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Studies on Aromatic Nitro Compounds. I. Reaction of 6-Nitroquinoline with Active Methylene Compounds in the Presence of Bases[1]

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The reactions of 6-nitroquinoline (I) with some cyanomethylene compounds in the presence of a base were investigated. I reacted with ethyl cyanoacetate in the presence of potassium cyanide to produce 6-ethoxalylaminoquinoline-5-carbonitrile (IIa) and diethyl 2-cyano-3-(5-cyano-6-quinolylamino)fumarate (IIIa) in 56 and 6.3% yields, respectively. When potassium *tert*-butoxide or potassium hydroxide was used as a base, IIa was obtained as a sole product. Potassium hydroxide was the most effective in the formation of IIa (66.5%). Similarly, the reactions of I with methyl cyanoacetate, *p*-nitrophenylacetonitrile, ω-cyanoacetophenone and 1-cyanoacetylpyrrolidine in the presence of potassium hydroxide gave the 6-aminoquinoline-5-carbonitrile derivatives (IIb, IIc, IId and IIf) corresponding to IIa. In the reaction of I with α-cyanoacetamide, α-cyano-β-carbamoyl-β-(5-cyano-6-quinolylamino)acrylamide (IIIe) and 3-cyano-4-(5-cyano-6-quinolylamino)-1H-pyrrole-2,5-dione (VI) were obtained as minor products together with IIe.

Keywords——6-nitroquinoline; base; cyanomethylene compounds; 6-acylaminoquinoline-5-carbonitriles; hydrolysis; 6-aminoquinoline-5-carbonitrile; acid chlorides

It has been reported that 4-nitroquinoline 1-oxides react with some nucleophiles in the presence of potassium cyanide to give the corresponding 4-substituted quinoline-3-carbonitriles.[2] As an extension of this study, we examined the reaction of 6-nitroquinoline (I) with some cyanomethylene compounds in the presence of a base, and different results were obtained.

A solution of I in dimethylformamide (DMF) was added to a stirred suspension of ethyl cyanoacetate (3 equiv.) and potassium cyanide (3 equiv.) in DMF, and the resulting mixture was stirred at room temperature for 30 min. Successive treatment of the reaction mixture with ice water and 10% hydrochloric acid afforded 6-ethoxalylaminoquinoline-5-carbonitrile (IIa) and diethyl 2-cyano-3-(5-cyano-6-quinolylamino)fumarate (IIIa) in 56.0 and 6.3% yields, respectively (Chart 1).

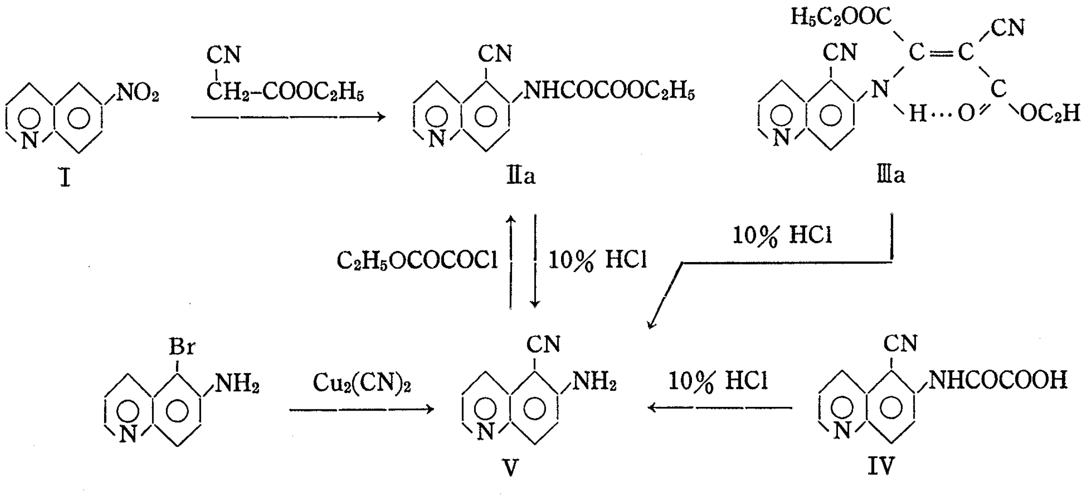


Chart 1

Table I. Reaction of 6-Nitroquinoline (I) with Ethyl Cyanoacetate

Reaction conditions[a)		Products, % yield			
Base	Time (hr)	IIa	IIIa	IV	V
KCN	0.5	56.0	6.3	—	—
KCN	1	57.2	1.9	—	—
KCN	5	54.2	4.1	—	—
KCN	24	2.5	16.5	38.5	4.0
NaH	48	36.5	1.9	—	—
tert-BuOK	5	42.9	—	—	—
KOH	5	66.5	—	—	—

