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Studies on 4-Hydroxyaminoquinoline 1-Oxide and Its Related Compounds. Synthesis of 3-Chloro- and 3-Bromo-4-aminoquinoline 1-Oxide and Presentation of Chemical Evidence for a New Type of Aromatic Rearrangement of N,O-Diaryl-hydroxylamines*

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The present paper deals with thermolyses of 4-hydroxyaminoquinoline 1-oxide (4HAQO) in acidic media and a new type of rearrangement of N,O-diarylhydroxylamine derived from 4HAQO and 4-hydroxyaminoquinoline. Thermolyses of 4-hydroxyamino-quinoline or -pyridine derivatives in hydrochloric or hydrobromic acid gave corresponding 3-halo-4-amino derivatives in relatively high yield. It was also found that N,O-di(4-quinolyl)hydroxylamine and N-(4-quinolyl)-O-(2,4-dinitrophenyl)hydroxylamine were rearranged to a corresponding diaryl derivative, 3,3′-(4-amino-4′-hydroxy)biquinoline and 3-(2′-hydroxy-3′,5′-dinitrophenyl)-4-aminoquinoline, respectively. Those facts presented the first chemical evidences for an aromatic rearrangement of N,O-diarylhydroxylamine which had already been predicted by Dewar.

After the discovery of carcinogenic activity of 4-nitroquinoline 1-oxide[2] and 4-hydroxy-aminoquinoline 1-oxide[3] (4HAQO), many efforts have been made to elucidate the relation-ship between their chemical reactivity and carcinogenicity.[4] In our previous papers,[5] it has been reported that free radicals were found as intermediates in air oxidation or pyrolysis of 4HAQO to give diquinoline derivatives. The present paper deals with thermolyses of 4HAQO in acidic media and a new type of rearrangement of N,O-diarylhydroxylamine derived from 4HAQO and 4-hydroxyaminoquinoline (4HAQ).

1) Thermolyses of 4HAQO and related compounds in acidic media.

Thermolyses of 4-hydroxyamino-quinoline or -pyridine derivatives in hydrochloric or hydrobromic acid gave corresponding 3-halo-4-amino derivatives in relatively high yield.

A solution of 4HAQO·hydrochloride in 1N HCl was heated at 200° for 3 hours in a sealed tube. Purification with chromatography on silica gel afforded chloro-compound (**1**), mp 220° (decomp.), $C_9H_7ON_2Cl$, UV λ_{max}^{MeOH} mμ (ε): 223 (27600), 260 (12300), 372 (8750), in 79% yield. Treatment of **1** with *n*-butylnitrite in a mixture of acetic acid and conc. H_2SO_4, followed by refluxing in C_2H_5OH to give (**2**),[6] mp 100—101°, Mass Spectrum *m/e*: 179 (M^+). Catalytic

* Dedicated to the memory of Prof. Eiji Ochiai.

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2) W. Nakahara, F. Fukuoka, and T. Sugimura, *Gann*, **48**, 129 (1957).

3) H. Endo and F. Kume, *Naturwissenshaften*, **50**, 525 (1963); *idem*, *Gann*, **54**, 443 (1963).

4) Y. Kawazoe, M. Tachibana, K. Aoki, and W. Nakahara, *Biochem. Pharmacol.*, **16**, 631 (1967); T. Okamoto and M. Mochizuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 987 (1969); M. Tachibana, S. Sawaki, and Y. Kawazoe, *ibid.*, **15**, 1112 (1967); Y. Kawazoe and M. Araki, *ibid.*, **16**, 839 (1968); M. Araki, Y. Kawazoe, and C. Nagata, *ibid.*, **17**, 1344 (1968); Y. Kawazoe and M. Araki, "Chemical Tumor Problems," ed. by W. Nakahara, pp. 43—104; C. Nagata, N. Kataoka, A. Imamura, Y. Kawazoe, and G. Chihara, *Gann*, 57, 323 (1966).

5) T. Kosuge, H. Zenda, and H. Sawanishi, *Chem. Pharm. Bull.* (Tokyo), **17**, 2389 (1969); *idem*, *ibid.*, **19**, 1291 (1971).

6) T. Kauffman and J. Schulz, *Chem. Ber.*, **99**, 1837 (1966).

hydrogenation of **2** over Raney nickel afforded a liquid (**3**), mp 185—186° (picrate), Mass Spectrum *m/e*: 163 (M^+). **3** was found to be identical with authentic sample[7] of 3-chloroquinoline in comparison with their spectral data and mixed melting point of their picrates. Thus, the structure of **1** was confirmed to be 3-chloro-4-aminoquinoline 1-oxide, as shown in Chart 1.

