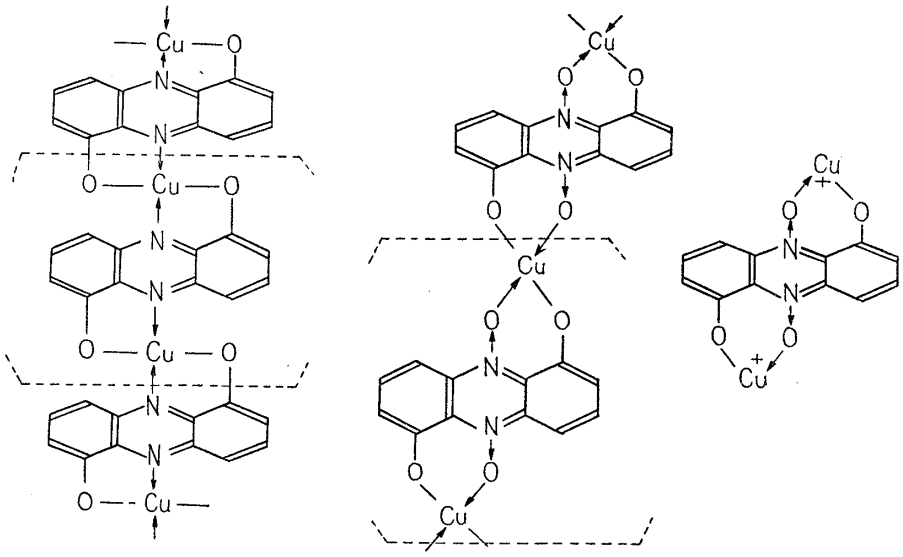

Chart. 1.

The author wishes to express his deep gratitude to Prof. M. Ishidate of the University of Tokyo for his encouragements and helpful advices. The author is also very grateful to Prof. T. Sakaguchi of the University of Chiba for his valuable suggestions and encouragement. A part of the expenses for this work was defrayed by a Grant in Aid for Scientific Research from the Ministry of Education to which the author's thanks are due.

**Summary**

Copper chelates of 1, 6-dihydroxyphenazine and its di-N-oxide, which possess two functional groups, were examined by spectrophotometric method concerning their properties and compositions in solution, as well as their dissociation constants. 1, 6-Dihydroxyphenazine forms a five-membered chelate ring, indicating the molar ratio of 1:1, a normal complex. The N-oxide derivative also form a chelate with molar ratio of 1:1, forming a six-membered chelate ring.

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## 114. **Hirotaka Otomasu and Shoichi Nakajima:** On the Nitration of Quinoxalines.

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Some reports on substitution reaction of quinoxalines with nucleophilic reagents have appeared but not those dealing with electrophilic reagents. In a series of earlier papers,[1] one of the authors (H. O.) established the nitro substitution reaction of phenazine and its derivatives. In this connection, nitration reaction of quinoxaline compounds, structurally related to phenazines, was examined in order to find the reaction mechanism of electrophilic reagents, and some experimental results obtained are reported in this paper.

Generally speaking, the present series of experiments on quinoxaline derivatives has proved that the derivatives are quite stable to nitration and only a few of them could be nitrated.

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1) H. Otomasu: This Bulletin, **2**, 283(1954); **4**, 117(1956); **6**, 77(1958).

Quinoxaline (I) and 2, 3-dimethylquinoxaline (II) resisted nitration, and even if the reaction was carried out with conc. sulfuric and fuming nitric acid at 100°, the reaction did not occur, merely the starting materials being recovered. Accordingly, it was found impossible to obtain those nitro compounds by nitration. On the other hand, nitration reaction proceeded readily in quinoxaline derivatives containing polar functions in their molecules. First attempt for nitration was made with derivatives having polar functions in the benzene ring.

