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Syntheses of Nitrogen-containing Compounds. XVIII.[1] Syntheses of Naphthyridines by Improved One-Step Process

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1,5-Naphthyridine (I) and 1,8-naphthyridines (III to VI) were synthesized by the reaction of 3- or 2-aminopyridines with glycerol, in the presence of sodium *m*-nitrobenzenesulfonate, boric acid, and ferrous sulfate, in sulfuric acid. Application of the same method to 3- and 4-aminoqinolines afforded 4,6-phenanthroline (VIII) and 5-methyl-1,-6-phenanthroline (IX). 1,6-Naphthyridine (II) was obtained in a high yield by the reaction of 4-aminopyridine and glycerol, in the presence of sulfo–mix, boric acid, and ferrous sulfate.

In a previous work on antibacterial substances,[3] it was shown that 1,5-naphthridine (I) and 1,6-naphthyridine (II) behaved differently to N-oxidation with hydrogen peroxide in acetic acid solution. The preceding paper of this series[1] reported an improved method for the synthesis of 1,8-naphthyridines (III) and the reactivity of I, II, and III in the presence of the base of dimethyl sulfoxide. In the present series of work, further improvement was effected in the one–step synthesis of I and III, using a catalyst, and this improved process was used for amino-quinolines to obtain phenanthrolines, which are reported herein.

In the preceding work, the improved method for the synthesis of 1,8-naphthyridines was the Skraup reaction using sodium *m*-nitrobenzenesulfonate in place of the sulfo–mix,[4] and 1,8-naphthyridines were obtained in higher yield than that reported to date.[5] Clark and Davis[6] reported that ferrous sulfate is a good catalyst for Skraup's quinoline synthesis, and Cohn[7] recommended the use of boric acid as a catalyst, and Tamura and others[8] reported a similar method using hydrochloric or acetic acid instead of sulfuric acid. Based on these observations, use of a catalyst in addition to sodium *m*-nitrobenzenesulfonate was considered. First, as a method for the synthesis of III, the Skraup reaction of 2-aminopyridine and glycerol was carried out in either sulfuric or acetic acid, using boric acid or ferrous sulfate as a catalyst, but the expected result was not obtained. The reaction was then carried out in sulfuric acid, using a mixture of boric acid and ferrous sulfate, and the objective III was obtained in a higher yield than that obtained in the preceding work.[1] Some examinations were made on the ratio of boric acid and ferrous sulfate in this reaction but no definite tendency was observed. Therefore, 6-methyl-, 5-methyl-, and 4-methyl-2-aminopyridines were each reacted with glycerol, sulfuric acid, and sodium *m*-nitrobenzenesulfonate, in the presence of a mixture of boric acid and ferrous sulfate, under the same conditions as above, and 2-methyl-(IV), 3-metyl-(V), and 4-methyl-1,8-naphthyridine (VI) were respectively obtained in a higher yield

1) Part XVII: Y. Hamada, I. Takeuchi, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **19**, 1751 (1971).
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3) T. Takahashi, Y. Hamada, I. Takeuchi, and H. Matsuoka, *Yakugaku Zasshi*, **89**, 1260 (1969).
4) W.P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).
5) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **32**, 832 (1967); W.W. Paudler and T.J. Kress, *J. Heterocyclic Chem.*, **4**, 284 (1967).
6) H.T. Clarku and A.W. Davis, *Org. Syntheses*, **2**, 79 (1922); Coll. Vol. **1**, 478 (1941).
7) E.W. Cohn, *J. Am. Chem. Soc.*, **52**, 3685 (1930).
8) S. Tamura, *Yakugaku Zasshi*, **80**, 559 (1960); S. Tamura, T. Kudo, and Y. Yanagihara, *ibid.*, **80**, 562 (1960).

than that reported previously. These reaction routes are shown in Chart 1 and detailed experimental conditions are summarized in Table I.