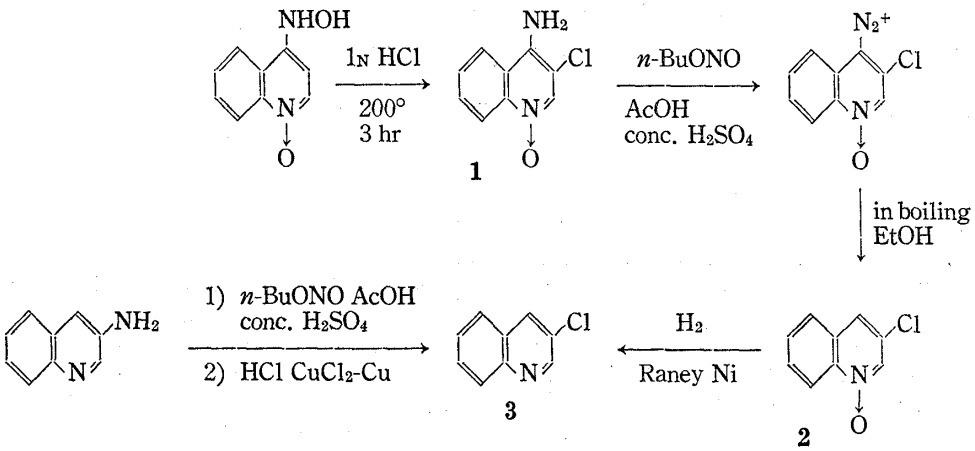


Chart 1

Table I. Termolysis of 4HAQO in 1N HCl at Various Temperature

Temp. (°C)	hr	Yield of **1** (%)
200	3	79
150	3	88
125	3	83
100	18	64
60	18	trace

Furthermore, the thermolyses of 4HAQO in 1N HCl at lower temperature were investigated and the results were shown in Table I. It was noteworth that **1** was obtained in 64% yield even at 100°. This finding to give 3-chloro derivatives in high yield on thermolyses of 4HAQO in hydrochloric acid prompted us to proceed the same reaction in the other 4-hydroxyamino-quinoline and -pyridine derivatives. It would be expected to be better method for the direct introduction of chlorine at 3-position in quinolines than method of chlorination with S_2Cl_2.[8] The results of the thermolyses of 4-hydroxyamino-quinoline and -pyridine derivatives in various concentration of hydrochloric acid were summarized in Table II. The structures of products were confirmed by comparison with authentic sample or analyses of their spectral data, the details of reactions will be described in experimental part.

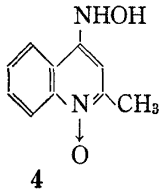
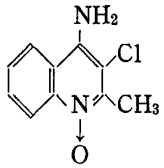
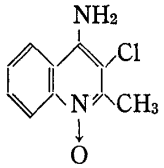
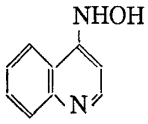
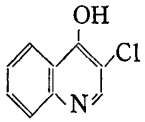
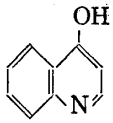
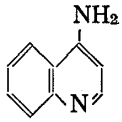
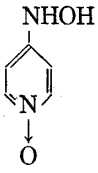
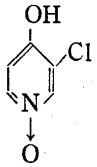
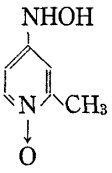
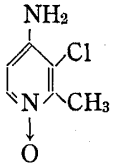
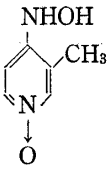
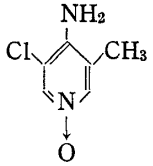
In all compounds which were examined in this paper, reactions occurred in ortho position of hydroxylamine, namely in β-substitution of quinolines or pyridines. The reactions of 4HAQ and **9** were accompanied by hydrolyses of amine to afford 4-hydroxy derivatives.

Thermolyses of 4HAQO, **4** and 4HAQ in 2N HBr were examined, and did not give any bromo compounds, but reduction of hydroxyamino to amino was observed as shown in Table III. But in conc. HBr, the thermolysis of 4HAQO was performed to give 3-bromo-4-amino-quinoline 1-oxide (**19**) in 71% yield, as such as chlorination. The structure of the bromo

7) J.C. Cochran and W.F. Little, *J. Org. Chem.*, **26**, 808 (1961).
8) Edinger and Lubberger, *J. Prakt. Chem.*, **54**, 348; Edinger, *Chem. Ber.*, **29**, 2456 (1896) [*Beilstein*, **20**, 359]; R.H. Baker, C.J. Albisetti, Jr., R.H. Dodson, G.R. Lappin, and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1532 (1946); F.H. Case, S. Catino, and F. Scholnick, *J. Org. Chem.*, **19**, 31 (1954); W.O. Sykes, *J. Chem. Soc.*, **1958**, 825; *etc.*

compound (**19**) was confirmed by comparison with the authentic sample.[9] It was well known as Bamberger reaction[10] that arylhydroxylamine is easily rearranged to *o*- or *p*-hydroxyaniline derivative in acidic medium, however in a field of N-heteroaromatic compound this kind of reaction has not been reported before our finding in this paper. Recent reports[11,12a] studied

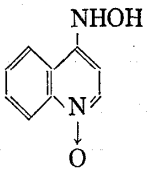
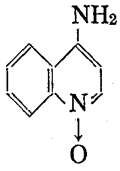
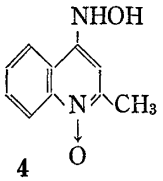
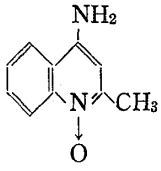
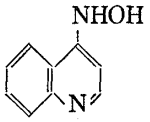
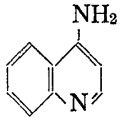
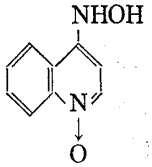
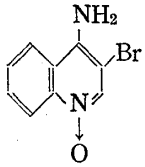
Table II. Thermolyses of Hydroxylamine Derivatives in Various Concentration of Hydrogen Chloride