6-Methoxyquinoxaline[2] (III) was nitrated with potassium nitrate in conc. sulfuric acid, forming a mononitro compound of m.p. 203° (IV) in 82% yield. This was reduced catalytically to the amino compound of m.p. 96° and identified with 5-amino-6-methoxyquinoxaline (V), which was prepared by the condensation of glyoxal with the reduction product (VII) of 2, 3-dinitro-*p*-anisidine (VI). From the above results, it was confirmed that the 6-methoxyquinoxaline was substituted in 5-position with the nitro group. No corresponding 5-methoxy-8-aminoquinoxaline (IX′) was produced in this reaction. To obtain 5-methoxy-8-aminoquinoxaline, 1-acetamido-2, 3-diamino-4-methoxybenzene (VIII) was condensed with glyoxal and the resulting 5-methoxy-8-acetamidoquinoxaline (IX) was hydrolysed as shown in Chart 1.

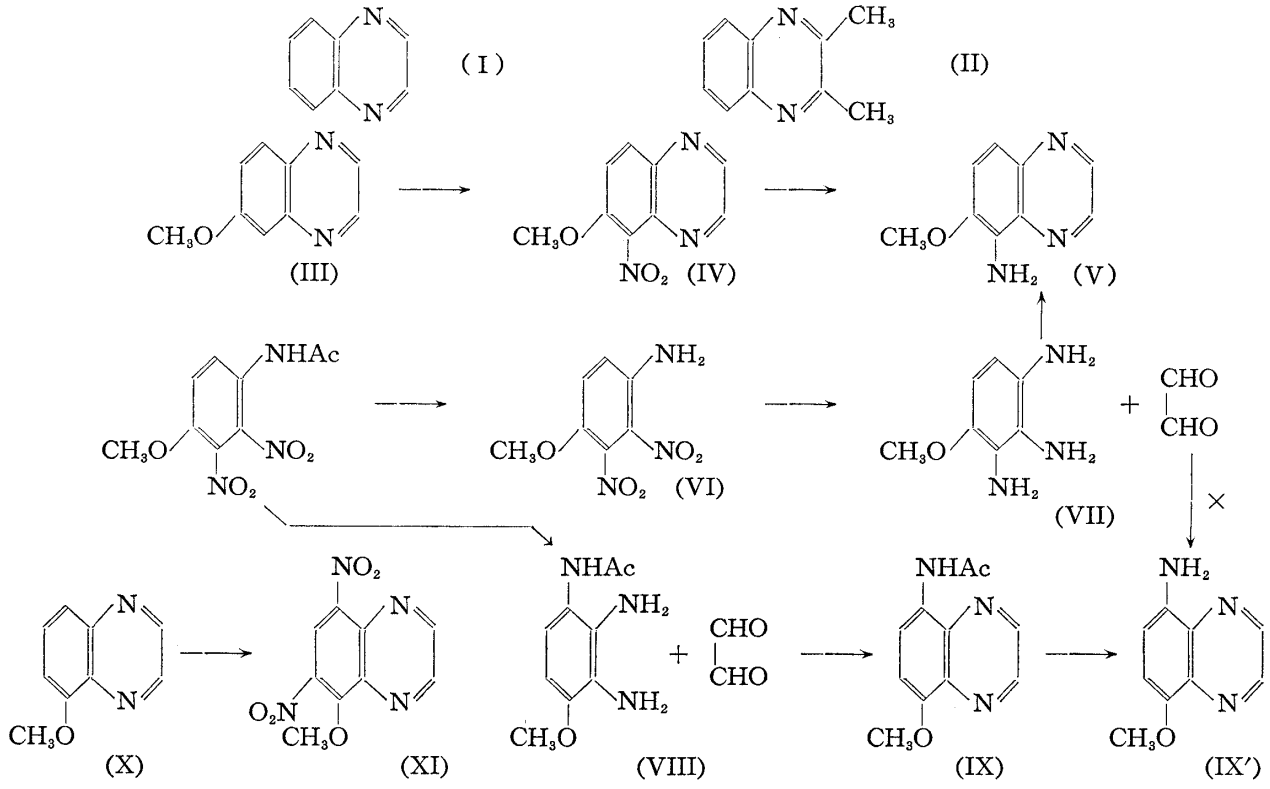



Chart 1.