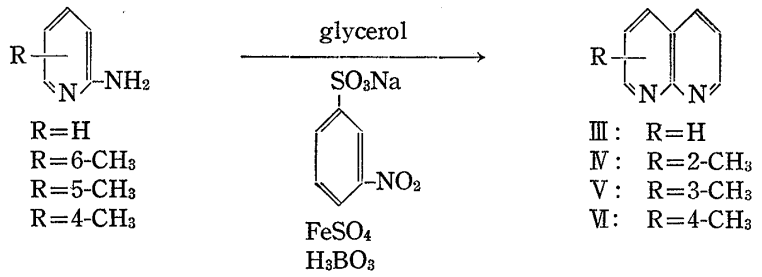


Chart 1

TABLE I

Compound No.	Raw material (g)	Method	Reagent	Yield (%)	Yield lit.[a] (%)	mp (°C)
III	2-aminopyridine (3.75)	A	glycerol	70	(45)[1]	95— 97
IV	2-amino-6-methylpyridine (4.3)	A	glycerol	50	(28)[1]	97— 99
V	2-amino-5-methylpyridine (4.3)	A	glycerol	87	(52)[1]	117—118
VI	2-amino-4-methylpyridine (4.3)	A	glycerol	38	(35)[1]	56— 57

Compound No.	Picrate mp (°C)	Appearance	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
III		colorless plates	$C_8H_6N_2$	73.83	4.65	21.53	73.67	4.52	21.39
IV		white cottony needles	$C_9H_8N_2$	74.97	5.59	19.43	75.15	5.70	19.61
V		colorless prisms	$C_9H_8N_2$	74.97	5.59	19.43	75.22	5.52	19.54
VI	202—204	colorless needles	$C_9H_8N_2$	74.97	5.59	19.43	74.93	5.57	19.53

a) literature

As will be seen in Table I, the yield of V showed greater increase than the others. These results seem to suggest that either of these catalysts alone would not be effective and that the increased yield was due to the synergetic action of boric acid and ferrous sulfate.

Synthesis of I was carried out under the same condition, that is, 3-aminopyridine and glycerol were submitted to the Skraup reaction using sodium *m*-nitrobenzenesulfonate, boric acid, ferrous sulfate, and sulfuric acid, and I was obtained in a quantitative yield, far exceeding that reported in past literature.[9]

Attempts were made for synthesis under these conditions using reagents other than acrolein. In the synthesis of IV, the reaction of 2-aminopyridine and sodium *m*-nitrobenzenesulfonate with crotonaldehyde, in the presence of sulfuric acid, resulted in total recovery of the starting 2-aminopyridine, but the addition of boric acid–ferrous sulfate catalyst afforded the objective IV, though in a lower yield than that by the usual method of using the sulfo–mix. The reaction of 3-aminopyridine and sodium *m*-nitrobenzenesulfonate, in the presence of boric acid, ferrous sulfate, and sulfuric acid, with methyl vinyl ketone also ended in the recovery of the starting material. These results suggest that the mixed catalyst of

9) A. Albert, *J. Chem. Soc.*, **1960**, 1790.