Starting material	Acid concentration	Reaction temp. (°C)	Reaction time (hr)	Product (%)		
 **4**	1N	180	6	 **5**[a] (63.2)		
	6N	180	6	 **5**[a] (79.5)		
	1N	220	7	 **6** (9.4)	 **7** (42.1)	 **8** (39.9)
 **9**	3N	210	3	 **10** (20.9)	 **11** (16.1)	
 **12**	3N	210	3	 **13**[a] (5.2)	dimer **14** (30.9)	
 **15**	3N	210	3	 **16**[a] (53.6)		

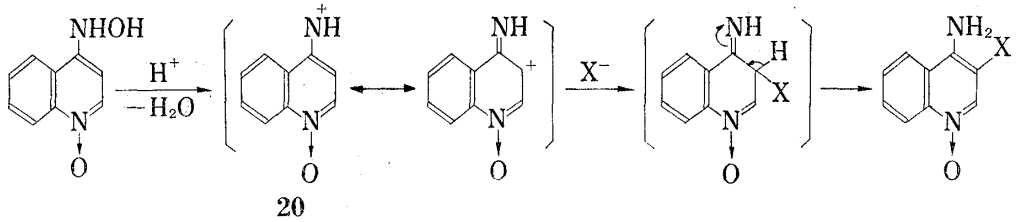
a) The structure was confirmed by spectral data listed in experimental part.

9) T. Naito, *Yakugaku Zasshi*, **67**, 246 (1964).
10) E. Bamberger, *Chem. Ber.*, **27**, 1347 (1894); *idem*, *Ann.*, **424**, 233 (1921).
11) H.E. Heller, E.D. Hughes, and C.K. Ingold, *Nature*, **168**, 909 (1951); Y. Yukawa, *Nippon Kagaku Zasshi*, **71**, 603 (1950); K. Shudo, *Yuki Gosei Kagaku Kyokai Shi*, **31**, 395 (1973).
12) *a*) M.J.S. Dewar, "Molecular Rearrangement," Vol. I ed. by P. De Mayo, Interscience, New York and London, 1963, p. 308; *b*) *Idem*, *ibid.*, p. 344.

Table III. Thermolyses of Hydroxylamine Derivatives in 2N and conc. Hydrogen Bromide

Starting material	Acid concentration	Reaction temp. (°C)	Reaction time (hr)	Product (%)
	2N	240	3	 **17** (50.1)
 **4**	2N	220	7	 **18** (49.2)
	2N	180	6	 **8** (89.3)
	conc.	180	3	 **19** (71.4)

on the mechanism for Bamberger reaction prompted us to propose a plausible mechanism for the formation of 3-halo-4-amino compounds, namely these reactions were considered to proceed *via* nitrenium ion (**20**) resulted from heterolytic fission of N–O bond, as shown in Chart 2 in the case of 4HAQO.



20

Chart 2

Further investigation of this series and more precise study on the mechanism are in progress.

2) Presentation of chemical evidences for a new aromatic rearrangement of N,O-diaryl-hydroxylamines.

As further study on the heterolytic N–O bond fission, it was found that N,O-diquinolyl-hydroxylamine was easily rearranged to biquinoline derivatives. This section in the paper deals with the new type of reaction in 4HAQ.

A mixture of 4-chloroquinoline (**21**) and hydroxylamine in CH_3OH was heated under refluxing for 5.5 hours to give (**22**), mp>300° (HCl salt), $C_{18}H_{13}ON_3 \cdot 3HCl \cdot H_2O$, Mass Spectrum *m/e*: 287 (M^+), and (**23**), mp 168° (decomp.), $C_{18}H_{13}ON_3 \cdot HCl \cdot 2H_2O$, Mass Spectrum *m/e*:

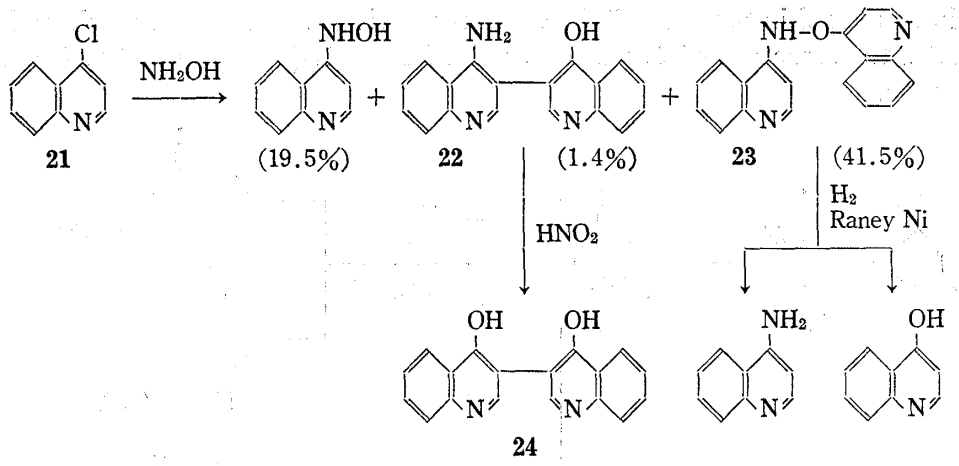


Chart 3

287 (M^+), in addition to 4HAQ (Chart 3). Treatment of **22** with sodium nitrite gave (**24**), which was identical with an authentic sample[13] of 4,4′-dihydroxy-3,3′-biquinoline, thus the structure of **22** was confirmed to be 3,3′-(4-amino-4′-hydroxy)biquinoline. Catalytic hydrogenation of **23** over Raney Ni gave 4-hydroxyquinoline and 4-aminoquinoline in high yield. It was found that **23** was identical with N,O-di(4-quinolyl)hydroxylamine derived from the reaction of 4-nitroquinoline with hydroxylamine by Hasegawa and Okamoto.[14]

23 would be formed from the reaction of 4-chloroquinoline and once produced 4-hydroxyaminoquinoline, since reaction of 4HAQ and 4-chloroquinoline gave **23** in relatively high yield. 4HAQO was also converted into the same compound **23** by the reaction with 4-chloroquinoline, followed by deoxygenation of N-oxide. **23** rearranged to **22** in CH_3OH by thermolysis at 100°.