a) Procedure: A solution of I (0.01 mol) in DMF (15 ml) was added to a solution of ethyl cyanoacetate (0.03 mol) and a base (0.03 mol) in DMF (15 ml), and the mixture was stirred at room temperature.

The reaction was completed in about 1 hr. However, when this reaction was carried out at room temperature for 24 hr, the yield of IIa decreased to only 2.5% and N-(5-cyano-6-quinolyl)oxamic acid (IV) and 6-aminoquinoline-5-carbonitrile (V) were additionally formed in yields of 38.5 and 4%, respectively. Various conditions were examined, and Table I summarizes the results. It was found that no reaction occurred in the absence of potassium cyanide, but the reaction proceeded significantly with other bases instead of potassium cyanide. With sodium hydride as a base, IIa and IIIa were obtained in somewhat lower yields of 36.5 and 1.9%, respectively. When potassium *tert*-butoxide or potassium hydroxide was used as a base, IIa was obtained as a sole product, but no formation of IIIa was apparent in these cases. Potassium hydroxide was the most effective base for the formation of IIa.

On acidic or alkaline hydrolysis, IIa gave 6-aminoquinoline-5-carbonitrile (V), which was identical with an authentic sample prepared from 6-amino-5-bromoquinoline[3)] and copper(I) cyanide. The structure of IIa was confirmed by direct comparison with an authentic sample obtained by the reaction of V with ethoxalyl chloride (Chart 1).

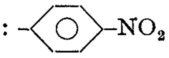
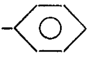
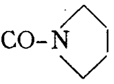
Compound IIIa was hydrolyzed by refluxing it with 10% hydrochloric acid to yield V. The mass spectrum (M^+, *m*/*e* 364) and the results of elemental analysis of IIIa indicated that IIIa was formed from IIa through condensation with another mole of ethyl cyanoacetate. However, an attempt to prepare IIIa by the reaction of IIa with ethyl cyanoacetate in the presence of potassium cyanide was unsuccessful. The infrared (IR) spectrum of IIIa exhibited a characteristic nitrile band at 2210 cm^{-1} and two strong bands at 1737 cm^{-1} and 1670 cm^{-1} indicative of a carbonyl group and a chelated carbonyl group. Its proton magnetic resonance (PMR) spectrum showed a broad signal at δ 11.61 (1H) due to a chelated amino proton, in addition to signals due to five aromatic protons and ten protons of two ethoxycarbonyl groups. On the basis of these data, IIIa was assigned as diethyl 2-cyano-3-(5-cyano-6-quinolylamino)-fumarate.

Product IV underwent hydrolysis to 6-aminoquinoline-5-carbonitrile on heating with 10% hydrochloric acid. The structure of IV was deduced on the basis of the spectral data (see "Experimental").

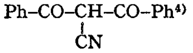
Subsequently, the reactions of I with some other cyanomethylene compounds were examined in the presence of a base, and the results listed in Table II were obtained.

Methyl cyanoacetate, *p*-nitrophenylacetonitrile, ω-cyanoacetophenone, α-cyanoacetamide and 1-cyanoacetylpyrrolidine reacted with I to produce the 6-aminoquinoline-5-carbonitrile derivatives (IIb, IIc, IId, IIe and IIf) corresponding to IIa. The structures of 6-methoxalylaminoquinoline-, 6-*p*-nitrobenzoylaminoquinoline-, and 6-phenyloxalylaminoquinoline-5-carbonitriles (IIb, IIc and IId) were confirmed by direct comparison with the corresponding authentic specimens prepared from V and methoxalyl, *p*-nitrobenzoyl, and phenyloxalyl[5)] chlorides, respectively (Chart 2). On hydrolysis with 10% hydrochloric acid, compounds

Table II. Reaction of 6-Nitroquinoline with Some Cyanomethylene Compounds

$CH_2(CN)-R$ R	Reaction conditions[a] Base	 Time (hr)	Products, % yield II	 Others
b: $-COOCH_3$	KCN	3	19.6	—
	KOH	6	32.3	—
c: 	KCN	24	50.5	—
	KOH	24	58.2	—
d: -CO- 	KCN	6	22.9[b]	—
e: $-CONH_2$	KOH	5	43.0	1.1(IIIe), 7.9(VI)
	tert-BuOK	4	33.9	5.6(IIIe), 6.8(VI)
f: -CO- 	KOH	20	14.2	—

[a] The experimental procedure was the same as described in Table I, except in the last experiment, in which reaction temperature was 70°.

