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Studies on Quinoline and Isoquinoline Derivatives. IV.[1] Reaction of Quinoline and Isoquinoline N-Oxides with 3-Aminocrotononitrile and Related Compounds

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The reaction of quinoline 1-oxide with 3-aminocrotononitrile or 3-aminocinnamonitrile in the presence of benzoyl chloride afforded 2-methyl- or 2-phenyl-imidazo[1,2-*a*]quinoline-1-carbonitriles along with the 2-substituted quinoline derivatives. This reaction was also observed on isoquinoline 2-oxide and 1-methyl- and 1-phenyl-imidazo[2,1-*a*]isoquinoline-2-carbonitriles were obtained.

The mechanism of the reaction was described tentatively.

Keywords——2-methylimidazo[1,2-*a*]quinoline-1-carbonitrile; 2-phenylimidazo[1,2-*a*]quinoline-1-carbonitrile; 1-methylimidazo[2,1-*a*]isoquinoline-2-carbonitrile; 1-phenylimidazo[2,1-*a*]isoquinoline-2-carbonitrile; Vilsmeier reaction of 1-phenylimidazo[2,1-*a*]-isoquinoline

In the preceding paper,[1] we have reported that the primary enamines, such as ethoxycarbonylacetamidine and ethyl ethoxycarbonylacetimidate, reacted with quinoline and isoquinoline N-oxides yielding the products which contain a bifunctional side-chain at the α-position of the rings. In order to extend this reaction to other primary enamines, we examined the raction of the N-oxides with 3-aminocrotonic acid derivatives, and found that an unusual ring closure reaction occurred when the reagents possess a conjugated nitrile group to the enamine moiety. This paper deals with the details of the above reaction.

As well as ethoxycarbonylacetamidine, ethyl 3-aminocrotonate readily condensed with quinoline 1-oxide (I) in the presence of benzoyl chloride to give pale yellow needles, mp 111—112°, in 55% yield. This compound was identical with ethyl 3-amino-2-(2-quinolyl)crotonate (IIa) prepared by the catalytic reduction of 2-(5-ethoxy-3-methyl-4-isoxazolyl)quinoline (III) according to the reported procedure.[3] Similarly, 3-aminocrotonamide was allowed to react

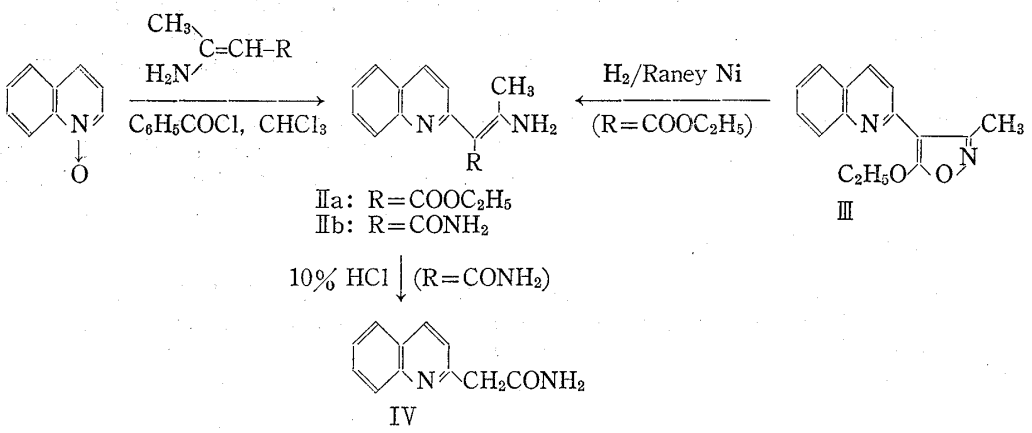

Chart 1

1) Part III: H. Yamanaka, M. Komatsu, S. Ogawa, and S. Konno, *Chem. Pharm. Bull.* (Tokyo), **27**, 806 (1979).
2) Location: *Aobayama, Sendai 980, Japan.*
3) H. Yamanaka, H. Egawa, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 2759 (1978).

with I affording the crystals, $C_{13}H_{13}N_3O$, mp 143°, in 57% yield. Hydrolysis of this product with dilute hydrochloric acid at room temperature gave rise to quinoline-2-acetamide (IV) which was identical with the authentic sample[4] in every respect. Based on the spectral data and the result of this reaction, the product has been assigned to the 3-amino-2-(2-quinolyl)-crotonamide structure (IIb).