Similar reaction with 5-methoxyquinoxaline[3] (X) failed to produce a mononitro compound but a disubstituted substance of m.p. 204~206° formed at the rate of 55% yield. In this case, the reaction did not take place at 0° to 5°, and began only when warmed to 60°. This was assumed to be 5-methoxy-6, 8-dinitroquinoxaline (XI) from the consideration of naphthoid activity, although the positions substituted with nitro group were not determined experimentally.

Subsequently, to find the polarization effect of pyrazine ring, quinoxaline N-oxide[4] (XII)

2) G. Körner: Ber., **17**, Ref. 573(1884).
3) F. E. King, N. G. Clark, P. M. H. Davis: J. Chem. Soc., **1949**, 3014.
4) J. K. Landquist: J. Chem. Soc., **1953**, 2816.

was synthesized and nitration was attempted, but this did not react under the same conditions as for (I), and the starting material was recovered. However, in the case of quinoxaline derivatives containing two functions of different polarizability at 2- and 3-positions of the pyrazine ring, the reaction seemed to proceed rather smoothly and 2-hydroxy-3-methylquinoxaline[5] (XV) was nitrated with potassium nitrate in conc. sulfuric acid at 0° to 5°.

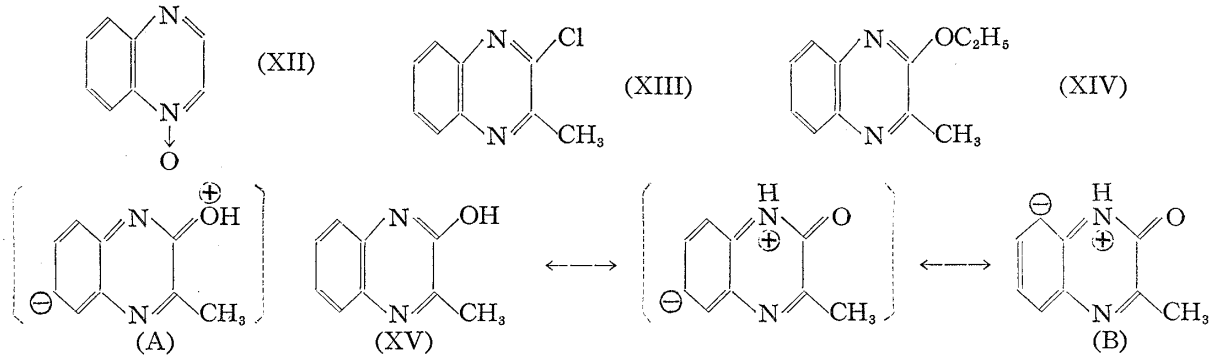
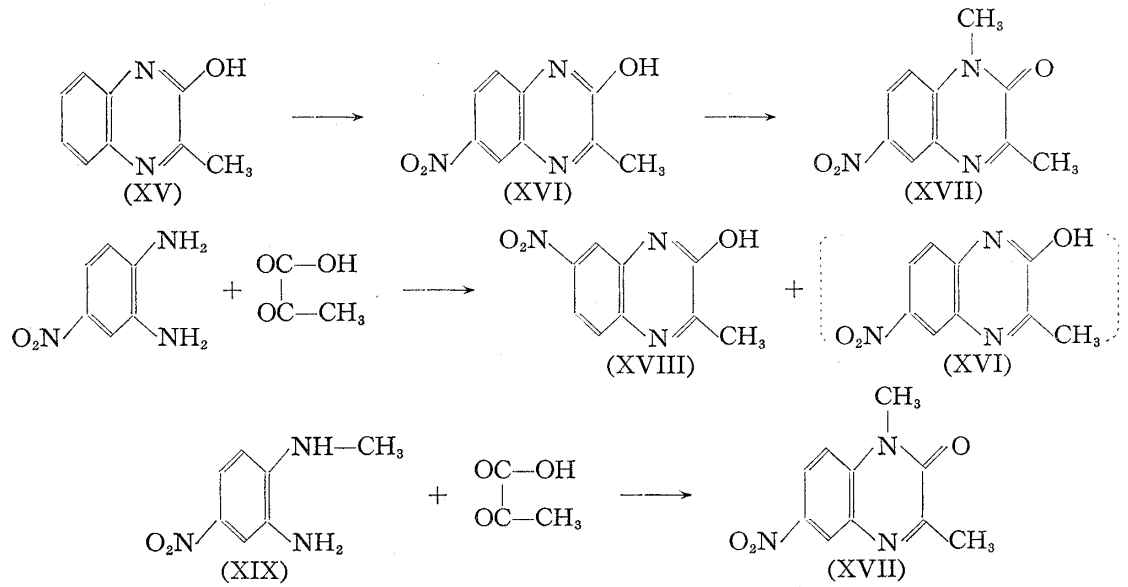