[b]  $Ph-CO-\underset{CN}{CH}-CO-Ph$[4] (650 mg, mp 158°) was isolated as a by-product.

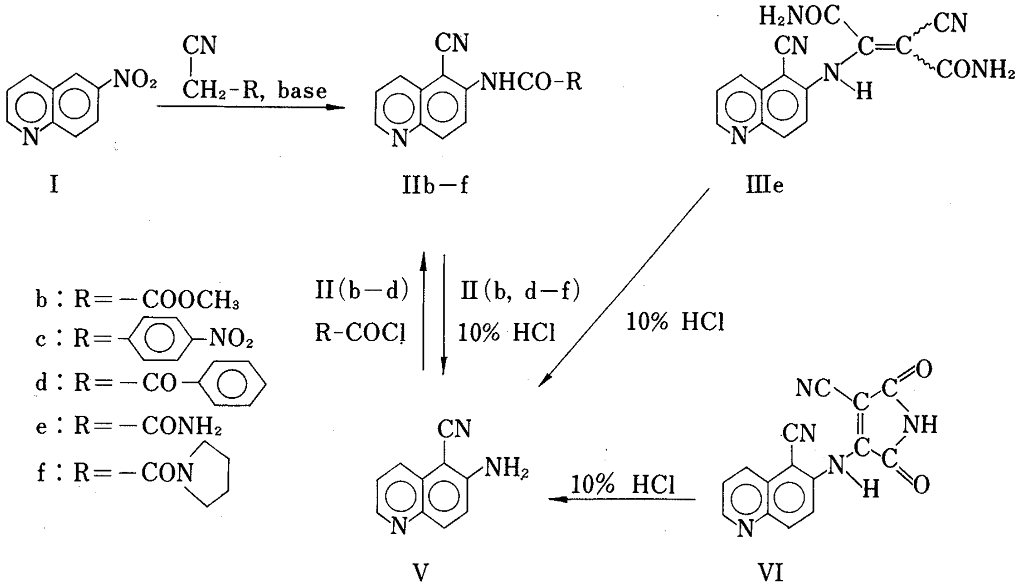


Chart 2

(IIb and IId) gave the same compound, 6-aminoquinoline-5-carbonitrile, whereas IIc was recovered unchanged under the same conditions. These structures were also supported by the analytical (Table III) and spectral data (Table IV).

The structure assignments of 6-oxamoylaminoquinoline-5-carbonitrile (IIe) and 6-(1-pyrrolidineoxalylamino)quinoline-5-carbonitrile (IIf) were based on the satisfactory elemental analyses and the spectral data shown in Tables III and IV. α-Cyanoacetamide reacted with I in the presence of potassium hydroxide or potassium *tert*-butoxide to give α-cyano-β-carbamoyl-β-(5-cyano-6-quinolylamino)acrylamide (IIIe) and 3-cyano-4-(5-cyano-6-quinolylamino)-1H-pyrrole-2,5-dione (VI) as minor products besides IIe. Both IIIe and VI were hydrolyzed by heating them with 10% hydrochloric acid to provide the same compound V. Compound IIIe gave analytical values in agreement with the empirical formula $C_{15}H_{10}N_6O_2 \cdot H_2O$ and the mass spectrum exhibited a molecular ion at m/e 306. The PMR spectrum of IIIe was not distinct because of the sparing solubility of IIIe in DMSO-d_6 and its IR spectrum displayed bands due to the amino group at 3160 cm^{-1}, 3295 cm^{-1} and 3420 cm^{-1}, the nitrile group at

2202 cm^{-1} and the carbonyl groups at 1751 cm^{-1} and 1679 cm^{-1}. These observations were consistent with the assigned structure, but its stereochemistry was not established. Compound VI was recrystallized from methanol as yellow prisms, mp 280°, which showed absorption bands at 1776 cm^{-1} and 1720 cm^{-1} attributable to an imido carbonyl group in its IR spectrum.