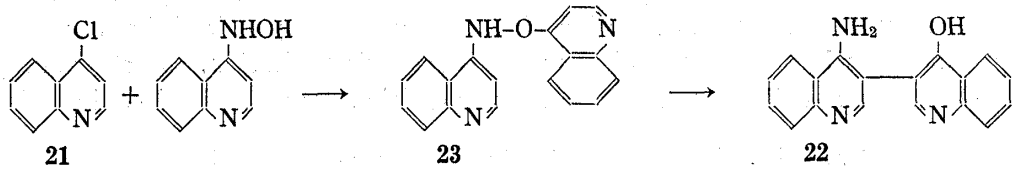


Chart 4

In 1963, Dewar[12b] predicted that N,O-diarylhydroxylamine should be rearranged in the same manner as hydrazobenzenes to give corresponding biphenyl derivatives, but any report had not been published to prove this proposal before our work. Among the efforts related with the proposal, Cox, *et al.*[15] and Sheradsky, *et al.*[16] reported independently that N,O-diarylhydroxylamine would be present as an intermediate in the syntheses of biphenyl derivatives. These reports prompted us to study more, namely the reaction of 4HAQ with 2,4-dinitrochlorobenzene having active nucleophilic center was examined, as follows.

Reaction of 4HAQ with 2,4-dinitrochlorobenzene in CH_3OH under refluxing for 20 minutes afforded (**25**), mp 185—190° (decomp.), $C_{15}H_{10}O_5N_4$, Mass Spectrum *m/e*: 326 (M^+), NMR Spectrum (in DMSO) δ: 8.80 (1H, doublet, J=3 cps), 8.55 (1H, double doublet, J=9 cps, J=3 cps), 8.15 (2H, two doublet, J=9 cps), 7.80—7.05 (4H, multiplet), 6.43 (1H, doublet, J=9 cps), in 33% yield. Catalytic hydrogenation of **25** over Raney Ni gave 4-aminoquinoline

13) T. Kosuge, H. Zenda, H. Sawanishi, and Y. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 2178 (1969).
14) M. Hasegawa and T. Okamoto, *Yakugaku Zasshi*, **93**, 1019 (1973). N,O-diarylhydroxylamines were also reported in following papers. A.S. Bailey, M. Manny, G.W.F. Orpwood, and J.E. White, *Tetrahedron*, **22**, 995 (1966); S. Hashimoto, K. Kano, and I. Takada, *Nippon Kagaku Zasshi*, **1972**, 1960.
15) J.R. Cox and M.F. Dunn, *Tetrahedron Letters*, **1963**, 985.
16) J. Sheradsky and G. Solemnick, *Tetrahedron Letters*, **1971**, 645; *idem*, *Isurael Journal of Chemistry*, **10**, 857 (1972).

and 2,4-dinitrophenol in 82% and 73% yield, respectively. From the result and analyses of spectral data, the structure of **25** was determined to be N-(4-quinolyl)-O-(2,4-dinitrophenyl)-hydroxylamine.