On the contrary, the reaction of I with 3-aminocrotononitrile under identical conditions afforded a different result. For instance, when I was treated with 3-aminocrotononitrile in the presence of benzoyl chloride and the crude product was purified through column chromatography, the following two compounds were isolated: main product, $C_{13}H_9N_3$, mp 137—138° (24%); minor product, $C_{13}H_{11}N_3$, mp 230—233°, (5%).

The spectral data demonstrated that the minor product has a 3-amino-2-(2-quinolyl)-crotononitrile structure (VIa) corresponding to IIa, b. In the infrared (IR) spectrum of the main product no absorption band assignable to an N–H bond is observed and the nuclear magnetic resonance (NMR) spectrum reveals that this compound has one methyl group in addition to six aromatic protons. Based on these spectral data and those of mass spectrum (MS) (m/e=207) the structure of the main product was uniquely proposed to be 2-methyl-imidazo[1,2-*a*]quinoline-1-carbonitrile (Va).

The same result was obtained by the reaction of I with 3-aminocinnamonitrile giving 2-phenylimidazo[1,2-*a*]quinoline-1-carbonitrile (Vb), mp 176—177°, in 21% yield, together with a small amount of 3-amino-2-(2-quinolyl)cinnamonitrile (VIb), mp 203—206° (7%). Furthermore, the similar products were also obtained through the reaction of isoquinoline 2-oxide (VII) with the enaminonitriles, as shown in Chart 2. Namely, 3-aminocrotononitrile and 3-aminocinnamonitrile were allowed to react with VII in the presence of benzoyl chloride to give the imidazolo[2,1-*a*]isoquinolines (VIIIa, b) and the 1-substituted isoquinolines (IXa, b), respectively.

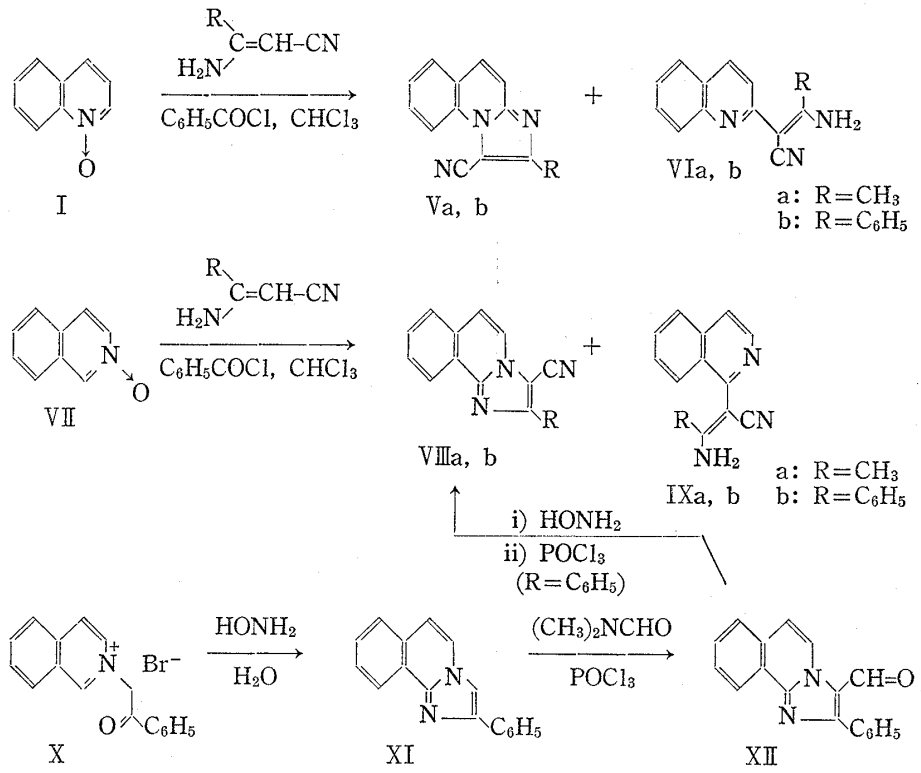

Chart 2

4) F. Zymalkowski and W. Schauer, *Arch. Pharm.*, **290**, 218 (1957).

