Notes

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Hirotaka Otomasu and Kei Yoshida : On the Nitration of Quinoxalines (Addendum).

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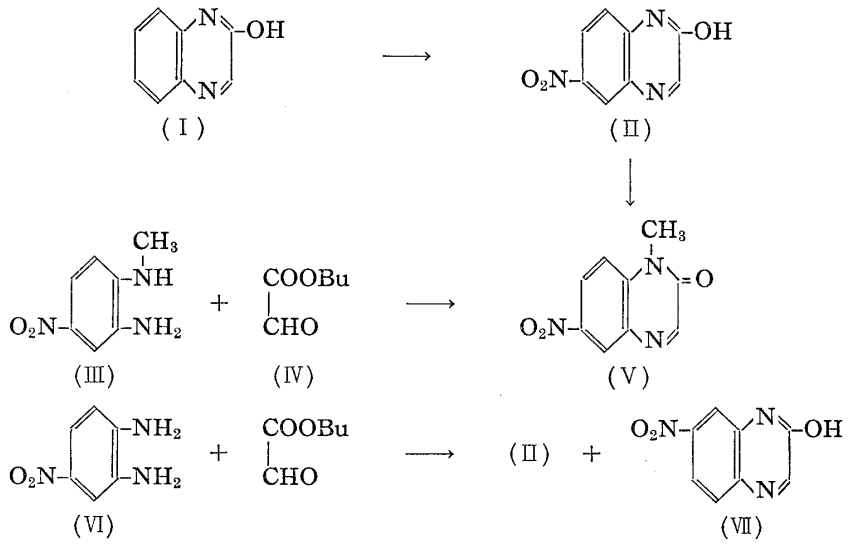
In a previous paper,[1] one of the present authors (H. O.), together with Nakajima, reported that in nitration of quinoxalines, the substitution of nitro group was found to take place at the 6-position in a 2-hydroxy-3-methylquinoxaline. In this present work, nitration of 2-hydroxyquinoxaline was attempted and an interesting fact was found that the substitution position differed according to the nitration conditions. The results are reported herein together with some addition to the work described in the preceding paper.[1]

2-Hydroxyquinoxaline (I) was nitrated with potassium nitrate in conc. sulfuric acid, forming a mononitro compound of m.p. 306° in 77% yield. This was treated with phosphoryl chloride and formed colorless needles of m.p. 202°, which agreed with the data for 2-chloro-6-nitroquinoxaline by Horner, *et al.*[2] The afore-mentioned nitration



product (II) was methylated with dimethyl sulfate and yielded the N-methyl derivative of m.p. 213°, which was consistent with the product prepared from the condensation of 1-methylamino-2-amino-4-nitrobenzene with butyl glyoxylate. This compound therefore is 1-methyl-2-oxo-6-nitro-1,2-dihydroquinoxaline (V).

On the other hand, 2-hydroxy-7-nitroquinoxaline (VII) had been obtained by Asano[3] in 65% yield by direct nitration of 2-hydroxyquinoxaline (I) with conc. nitric acid in glacial acetic acid at room temperature. He verified the structure, which, when reduced to the amino derivative, was consistent with the authentic specimen of 2-hydroxy-7-aminoquinoxaline prepared by the method of Atkinson, *et al.*[4]

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1) H. Otomasu, S. Nakajima : This Bulletin, **6**, 566(1958).
2) L. Horner, U. Schwenk, E. Junghanns : Ann., **597**, 212(1953).
3) K. Asano : Yakugaku Zasshi, **79**, 658(1959).
4) C. M. Atkinson, C. W. Brown, J. C. E. Simpson : J. Chem. Soc., **1956**, 26.

