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Syntheses of Nitrogen-containing Heterocyclic Compounds. XXV.[1] Chemical Reactivity of 4,6-Phenanthroline. (1)

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4,6-Phenanthroline 6-oxide (II), 4-oxide (IV), and 4,6-dioxide (III) were synthesized from 4,6-phenanthroline by various methods. The reaction of II, III, and IV with phosphoryl chloride gave some chlorinated compounds (V to IX), and the reaction of II with acetic anhydride gave 4,6-phenanthrolin-5(6*H*)-one (X) and 6-(5′-4′,6′-phenanthrolinyl)-4,6-phenanthrolin-5(6*H*)-one (XI). These results were compared with the same reaction of 1,6-phenanthroline.

As a part of studies on nitrogen-containing heterocyclic compounds, we have synthesized various heterocycles by the development of an improved one-step synthesis.[3] Chemical reactivity of one of these compounds, 4,6-phenanthroline, has not been elucidated fully beyond its amination[3c] and iodomethylation.[3c] In the present series of work, the monoxide and dioxide of 4,6-phenanthroline were synthesized, their Meisenheimer reaction, and reaction with acetic anhydride of the synthesized 4-oxide were carried out, and their reactivity was compared with that of 1,6-phenanthroline N-oxides.[4]

Synthesis of 4,6-Phenanthroline N-Oxide

A mixture of 4,6-phenanthroline[3c] (I) and *m*-chloroperbenzoic acid in chloroform was heated at 60—70° for 1 hr and a compound (II), mp 162—164°, $C_{12}H_8ON_2$, *m/e* 196 (M^+) and 180 (M^+-O), IR ν_{max}^{KBr} 1180 cm^{-1} (N–O), and a compound (III), mp 284—286°, $C_{12}H_8O_2N_2$, *m/e* 212 (M^+), 196 (M^+-O), and 180 ($M^+-2\,O$), IR ν_{max}^{KBr} 1277 and 1230 cm^{-1} (N–O), were obtained in respective yield of 57.2% and 21.4%. On the other hand, 4,6-phenanthroline 6-oxide (II′) was obtained in 27% yield by the application of ferrous sulfate and boric acid with glycerol to 3-aminoquinoline 1-oxide,[5] in the presence of Sulfo-mix.[6] Mixed fusion of II′ with II obtained by the oxidation of I showed no depression of the melting point and their infrared (IR) spectra were identical. Therefore, II was identified as 4,6-phenanthroline 6-oxide. 4,6-phenanthroline 4-oxide was not obtained by the oxidation of I with *m*-chloroperbenzoic acid. Heating of I with hydrogen peroxide and sodium tungstate at 50° for 15 hr gave a compound (III′) of mp 284—286°, $C_{12}H_8O_4N_2$, in 83.3% yield. Mixed fusion of this III′ with III obtained by oxidation of I with *m*-chloroperbenzoic acid showed no depression of the melting point and their spectra were identical. The nuclear magnetic resonance (NMR) spectrum of III indicated it to be 4,6-phenanthroline 4,6-dioxide.

These experimental results suggested that direct synthesis of 4,6-phenanthroline 4-oxide would be difficult and, therefore, partial reduction of III with Raney nickel was carried out

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[1] Part XXIV: Y. Hamada, T. Ito, and M. Hirota, *Yakugaku Zasshi*, **96**, 1265 (1976).

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[3] *a*) Y. Hamada, I. Takeuchi, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **19**, 1751 (1971); *b*) Y. Hamada and I. Takeuchi, *ibid.*, **19**, 1857 (1971); *c*) Y. Hamada, I. Takeuchi, and M. Hirota, *ibid.*, **22**, 485 (1974); *d*) Y. Hamada, I. Takeuchi, and M. Sato, *Yakugaku Zasshi*, **94**, 1328 (1974); *e*) Y. Hamada, M. Sato, and I. Takeuchi, *ibid.*, **95**, 1492 (1975).

[4] Y. Kobayashi, I. Kumadaki, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **17**, 1511 (1969).

[5] E. Ochiai and C. Kaneko, *Yakugaku Zasshi*, **78**, 584 (1958).