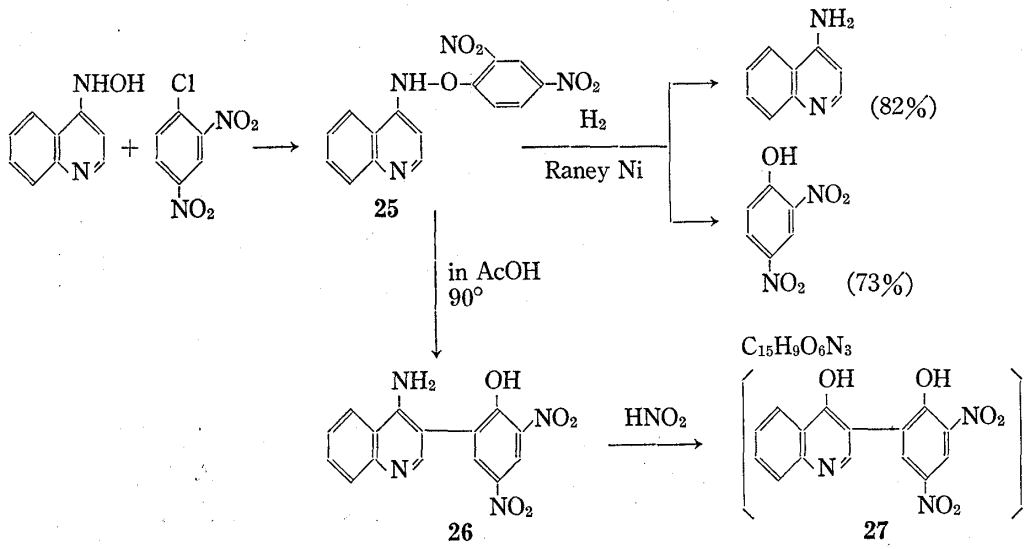


Chart 5

Treatment of **25** in acetic acid at 90° for 3 hours gave (**26**), mp 262—263° (HCl salt), $C_{15}H_{10}O_5N_4 \cdot HCl$, Mass Spectrum *m/e*: 326 (M^+), NMR Spectrum (in CD_3OD) δ: 8.95 (1H, doublet, J=3 cps), 8.55 (1H, doublet, J=3 cps), 8.30 (1H, singlet), 7.95—7.40 (4H, multiplet), in 49% yield. Reaction of **26** with sodium nitrite gave (**27**), mp 283—284°, $C_{15}H_9O_6N_3$, Mass Spectrum *m/e*: 327 (M^+). From the finding and analyses of spectral data of **26** and **27**, the structure of **26** was determined to be 3-(2′-hydroxy-3′,5′-dinitrophenyl)-4-aminoquinoline.

From the above results and the reaction of **23**, it would be emphasized that our information reported in this paper is the first chemical proof to Dewar's prediction. Further study on the rearrangement of **23** and **25** in various reaction conditions are summarized in Table IV.

Table IV. Rearrangement of **23** and **25** in Various Medium

	Temp. (°C)	Time (min)	Solvent and yield		
			in MeOH	in 0.25M HCl–MeOH	in 0.25M NaOH–MeOH
23→**22**	60	80	81%	0%	73%
	90	120		60%	
25→**26**	70	30		40%	81%

The yield was determined from the ultraviolet spectrum.

As shown in Table IV, it was some of interest that the rearrangement favorably proceeded in neutral medium and also in basic medium, in contrast with benzidine rearrangement of hydrazobenzene which required protonation of nitrogen. It was also found that free radical pathway might be excluded in the reaction, since any signal has not been observed in ESR spectra during the thermolysis of **23** and **25**. Unfortunately, reasonable mechanism for the rearrangement has not been elucidated yet, but further studies of this series on reaction mechanism and in relation to their carcinogenic activity are in progress.

Experimental

All melting points are determined in open capillary tube and are uncorrected.

Thermolysis of 4HAQO in 1N HCl——A solution of 4HAQO·HCl[17] (300 mg) in 1N HCl (5 ml) was heated at 200° for 3 hr in a sealed tube. After removal of the solvent, soluble fraction in $CHCl_3$ with MeOH (5%)

17) E. Ochiai and H. Mitarashi, *Ann. Rept. ITSUU Lab.*, 13, 19 (1963).

was subjected to column chromatography[18] on silica gel eluted with the same solvent to give yellow powders. After neutralization with 1N NaOH, recrystallization from MeOH–AcOEt gave 3-chloro-4-aminoquinoline 1-oxide (**1**), mp 220° (decomp.). Mass Spectrum *m/e*: 194 (M^+). *Anal.* Calcd. for $C_9H_7ON_2Cl$: C, 55.52; H, 3.60; N, 14.40. Found: C, 54.52; H, 3.66; N, 13.98. UV λ_{max}^{MeOH} mμ (ε): 223 (27600), 260 (12300), 372 (8750), (223 mg, 79%).

The same procedure was taken in those cases of reaction temperature at 150°, 125°, 100°, or 60°.

Diazotization and Reduction of (1)——To a solution of **1** (400 mg) in a mixture of glacial AcOH (4 ml) and conc.H_2SO_4 (3 ml), *n*-butylnitrite (6 ml) was added under cooling with ice water and stirred for 30 min. Cold acetone (50 ml) and ether (about 300—400 ml) were added to the reaction mixture to make precipitation. The diazonium salt was collected by filtration and was reduced by boiling in EtOH (30 ml) for 30 min. After removal of the solvent, the residue was made alkaline with 1N NaOH and extracted with $CHCl_3$. The product was subjected to column chromatography on silica gel eluted with $CHCl_3$ to give **2**, mp 100—101° (recrystallized from a mixture of petr. ether–benzene). Mass Spectrum *m/e*: 179 (M^+), monochloride (50 mg, 13.5%).

Reduction of 2——**2** (80 mg) in MeOH was hydrogenated over Raney Ni prepared from nickel aluminum alloy (300 mg). After removal of the catalyst by filtration and of the solvent by evaporation, the residue was subjected to column chromatography on silica gel eluted with $CHCl_3$ to give 3-chloroquinoline (**3**), mp 185—186° (picrate)(45 mg, 61.8%). The product was identified with the authentic sample synthesized by the method of J.C. Cochran.[7]

Thermolysis of 4-Hydroxyaminoquinaldine 1-Oxide (4) in 1N HCl——A suspension of **4**·HCl[19] (445 mg) in 1N HCl (8 ml) was heated at 180° for 6 hr in a sealed tube. After removal of the solvent, the soluble fraction of the residue in MeOH was subjected to column chromatography on silica gel eluted with MeOH–$CHCl_3$ to give yellow powders. The salt isolated was made free by treatment with 1N NaOH. Recrystallization from MeOH–AcOEt gave (**5**), mp 222°. Mass Spectrum *m/e*: 208 (M^+). *Anal.* Calcd. for $C_{10}H_9ON_2Cl \cdot CH_3OH$: C, 54.97; H, 5.41; N, 11.66. Found: C, 54.31; H, 5.20; N, 11.68. UV λ_{max}^{MeOH} mμ (ε): 221 (33500), 258 (20900), 263 (20400), 364 (9880), (298.6 mg, 63.2%).