TABLE III. Some Properties of 6-Substituted Quinoline-5-carbonitriles

Compd. No.	mp (°C) ( ): Recrystn. solvent	Appearance	Formula	Analysis (%) Calcd (Found)		
				C	H	N
IIa	182 (acetone)	Colorless needles	$C_{14}H_{11}N_3O_3$	62.45 (62.14	4.12 4.04	15.61 15.46)
IIb	175 (acetone)	Colorless needles	$C_{13}H_9N_3O_3$	61.17 (61.25	3.55 3.41	16.47 16.53)
IIc	240—241 (MeOH)	Pale yellow scales	$C_{17}H_{10}N_4O_3$	64.14 (64.11	3.17 2.88	17.60 17.38)
IId	197—199 (MeOH)	Colorless needles	$C_{18}H_{11}N_3O_2$	71.75 (71.56	3.68 3.53	13.95 13.89)
IIe	289—290 (MeOH)	Colorless needles	$C_{12}H_8N_4O_2$	60.00 (59.95	3.32 3.35	23.33 23.52)
IIf	207 (MeOH)	Colorless needles	$C_{16}H_{14}N_4O_2$	65.29 (65.12	4.80 4.64	19.04 19.37)
IIIa	184 (acetone)	Light yellow prisms	$C_{19}H_{16}N_4O_4$	62.63 (62.60	4.43 4.30	15.38 15.10)
IIIe	273—275 (MeOH)	Light red columns	$C_{15}H_{10}N_6O_2 \cdot H_2O$	55.55 (55.54	3.73 3.69	25.92 25.49)
VI	293—294 (MeOH)	Yellow prisms	$C_{15}H_7N_5O_2$	62.28 (62.37	2.44 2.30	24.21 23.95)

TABLE IV. Spectral Data for 6-Substituted Quinoline-5-carbonitriles

Compd. No.	IR ν_{max}^{KBr} cm^{-1}			Proton NMR spectra ppm(J in Hz)						MS m/e (M$^+$)
	NH	CN	CO	C_2	C_3	C_4	C_7	C_8	others	
IIa	3358 3130	2205	1731	$^{a)}$9.04 (d.d, $J_{2,3}=4.5$, $J_{2,4}=1$, $J_{3,4}=9$) (d, $J_{7,8}=9$)	7.78	8.48	8.00	8.38	1.36 (–OCH$_2$–C$\underline{H}_3$) 4.38 (–OC$\underline{H}_2$–CH$_3$), 11.33 (NH)	269
IIb	3355 3138	2206	1723	$^{b)}$9.08 (d.d, $J_{2,3}=4.5$, $J_{2,4}=1$, $J_{3,4}=9$) (d, $J_{7,8}=9$)	7.87	8.56	8.29	8.46	4.11 (–OCH$_3$) 10.23 (NH)	255
IIc	3225 3110	2215	1658	$^{a)}$9.11 (d.d, $J_{2,3}=4.5$, $J_{2,4}=1$) (d, $J_{7,8}=9$)	7.83		8.05		8.20—8.80 (6H, m), 11.40 (NH)	318
IId	3320	2204	1706 1658	$^{c)}$8.97 (d.d, $J_{2,3}=4.5$, $J_{2,4}=1$, $J_{3,4}=9$)		8.87			7.44—7.78 (4H, m) 8.32—8.48 (4H, m), 9.87 (NH)	301
IIe	3370 3280 3180	2200	1712	$^{a)}$8.81 (d.d, $J_{2,3}=4.0$, $J_{2,4}=1.5$, $J_{3,4}=8.8$) (d, $J_{7,8}=9.4$)	7.68	8.27	8.05	8.21	8.24 (NH$_2$), 10.81 (NH)	240
IIf	3270	2190	1708 1642	$^{d)}$						294
IIIa		2210	1737 1670	$^{b)}$9.05 (d.d, $J_{2,3}=4.5$, $J_{2,4}=1$, $J_{3,4}=9$) (d, $J_{7,8}=9$)	7.79	8.51	7.70	8.37	1.13, 1.35 (–OCH$_2$–C$\underline{H}_3$) × 2 4.28 (–OC$\underline{H}_2$–CH$_3$) × 2, 11.61 (NH)	364
IIIe	3420 3295 3160	2202	1751 1679	$^{d)}$						306
VI	3265	2210	1776 1720	$^{a)}$9.11 (d.d, $J_{2,3}=4.0$, $J_{2,4}=1.3$, $J_{3,4}=8.1$) (d, $J_{7,8}=9$)	7.73	8.32	7.88	8.27	11.45 (NH)	289

