison.

The fact that the direction of ring closure occurs preferentially at C_4-position of benzimidazole ring may suggest that the σ complex of the corresponding intermediate for type-A exists as a resonance hybrid between Xa and Xb, and is more thermodynamically stabilized than that (XI) of the corresponding intermediate for type-B (Chart 3). It may be considered that the position of cyclization mainly depends on the stability of the intermediate rather than electron density at position of cyclization.



Xa Xb XI

Chart 3

Experimental[8]

6-Methylamino-5-nitroquinaldine (IXa)——A mixture of 6-iodo-5-nitroquinaldine[9] (VIII) (1 g) and 40% aqueous methylamine solution (6 ml) was heated in a sealed tube on a water bath for 3 hr and poured into cold H_2O. The precipitate was filtered, washed with H_2O and recrystallized from EtOH to give 0.64 g (93%) of reddish yellow crystals, mp 167.5—168°. *Anal.* Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.41; H, 5.52; N, 19.42. IR cm^{-1} (KBr): ν_{NH} 3260.

6-Ethylamino-5-nitroquinaldine (IXb)——Prepared from VIII (0.5 g) and 70% aqueous ethylamine solution (2 ml) as described for IXa. Recrystallization from EtOH gave 0.31 g (84%) of reddish yellow crystals, mp 115.5—116.5°. *Anal.* Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.17; H, 5.83; N, 18.17. IR cm^{-1} (KBr): ν_{NH} 3280.

2,3,7-Trimethyl-3*H*-imidazo[4,5-*f*]quinoline (IIa)——a) From 1,2-dimethyl-5-aminobenzimidazole[10] (Ia). A solution of Ia (0.5 g) and crotonaldehyde (1 ml) in conc. HCl (20 ml) was heated under reflux for 2 hr and filtered. The filtrate was made alkaline with conc. NH_4OH under cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. K_2CO_3, evaporated *in vacuo*, the residue was dissolved in $CHCl_3$ and the solution was chromatographed on a silica gel (5 g) column in order to remove the tar. The eluate was evaporated *in vacuo* and the residue was recrystallized from H_2O to give 0.49 g (75%) of colorless needles, mp 201.5—202.5°. *Anal.* Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.23; H, 6.37; N, 19.72. UV λ_{max}^{EtOH} mμ (ε): 255 (36000) (shoulder), 258.5 (39000), 310 (4000). NMR: (see Table I).

A small amount of by-product was obtained by the preparative TLC of the tar. The UV spectrum of this by-product did not show the characteristic absorption of type-B.

b) From the chloro compound (Va). The chloro compound (Va) (0.3 g) in EtOH (50 ml) was hydrogenated over Pd–C (1%, 0.3 g) at room temperature. The catalyst was filtered off, the filtrate was evaporated *in vacuo* and the residue was dissolved in a small portion of H_2O. The solution was made alkaline with conc. NH_4OH, extracted with $CHCl_3$, the extract was washed with H_2O, dried over anhyd. K_2CO_3, evaporated *in vacuo* and the residue was recrystallized from H_2O to give 0.225 g (87%) of colorless needles, mp 201.5—202.5°.

c) From the nitro compound (IXa). The nitro compound (IXa) (0.3 g) was dissolved in AcOH (50 ml), hydrogenated over Pd–C (1%, 0.3 g) until uptake ceased and 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 evapo-

8) Melting points were measured on a Yanagimoto Micro Melting Point Apparatus and were uncorrected. NMR spectra were taken on a JNM-4H-100 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. IR and UV spectra were measured on a JASCO DS-301 IR spectrophotometer and on a Hitachi EPS-3 UV spectrophotometer.

9) V. Petrow and B. Sturgeon, *J. Chem. Soc.*, **1954**, 570.

10) A. Schuster and J. Pinnow, *Ber.*, **29**, 1053 (1896).

rated *in vacuo*. The residue was dissolved in 4N HCl (10 ml) and the solution was heated under reflux for 0.5 hr. After cooling, the solution was made alkaline with conc. NH_4OH, extracted with $CHCl_3$, the extract was washed with H_2O, dried over anhyd. K_2CO_3 and evaporated to dryness *in vacuo*. The residue was recrystallized from H_2O to give 0.23 g (79%) of colorless crystals, mp 201.5—202.5°.