5 (200 mg) in MeOH was hydrogenated over Raney Ni, prepared from nickel aluminum alloy (300 mg), to give a deoxygenated compound, 3-chloro-4-aminoquinaldine, mp 209—210°. Mass Spectrum *m/e*: 192 (M^+). UV λ_{max}^{MeOH} mμ (ε): 218(33100), 243(31000), 313(8050). NMR (in CD_3OD) δ: 7.23—8.23 (4H, multiplet), 2.58 (3H, singlet). (140 mg, 75%).

Thermolysis of 4 in 6N HCl——A suspension of **4**·HCl (480 mg) in 6N HCl (10 ml) was heated at 180° for 6 hr in a sealed tube. Procedure for isolation of the product was carried out as same as the above reaction to give **5** (405.4 mg, 79.5%).

Thermolysis of 4HAQ in 1N HCl——A solution of 4HAQ·HCl[20] (201.7 mg) in 1N HCl (5 ml) was heated at 220° for 7 hr in a sealed tube. After cooling, the precipitate was collected by filtration and extracted with MeOH. From MeOH solution was given 4HAQ·HCl (82.4 mg).

MeOH insoluble part was subjected to column chromatography on silica gel, eluted with MeOH–$CHCl_3$ to give the following three compounds.

3-chloro-4-hydroxyquinoline (**6**)[21] (12.6 mg, 9.4%).

4-hydroxyquinoline (**7**)[22] (45.5 mg, 42.1%).

4-aminoquinoline (**8**)[23] (43.7 mg as HCl salt, 39.9%).

These yields are based on the reacted starting material.

Thermolysis of 4-Hydroxyaminopyridine 1-Oxide (9) in 3N HCl——A solution of **9**[24] (644.2 mg) in 3N HCl (12 ml) was heated at 210° for 3 hr in a sealed tube. After removal of the solvent, soluble fraction of the residue in MeOH was subjected to column chromatography on silica gel, and a fraction eluted with 2% MeOH in $CHCl_3$ was subjected to column chromatography on Sephadex LH-20 eluted with MeOH to give 3-chloro-4-hydroxypyridine 1-oxide (**10**),[25] mp 258—259° (recrystallized from MeOH). Mass Spectrum *m/e*: 145 (M^+). *Anal.* Calcd. for $C_5H_4O_2NCl$: C, 42.76; H, 2.79; N, 9.66. Found: C, 41.56; H, 2.96; N, 9.51 (138.0 mg, 20.9%).

A fraction eluted with 4% MeOH in $CHCl_3$ on silica gel column chromatography was purified by chromatography on Sephadex LH-20 eluted with MeOH to give 4-hydroxypyridine (**11**)[26] (78.2 mg, 16.1%).

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18) Only this procedure succeeded in the isolation of desirable product without any trouble caused by unreacted 4HAQO.
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Thermolysis of 4-Hydroxyamino-2-picoline 1-Oxide (12) in 3N HCl——A solution of **12**[19] (301.8 mg) in 3N HCl (6 ml) was heated at 210° for 3 hr in a sealed tube. After removal of the solvent, the residue was extracted with EtOH, and recrystallization from MeOH–AcOEt gave 4-amino-3-chloro-2-picoline 1-oxide (**13**) in 5.2% yield. mp 230° (decomp.). Mass Spectrum *m/e*: 158 (M^+). *Anal.* Calcd. for $C_6H_7ON_2Cl \cdot HCl$: C, 37.11; H, 4.16; N, 14.33. Found: C, 36.91; H, 4.14; N, 14.49. UV λ_{max}^{MeOH} mμ (ε): 280 (14800). NMR (in 6*d*-DMSO) δ: 8.23 (1H, doublet, $J=8$ cps), 7.95 (2H, broad singlet), 6.93 (1H, doublet, $J=8$ cps), 2.63 (3H, singlet).

Recrystallization of the insoluble part in EtOH gave colorless needles (**14**), mp 239° (decomp.). Mass Spectrum *m/e*: 244 (M^+). *Anal.* Calcd. for $C_{12}H_{14}O_2N_4 \cdot 2H_2O \cdot HCl$: C, 45.57; H, 6.01; N, 17.72. Found: C, 45.82; H, 6.12; N, 17.27. UV λ_{max}^{MeOH} mμ (ε): 284 (28000). (105.5 mg, 30.9%). The structure of the compound has not been clarified yet.

Thermolysis of 4-Hydroxyamino-3-picoline 1-Oxide (15) in 3N HCl——A solution of **15**[19] (2.00 g) in 3N HCl (20 ml) was heated at 220° for 3 hr in a sealed tube. After removal of the solvent, the residue was washed with EtOH (10 ml) and with 5% EtOH in $CHCl_3$ (10 ml), and the insoluble part was subjected to column chromatography on silica gel eluted with MeOH–$CHCl_3$ to give 4-amino-5-chloro-3-picoline 1-oxide (**16**), mp 218° (decomp.). Mass Spectrum *m/e*: 158 (M^+). *Anal.* Calcd. for $C_6H_7ON_2Cl \cdot HCl$: C, 37.11; H, 4.16; N, 14.43. Found: C, 38.65; H, 4.83; N, 14.48. UV λ_{max}^{MeOH} mμ (ε): 216 (21600), 286 (18800). NMR (in 6*d*-DMSO) δ: 8.35 (1H, singlet), 8.00 (1H, singlet), 7.10 (2H, broad singlet), 2.10 (3H, singlet) (1.21 g, 53.6%).