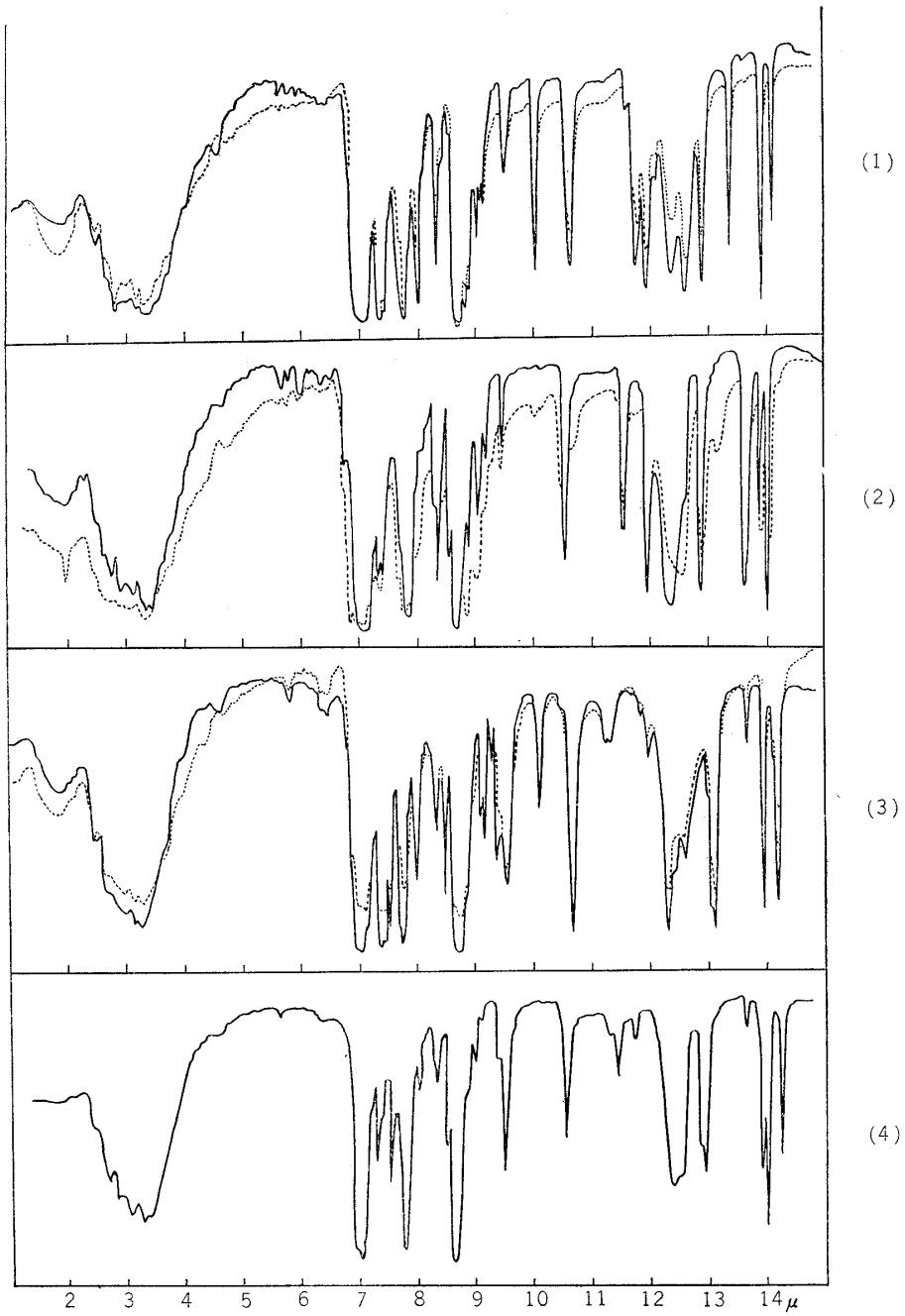


Fig. 1. Infrared Absorption Spectra of 2-Hydroxy-6- and -7-nitroquinoxaline (KBr disc)

—— Nitration product
------ Condensation product

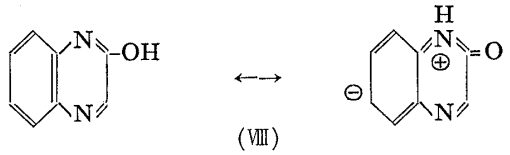
(1) 2-Hydroxy-6-nitroquinoxaline
(2) 2-Hydroxy-7-nitroquinoxaline
(3) 2-Hydroxy-3-methyl-6-nitroquinoxaline
(4) 2-Hydroxy-3-methyl-7-nitroquinoxaline

Various workers[2~5] reported the synthesis of 6- or 7-nitroquinoxaline. Horner, *et al.*[2] isolated two substances, 2-hydroxy-6- and -7-nitroquinoxalines from the condensation product of 1,2-diamino-4-nitrobenzene with ethyl glyoxylate diethyl acetal.

5) F. J. Wolf, K. Pfister, 3rd., R. H. Beutel, R. M. Wilson, Jr., C. A. Robinson, J. R. Stevens: J. Am. Chem. Soc., **71**, 6(1949).