By mixed melting point determination and by IR and NMR spectral comparison, this compound was respectively identified with both products derived from the route a) and b).

2,7-Dimethyl-3-ethyl-3*H*-imidazo[4,5-*f*]quinoline (IIb)——a) From 1-ethyl-2-methyl-5-aminobenzimidazole[11] (Ib). A solution of Ib (0.5 g) and crotonaldehyde (1 ml) in conc. HCl (20 ml) was treated by procedure similar to that used for a) of IIa. Recrystallization from dil. EtOH gave 0.52 g (81%) of colorless needles, mp 149.5—150.5°. *Anal.* Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.40; H, 6.99; N, 18.36. UV λ_{max}^{EtOH} mμ (ε): 255 (40000) (shoulder), 258.5 (42000), 310 (4200). NMR: (see Table I).

b) From the chloro compound (Vb). Hydrogenation of Vb (0.3 g) in EtOH (50 ml) was carried out by procedure as described for b) of IIa. Recrystallization from dil. EtOH gave 0.21 g (81%) of crystals, mp 149.5—150.5°.

c) From the nitro compound (IXb). The nitro compound (IXb) (0.3 g) in AcOH (50 ml) was hydrogenated over Pd–C (1%, 0.3 g) under atmospheric pressure at room temperature. After treatment as described for c) of IIa, crude IIb was recrystallized from dil. EtOH to give 0.24 g (82%) of crystals, mp 149.5—150.5°.

By mixed melting point determination and by IR and NMR spectral comparison, this compound was respectively identified with both products derived from the route a) and b).

2,3,7-Trimethyl-9-chloro-3*H*-imidazo[4,5-*f*]quinoline (Va) and 1,2,6-Trimethyl-8-chloro-1*H*-imidazo-[5,4-*g*]quinoline (VIa)——a) The crotonate (IIIa). A mixture of Ia (1 g), ethyl acetoacetate (0.9 g), anhyd. EtOH (10 ml), anhyd. Na_2SO_4 (4 g), and AcOH (3 drops) was heated under reflux for 4 hr, filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was washed with a little portion of ether and dried; Yield 1.49 g (crude). IR cm^{-1} (KBr): ν_{NH} 3250, $\nu_{C=O}$ 1650. NMR: (see Fig. 1).

b) Cyclization of IIIa. To a mixture of diphenyl (10 g) and diphenyl ether (10 g) heated at 250—260° under stirring, IIIa (1.49 g) was added in one portion. The reaction mixture was stirred at the same temperature for 15 min and then allowed to stand at room temperature until a solid separated. To the reaction mixture, petroleum ether (50 ml) was added and the precipitate (IVa) was filtered by suction and dried; Yield 0.985 g (crude). IR cm^{-1} (KBr): $\nu_{C=O}$ 1635.

c) Treatment of IVa with $POCl_3$. A mixture of IVa (0.985 g) and $POCl_3$ (10 ml) was heated under reflux for 3 hr and excess $POCl_3$ was evaporated *in vacuo*. The residue was dissolved in H_2O, the solution was made alkaline with conc. NH_4OH under ice–cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. K_2CO_3 and evaporated to dryness *in vacuo*. The residue, which showed two spots on a TLC (silica gel; $CHCl_3$–MeOH, (10:1)), was dissolved in $CHCl_3$ and the solution was chromatographed on a silica gel (10 g) column. The early fraction eluated with the same solvent was evaporated *in vacuo* and the residue was recrystallized from benzene to give 0.535 g (over-all yield, 35%) of Va, mp 220.5—221.5°. *Anal.* Calcd. for $C_{13}H_{12}N_3Cl$: C, 63.53; H, 4.93; N, 17.10. Found: C, 63.97; H, 5.24; N, 17.42. UV λ_{max}^{EtOH} mμ (ε): 256 (40000) (shoulder), 260 (44000), 320 (3000). NMR: (see Table I).