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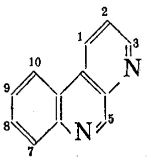
but 4,6-phenanthroline 4-oxide was not obtained and a mixture of I and II in 1:1 ratio was obtained. After due consideration, III was heated with carbon disulfide in N,N-dimethylformamide at 90° for 2 hr and (IV) was obtained in 97% yield. The identity of IV with 4,6-phenanthroline 4-oxide was made through mass, IR, and NMR spectral analyses, and from the Meisenheimer reaction to be described later. In this reduction, use of solvents other than N,N-dimethylformamide did not give a good yield. Application of this partial reduction of III to IV for other compounds is now being examined.

Meisenheimer Reaction

It has been reported that the application of phosphoryl chloride to the N-oxides of pyridine, quinoline, naphthyridine, and 1,6-phenanthroline results in deoxygenation and chlorination of the position α or γ to the N-oxide function.[4,8] Therefore, for the structural identification of N-oxides and examination of their reactivity, II was reacted with phosphoryl chloride, as shown in Chart 2, and a product (V) of mp 113—115° was obtained in 85.7% yield. Its molecular formula corresponded to $C_{12}H_7N_2Cl$, with m/e 214 (M^+) and 179 (M^+-Cl). There was no depression of the melting point by fusion of this V with the product obtained by chlorination of 4,6-phenanthrolin-5(6*H*)-one[3c] with phosphoryl chloride, which will be described later. Therefore, V was identified as 5-chloro-4,6-phenanthroline.

Reaction of IV with phosphoryl chloride gave three products (VI, VII, and VIII), which had a common molecular formula of $C_{12}H_7N_2Cl$, with m/e 214 (M^+) and 179 (M^+-Cl), indicating that they are compounds formed by deoxygenation and chlorination of the pyridine ring. From the NMR spectral data given in Table I, these compounds were identified as 3-chloro (VI), 2-chloro VII), and 1-chloro (VIII) derivatives of 4,6-phenanthroline. Their yield ratio was 61:2.3:6.8. VIII was identified with 1-chloro-4,6-phenanthroline synthesized by the method given in the literature[9] through mixed fusion and IR spectral comparison.

Table I. NMR Spectral Data[a] of N-oxide (II—IV) and Chloro Compound (V—IX) in $CDCl_3$

Compound No.	Chemical shift (δ)								Coupling constants (Hz)		
	1H	2H	3H	5H	8H	9H	7H	10H	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
	8.82	7.70	9.00	9.48	7.74	7.74	8.22	8.44	8.4	2.0	4.4
II	8.64	7.52	8.86	8.93	7.76	7.76	8.78[b]	8.42	8.8	1.2	4.8
III	8.32	7.53	8.57	9.72	7.97	7.97	8.93[b]	8.57	8.8	1.2	6.4
IV	8.35	7.61	8.53	10.10[b]	7.78	7.78	8.26	8.46	8.8	1.2	6.4
V	8.80	7.66	9.08	—	7.76	7.76	8.03	8.37	8.8	1.8	4.2
VI	8.63	7.58	—	9.27	7.70	7.70	8.12	8.28	8.8	—	—
VII	8.80	—	8.93	9.45	7.77	7.77	8.23	8.42	—	2.0	—
VIII[9]	—	7.76	8.84	9.46	7.76	7.76	8.25	9.62[c]	—	—	4.8
IX	8.74	7.74	—	—	7.74	7.74	8.05	8.34	8.8	—	—

a) JEOL-PS-100 (100 MHz) High Resolution Spectrometer
b) the anisotropic effect of the N-O group[10]
c) the anisotropic effect of the Cl group

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8) *a*) B. Bobranski, *Chem. Ber.*, **71**, 578 (1938); *b*) W.W. Paudler and D.J. Pokorny, *J. Org. Chem.*, **36**, 1720 (1971); *c*) D.J. Pokorny and W.W. Paudler, *J. Org. Chem.*, **37**, 3101 (1972).

9) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **32**, 2616 (1967).

10) K. Tori, M. Ogata, and H. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **11**, 681 (1963).