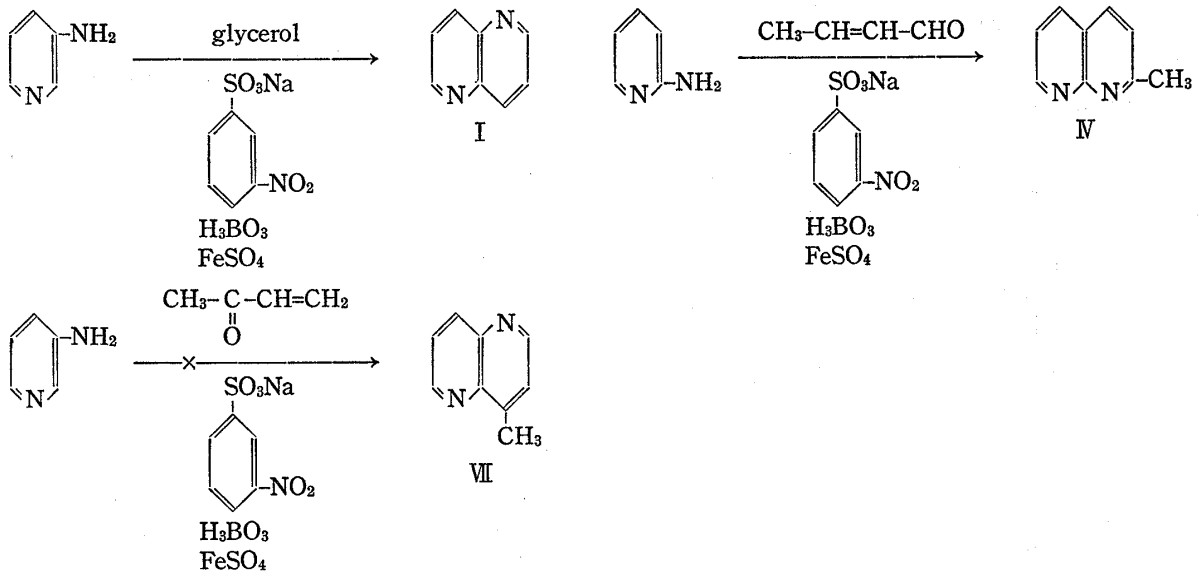


Chart 2

TABLE II

Compound No.	Raw material (g)	Method	Reagent	Yield (%)	mp (°C)
I	3-aminopyridine (3.75)	A	glycerol	90	73—75
IV	2-aminopyridine (3.75)	B	crotonaldehyde	0.6	97—99
VII	3-aminopyridine (3.75)	B	methylvinylketon	recovery	

Compound No.	Appearance	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
I	colorless needles	$C_8H_6N_2$	73.83	4.65	21.53	73.96	4.60	21.66
IV	white cottony needles	$C_9H_8N_2$	74.97	5.59	19.43	75.08	5.65	19.23

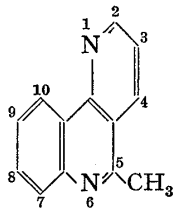
boric acid and ferrous sulfate is effective only in the Skraup reaction with acrolein (dehydration product of glycerol). These reaction routes are shown in Chart 2 and experimental details are summarized in Table II.

These reaction conditions were then applied to amino-quinolines. 4,6-Phenanthroline[10] (VIII) had hitherto been obtained from 3-aminoquinoline in the presence of arsenic pentoxide and sulfuric acid, or by the Skraup reaction using the sulfo-mix, but the yield was poor in either case, being 0.8% and 10%, respectively. The reaction of 3-aminoquinoline with glycerol was therefore carried out in the presence of sodium *m*-nitrobenzenesulfonate, boric acid, ferrous sulfate, and sulfuric acid, and a substance (VIII′) with a molecular formula of $C_{12}H_8N_2$, *m/e* 180 (M^+), was obtained. VIII′ was identified by mixed melting point fusion and by infrared (IR) and nuclear magnetic resonance (NMR) spectra with 4,6-phenanthroline, synthesized according to the report of Paudler, *et al.*[10a]

5-Methyl-1,6-phenanthroline[11] (IX) had been obtained by the Skraup reaction of 2-methyl-4-aminoquinoline (X) in the presence of arsenic pentoxide but its yield was only 4.9%.

10) *a*) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **32**, 2616 (1967); *b*) N.P. Buu-Hoï, R. Royer, and M. Hubert, *J. Chem. Soc.*, **1956**, 2048.
11) F. Lions and E. Ritchi, *J. Proc. Roy. Soc. N.S. Wales*, **74**, 443 (1941).

Table III. NMR Spectral Data of 5-Methyl-1,6-phenanthroline (in $CDCl_3$)

Compound	Chemical shifts (δ)								Coupling constants (cps)		
	2H	3H	4H	7H	8H	9H	10H	CH_3	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$
	9.04	7.45	8.28	8.03	7.75	7.75	9.04	2.95	4.5	2.0	8.2