Next, 0.095 g (over-all yield, 6%) of VIa was obtained and recrystallized from benzene, mp 203—204°. *Anal.* Calcd. for $C_{13}H_{12}N_3Cl$: C, 63.53; H, 4.93; N, 17.10. Found: C, 63.56; H, 4.88; N, 17.08. UV λ_{max}^{EtOH} mμ (ε): 247.5 (58000), 332 (10000). NMR: (see Table I).

2,7-Dimethyl-3-ethyl-9-chloro-3*H*-imidazo[4,5-*f*]quinoline (Vb) and 2,6-Dimethyl-1-ethyl-8-chloro-1*H*-imidazo[5,4-*g*]quinoline (VIb)——a) The crotonate (IIIb). A mixture of Ib (1 g), ethyl acetoacetate (0.9 g), anhyd. EtOH (10 ml), anhyd. Na_2SO_4 (4 g), and AcOH (3 drops) was treated as in the case of IIIa. The obtained crotonate (IIIb) was washed with a little portion of ether and dried; Yield 1.52 g (crude). IR cm^{-1} (KBr): ν_{NH} 3250, $\nu_{C=O}$ 1660.

b) Cyclization of IIIb. Cyclization of IIIb (1.52 g) was carried out by procedure similar to that used for IIIa and 1.08 g of IVb was obtained. IR cm^{-1} (KBr): $\nu_{C=O}$ 1635.

c) Treatment of IVb with $POCl_3$. A mixture of IVb (1.08 g) and $POCl_3$ (10 ml) was heated under reflux for 3 hr. The major product (Vb), isolated in the manner described for same treatment of Va, was recrystallized from benzene to give 0.585 g (over-all yield, 39.4%) of colorless crystals, mp 182.5—183°. *Anal.* Calcd. for $C_{14}H_{14}N_3Cl$: C, 64.73; H, 5.44; N, 16.18. Found: C, 64.22; H, 5.58; N, 16.08. UV λ_{max}^{EtOH} mμ (ε): 256 (40000) (shoulder), 260 (44000), 320 (3700). NMR: (see Table I).

Next, 0.095 g (over-all yield, 6.4%) of the minor product (VIb) was obtained and recrystallized from benzene–*n*-hexane, mp 175—176°. *Anal.* Calcd. for $C_{14}H_{14}N_3Cl$: C, 64.73; H, 5.44; N, 16.18. Found: C, 64.37; H, 5.55; N, 16.11. UV λ_{max}^{EtOH} mμ (ε): 247.5 (58000), 332 (10000). NMR: (see Table I).

2,3,7,9-Tetramethyl-3*H*-imidazo[4,5-*f*]quinoline (VIIa)——A solution of Ia (0.5 g) and methyl propenyl ketone (1 ml) in conc. HCl (20 ml) was refluxed for 2 hr, filtered, the filtrate was made alkaline with conc. NH_4OH under ice–cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd.

11) R. Foster, *J. Chem. Soc.*, **1957**, 4687.

K_2CO_3, evaporated *in vacuo* and the residue was recrystallized from dil. EtOH to give 0.53 g (76%) of colorless needles, mp 171—172°. *Anal.* Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.95; H, 6.78; N, 18.85. UV λ_{max}^{EtOH} mμ (ε): 253 (39000) (shoulder), 256.5 (41000), 310 (4500). NMR: (see Table I).

2,7,9-Trimethyl-3-ethyl-3*H*-imidazo[4,5-*f*]quinoline (VIIb)——Prepared from Ib (0.5 g), methyl propenyl ketone (1 ml), and conc. HCl (20 ml) as described for VIIa. Recrystallization from dil. EtOH gave 0.595 g (87.1%) of colorless needles, mp 141.5—142.5°. *Anal.* Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.58; H, 7.49; N, 17.41. UV λ_{max}^{EtOH} mμ (ε): 253 (41000) (shoulder), 256.5 (43000), 310 (4700). NMR: (see Table I).

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