Thermolysis of 4HAQO in 2N HBr——A solution of 4HAQO·HBr (300 mg) in 2N HBr (5 ml) was heated at 240° for 3 hr in a sealed tube. After removal of the solvent, the residue was subjected to column chromatography on cellulose eluted with MeOH to give a yellow powder. The HBr salt was made free by treatment with 1N NaOH, and recrystallization from MeOH–AcOEt gave 4-aminoquinoline 1-oxide (**17**),[23] mp 274° (decomp.). (141.0 mg, 50.1%).

Thermolysis of 4 in 2N HBr——A solution of **4**·HBr (300 mg) in 2N HBr (8 ml) was heated at 180° for 6 hr in a sealed tube. After removal of the solvent, soluble fraction of the residue in MeOH was subjected to column chromatography on silica gel eluted with MeOH–$CHCl_3$ to give yellow powders (**18**), mp 240° (decomp.) (recrystallized from the mixture of MeOH–AcOEt). Mass Spectrum *m/e*: 174 (M^+). *Anal.* Calcd. for $C_{10}H_{10}ON_2 \cdot HBr \cdot H_2O$: C, 43.95; H, 4.81; N, 10.25. Found: C, 43.52; H, 4.79; N, 10.20. (139.0 mg, 49.2%).

18 (100 mg) in MeOH was hydrogenated over Raney Ni, prepared from nickel aluminum alloy (200 mg). The reaction mixture was made alkaline by treatment with 1N NaOH, evaporated to dryness, and the residue was subjected to column chromatography on silica gel using MeOH–$CHCl_3$ to give 4-aminoquinaldine,[27] mp 163° (recrystalized from benzene). Mass Spectrum *m/e*: 158 (M^+) (48.3 mg, 78.0%).

Thermolysis of 4HAQ in 2N HBr——A solution of 4HAQ·HBr (205.1 mg) in 2N HBr (5 ml) was heated at 220° for 7 hr in a sealed tube. The precipitate was collected by filtration and was extracted with MeOH to give 4HAQ·HBr. (128.3 mg). After the removal of the solvent of the filtrate *in vacuo*, the residue was subjected to column chromatography on silica gel using 5% MeOH in $CHCl_3$ to give yellow powders. The HBr salt was made free by treatment with 1N NaOH, and recrystallization from benzene gave **8**. mp 153—154° (64 mg, 89.3%). This yield is based on the reacted starting material.

Thermolysis of 4HAQO in conc. HBr——A solution of 4HAQO (300 mg) in conc. HBr (6 ml) was heated at 180° for 3 hr in a sealed tube. After the reaction mixture was neutralized, precipitate was collected by filtration, and was subjected to column chromatography on silica gel eluted with MeOH–$CHCl_3$ to give 3-bromo-4-aminoquinoline 1-oxide (**19**). mp 202—203° (recrystallized from EtOH). (297.1 mg, 71.4%). The structure of the product was identified with the authentic sample.[9]

Reaction of 4-Chloroquinoline (21)[22] and Hydroxylamine——To a solution of hydroxylamine·HCl (6.31 g) in MeOH (100 ml), MeOH saturated with K_2CO_3 was added to neutralize the solution, and the precipitated KCl was removed by filtration. To the filtrate, a solution of **21** (3 g) in MeOH (20 ml) was added and the mixture was refluxed for 5.5 hr. The red needles precipitated was collected by filtration, washed with small amount of MeOH and recrystallized from MeOH to give N,O-di(quinolyl)hydroxylamine (**23**)·HCl. (1.37 g, 41.5%). mp 168° (decomp.). *Anal.* Calcd. for $C_{18}H_{13}ON_3 \cdot 2H_2O \cdot HCl$: C, 60.18; H, 5.02; N, 11.71. Found: C, 61.21; H, 5.08; N, 11.99. Mass Spectrum *m/e*: 287 (M^+). UV λ_{max}^{MeOH} mμ (ε): 225 (38900), 380 (13600).

Concentration of the mother liquid yielded 4HAQ·HCl (701 mg, 19.5%), identified with an authentic sample.[20]

Further concentration of the mother liquid removed 4HAQ·HCl gave 3,3′-(4-amino-4′-hydroxy)biquinoline·HCl (**22**), mp>300°. (recrystallized from H_2O–MeOH). *Anal.* Calcd. for $C_{18}H_{13}ON_3 \cdot H_2O \cdot 3HCl$: C, 52.11; H, 4.34; N, 10.13. Found: C, 51.96; H, 4.46; N, 9.60. Mass Spectrum *m/e*: 287 (M^+). UV λ_{max}^{MeOH} mμ (ε): 216 (55100), 332 (28300). (54 mg, 1.4%).

Reaction of 22 with $NaNO_2$——To a solution of **22** (208 mg) in a mixture of glacial AcOH (4 ml) and conc. H_2SO_4 (2 ml), $NaNO_2$ (1 g) in cold water (2 ml) was added dropwise under cooling with ice water. After

27) G. Buchmann, Ger. (East) 24330 (Cl. 12p), Nov. 28, (1962), Appl. Mar. 11, (1959); 2pp [*C.A.*, **59**, 10008*a* (1963)].

standing for 24 hr at room temperature, the mixture was neutralized with conc. NaOH solution. Produced precipitates were collected by filtration, washed with water, and recrystallized from MeOH–AcOEt after treatment with HCl to give 3,3′-(4,4′-dihydroxy)biquinoline·HCl (**24**). mp>300°. (60 mg).