In order to confirm the tricyclic structure of the main products, 1-phenylimidazo[2,1-*a*]-isoquinoline-2-carbonitrile (VIIIb) was independently synthesized as follows. According to the manner reported in the literature,[5] 1-phenylimidazo[2,1-*a*]isoquinoline (XI) was prepared from the ioquinolinium salt (X). The reaction of XI with a Vilsmeier reagent (dimethylformamide and phosphoryl chloride) afforded 1-phenylimidazo[2,1-*a*]isoquinoline-2-carboxaldehyde (XII), mp 163—165°, in good yield. The aldoxime obtained from XII by the standard method, was dehydrated by means of phosphoryl chloride to 1-phenylimidazo[2,1-*a*]isoquinoline-2-carbonitrile which was identical with VIIIb.

In connection with the reaction mechanism on the formation of tricyclic compounds (Va, b and VIIIa, b), two pathways (routes A and B) are presumable. As shown in Chart 3, route A involves the formation of an aziridine intermediate whereas route B does not.

Route A: As well as other enamines, 3-aminocrotononitrile attacks to the α-position of I to give the usual intermediate (XIII). The elimination of benzoic acid from XIII gives rise to the minor product (VIa). When XIII is transformed into the aziridine intermediate (XIV), the subsequent ring-opening of XIV affords the ylide (XV) which recyclizes to the dihydro compound (XVI).

Route B: Since the nucleophilic character of the enamine carbon atom is reduced by the presence of a cyano group, 3-aminocrotononitrile, unlike other enamines, reacts with I at the amino group to give the intermediate (XVII) which may be changed to XVIII by the elimination of benzoic acid.

At the final step of both routes A and B, the participation of an oxidizing agent is necessary to give Va. In the reaction of I with 3-aminocrotononitrile, the use of excess I