Abbrevaiations: d, doublet; d.d, doublet of doublets; m, multiplet.

a) In $(CD_3)_2SO$. *b*) In $(CD_3)_2CO$. *c*) In $CDCl_3$.

d) The PMR spectra of IIf and IIIe could not be obtained clearly because of the sparing solubilities of IIf and IIIe in DMSO-d_6.

Elemental analysis and the mass spectrum (M^+, m/e 289) accorded with the molecular formula $C_{15}H_7N_5O_2$. Its PMR spectrum was also consistent with the assigned structure. Thus VI was identified unequivocally as 3-cyano-4-(5-cyano-6-quinolylamino)-1H-pyrrole-2,5-dione.

Although the details of the reaction mechanism have not been established, the formation of II from the reactions of I with cyanomethylene compounds in the presence of bases other than potassium cyanide indicates that the 5-cyano group of II may originate from the cyanomethylene group, and potassium cyanide seems to behave only as a base. In order to elucidate the reaction mechanism and also to explore the scope of the reaction, further studies of the reaction using other aromatic and heteroaromatic nitro compounds and active methylene compounds are in progress under various conditions.

Experimental

DMF was prepared by distillation from calcium hydride and was stored over molecular sieve 4A. All melting points are uncorrected. IR spectra were recorded on an IRA-2 spectrophotometer. PMR spectra were taken on a Hitachi R-22 spectrometer at 90 MHz or a JNM-MH-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL model JMS-01SG spectrometer.

Reaction of 6-Nitroquinoline (I) with Cyanomethylene Compounds. General Procedure for the Preparation of II (a—d and f)——A solution of I (0.01 mol) in DMF (15 ml) was slowly added to a stirred solution of the cyanomethylene compound (0.03 mol) and a base (0.03 mol) in DMF (15 ml). The stirring was continued for the specified time (Tables I and II) at room temperature. The mixture was poured into ice water, and neutralized with 10% HCl. The precipitate was collected, washed with water, dried, and recrystallized from the solvent indicated in Table III. In the case of II (c and d), the precipitate was washed with water, and then with ether to remove the unchanged cyanomethylene compounds, dried and recrystallized from MeOH. The yields, the elemental analyses and the spectral data of II are shown in Tables I—IV.

Reaction of I with Ethyl Cyanoacetate——A solution of I (0.01 mol) in DMF (15 ml) was added dropwise to a stirred solution of ethyl cyanoacetate (0.03 mol) and KCN (0.03 mol) in DMF (15 ml). The reaction mixture was stirred for 24 hr at room temperature. After the solvent had been removed *in vacuo*, the residue was dissolved in water (*ca.* 30 ml), acidified with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel. The first fraction eluted with $CHCl_3$ gave IIa, 66 mg (2.5%). Further elution with $CHCl_3$ gave IIIa, 600 mg (16.5 %). The last fraction eluted with $CHCl_3$–MeOH (9: 1) gave 6-aminoquinoline-5-carbonitrile (V), 67 mg (4%). The mother liquor from $CHCl_3$ extraction was salted out with NaCl, and cooled. The precipitate was collected, washed with small amounts of cold water, and recrystallized from H_2O–acetone to give N-(5-cyano-6-quinolyl)oxamic acid (IV) as brown grainy crystals, 930 mg (38.5%). mp 197° (dec.). *Anal.* Calcd for $C_{12}H_7N_3O_3$: C, 59.75; H, 2.96; N, 17.42. Found: C, 59.82; H, 3.18; N, 17.32. MS m/e: 241 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 2200 (CN), 2680—2440, 1718 (–COOH), 1656 ($-NH\underline{CO}-$).

Reaction of I with α-Cyanoacetamide——A solution of I (0.01 mol) in DMF (15 ml) was added slowly to a solution of α-cyanoacetamide (0.03 mol) and KOH (0.03 mol) in DMF (15 ml), and the mixture was stirred for 5 hr at room temperature. The reaction mixture was neutralized with 10% HCl, and the deposited crystals were collected and dried (2.165 g). Fractional crystallization (several times) of the crystals from MeOH afforded IIe, 1.032 g (43%), yellow needles, mp 281—282° (dec.). The mother liquor of crystallization of IIe was evaporated to dryness. The fractional crystallization of the residue from MeOH gave IIIe, 0.036 g (1.1%), light red columns, mp 273—275° (dec.) and VI, 0.23 g (7.9%), yellow prisms, mp 293—294°.

