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Synthesis of Nitrogen-containing Heterocyclic Compounds. XX.[1] Improvement of One-step Synthesis of Phenanthrolines and Some Reactions of 4,6-Phenanthroline

Yoshiki Hamada, Isao Takeuchi,[2a] and Minoru Hirota[2b]

Faculty of Pharmacy, Meijo University,[2a] and Faculty of Engineering, Yokohama National University[2b]

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1,9-Diazaanthracene (IV), 4-methyl-1,9-diazaanthracene (V), 4,6-phenanthroline (I), 1,6-phenanthroline (III), and 5-methyl-1,6-phenanthroline (II) were synthesized by the reaction of 2-, 3-, or 4-aminoquinolines with glycerol or methyl vinyl ketone, in the presence of sulfo-mix, ferrous sulfate, and boric acid. Methylation of I with methyl iodide afforded the monomethiodide (VI) in which methyl iodide was proved to have reacted with the nitrogen in 6-position. Chichibabin amination of I afforded 5-amino-4,6-phenanthroline (VIII) and this amination was examined by comparison of reaction indices by the Hückel molecular orbital method.

We became interested in the difference in chemical properties of naphthyridines according to the position of the nitrogen atom from the different products obtained by the N-oxidation of 1,5- and 1,6-naphthyridines,[3] and difference in the reactivity of naphthyridines to methylation of 1,5-, 1,6-, and 1,8-naphthyridines with dimethyl sulfoxide.[4] We have also reported the improved syntheses of 1,5-, 1,6-, and 1,8-naphthyridine and phenanthrolines from aminopyridines and aminoquinolines with glycerol in the presence of sodium *m*-nitrobenzenesulfonate and a catalyst.[5]

In order to examine the applicable limit of the improved method[5] with the use of the sulfo-mix[6] and a catalyst, the Skraup reaction of 2-, 3-, and 4-aminoquinolines was carried out in the present series of work. In order, also, to examine the reactivity of phenanthrolines according to the position of nitrogen atom in the ring, methylation of 4,6-phenanthroline (I) with methyl iodide, and its Chichibabin amination were carried out. Comparative examination was made on the reactivity index in the Chichibabin amination of I by Hückel's molecular orbital (HMO) method.

Reaction of 3-aminoquinoline and 4-aminoquinaldine with glycerol, in the presence of sulfo-mix, ferrous sulfate, and boric acid afforded I and 5-methyl-1,6-phenanthroline (II),

1) Part XIX: Y. Hamada, Y. Ito, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **20**, 2678 (1972).
2) Location: *a) Yagoto-Urayama, Tempaku-cho, Showa-ku, Nagoya, 468, Japan; b) Ooka, Minamiku, Yokohama, 233, Japan.*
3) T. Takahashi, Y. Hamada, I. Takeuchi, and H. Matuoka, *Yakugaku Zasshi*, **89**, 1260 (1969).
4) Y. Hamada, I. Takeuchi, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **19**, 1751 (1971).
5) Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1857 (1971).
6) W.P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

respectively, in better yield than previously.[5] In a similar manner, 1,6-phenanthroline (III) was obtained in a good yield from 4-aminoquinoline by the sole use of sulfo-mix.[7]

There is as yet no report on the successful Skraup reaction of 2-aminoquinoline and the parent skeleton of 1,9-diazaanthracene, thought to be formed by this reaction, has been synthesized. Therefore, the reaction of 2-aminoquinoline with glycerol, in the presence of sulfo-mix, ferrous sulfate, and boric acid, was carried out and a compound (IV), $C_{12}H_8N_2$, *m/e* 180 (M^+), was obtained. The compound (IV) was found to be 1,9-diazaanthracene from its nuclear magnetic resonance (NMR) spectrum. Further, its ultraviolet (UV) spectrum was similar to linear acridines than angular I and III, and the assignment of IV to 1,9-diazaanthracene was confirmed. The UV spectrum of (V) was also similar to that of IV. These results are shown in Chart 1, Table I, and Fig. 1.