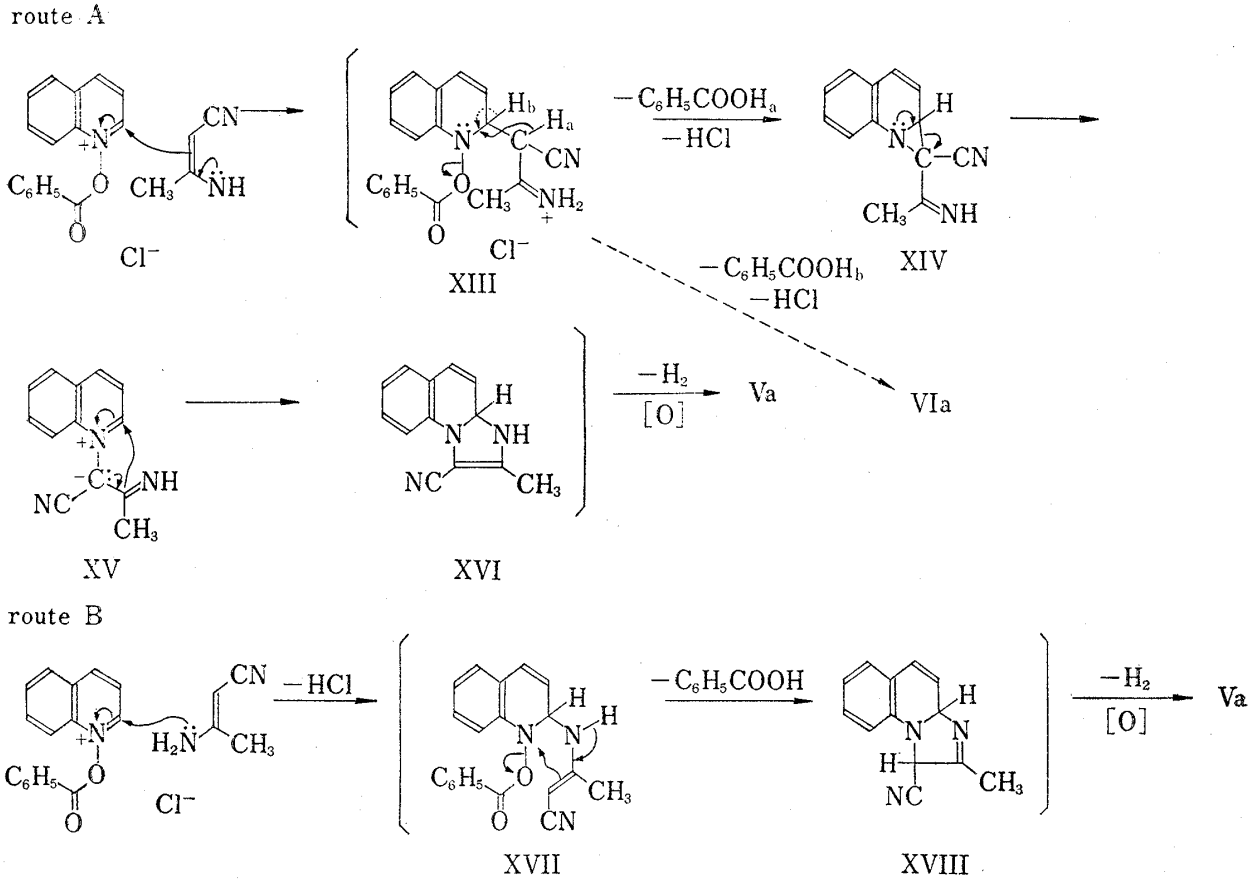

Chart 3

5) F. Kroehnke and W. Zecher, *Chem. Ber.*, **95**, 1128 (1962).

did not increase the yield of Va significantly. Quinoline itself was never detected in the reaction mixture. When air was blown through the warm reaction mixture, the yield of Va rather decreased.

Based on these observations, the disproportionation of XVI or XVIII might be reasonable for the formation of Va, although a tetrahydro derivative of Va was not isolated. By reference to the report[6] which described the formation of the similar aziridine intermediate to XIV, it may be seen that route A is more likely than route B.

Experimental[7]

Ethyl 3-Amino-2-(2-quinolyl)crotonate (IIa)——To a $CHCl_3$ (10 ml) solution of quinoline 1-oxide (1.45 g, 0.01 mol) was added a $CHCl_3$ (10 ml) solution of benzoyl chloride (1.68 g, 0.012 mol) and the mixture was allowed to stand at room temperature over night. To the mixture a $CHCl_3$ (20 ml) solution of ethyl 3-aminocrotonate (2.60 g, 0.02 mol) was added under stirring. The reaction mixture was allowed to stand again at room temperature over night, washed with 10% NaOH, and dried over anhyd. K_2CO_3. Purification of the crude product by cloum chromatography (Al_2O_3–ether) gave colorless prisms, mp 111—112°, which was identical with authentic specimen.[3] Yield 1.40 g (55%).

3-Amino-2-(2-quinolyl)crotonamide (IIb)——To a $CHCl_3$ (10 ml) solution of quinoline 1-oxide (1.45 g, 0.01 mol) was added a $CHCl_3$ (20 ml) solution of benzoyl chloride (1.68 g, 0.012 mol) and the mixture was allowed to stand at room temperature over night. To the mixture was added 3-aminocrotonamide (2.00 g, 0.02 mol) under stirring. The reaction mixture was allowed to stand at room temperature over night, washed with 10% NaOH, and dried over anhyd. K_2CO_3. Recrystallization of the crude product from AcOEt gave pale yellow needles, mp 143°. Yield, 1.30 g (57%). *Anal.* Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.38; H, 5.74; N, 18.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3410, 3280, 1650. NMR ($CDCl_3$): 1.88 (3H, s), 5.50—6.50 (2H, broad), 6.80—8.18 (8H, m).

Hydrolysis of IIb——A mixture of IIb (1.13 g, 0.005 mol) and 10% HCl (20 mol) was allowed to stand at room temperature over night. Making the reaction mixture alkaline with saturated K_2CO_3 aq. solution gave the precipitates which were filtered and dried. Recrystallization of the precipitates from EtOH gave 2-quinolineacetamide (IV) as pale yellow prisms, mp 91°, which was identical with the authentic specimen.[5] Yield 0.51 g (55%).

Reaction of Quinoline 1-Oxide (I) with 3-Aminocrotononitrile in the Presence of Benzoyl Chloride——To a $CHCl_3$ (20 ml) solution of I (2.9 g, 0.02 mol) was added a $CHCl_3$ (10 ml) solution of benzoyl chloride (2.8 g, 0.02 mol) under ice-cooling, and the mixture was stirred for 2 hr at room temperature. A $CHCl_3$ (10 ml) solution of 3-aminocrotononitrile (2.0 g, 0.024 mol) was added to this mixture and the resulting reaction mixture was allowed to stand at room temperature over night. The resulting precipitates were filtered, dissolved in 3 N Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was purified by column chromatography (Al_2O_3) using benzene, ether, and $CHCl_3$ as eluants. The benzene eluate afforded colorless needles which were recrystallized from benzene–petr. ether, mp 137—138°. Yield 1.1 g (24%). *Anal.* Calcd. for $C_{13}H_9N_3$ (Va): C, 75.34; H, 4.38, N, 20.28. Found: C, 75.56; H, 4.20; N, 20.34. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220. NMR ($CDCl_3$): 2.60 (3H, s), 7.30—8.00 (5H, m), 8.37 (1H, dd, J=1.5, 7.5).