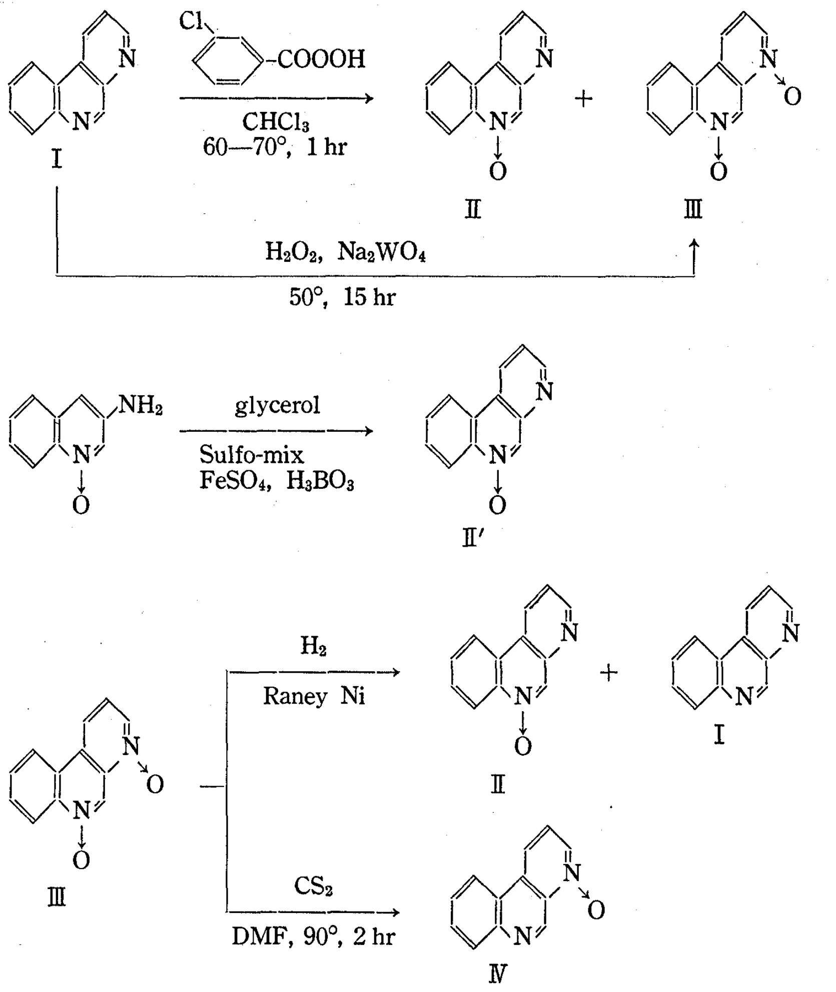

Chart 1

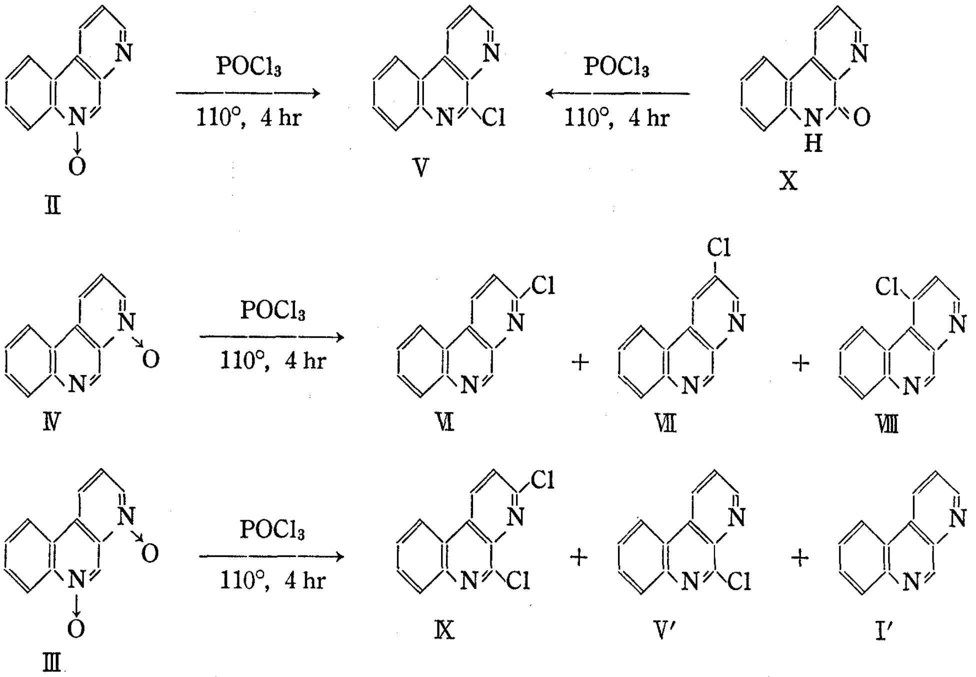

Chart 2

Reaction of III with phosphoryl chloride also gave three products; IX, mp 186—187°, $C_{12}H_6N_2Cl_2$, *m/e* 248 (M^+), 213 ($M^+—Cl$), and 178 ($M^+—2Cl$), in 30% yield: V, mp 113—115°, $C_{12}H_6N_2Cl$, *m/e* 214 (M^+) and 179 ($M^+—Cl$), in 18% yield; and a small amount of I′, mp 112—114°, $C_{12}H_8N_2$, *m/e* 180 (M^+). V′ and I′ were respectively identified with V and I through mixed fusion and IR spectral comparison. IX was identified with 2,5-dichloro-4,6-phenanthroline from NMR spectral data shown in Table I. This result further confirms that III is a dioxide. The fact that I was obtained, though in a small amount, indicates that both oxide functions were deoxygenated, and this phenomenon is rather interesting since such a reaction has not been witnessed with 1,6-phenanthroline 1,6-dioxide and other N-oxides.

Reaction with Acetic Anhydride

It is known that reaction of quinoline 1-oxide and various other N-oxides with acetic anhydride results in the introduction of an acetoxyl group into the position α to the N-oxide and this group easily undergoes hydrolysis and is converted to a hydroxyl group.[4,11] Refluxing of II with acetic anhydride for 1 hr gave a 5-oxo compound (X) in 71.4% yield, while prolongation of this refluxing for 3 hr gave X and a structurally unknown compound (XI) in 1: 3 ratio. Further refluxing of the mixture for 5 hr gave only XI in 21.2% yield. From its elemental analysis and mass spectrum, XI, mp above 300°, was given a molecular formula of $C_{24}H_{14}ON_4$, with *m/e* 374 (M^+), IR $\nu_{\max}^{\mathrm{KBr}}$ 1660 cm^{-1} (NH–CO), and was considered to have