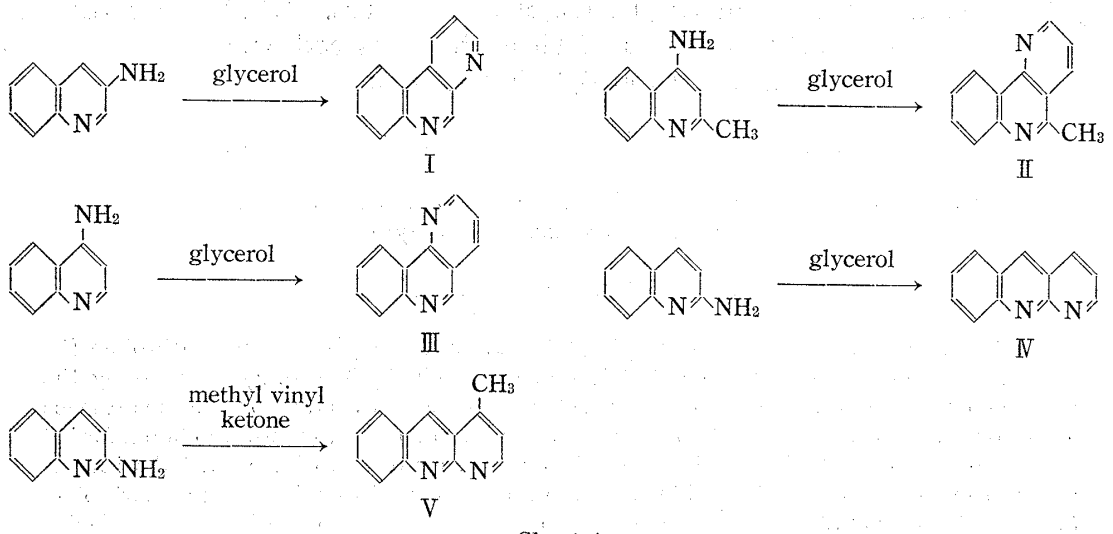


Chart 1

TABLE I

Compound No.	Raw Material	Reagent	Oxidizing agent	Catalyst	Temp. (°C)	Time (hr)	Yield (%)	Yield lit[a] (%)
I	3-aminoquinoline	glycerol	sulfo-mix	$FeSO_4$, H_3BO_3	130	5	60	(50)[5]
II	4-aminoquinaldine	glycerol	sulfo-mix	$FeSO_4$, H_3BO_3	130	5	70	(35)[5]
III	4-aminoquinoline	glycerol	sulfo-mix	$FeSO_4$, H_3BO_3	130	5	73	(50)[7]
IV	2-aminoquinoline	glycerol	sulfo-mix	$FeSO_4$, H_3BO_3	130	5	25	
V	2-aminoquinoline	M.V.K.[b]	sulfo-mix	$FeSO_4$, H_3BO_3	130	5	trace	

Compound No.	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I	112—114	white cottony needles	$C_{12}H_8N_2$	79.98	4.48	15.55	79.84	4.63	15.65
II	110—112	pale yellow cottony needles	$C_{13}H_{10}N_2$	80.38	5.19	14.42	80.32	5.22	14.60
III	95—96	colorless needles	$C_{12}H_8N_2$	79.98	4.48	15.55	79.82	4.45	15.49
IV	190—192	pale yellow needles	$C_{12}H_8N_2$	79.98	4.48	15.55	80.01	4.22	15.79
V	128—129	white cottony needles	$C_{13}H_{10}N_2$	80.38	5.19	14.42	80.44	5.23	14.27

a) literature
b) methyl vinyl ketone

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

The compound (I) has different nitrogen atoms in 4- and 6-positions and it seemed of interest to see which of these nitrogens showed reactivity to reagents, and methylation of I with methyl iodide and the Chichibabin amination were attempted. Past reports on the reaction of phenanthrolines with methyl iodide indicated that the nitrogen in 1-position of 1,10-phenanthroline and that in 7-position of 1,7-phenanthroline reacted to form a monomethiodide, while the nitrogen atom in both 4- and 7-positions of 4,7-phenanthroline reacted to form a dimethiodide.[8] Reaction of I with methyl iodide gave a compound (VI) whose elemental analytical values corresponded to the molecular formula, $C_{13}H_{11}N_2I$, for a monomethiodide. Oxidation of VI with potassium ferricyanide and sodium hydroxide produced a compound (VII), *m/e* 210 (M^+), with a carbonyl band in its infrared (IR) spectrum. Comparison of its NMR spectrum with that of I showed the disappearance of a signal for 5-H, indicating that methyl iodide had reacted with nitrogen in the 6-position. Consequently, VI would be 4,6-phenanthroline 6-methiodide and VII, 6-methyl-4,6-phenanthrolin-5-one.