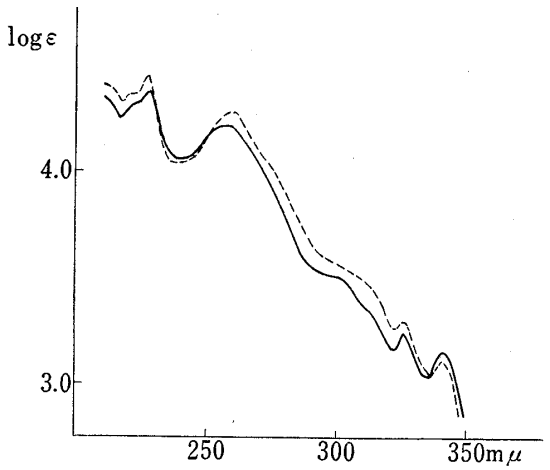


Fig. 1. Ultraviolet Absorption Spectra in EtOH

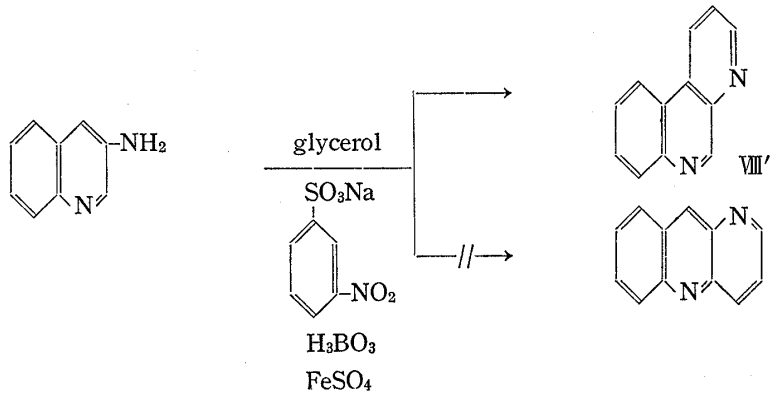
——: 1,6-phenanthroline (XI)
------: 5-methyl-1,6-phenanthroline (IX)

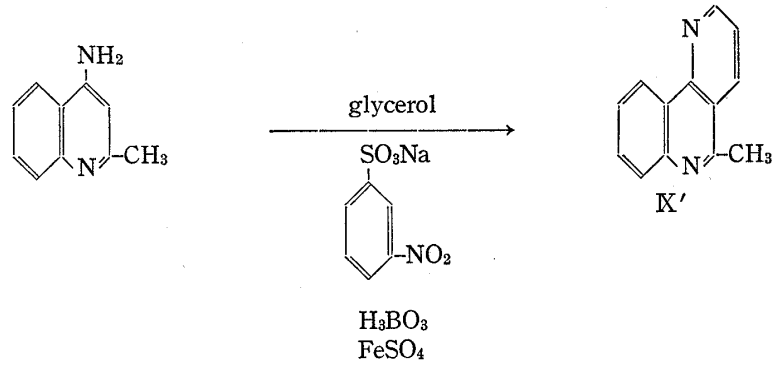
Using the same conditions as above, X was reacted with glycerol and sodium *m*-nitrobenzenesulfonate, in the presence of boric acid, ferrous sulfate, and sulfuric acid, and a substance (IX′) of mp 105—107°, differing from the reported mp of 206°, was obtained in 40% yield. Its mass spectrum revealed *m/e* 194 (M^+), 179 (M^+-CH_3), and 167 (M^+-HCN), and its elemental analysis indicated the molecular formula of $C_{13}H_{10}N_2$. The NMR spectrum of IX′ was identical with that of the fundamental skeleton of 1,6-phenanthroline[12] (XI), except for 5-methyl group. Its ultraviolet (UV) spectra was similar to that of XI. Results of the above experiments and its IR spectrum also indicated that IX′ is IX. In order to determine its structure, some chemical reactions were carried out, the result of which will be reported at a later date. NMR and UV spectra of IX were given in Table III and Fig. 1.

It was shown in the preceding report[1] that sulfo–mix gave a better result than sodium *m*-nitrobenzenesulfonate for the synthesis of II, and the reaction of 4-aminopyridine and glycerol was carried out with the sulfo–mix, in the presence of boric acid and ferrous sulfate. II was obtained in a higher yield than that in the synthesis by Kress and Paudler,[13] and therefore, synthesis of other naphthyridines under this condition is now being examined. Results of the above reaction are shown in Chart 3 and its experimental details are summarized in Table IV.

These experiments have shown that the improved process with sodium *m*-nitrobenzenesulfonate, using a mixed catalyst of boric acid and ferrous sulfate, is effective for the syntheses of 1,5- and 1,8-naphthyridines, as well as quinolines, and that the use of sulfo–mix is effective in obtaining 1,6-naphthyridines.

12) Y. Kobayashi, I. Kumadaki, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **17**, 1511 (1969).
13) T.J. Kress and W.W. Paudler, *Chem. Commun.*, **1**, 3 (1967).