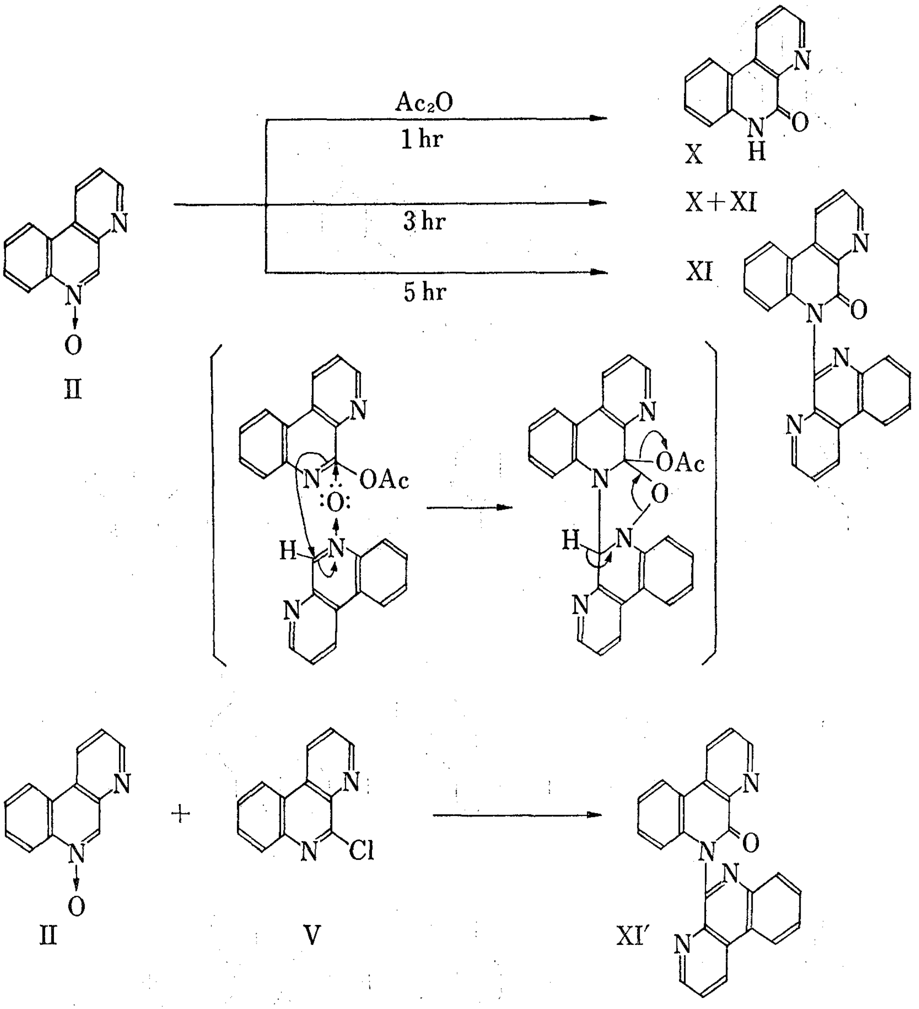

Chart 3

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11) *a*) K. Katada, *Yakugaku Zasshi*, **67**, 15 (1947); *b*) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 1045 (1969).

been formed by condensation of 2 molecules. Therefore, X was chlorinated with phosphoryl chloride to V and this was fused with II, and its product (XI′) was found to be identical with XI by mixed fusion and IR spectral comparison. Therefore, XI was identified as 6-(5′-4′,6′-phenanthrolinyl)-4,6-phenanthrolin-5(6*H*)-one. As for the formation of XI, it was surmised that the oxygen atom of the 6-oxide made a nucleophilic attack on the intermediate acetoxyl compound, as shown in Chart 3. A reaction like this, with the formation of XI, has not been experienced with 1,6-phenanthroline N-oxide. It is interesting that there is a difference in the reactivity of diazaphenanthrene N-oxides according to the position of the ring nitrogen, and further examinations will be undertaken in this kind of compounds.

Experimental

Oxidation of 4,6-Phenanthroline (I) with *m*-Chloroperbenzoic Acid——To a solution of 90 ml of $CHCl_3$, 1.2 g of I and 1.5 g of *m*-chloroperbenzoic acid were dissolved and this mixture was heated at 60—70° for 1 hr. The reaction miuture was cooled, $CHCl_3$ was added, and the $CHCl_3$ solution was extracted with saturated aqueous solution of $NaHCO_3$. The resulting aqueous solution was continuously extracted with $CHCl_3$. Combined $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed over silica gel. The column was eluted with benzene–$CHCl_3$ (7: 3) and the first effluent fraction was recrystallized from benzene to give 0.75 g (57.2%) of II as white prisms, mp 162—164°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1180 (N–O). Mass Spectrum *m/e*: 196 (M^+), 180 (M^+–O). *Anal.* Calcd. for $C_{12}H_8ON_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.56; H, 3.88; N, 14.14. II was identified with 4,6-phenanthroline 6-oxide (II′), synthesized by the Skraup reaction of 3-aminoquinoline 1-oxide, by mixed mp and by the comparison of IR spectra. The second effluent fraction with $CHCl_3$ was recrystallized from $CHCl_3$–MeOH (7: 3) to give 0.3 g (21.4%) of III as yellow needles, mp 284—286°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1277, 1230 (N–O). Mass Spectrum *m/e*: 212 (M^+), 196 (M^+-O), 180 (M^+-2O). *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.27; H, 3.60; N, 13.12.

4,6-Phenanthroline 6-Oxide (II′)——A mixture of 30 g of Sulfo-mix[6] (prepared from 27 g of $H_2SO_4\cdot SO_3$ (20%) and 3 g of nitrobenzene), 1.4 g of $FeSO_4\cdot 7H_2O$, and 2.4 g of H_3BO_3 was chilled to 0—5°, 5 ml of anhyd. glycerol was added, followed by 1.5 g (0.093 mole) of 3-aminoquinoline 1-oxide and 8 ml of warmed water (50°), and the mixture was stirred at 135° for 4 hr. The reaction mixture was neutralized with NH_3 water and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed over silica gel. The column was eluted with benzene–$CHCl_3$ (7: 3) and the effluent fraction was recrystallized from benzene to give 0.5 g (27%) of II′ as white prisms, mp 162—164°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1180 (N–O). Mass Spectrum *m/e*: 196 (M^+), 180 (M^+–O). *Anal.* Calcd. for $C_{12}H_8ON_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.64; H, 3.94; N, 14.22. II′ was identified with II, obtained by oxidation of 4,6-phenanthroline with *m*-chloroperbenzoic acid, by mixed mp and by the comparison of IR spectra.