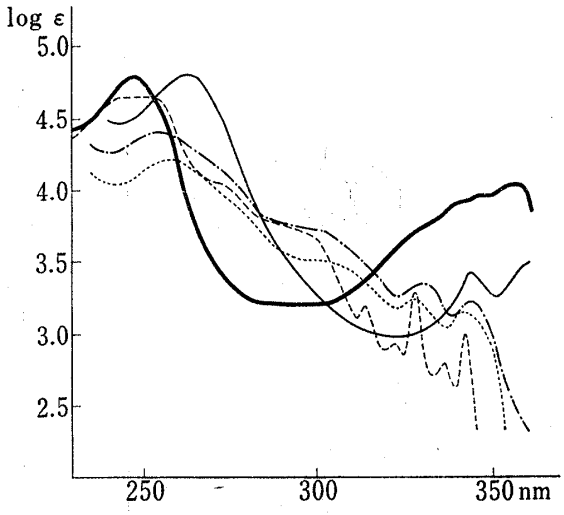
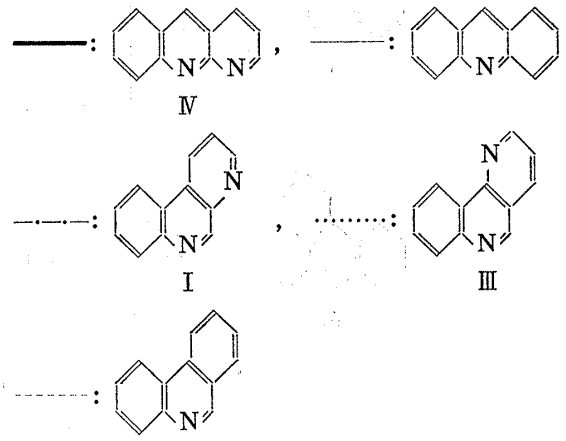


Fig. 1. Ultraviolet Absorption Spectra in EtOH



As for the Chichibabin amination of phenanthrolines, amination of the parent ring has not been known to date. Therefore, examinations were made on whether the amino group would react with the position next to the nitrogen atom in 4- or 6-position. The compound (I) was reacted with potassium amide in liquid ammonia and a monoamino compound (VIII) of mp 229—230°, $C_{12}H_9N_3$, *m/e* 195 (M^+), and a compound (IX) of mp 312—313°, $C_{12}H_8ON_2$, *m/e* 196 (M^+), were obtained. The NMR spectrum of VIII no longer showed the singlet signal for 5-H present in I and the signal for deuterated amino group appeared at 7.18 δ, indicating that the amino group reacted at the 5-position, next to the nitrogen in 6-position. Consequently, VIII would be 5-amino-4,6-phenantroline.

The IR spectrum of IX showed a carbonyl absorption at 1665 cm^{-1}, and its NMR spectrum had a signal for deuterated NH at 11.87 δ, with disappearance of the signal for 5-H present in I, suggesting that IX might be 4,6-phenanthrolin-5(6H)-one. 4,6-Phenanthrolin-5(6H)-one was synthesized by diazotization of VIII with sodium nitrite in sulfuric acid and admixture of this compound with IX indicated no depression of the melting point. The IR spectra of IX and the synthesized compound were in good agreement. Since the Chichibabin amination of I resulted in the formation of a carboxide (IX) as a by-product, conditions of this amination were examined by varying the molar quantity of potassium amide to 1.2, 2.3, 4.6, and 6.1 moles. Details of this result are given in Chart 2 and Table II.