The $CHCl_3$ eluate afforded pale yellow needles which were recrystallized from MeOH, mp 230—233°. Yield, 0.05 g. *Anal.* Calcd. for $C_{13}H_{11}N_3$ (VIa): C, 74.69; H, 5.40; N, 19.84. Found: C, 74.62; H, 5.30; N, 20.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1995. NMR ($CDCl_3$): 2.43 (3H, s), 4.00—6.00 (2H, broad), 7.30—8.20 (6H, m).

The mother liquor was washed with 3 N Na_2CO_3 and extracted with 3 N HCl. The HCl layer was made alkaline with 3 N Na_2CO_3, and extracted with $CHCl_3$, and the $CHCl_3$ layer was dried over anhyd. K_2CO_3. The $CHCl_3$ was removed and the residue was purified by column chromatography (Al_2O_3) using benzene, ether and $CHCl_3$ as eluants. The $CHCl_3$ eluate gave pale yellow needles (MeOH), mp 230—233°, which were identical with VIa. Yield 0.25 g. Total yield 0.30 g (5%).

Reaction of Quinoline 1-Oxide (I) with 3-Aminocinnamonitrile in the Presence of Benzoyl Chloride——According to the procedure for the reaction of I with 3-aminocrotononitrile, I (2.9 g, 0.02 mol) was allowed to react with benzoyl chloride (2.8 g, 0.02 mol) and 3-aminocinnamonitrile (2.9 g, 0.02 mol) in $CHCl_3$. The resulting precipitates were filtered and dissolved in 3 N Na_2CO_3. The 3 N Na_2CO_3 solution was extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was purified by column chromatography (Al_2O_3) using

6) K. Funakoshi, H. Sonoda, Y. Sonoda, and M. Hamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 3504 (1978).

7) All melting points are uncorrected. The IR spectra were taken with a JASCO IRA-1 spectrometer and the NMR spectra with a Hitachi-Perkin-Elmer R-20 spectrometer. The chemical shifts are expressed by the ppm downfield from tetramethylsilane used as an internal standard and the coupling constants by Herz (Hz). Following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m).

benzene as an eluant. The benzene eluate gave colorless needles which were recrystallized from benzene, mp 176—177°. Yield 0.87 g. *Anal.* Calcd. for $C_{18}H_{11}N_3$ (Vb): C, 80.28; H, 4.12; N, 15.61. Found: C, 80.49; H, 4.02; N, 15.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210. NMR ($CDCl_3$): 7.30—7.90 (8H, m), 8.00—8.30 (2H, m), 8.90 (1H, dd, J=1.5, 7.5).

After the mother liquor had been washed with 3 N Na_2CO_3, the $CHCl_3$ was removed. The residue was purified by column chromatography (Al_2O_3) using benzene, ether, and $CHCl_3$ as eluants. The benzene eluate afforded colorless needles (benzene), mp 176—177°, which were identical with Vb. Yield 0.28 g. Total yield 1.15 g (21%).

The $CHCl_3$ eluate gave pale yellow needles which were recrystallized from MeOH, mp 203—206°. Yield 0.38 g (7%). *Anal.* Calcd. for $C_{18}H_{13}N_3$ (VIb): C, 79.68; H, 4.83; N, 15.49. Found: C, 79.62; H, 4.84; N, 15.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 2000. NMR ($CDCl_3$) : 5.30—6.20 (1H, broad), 7.40—8.30 (11H, m), 11.00—12.00 (1H, broad).

Reaction of Isoquinoline 2-Oxide (VII) with 3-Aminocrotonitrile in the Presence of Benzoyl Chloride——According to the procedure for the reaction of I with 3-aminocrotononitrile, VII (2.9 g, 0.02 mol) was allowed to react with benzoyl chloride (2.8 g, 0.02 mol) and 3-aminocrotononitrile (2.0 g, 0.024 mol) in $CHCl_3$. The resulting precipitates were filtered and dissolved in 3 N Na_2CO_3. The 3 N Na_2CO_3 solution was extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was purified by column chromatography (Al_2O_3) using benzene, ether, and $CHCl_3$ as eluants. The benzene eluate gave colorless needles which were recrystallized from benzene–petr. benzine, mp 203—204°. Yield 1.0 g (24%). *Anal.* Calcd. for $C_{13}H_9N_3$ (VIIIa): C, 75.34; H, 4.38; N, 20.28. Found: C, 75.31; H, 4.30; N, 20.62. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210. NMR ($CDCl_3$): 2.60 (3H, s), 7.18 (1H, d, J=7.5), 7.50—7.80 (3H, m), 7.92 (1H, d, J=7.5), 8.40—8.70 (1H, m).