Chart 2.

Nitration of 2-chloro-3-methyl-[6] (XIII) and 2-ethoxy-3-methylquinoxalines[6] (XIV) did not take place under the same conditions.

As for the electronic configuration of 2-hydroxy-3-methylquinoxaline, examples (XIII) and (XIV) are likely to deny its *amphi*-quinoid sutructure (A), and the contribution of the two principal resonance formulae (B) to the reaction may be considered, as shown in Chart 2. Consequently it is supposed that the nitro substitution will probably take place at 6- or 8-position in the benzene ring and taking the case of phenazine N-oxide into account the yield of 8-nitro would be much less than that of the 6-nitro derivative.




In an attempt to synthesize 2-hydroxy-3-methyl-6-nitroquinoxaline, condensation reaction between 1,2-diamino-4-nitrobenzene and pyruvic acid was carried out and slightly yellow needles of m.p. 255°, which was not identical with the nitration product (XVI), m. p. 270°, of 2-hydroxy-3-methylquinoxaline, were obtained. Methylation of the nitration product (XVI) with dimethyl sulfate gave its N-methyl derivative (XVII), m.p. 218°, which agreed with the condensation product, 1, 3-dimethyl-2-oxo-6-nitro-1, 2-dihydroquinoxaline (XVII), of 1-methyl-

5) O. Hinsberg: Ann., **292**, 245(1896).
6) G. T. Newbold, F. S. Spring: J. Chem. Soc., **1948**, 521.

amino-2-amino-4-nitrobenzene[7] (XIX) and pyruvic acid. Accordingly, the location of the nitro group in the benzene ring was shown to be at 6-position.

In addition, the condensation product of m.p. 255°, prepared from 1,2-diamino-4-nitrobenzene and pyruvic acid, was assumed to be 2-hydroxy-3-methyl-7-nitroquinoxaline (XVIII). Though the formation of a small amount of 2-hydroxy-3-methyl-6-nitroquinoxaline (XVI) seemed to be possible in the course of this condensation reaction, it was not separated from the reaction mixture.

Our deep thanks are due to Prof. Dr. M. Ishidate, University of Tokyo, for his encouragement and to Prof. Dr. I. Yosioka, University of Osaka, for his kind advices. We are indebted to Misses T. Oshibe and E. Takahashi for microanalyses.

## Experimental[8]

Quinoxaline (I), quinoxaline N-oxide (XII) and 2,3-dimethylquinoxaline (II) were each nitrated with conc. $H_2SO_4$ and fuming nitric acid (d. 1.52) at 100°. The reaction mixture was poured into cold water, basified with NaOH, then extracted with $CHCl_3$, and the extract was evaporated to dryness. The residual substance was consistent with the starting material, in each case.