8) *a*) B.E. Halcrow and W.O. Kermack, *J. Chem. Soc.*, **1946**, 155; *b*) A. Kaufmann and R. Radosevic, *Chem. Ber.*, **42**, 2612 (1909); *c*) P. Karr, A. Pletsher, and W. Manz, *Helv. Chim. Acta*, **30**, 1146 (1947); *d*) *Idem*, *ibid.*, **31**, 1431 (1948); *e*) Skraup and Vortmann, *Monatsh.*, **4**, 570 (1883).

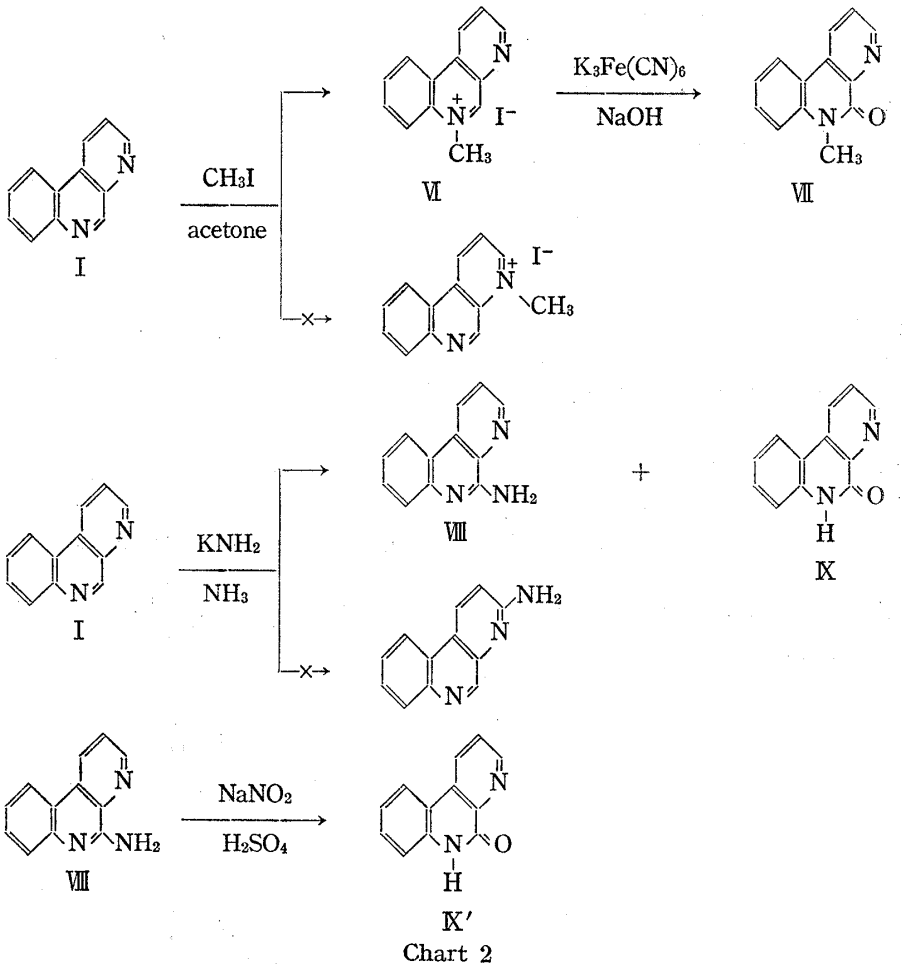


Chart 2

TABLE II

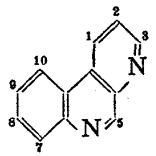
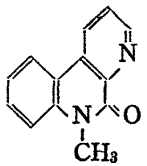
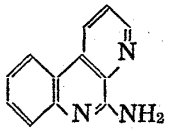
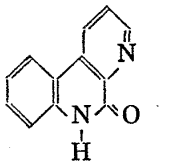
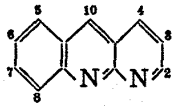
Conditions No.	Raw material I (g)	Solvent liquid NH_3 (ml)	K g (mole)	KNO_3 (g)	Catalyst $FeCl_3$ (g)	Temp. (°C)	Time (days)	Product g (%) Ⅷ	IX	Recovery I
1[a]	1.0	17	0.7 (3.2)	0.76	0.7	50—70	18 hr	0.1 (9.2)	—	0.8 (80)
2	1.51	25	0.42 (1.2)	1.14	1.05	20	8	0.03 (1.8)	—	1.0 (66.2)
3	1.51	25	1.05 (3.2)	1.14	1.05	20	8	0.1 (6.1)	0.1 (6.1)	0.8 (53)
4	1.51	25	1.5 (4.6)	1.14	1.05	20	10	0.73 (44.5)	0.3 (18.3)	0.15 (9.9)
5[b]	1.51	25	2.0 (6.1)	1.14	1.05	20	8	0.65 (39.6)	0.61 (37.2)	—

Compound No.	mp (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (NH_2)	(C=O)
Ⅷ	229—230	colorless plates	$C_{12}H_9N_3$	73.83	4.65	21.55	73.97	4.33	21.42	3250, 3420[s]	
IX	312—313	white needles	$C_{12}H_8ON_2$	73.46	4.11	14.28	73.43	3.76	14.05		1665
IX′	312—313	white needles	$C_{12}H_8ON_2$	73.46	4.11	14.28	73.06	3.91	13.81		1663

a) condition of quinoline amination[9]
b) condition of naphthyridine amination[c]
c) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **33**, 1384 (1968).

9) F.W. Bergstrom, *J. Org. Chem.*, 2, 411 (1937).

TABLE III. NMR Spectral Data

Compound		Solvent	Chemical shift (δ)												Coupling constants (cps)				
			1H	2H	3H	4H	5H	6H	8H	9H	7H	10H	N-C<u>H</u>$_3$	N<u>H</u>$_2$	N<u>H</u>	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$