The $CHCl_3$ eluate gave pale yellow needles which were recrystallized from MeOH, mp 177—178°. Yield 0.38 g (9%). *Anal.* Calcd. for $C_{13}H_{11}N_3$ (IXa): C, 74.62; H, 5.30; N, 20.08. Found: C, 74.77; H, 5.24; N, 20.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1995. NMR ($CDCl_3$): 2.43 (3H, s), 7.30—8.00 (6H, m), 8.30 (1H, d, J=7.5), 8.80—9.20 (1H, m).

Reaction of Isoquinoline 2-Oxide (VII) with 3-Aminocinnamonitrile in the Presence of Benzoyl Chloride——According to the procedure for the reaction of I with 3-aminocrotononitrile, VII (2.9 g, 0.02 mol) was allowed to react with benzoyl chloride (2.8 g, 0.02 mol) and 3-aminocinnamonitrile (3.5 g, 0.024 mol) in $CHCl_3$. The resulting precipitates were filtered and dissolved in 3 N Na_2CO_3. The 3 N Na_2CO_3 solution was extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue purified by column chromatography (Al_2O_3) using benzene as an eluant. The benzene eluate gave colorless needles which were recrystallized from benzene, mp 197—198°. Yield 0.85 g. *Anal.* Calcd. for $C_{18}H_{11}N_3$ (VIIIb): C, 80.28; H, 4.12; N, 15.61. Found: C, 80.16; H, 4.07; N, 15.70. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210. NMR ($CDCl_3$): 7.28 (1H, d, J=6.8), 7.40—7.90 (6H, m), 8.09 (1H, d, J=6.8), 8.20—8.50 (2H, m), 8.60—8.90 (1H, m).

After the mother liquor had been washed with 3 N Na_2CO_3, the $CHCl_3$ was removed. The residue was purified by column chromatography (Al_2O_3) using benzene, ether, and $CHCl_3$ as eluants. The benzene eluate gave colorless needles (benzene), mp 197—198°, which were identical with VIIIb. Yield 0.22 g. Total yield, 1.07 g (20%). The $CHCl_3$ eluate gave pale yellow needles which were recrystallized from MeOH, mp 197—198°. Yield 0.45 g (8%). *Anal.* Calcd. for $C_{18}H_{13}N_3$ (IXb): C, 79.68; H, 4.83; N, 15.49. Found: C, 80.00; H, 4.74; N, 15.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1995. NMR ($CDCl_3$): 7.40—8.10 (9H, m), 8.47 (1H, d, J=6.0), 8.90—9.20 (1H, m).

1-Phenylimidazo[2,1-*a*]isoquinoline-2-carboxaldehyde (XII)——To a cold mixture of dimethylformamide (1.46 g, 0.02 mol), $POCl_3$ (1.23 g, 0.008 mol), and $CHCl_3$ (20 ml) was added 1-phenylimidazo[2,1-*a*]isoquinoline (XI) (1.2 g, 0.005 mol). The mixture was refluxed for 5 hr, poured into a cold NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was recrystallized from acetone to give colorless needles, mp 187—189°. Yield 1.2 g (88%). *Anal.* Calcd. for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.62; H, 4.32; N, 10.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR ($CDCl_3$): 7.36 (1H, d, J=8.3), 7.55—8.15 (8H, m), 8.80—9.10 (1H, m), 9.42 (1H, d, J=8.3), 10.06 (1H, s). Oxime, mp>300° (EtOH).

1-Phenylimidazo[2,1-*a*]isoquinoline-2-carbonitrile (VIII)——A mixture of 1-phenylimidazo[2,1-*a*]isoquinoline-2-aldoxime (0.86 g, 0.003 mol) and $POCl_3$ (10 ml) was refluxed for 1 hr. Excess $POCl_3$ was removed under reduced pressure and the residue was poured into a cold NH_4OH and extracted with $CHCl_3$. The crude product was recrystallized from benzene to give colorless needles, mp 197—198°. Yield, 0.60 g (74%).

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