**Nitration of 6-Methoxyquinoxaline (III) (Formation of 5-Nitro-6-methoxyquinoxaline (IV))**—6-Methoxyquinoxaline[2] (III) (0.43 g.) was dissolved in conc. $H_2SO_4$ (4 cc), cooled to 0°, and powdered $KNO_3$ (0.5 g.) was added in small portions under good agitation. After the addition was completed, the solution was allowed to stand for 2 hrs. at room temperature and the reaction mixture was poured on ice, whereupon orange-yellow precipitate separated. It weighed 0.45 g. after drying. This was recrystallized from acetone to yield 5-nitro-6-methoxyquinoxaline (IV) as very slightly yellow pillars, m.p. 203°. *Anal.* calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.58; H, 3.53; N, 20.02.

**5-Amino-6-methoxyquinoxaline (V)**—(i) Reduction of 5-nitro-6-methoxyquinoxaline: (IV) (1.42 g.) was catalytically reduced over 10% Pd-C in MeOH (250 cc.). When the absorption of $H_2$ ended, the reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness. The crude product obtained was recrystallized from ligroine to orange pillars, m.p. 96°. *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.59; H, 4.99; N, 23.55.

(ii) Condensation of 2,3,4-Triaminoanisole with Glyoxal: 1-Amino-2,3-dinitro-4-methoxybenzene (5 g.) was dissolved in MeOH (250 cc.) and reduced catalytically over Pd-C. After the $H_2$ absorption had subsided, a solution of glyoxal bisulfite (10 g.) dissolved in hot water (200 cc.) was added to this mixture, which was then warmed for 30 mins. under $H_2$ stream, and refluxed on water bath for the following 1.5 hrs. After MeOH was evaporated *in vacuo*, the solution was made strongly alkaline with NaOH and the resinous substance that precipitated was extracted with $CHCl_3$. The extract was dried and concentrated to yield 1.2 g. of reddish-brown resin, which gave orange pillars of m.p 96° after recrystallization from ligroine. The m.p. of this substance was not depressed when admixed with the reduction product of 5-nitro-6-methoxyquinoxaline. *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99. Found: C, 62.01; H, 5.49; N, 23.50.

**Nitration of 5-Methoxyquinoxaline (X)**—To a solution of 5-methoxyquinoxaline[3] (0.5 g.) in conc. $H_2SO_4$ (5 cc.), $KNO_3$ (1 g.) was added and the mixture was warmed for 15 mins. at 60°. The mixture was poured into ice-water (80 cc.), which was adjusted to weak acidity with NaOH and 0.6 g. of crude crystals that separated were recrystallized from MeOH to 5-methoxy-6,8-dinitroquinoxaline (IX) as slightly yellow needles, m.p. 204~206°. *Anal.* Calcd. for $C_9H_6O_5N_4$: C, 43.20; H, 2.40; N, 22.40. Found: C, 43.25; H, 2.28; N, 21.98.

**5-Methoxy-8-acetamidoquinoxaline (IX)**—1-Acetamido-2,3-dinitro-4-methoxybenzene (4 g.) was reduced catalytically over Pd-C in MeOH (250 cc.). After reduction had been completed, glyoxal bisulfite (8 g.) was added and the mixture was refluxed for 2 hrs. After the catalyst was removed and MeOH evaporated, the residue was made strongly alkaline with NaOH, when orange resinous substance precipitated. This was extracted with $CHCl_3$, the extract was evaporated to dryness to give the crude product (1.8 g.), and its recrystallization from benzine gave yellow rhombic crystals (IX), m.p. 149°. *Anal.* Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.83; H, 5.07; N, 19.36. Found: C, 60.38; H, 4.65; N, 19.09.

**5-Methoxy-8-aminoquinoxaline (IX′)**—The foregoing (IX) was warmed with 20% NaOH solution on a water bath for 1 hr., cooled, and the reaction mixture was extracted with $CHCl_3$. The crude product that deposited was recrystallized from benzene to orange-red plates, m.p. 125°. *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99 Found: C, 61.54; H, 4.55; N, 24.26.