	I	$CDCl_3$[10]	8.77	7.67	8.98	—	9.50	—	8.28	8.28	7.73	7.73				8.2	1.5	4.5		
		DMSO-d_6	9.27	7.97	9.15	—	9.48	—	7.91	7.91	(8.83 or 8.24)					8.3	1.6	4.5		
		CF_3COOH	10.03	8.82	9.74	—	10.53	—	8.55	8.55	(8.55 or 9.22)					8.5	0.8	5.0		
	VII	$CDCl_3$	8.52	7.62	8.93	—	—	—	7.40	7.40	(8.13 or 7.28)		3.79			8.3	1.5	4.5		
	VIII	DMSO-d_6	9.08	7.90	8.95				7.63	7.63	(8.48 or 7.36)			7.18		7.8	1.5	4.5		
	IX	DMSO-d_6[a] CF_3COOH	9.78	8.65	9.27				7.85	7.85	(8.60 or 7.85)				11.87	8.5	1.5	5.5		
	IV	$CDCl_3$	—	9.22	7.37	8.33	(		multiplet			) 8.72						4.3	2.4	8.8

a) Assign is difficult.

It is seen from Table II that yield of VIII is the greatest when 4.6 moles of potassium amide is used and the yield decreases with excess of the reagent, with increase in the formation of IX. When the reaction temperature was brought to the condition of amination of quinolines[9] by heating at 50—70°, yield of the VIII was only 9.2%. In the present series of work, only the reactivity of I to amination was examined, and the formation mechanism of the IX is left for future examinations. NMR spectral data of the compounds obtained are given in Table III.

Paudler and Kress[10] reported the mass spectra of phenanthrolines and stated that 2 molecules of HCN would be liberated from the angular I but only one molecule of HCN is expected to be liberated from linear benzo-1,5-naphthyridine. Based on this report, we were interested in the behavior of linear IV and its mass spectrum was measured. From M^+-HCN (20.1%) and (M^+-HCN)-HCN (12.1%) are supported by the presence of metastable ions at *m/e* 130.0 (calcd. 130.1) and *m/e* 103.8 (calcd. 103.8), it was found that there is a tendency for liberation of 2 molecules of HCN, same as in I. It is interesting that the same tendency was seen in the mass spectrum of V. Mass spectra of angular II, III, VII, VIII, and IX were also measured and their results are shown in Fig. 2 and Table IV.