In order to obtain the same compounds, 2-hydroxy-6- and -7-nitroquinoxalines, condensation reaction of 1,2-diamino-4-nitrobenzene with butyl glyoxylate was carried out and two substances, (II), m.p. 306°, and (VII), m.p. 275°, were obtained, both of which agreed with those of Horner's description. These compounds were identical with the nitration product obtained by the nitration of 2-hydroxyquinoxaline (I) with a mixture of nitric and sulfuric acids or with conc. nitric acid in glacial acetic acid. The identity of 2-hydroxy-6- and -7-nitroquinoxaline was confirmed by admixture of the 2-chloro derivatives and also by comparison of their infrared spectra. Accordingly, the location of the nitro group in 2-hydroxyquinoxaline prepared by nitration with a mixture of nitric and sulfuric acids was shown to be the 6-position.

It may be supposed that the different results by the nitration condition with a mixture of nitric and sulfuric acids is caused by the electronic configuration of 2-hydroxyquinoxaline contributing to the structure of (VIII) formulae, as shown.



(VIII)

As was reported in a previous paper,[1] 2-hydroxy-3-methyl-7-nitroquinoxaline was produced by the condensation of 1,2-diamino-4-nitrobenzene and pyruvic acid, but when the reaction was followed in more detail, it was found that a small amount of another isomer, 2-hydroxy-3-methyl-6-nitroquinoxaline, was also obtained by the fractional recrystallization of the condensation product, and moreover, this compound was identical with the nitration product of 2-hydroxy-3-methylquinoxaline.

Experimental*2

Nitration of 2-Hydroxyquinoxaline (I) (Formation of 2-Hydroxy-6-nitroquinoxaline (II))—To a solution of 2-hydroxyquinoxaline (I) (0.5 g.) in conc. H_2SO_4 (5 cc.), well powdered KNO_3 (0.35 g.) was added and the mixture was warmed for 10 min. at 40° with good agitation. The reaction mixture was poured into cold water, whereupon yellow precipitate separated. The crude product was washed with water and dried (0.5 g.). Yield, ca. 77%. Recrystallization from MeOH gave yellow needles, m.p. 306° (reported[2] m.p. 294°). *Anal.* Calcd. for $C_8H_5O_3N_3$: C, 50.26; H, 2.64; N, 21.98. Found: C. 49.77; H, 2.23; N, 21.60.

1-Methyl-2-oxo-6-nitro-1,2-dihydroquinoxaline (V)—i) 2-Hydroxy-6-nitroquinoxaline (II) (1 g.) was dissolved in hot water and basified with NaOH solution. To this solution was added Me_2SO_4 (3.5 cc.) and the mixture was shaken vigorously at room temperature. The precipitate that separated out was collected and recrystallized from MeOH to pale yellow needles, m.p. 213°. *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.69; H, 3.41; N, 20.50. Found: C, 52.29; H, 3.34; N, 20.61.

ii) To a solution of 1-methylamino-2-amino-4-nitrobenzene (1 g.) dissolved in EtOH (10 cc.), butyl glyoxylate (1.7 g.) was added and the mixture was refluxed for 1 hr. After removal of the solvent, the residue was recrystallized from MeOH to 1-methyl-2-oxo-6-nitro-1,2-dihydroquinoxaline (0.8 g.), m.p. 213°, undepressed on admixture with the sample obtained as described in (i).

2-Chloro-6-nitroquinoxaline—2-Hydorxy-6-nitroquinoxaline (II) (0.3 g.) was heated with $POCl_3$ (8 cc.) in an oil-bath for 2 hr. $POCl_3$ was removed by distillation under a reduced pressure and the residue was washed with water. By recrystallization from MeOH, 2-chloro-6-nitroquinoxaline was obtained as colorless needles, m.p. 202°. *Anal.* Calcd. for $C_8H_4O_2N_3Cl$: N, 20.05. Found: N, 20.04.