**Nitration of 2-Hydroxy-3-methylquinoxaline (XV) (Formation of 2-Hydroxy-3-methyl-6-nitroquinoxaline (XVI))**—The solution of 2-hydroxy-3-methylquinoxaline[5] (XV) (5 g.) dissolved in conc. $H_2SO_4$ (50 cc.), cooled to 0° to 5°, was added with powdered $KNO_3$ (2.8 g.) in small portions and the solution was kept at room temperature for 2 hrs. The reaction mixture was poured into ice water,

7) K. Brand, E. Wild: Ber., **56**, 115 (1923).
8) All melting points are uncorrected.

whereupon 4.5 g. of orange-yellow precipitate separated. Further 0.5 g. was obtained from the mother liquor. These were combined and recrystallized from acetone to yellow needles of m. p. 270° (darken. at about 250°). *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.41; N, 20.97. Found: C, 53.18; H, 3.29; N, 20.24.

2-Chloro-3-methyl-[6] (VIII) and 2-ethoxy-3-methylquinoxalines[6] (IX) were nitrated by the same procedure as above, but no nitration product was obtained.

**Condensation Reaction of 1, 2-Diamino-4-nitrobenzene and Pyruvic Acid (Formation of 2-Hydroxy-3-methyl-7-nitroquinoxaline (XVIII))**—To a solution of 1, 2-diamino-4-nitrobenzene (1.5 g.) in MeOH (200 cc.), pyruvic acid (1 g.) was added. After boiling for 1 hr., MeOH was evaporated and the residue was washed with water and dried, which weighed 1.85 g. This was recrystallized four times from MeOH to slightly yellow needles, m.p. 255°. *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.41; N, 20.97. Found: C, 52.68; H, 3.44; N, 20.39.

**1, 3-Dimethyl-2-oxo-6-nitro-1, 2-dihydroquinoxaline (XVII)**—(i) To a solution of 2-hydroxy-3-methyl-6-nitroquinoxaline (XVI) (1 g.) dissolved in 20% NaOH (20 cc.), $Me_2SO_4$ (4 cc.) was added, the mixture was agitated at room temperature, and cooled. The precipitate that separated out was collected (0.55 g.), dissolved in hot acetone, treated with carbon, and cooled to give yellow prisms of m.p. 218°. *Anal.* Calcd. for $C_{10}H_9O_3N_3$: C, 54.80; H, 4.11; N, 19.18. Found: C, 54.87; H, 3.85; N, 19.18.

(ii) To a solution of 1-methylamino-2-amino-4-nitrobenzene[7] (XIX) (0.2 g.) dissolved in MeOH (50 cc.), pyruvic acid (0.2 g.) was added and the mixture was refluxed for 1 hr. The residue obtained on evaporation of MeOH was recrystallized from acetone to yellow prisms (0.16 g.), m. p. 218°, undepressed on admixture with 1, 3-dimethyl-2-oxo-6-nitro-1, 2-dihydroquinoxaline (XVIII), obtained by the methylation of nitration product of 2-hydroxy-3-methylquinoxaline. *Anal.* Calcd. for $C_{10}H_9O_3N_3$: C, 54.80; H, 4.11; N, 19.18. Found: C, 54.97; H, 3.83; N, 19.26.

## Summary

Quinoxaline, quinoxaline N-oxide, and 2, 3-dimethylquinoxaline were resistant to nitration, but the quinoxaline derivatives containing polar functions, either in benzene or pyrazine ring, were readily nitrated. Thus, 5-methoxy-, 6-methoxy-, and 2-hydroxy-3-methyl-quinoxalines yielded upon nitration 5-methoxy-6, 8-dinitro-, 5-nitro-6-methoxy- and 2-hydroxy-3-methyl-6-nitro-quinoxalines, respectively.

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