4,6-Phenanthroline 4,6-Dioxide (III′)——A solution containing 1 g of 4,6-phenanthroline, 0.3 g of $Na_2WO_4\cdot 2H_2O$, and 8 ml of 30% H_2O_2 was stirred and heated at 50° for 15 hr. After the reaction was completed, the precipitated solid was collected by filtration and washed with H_2O. The precipitate was dried and recrystallized from $CHCl_3$–MeOH (7: 3) to give 0.97 g (83.3%) of III′ as yellow needles, mp 284—286°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1277, 1230 (N–O). Mass Spectrum *m/e*: 212 (M^+), 196 (M^+-2O). *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.14; H, 3.66; N, 13.10. III′ was identified with III, obtained by oxidation of 4,6-phenanthroline with *m*-chloroperbenzoic acid, by mixed mp and by the comparison of IR spectra.

Catalytic Reduction of III with Raney Ni——A solution of 0.88 g (4.1 mmoles) of III in 400 ml of MeOH was viogorously stirred with 0.9 g of Raney Ni in H_2 atomosphere. After 160 ml (7.14 mmoles) of H_2 was absorbed, Raney Ni was filtered off, the solvent was evaporated, and the residue was chromatographed over silica gel. The first effluent fraction with benzene gave 0.34 g (45%) of I, the second effluent fraction with benzene–$CHCl_3$ (7: 3) gave 0.3 g (36.8%) of II, and the third effluent fraction with $CHCl_3$ 0.07 g of recovered III.

Preparation of 4,6-Phenanthroline 4-Oxide (IV) from III——A mixture of 100 mg (0.47 mmole) of III, 2 ml of N,N-dimethylformamide, and 53.2 mg (0.7 mmole) of CS_2 was heated at 90° for 2 hr. The reaction mixture was cooled and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from benzene to give 90 mg (97.3%) of IV as white needles, mp 212—212.5°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1230 (N–O). Mass Spectrum *m/e*: 196 (M^+), 180 (M^+-O). *Anal.* Calcd. for $C_{12}H_8ON_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.29; H, 3.93; N, 14.09.

Meisenheimer Reaction of II—II (200 mg, 1 mmole) was added in portions to 2 ml of well-stirred, ice-cold, freshly distilled $POCl_3$. After being stirred for 5 min, the mixture was refluxed for 4 hr. The excess $POCl_3$ was removed *in vacuo*, the residue was neutralized with 20 g of ice and 10% NaOH, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed over silica gel, and the column was eluted with $CHCl_3$. The effluent fraction was recrystallized from benzene-cyclohexane (1: 1) to give 150 mg (85.7%) of V as colorless needles, mp 113—115°. Mass

Spectrum *m/e*: 214 (M^+), 179 (M^+-Cl). *Anal.* Calcd. for $C_{12}H_7N_2Cl$: C, 67.14; H, 3.30; N, 13.05. Found: C, 67.24; H, 3.52; N, 13.14. V was identified with 5-chloro-4,6-phenanthroline (V′), synthesized by chlorination of 4,6-phenanthrolin-5(6*H*)-one[3c] (X) with $POCl_3$, by mixed mp and by comparison of IR and NMR spectra.

Meisenheimer Reaction of IV——IV (200 mg, 1 mmole) was added in portions to 3 ml of well-stirred, ice-cold, freshly distilled $POCl_3$. After being stirred for 5 min, the mixture was refluxed for 4 hr. The reaction mixture was treated as in the same way as in the case of II. The residue was chromatographed over silica gel and the column was eluted with $CHCl_3$. The first effluent fraction was recrystallized from benzene-cyclohexane (1: 1) to give 135 mg (61.7%) of VI as colorless plates, mp 154—155°. Mass Spectrum *m/e*: 214 (M^+), 179 (M^+-Cl). *Anal.* Calcd. for $C_{12}H_7N_2Cl$: C, 67.14; H, 3.30; N, 13.05. Found: C, 67.32; H, 3.20; N, 13.18. The second effluent fraction was recrystallized from benzene cyclohexane (1: 1) to give 5 mg (2.3%) of VII as colorless needles, mp 175—178°. Mass Spectrum *m/e*: 214 (M^+), 179 (M^+-Cl). *Anal.* Calcd. for $C_{12}H_7N_2Cl$: C, 67.14; H, 3.30; N, 13.05. Found: C, 67.02; H, 3.16; N, 13.22. The third effluent fraction was recrystallized from benzene-cyclohexane (1: 1) to give 15 mg (6.8%) of VIII as white needles, mp 115—117°. VIII was identified with 1-chloro-4,6-phenanthroline,[9] synthesized by the method repotred in the literature, by mixed mp and by the comparison of IR spectra. The structure of VI and VII were presumed to be 3- and 2-chloro-4,6-phenanthroline from their NMR spectra.