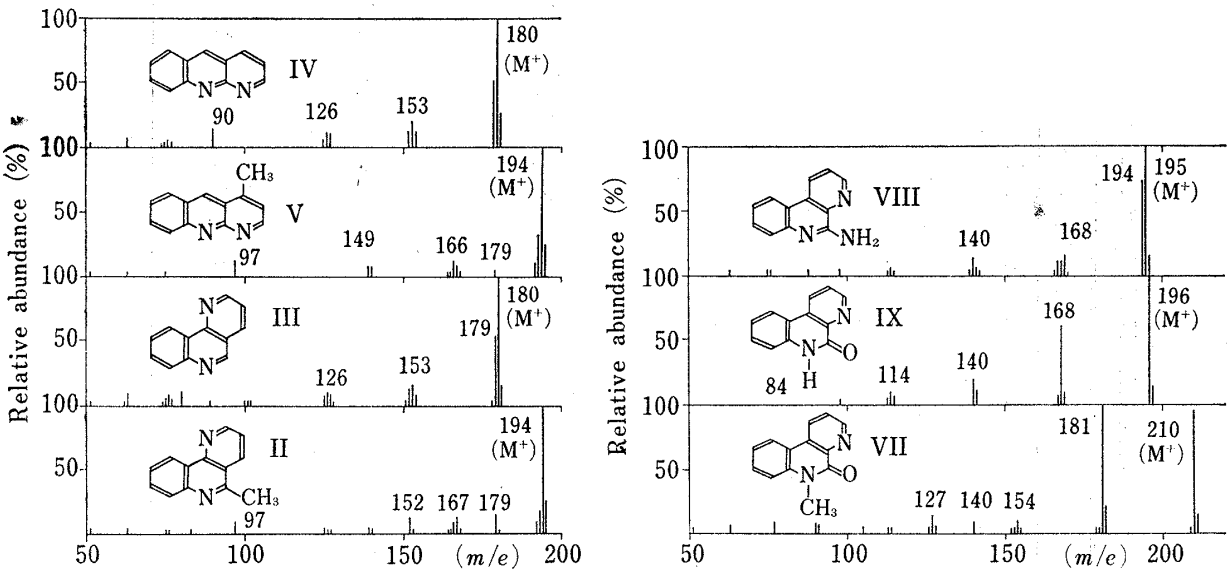


Fig. 2. Mass Spectra of IV, V, III, II, VIII IX, and VII at 70 eV

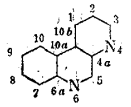
Table IV. Mass Spectral Data of Principal Fragments

Fragment	Relative abundance (%) IV	III	V	II	VIII	Fragment	Relative abundance (%) IX	VII
(M^+)	100	100	100	100	100	(M^+)	100	95.7
(M^+–H)	52.3	53.1	33.4	17.9	73.6	(M^+–CO)	59.9	22.1
(M^+–HCN)	20.1	16.7	8.4	14.7	10.6	(M^+–CO–H)		100
(M^+–2HCN)	12.1	10.9	7.5			(M^+–CO–HCN)	11.9	
(M^+–H–HCN)	12.6	8.6	11.2	9.7	11.4	(M^+–CO–H_2CN)	18.6	10.7
(M^+–H–2HCN)			9.0		12.9	(M^+–CO–2HCN)	9.7	
(M^+–CH_3)			5.4	15.9		(M^+–CO–H–2HCN)		14.9
(M^+–CH_3–HCN)			3.6	13.1				
(M^+–CH_3–2HCN)				5.1				

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

Considerations were then made on the reactivity index by the HMO method on the amination of I. Calculations were made with the Coulomb integrals proposed by Brown[11]; $\alpha = \alpha + 1.1\beta$ for nitrogen, $\alpha = \alpha + 0.4\beta$ for carbon next to nitrogen, and $\alpha = \alpha + 0.1\beta$ for carbon next but one to nitrogen. Resonance integral was taken as equal to C-C bond in the aromatic ring. Brown's parameter[11] is known to be one that reproduces comparatively well the reactivity of nitrogen-containing six-membered ring system fused to the benzene ring. Result of this calculation is given in Table V.