Hydrolysis of II——(a) A solution of II (a, b, d, e or f) (1 mmol) in 10% HCl (5 ml) was refluxed for 3 hr at 130—140° on an oil bath. The reaction mixture was cooled to room temperature and neutralized with 10% NaOH. The precipitate was collected, washed with water, dried and recrystallized from $CHCl_3$ to yield pale yellow prisms (V), mp 181°, which were identical with an authentic sample prepared from 6-amino-5-bromoquinoline³⁾ as described below. Yields were 75.1, 85.4, 82.3, 80.9 and 86.5%, respectively.

(b) IIa (0.15 g) was added to a solution of NaOMe in MeOH [prepared from Na (0.04 g) and abs. MeOH (10 ml)], and the mixture was stirred for 3 hr at room temperature. After removal of the solvent, the residue was purified by column chromatography on alumina with $CHCl_3$ as the eluent, and 0.06 g (63.4%) of V was obtained.

(c) A solution of IIa (0.35 g) in 10% K_2CO_3 (20 ml) was refluxed for 3 hr at 130°. The reaction solution was cooled, then the precipitate was collected, washed with water and dried; 0.05 g (25.1%) of V was obtained.

Hydrolysis of III——A solution of III (a or e) (1 mmol) in 10% HCl (10 ml) was refluxed for 3 hr at 130—140° on an oil bath and cooled. The resulting solution was neutralized with 10% NaOH. The precipitate was collected, washed with water, dried and recrystallized from $CHCl_3$ to give V. Yields were 71.8 and 64.1%, respectively.

Hydrolysis of IV——A solution of IV (400 mg) in 10% HCl (7 ml) was refluxed for 3 hr at 130—140° on an oil bath. The cooled solution was neutralized with 10% NaOH. The deposited crystals were collected, washed with water, dried and recrystallized from $CHCl_3$ to give V (210 mg) in 74.9% yield.

Hydrolysis of VI——A solution of VI (50 mg) in 10% HCl (4 ml) was refluxed for 7 hr at 140—150° on an oil bath. After work-up as described for the hydrolysis of IV, V (22 mg) was obtained in 75.9% yield.

Preparation of 6-Aminoquinoline-5-carbonitrile (V)——A suspension of 6-amino-5-bromoquinoline[3] (466 mg) and copper(I) cyanide (250 mg) in DMF (4 ml) was refluxed for 5 hr. After removal of the solvent under reduced pressure, the residue was dissolved in conc. NH_4OH, and the solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated. The residue was chromatographed on alumina. Elution with $CHCl_3$ gave 6-aminoquinoline-5-carbonitrile (V), which was recrystallized from $CHCl_3$ to give pale yellow prisms, mp 181°. Yield was 150 mg (44%). *Anal.* Calcd for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.71; H, 4.01; N, 24.67. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3470, 3398, 3350 (NH_2), 2201 (CN). PMR (in $CDCl_3$) δ: 5.02 (2H, br.s, $-NH_2$), 7.12 (1H, d, $J_{7,8}=9$ Hz, C_7–H), 7.42 (1H, d.d, $J_{2,3}=4.5$, $J_{3,4}=9$ Hz, C_3–H), 8.01 (1H, d, $J_{7,8}=9$ Hz, C_8–H), 8.20 (1H, d.d, $J_{2,4}=1$, $J_{3,4}=9$ Hz, C_4–H), 8.69 (1H, d.d, $J_{2,3}=4.5$, $J_{2,4}=1$ Hz, C_2–H).

Preparation of II (a—d) from V——A solution of V (1 mmol) and ethoxalyl, methoxalyl, *p*-nitrobenzoyl, or phenyloxalyl chloride (1.5 mmol) in pyridine (3 ml) was kept at room temperature overnight. The reactants were poured into ice water (10—20 ml), and the deposited crystals were collected, washed with water, dried and recrystallized from an appropriate solvent (Table III). Yields were 91.5, 98.0, 97.5 and 88.5%, respectively.

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