Condensation of 1,2-Diamino-4-nitrobenzene with Butyl Glyoxylate (Formation of 2-Hydroxy-6- (II) and -7-nitroquinoxaline (VII))—According to the method of Atkinson, *et al.*,[4] a mixture of 1,2-diamino-4-nitrobenzene (4 g.) in EtOH (8 cc.) and butyl glyoxylate (4 g.) was refluxed for 2 hr., cooled, and filtered. The product of mixed hydroxy compounds was washed with EtOH and dried (4.2 g.). The whole was refluxed with EtOH (1300 cc.) to complete solution, clarified with activated carbon, concentrated to about 800 cc., and cooled to room temperature. The crystals that separated out

*2 All m.p.s are uncorrected.

were collected (0.8 g.) and purified from Me_2CO to yield nearly colorless crystals of m.p. 306°. This was not depressed by admixture with 2-hydroxy-6-nitroquinoxaline (II) prepared by nitration of (I) with KNO_3 in conc. H_2SO_4.

The mother liquor of the product (II) was evaporated to dryness after purification with activated carbon and the residue was washed with MeOH (3 g.). After repeated recrystallization, the product that did not melt below 260° was collected and heated on a water-bath with excess of $POCl_3$ for 1 hr. $POCl_3$ was removed by distillation under a reduced pressure and the residue was washed with water. The solid product was recrystallized from benzene to colorless needles, m.p. 185~186°, of 2-chloro-7-nitroquinoxaline.

This chloro compound (0.5 g.) was refluxed for 2.5 hr. with *N* HCl (10 cc.) in EtOH (4 cc.). After cool, the product was recrystallized from Me_2CO to orange needles, m.p. 275~276°. *Anal.* Calcd. for $C_8H_5O_3N_3$: N, 21.98. Found: N, 21.93. This was identical with 2-hydroxy-7-nitroquinoxaline prepared by nitration of (I) with conc. HNO_3 in AcOH by Asano's method.[3] Structural confirmation of these compounds was made by mixed fusion of the respective 2-chloro derivatives and also by comparison of their IR spectra.

Condensation Reaction of 1,2-Diamino-4-nitrobenzene and Pyruvic Acid (Formation of 2-Hydroxy-3-methyl-6- and -7-nitroquinoxaline)—To a solution of 1,2-diamino-4-nitrobenzene (1.2 g.) in MeOH (70 cc.), pyruvic acid (0.8 g.) was added with warming. When cool, the crystals (0.8 g.) separated and were recrystallized twice from Me_2CO to 2-hydroxy-3-methyl-7-nitroquinoxaline as slightly yellow needles, m.p. 255° (reported[2] m.p. 252°). *Anal.* Calcd. for $C_9H_7O_3N_3$: N, 20.97. Found: N, 20.72.

From the recrystallization mother liquor, 0.2 g. of slightly yellow needles, m.p. ca. 280° (decomp.), was obtained (this compound was reported as melting at 270° in earlier paper[1]; reported[2] m.p. 282°). This compound was found to be identical with 2-hydroxy-3-methyl-6-nitroquinoxaline by mixed fusion and by the comparison of IR spectra. *Anal.* Calcd. for $C_9H_7O_3N_3$: N, 20.97. Found: N, 20.84.

2-Chloro-3-methyl-7-nitroquinoxaline—2-Hydroxy-3-methyl-7-nitroquinoxaline (0.15 g.) was heated with $POCl_3$ (4 cc.) on a water bath for 30 min. Excess of $POCl_3$ was removed by distillation under a reduced pressure and decomposed with water. The reddish brown precipitate (0.1 g.) was obtained and purified by sublimation in high vacuum to colorless needles, m.p. 153°. *Anal.* Calcd. for $C_9H_6O_2N_3Cl$: C, 48.34; H, 2.70; N, 18.8. Found: C, 48.89; H, 3.04; N, 18.60.

2-Chloro-3-methyl-6-nitroquinoxaline—2-Hydroxy-3-methyl-6-nitroquinoxaline (0.2 g.) was heated with $POCl_3$ (5 cc.). The reaction mixture was treated as above and colorless needles of m.p. 136° were obtained. *Anal.* Calcd. for $C_9H_6O_2N_3Cl$: C, 48.34; H, 2.70; N, 18.8. Found: C, 48.48; H, 2.70; N, 18.79.

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Summary

2-Hydroxyquinoxaline was nitrated with potassium nitrate in conc. sulfuric acid and formed 2-hydroxy-6-nitroquinoxaline, m.p. 306°, in 77% yield. This was treated with dimethyl sulfate and 1-methyl-2-oxo-6-nitro-1,2-dihydroquinoxaline, m.p. 213°, was obtained, which was also prepared by the condensation of 1-methylamino-2-amino-4-nitrobenzene with butyl glyoxylate.

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