Table V

Compound	Position of reaction (r)	π-Electron density (q_r)	Superdelocalizability (Sr^-)[a]	Frontier electron density (fr^-)[b]
	1	0.839	3.112	0.207
	2	0.940	1.969	0.106
	3	0.924	2.825	0.153
	4(N)	1.313		
	4*a*	1.022		
	5	0.925	5.232	0.441
	6(N)	1.271		
	6*a*	1.046		
	7	0.955	1.771	0.093
	8	0.968	1.101	0.013
	9	0.953	1.685	0.086
	10	0.974	1.181	0.020
	10*a*	0.965		
	10*b*	0.904		

parameters: $\alpha_N = \alpha_C + 1.1\beta$, $\alpha_{C_\alpha} = \alpha_C + 0.4\beta$, $\alpha_C\beta = \alpha_C + 0.1\beta$
a) Sr^-: superdelocalizability for nucleophilic substitution
b) fr^-: frontier electron density for nucleophilic substitution

These data in Table V indicate, however, that the attack of the anion occurs in the position with the smallest π-electron density of the r-th atom (qr). This would mean that the reaction is most facile in 1-position of I, followed by 3- and 5-positions in that order, and this would not explain the reactivity of I. In other reactivity indices, super delocalizability of the r-th atom (Sr^-) and frontier electron density of the r-th atom (fr^-), the values were large in 5-position, suggesting larger reactivity than other positions and well agreeing with experimental result. The HMO method with consideration on reagents will be reported elsewhere. And yet, considering that π-electron density would not explain the reactivity of I, steric hindrance is supposed as other factor. It is expected that 1-position is fairly suffered from steric hindrance by the proton of the 10-position.

These experimental results have indicated that the use of Sulfo-mix with ferrous sulfate and boric acid would be advantageous for the syntheses of phenanthrolines like I, II, and III by the Skraup reaction and shows the wide applicability of Sulfo-mix. It was also found through these reactions that methylation of I with methyl iodide takes place at the nitrogen in 6-position and the Chichibabin amination at 5-position, next to the nitrogen in 6-position.

Experimental

4,6-Phenanthroline (I)——Method (a): A mixture of 58.5 g of sulfo-mix[6] (prepared from 48 g of $H_2SO_4 \cdot SO_3$ (20%), and 11 g of nitrobenzene), 1.4 g of $FeSO_4 \cdot 6H_2O$, and 2.4 g of H_3BO_3 was chilled to 0—5°, 12.5 ml of anhyd. glycerol, was added, followed by 0.04 mole of 3-aminoquinoline and 22.5 ml of warmed water (50°), and the mixture was stirred at 130° for 5 hr. The reaction mixture was neutralized with 50%

11) *a*) D.A. Brown and M.J.S. Dewar, *J. Chem. Soc.*, **1953**, 2406; *b*) R.D. Brown and R.D. Harcourt, *J. Chem. Soc.*, **1959**, 3451.

NaOH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from cyclohexane. The obtained product was identified with I, synthesized by the route reported in literature,[5] by mixed mp, and its picrate, and by comparison of IR and NMR spectra. These experimental details are summarized in Table I.

5-Methyl-1,6-phenanthroline (II)——The same route of synthesis as method (a) was carried out using 0.05 mole of 4-aminoquinaldine and 21 ml of glycerol. The residue was recrystallized from cyclohexane, and the product was identified with II, synthesized by the route reported in literature,[5] by mixed mp, and by comparison of IR and NMR spectra. These experimental details are summarized in Table I.

1,6-Phenanthroline (III)——The same route of synthesis as method (a) was carried out using 0.008 mole of 4-aminoquinoline and 2.5 ml of glycerol. The residue was recrystallized from hexane, and the product was identified with III, synthesized by the route reported in literature,[7] by mixed mp, and by comparison of IR and NMR spectra. These experimental details are summarized in Table I.