Reduction of 23——A suspension of **23** (90 mg) in MeOH (20 ml) was hydrogenated over Raney Ni, prepared from nickel aluminum alloy (600 mg). After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the residue was subjected to column chromatography on silica gel to give two compounds, **7** (33 mg, 91%) (recrystallized from MeOH–AcOEt) and **8** (35 mg, 96%) (recrystallized from MeOH–benzene).

Reaction of 4HAQ and 21——To a solution of 4HAQ·HCl (1.25 g) in MeOH (30 ml), MeOH saturated with K_2CO_3 was added until the solution was neutralized, and precipitated KCl was removed by filtration. To the filtrate, a solution of **21** (1 g) in MeOH (20 ml) was added, and the mixture was refluxed for 5.5 hr. The red needle precipitates were collected by filtration, washed with small amount of MeOH and recrystallized from MeOH to give **23**·HCl (843 mg, 38% based on 4HAQ·HCl).

Reaction of 4HAQ and 21——A suspension of 4HAQO (352 mg) and **21** (328 mg) in MeOH (20 ml) was refluxed for 1 hr and evaporated to dryness. The residue was washed with $CHCl_3$, and recrystallized from HCl–MeOH to give **23**·HCl. (237 mg, 33% based on 4HAQO).

Rearrangement of 23——A suspension of **23** (300 mg) in MeOH (10 ml) was heated at 100° for 1.5 hr in a sealed tube. The resulted precipitates were collected by filtration and recrystallized from HCl–MeOH to give **22**, mp>300° (152 mg, 36%).

Preparation of N-(4-Quinolyl)-O-(2,4-dinitrophenyl)hydroxylamine (**25**)——To a solution of MeOH (120 ml) with K_2CO_3 (800 mg), 4HAQ·HCl (2000 mg) was added and the produced KCl was removed by filtration. To the filtrate, 2,4-dinitrochlorobenzene (2335 mg) was added and the mixture was refluxed for 20 min. Precipitates were collected by filtration, washed with MeOH to give red product, **25**, mp 185—190° (decomp.). *Anal.* Calcd. for $C_{15}H_{10}O_5N_4$: C, 55.21; H, 3.07; N, 17.18. Found: C, 55.18; H, 3.36; N, 17.28. Mass Spectrum *m/e*: 326 (M^+). UV λ_{max}^{MeOH} mμ (ε): 226 (50900), 385 (18400). NMR (in DMSO) δ: 8.80 (1H, doublet, J=3 cps), 8.55 (1H, double doublet, J=9 cps, J=3 cps), 8.15 (2H, two doublet, J=9 cps), 7.80—7.05 (4H, multiplet), 6.43 (1H, doublet, J=9 cps) (1100 mg, 33%).

Rearrangement of 25——A suspension of **25** (200 mg) in glacial AcOH (150 ml) was heated at 90° for 3 hr in a sealed tube. After removal of the solvent by evaporation *in vacuo*, the residue was recrystallized from MeOH–AcOEt with HCl to give 3-(2′-hydroxy-3′,5′-dinitrophenyl)-4-aminoquinoline·HCl (**26**). mp 262—263°. *Anal.* Calcd. for $C_{15}H_{10}O_5N_4$·HCl: C, 49.66; H, 3.03; N, 15.45. Found: C, 49.19; H, 3.22; N, 15.18. Mass Spectrum *m/e*: 326 (M^+). UV λ_{max}^{MeOH} mμ (ε): 245 (33000), 326 (18500). NMR (in CD_3OD) δ: 8.95 (1H, doublet, J=3 cps), 8.55 (1H, doublet, J=3 cps), 8.30 (1H, singlet), 7.95—7.40 (4H, multiplet) (109 mg, 49%).

Reduction of 25——A suspension of **25** (200 mg) in a mixture of 1N HCl (10 ml) and MeOH (200 ml) was hydrogenated over Raney Ni, prepared from nickel aluminum alloy (300 mg). After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the residue was acidified with 1N HCl and extracted with $CHCl_3$ to give 2,4-dinitrophenol (82 mg, 73%).

The $CHCl_3$ insoluble layer gave **8** (72 mg, 82%).

Reaction of 26 with $NaNO_2$——To a solution of **26** (80 mg) in diluted H_2SO_4 (0.5 ml→10 ml), $NaNO_2$ (0.5 g) in cold water (2 ml) was added dropwise under cooling with ice water and the reaction mixture was kept under cooling for 5 min, followed by at 60° for 10 min, and neutralized with conc. NaOH solution. The resulted precipitates were collected by filtration and recrystallized from MeOH–AcOEt to give **27**, mp 283—284°. *Anal.* Calcd. for $C_{15}H_9O_6N_3$: C, 55.05; H, 2.75; N, 12.88. Found: C, 55.25; H, 2.27; N, 12.94. Mass Spectrum *m/e*: 327 (M^+). UV λ_{max}^{MeOH} mμ (ε): 248 (27500).

Measurement of Electron Spin Resonance Spectra——When a solution of **23** or **25** dissolved in DMF was warmed at 60—100°, any spectra have not been observed.

Apparatus: Japan Electron Optics Laboratory JES-3BX spectrometer

Modulation: 100 Kc/s

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