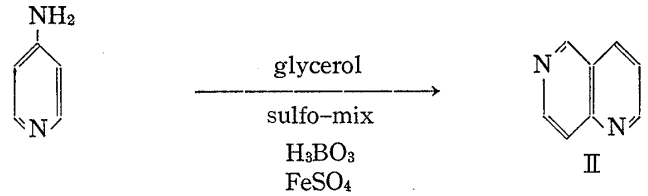


Chart 3

TABLE IV

Compound No.	Raw material (g)	Method	Reagent	Yield (%)	mp (°C)	Picrate mp (°C)
Ⅷ	3-aminoquinoline (5.76)	A	glycerol	50	112—114	
Ⅸ	4-aminioquinaldine (1.5)	A	glycerol	35	110—112	
Ⅱ	4-aminopyridine (3.75)	C	glycerol	70	28— 30	202—204

Compound No.	Appearance	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1}
Ⅷ	white cottony needles	$C_{12}H_8N_2$	79.98	4.48	15.55	79.72	4.56	15.71	
Ⅸ	pale yellow cottony needles	$C_{13}H_{10}N_2$	80.38	5.19	14.42	80.26	5.24	14.32	1580 (C=N) 1440, 2880(-CH_3), 771(C-H)[a]
Ⅱ	colorless needles	$C_8H_6N_2$	73.83	4.65	21.53	73.95	4.87	21.30	

a) adjoining 3 protons

Experimental

1,8-Naphthyridines (III to VI)——Method (A): A mixture of 41 g of H_2SO_4, 17.5 g of sodium *m*-nitrobenzenesulfonate, 2.4 g (2.3 mole) of H_3BO_3, and 1.4 g (0.53 mole) of $FeSO_4 \cdot 6H_2O$ was chilled to 0—5°, 12.5 ml of anhyd. glycerol, was added, followed by 0.04 mole of 2-aminopyridine or 2-amino- (4,5,6)-methylpyridine and 22.5 ml of warmed water (50°) and the mixture was stirred at 135° for 4 hr. The reaction mixture was basified with 50% 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 III to VI, 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.

1,5-Naphthyridine (I)——The same route of synthesis as for method A was carried out using 0.04 mole of 3-aminopyridine and 12.5 g of glycerol. The residue was recrystallized from cyclohexane. The obtained product was identified with I, synthesized by the route reported in literature,[9] by mixed mp, and by comparison of IR and NMR spectra. These experimental details are summarised in Table II.

2-Methyl-1,8-naphthyridine (IV)——Method (B): To a stirred mixture of 41 g of H_2SO_4, 17.5 g of sodium *m*-nitrobenzenesulfonate, 2.4 g of H_3BO_3, 1.4 g of $FeSO_4 \cdot 6H_2O$ and 22.5 ml of water, 9.5 g (0.135 mole) of crotonaldehyde was added over period of 30 min at 120°, and the mixture was stirred at 135° for 4 hr. The reaction mixture was basified with 50% 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 IV, 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 II.

4,6-Phenanthroline (VIII)——The same route of synthesis as for method (A) was carried out using 0.04 mole of 3-aminoquinoline and 12.5 g of glycerol. The residue was recrystallized from cyclohexane. The obtained product was identified with VIII, synthesized by the route reported in literature,[10a] by mixed mp, and by comparison of IR and NMR spectra. These experimental details are summarized in Table IV.

5-Methyl-1,6-phenanthlorine (IX)——The same route of synthesis as for method (A) was carried out on a quarter scale, using 0.01 mole of 4-aminoquinaldine and 4.2 g of glycerol. The residue was recrystallized from cyclohexane. Further the crystal was chromatographed on alumina (20 g) eluted with $CHCl_3$. These experimental details are summarized in Table IV.

1,6-Naphthyridine (II)——Method (C): A mixture of 58.5 g of sulfo-mix[4] (prepared from 48 g of $H_2SO_4 \cdot SO_3$ (20%), and 11 g of nitrobenzene), 2.4 g (0.04 mole) of H_3BO_3 and 1.4 g (0.0054 mole) of $FeSO_4 \cdot 6H_2O$ was chilled to 0—5°, 12.5 ml of anhyd. glycerol, was added, followed by 0.04 mole of 4-aminopyridine and 22.5 ml of warmed water (50°), and the mixture was stirred at 130° for 5 hr. The reaction mixture was basified with 50% 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 II, synthesized by the route reported in literature,[13] by mixed mp, and its picrate, and by comparison of IR and NMR spectra. These experimental details are summarized in Table IV.

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