1,9-Diazaanthracene (IV)——The same route of synthesis as method (a) was carried out using 0.008 mole of 2-aminoquinoline and 2.5 ml of glycerol. The residue was recrystallized from cyclohexane to give IV. These experimental details are summarized in Table I.

4-Methyl-1,9-diazaanthracene (V)——Method (b): To a stirring mixture of 0.008 mole of 2-aminoquinoline, 11.7 g of Sulfo-mix, 0.28 g of $FeSO_4 \cdot 6H_2O$, 0.48 g of H_3BO_3, and 4 ml of water, 0.01 mole of freshly distilled methyl vinyl ketone was added over a period of 30 min at 110°, and the mixture was stirred at 130° for 5 hr, and subsequently treated as in method (a). The residue was recrystallized from cyclohexane to V. UV λ_{max}^{EtOH} nm (log ε): 235 (4.36), 257 (4.37). These experimental details are summarized in Table I.

4,6-Phenanthroline 6-Methiodide (VI)——A solution of 1 g of I in acetone containing 0.8 ml of MeI was heated under reflux overnight. The resulting precipitate was collected and recrystallized from EtOH to 1.4 g (78%) of VI as orange needles, mp 250—251° (decomp.). *Anal.* Calcd. for $C_{13}H_{11}N_2I$: C, 48.47; H, 3.44; N, 8.70. Found: C, 48.32; H, 3.40; N, 8.35.

6-Methyl-4,6-phenanthrolin-5-one (VII)——To a stirring solution of 0.5 g of VI in 10 ml of water, cooled in an ice-methanol bath, a solution of 0.3 g of NaOH in 0.6 ml of water was added dropwise during 5 min, and 1 g of $K_3Fe(CN)_6$ in 2 ml of water during 30 min, both additions starting at the same time. After 1.5 hr, the ice bath was removed and stirring was continued for additional 5 hr at room temperature. The reaction mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from acetone to give 0.25 g (76%) of VII as colorless needles, mp 173—175°, *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.09; H, 4.75; N, 13.58. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=O).

Chichibabin Amination of I——Method (1): To 25 ml of liquid ammonia in an autoclave 2 g of freshly cut potassium metal and 1.05 g of $FeCl_3$ were added. After the evolution of hydrogen had ceased, 1.05 g of I and 1.14 g of KNO_3 were added simultaneously. The autoclave was sealed and allowed to stand at room temperature with occasional shaking for 8 days. The cooled autoclave was opened and 25 ml of benzene–ethanol (1: 1) solution was added in small portions. When ammonia had evaporated, 25 ml of water was added and the reaction mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed over alumina, and eluted with $CHCl_3$. First effluent fraction was recrystallized from benzene to 5-amino-4,6-phenanthroline (VIII). Second effluent fraction was recrystallized from $CHCl_3$ to 4,6-phenanthrolin-5(6H)-one, which was identified with IX′, synthesized through diazotization of VIII, by mixed mp, and by comparison of IR and NMR spectra. These experimental details are summarized in Table II.

Method (2): To 17 ml of liquid ammonia placed in an autoclave 0.7 g of freshly cut potassium metal and 1.05 g of $FeCl_3$ were added. After the evolution of hydrogen had ceased, 1 g of I and 0.76 g of KNO_3 were added simultaneously. The autoclave was sealed and heated at 50—70° for 18 hr, and subsequently treated as in method (1). First effluent fraction was recrystallized from cyclohexane to 0.8 g of I. Second effluent fraction was recrystallized from benzene and the product was identified with VIII, synthesized by the method (1), by mixed mp and by comparison of IR and NMR spectra. These experimental details are summarized in Table II.

4,6-Phenanthrolin-5(6H)-one (IX′)——To a stirring mixture of 0.2 g of VIII and 4 ml of H_2SO_4, 0.1 g of $NaNO_2$ was added at 0—5° and the mixture was stirred for 1 hr. To this reaction mixture, 10 ml of cooled water was added and the mixture was warmed until the evolutilon of gas had ceased. The mixture was neutralized with NH_4OH and extracted with hot $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from $CHCl_3$ to 0.19 g (95%) of IX′. These experimental details are summarized in Table II.

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