Meisenheimer Reaction of III——III (400 mg, 2 mmoles) was added in portions to 4 ml of well-stirred, ice-cold, freshly distilled $POCl_3$. After being stirred for 5 min, the mixture was refluxed for 4 hr. The reaction mixture was treated as for II. The residue was chromatographed over silica gel. The first effluent fraction with benzene gave 140 mg (30%) of IX as white needles, mp 186—187°. Mass Spectrum *m/e*: 248 (M^+), 213 (M^+-Cl), 178 (M^+-2Cl). *Anal.* Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.88; H, 2.43; N, 11.25. Found: C, 58.11; H, 2.14; N, 11.27. The structure of IX was presumed to be 3,5-dichloro-4,6-phenanthroline from its NMR spectra. The second effluent fraction with benzene–$CHCl_3$ (9: 1) gave 70 mg (18%) of V, and the third effluent fraction with benzene–$CHCl_3$ (4: 1) gave a trace of I.

Reaction of II with Ac_2O——Method (a): A solution of 70 mg (0.35 mmole) of II in 1.5 ml of Ac_2O was refluxed for 1 hr. After evaporation of Ac_2O *in vacuo*, the residue was treated with H_2O, neutralized with 10% NaOH, and extracted with CH_2Cl_2. After being dried over Na_2SO_4, the solvent was evaporated, and the residue was recrystallized from EtOH to give 50 mg (71.4%) of X as white needles, mp 312—313°. IR ν_{max}^{KBr} cm^{-1}: 1665 (NH–CO). X was identified with 4,6-phenanthrolin-5(6*H*)-one, synthesized by the method reported in the literature,[3c] by mixed mp and by comparison of IR and NMR spectra.

Method (b): A solution of 70 mg (0.35 mmole) of II in 1.5 ml of Ac_2O was refluxed for 3 hr. The reaction mixture was treated as in method (a). The residue was chromatographed over silica gel and the column was eluted with $CHCl_3$–acetone (9: 1). The first effluent fraction was recrystallized from $CHCl_3$ to give 15 mg (11.1%) of XI as white needles, mp 300°. IR ν_{max}^{KBr} cm^{-1}: 1660 (N–CO). Mass Spectrum *m/e*: 379 (M^+). *Anal.* Calcd. for $C_{24}H_{14}ON_4$: C, 76.99; H, 3.77; N, 14.97. Found: C, 76.78; H, 3.44; N, 14.86. XI was identified with XI′, obtained by condensation of IV and V, by mixed mp and by comparison of IR spectra. The second effluent fraction with $CHCl_3$–acetone (4: 1) gave 5 mg (3.4%) of X as white needles, mp 312—313°.

6-(5′-4′,6′-Phenanthrolinyl)-4,6-phenanthrolin-5(6*H*)-one (XI′)——A mixture of 100 mg (0.5 mmole) of II and 160 mg (0.765 mmole) of V was heated at 125° for 5 hr. The reaction mixture was cooled, the residue was chromatographed over silica gel, and the column was eluted with $CHCl_3$–acetone (7: 3). The effluent fraction was recrystallized from $CHCl_3$ to give 110 mg (57.9%) of XI′ as white needles, mp >300°. IR ν_{max}^{KBr} cm^{-1}: 1660 (N–CO). Mass Spectrum *m/e*: 374 (M^+). *Anal.* Calcd. for $C_{24}H_{14}ON_4$: C, 76.99; H, 3.77; N, 14.97. Found: C, 76.81; H, 3.54; N, 14.73.

Chlorination of X with $POCl_3$——To 2 ml of well-stirred, ice-cold, freshly distilled $POCl_3$, 200 mg of X was added in portions after being stirred for 5 min, the mixture was refluxed for 4 hr. The reaction mixture was treated as in the Meisenheimer reaction of II. The residue was chromatographed over silica gel, and the column was eluted with $CHCl_3$. The effluent fraction was recrystallized from benzene-cyclohexane (1: 1) to give 200 mg (95.2%) of V′ as colorless needles, mp 113—115°. Mass Spectrum *m/e*: 214 (M^+), 179 (M^+-Cl).

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