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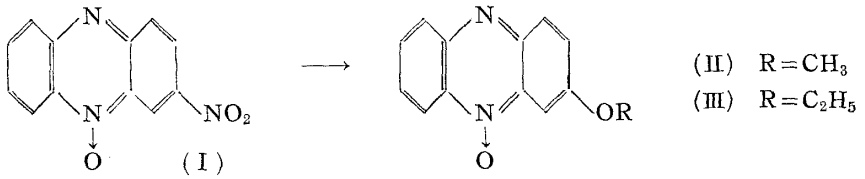
25. Hirotaka Otomasu: Studies on Phenazines. XI.* Nitration of Phenazine and Its Derivatives. (2).*

(*Hoshi College of Pharmacy***)

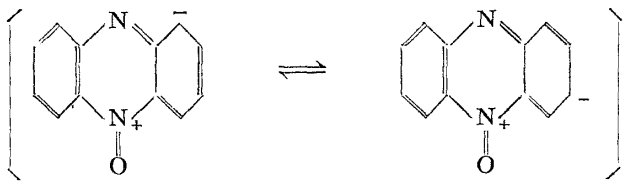
As described in Part VII[1] of this series, two mononitro compounds, orange red needles (I) of m.p. 204° and a small amount of yellow needles, m.p. 213°, were obtained by the nitration of phenazine N-oxide. These substances were assumed to be 3- and 1-nitrophenazine 5-oxide, because 1- and 3-positions of phenazine 5-oxide were activated by N-oxide against electrophilic reagents, and actually, the reduction product of these nitro compounds were found to be identical with 2- and 1-aminophenazine, respectively.

The present paper describes the experimental determination of the substituted position of nitro groups, together with the nitration of chlorophenazine derivatives.



By refluxing with methanolic potassium hydroxide solution, (I) was converted to 3(2)-methoxyphenazine 5(10)-oxide (II) in 50% yield, which had been previously prepared by Yosioka.[2] Therefore, another nitro compound of m.p. 213° should be 1-nitrophenazine 5-oxide. In this reaction, (I) was treated with ethanolic solution by the same method, and the yield of 3-ethoxyphenazine 5-oxide[3] (III) was far smaller and no corresponding substance was produced on using the higher alcohols than ethanol, such as propanol, butanol, or phenol. When the similar reaction was carried out with 2-nitrophenazine, instead of (I), both 2-methoxyphenazine and 2-hydroxyphenazine were obtained in a very poor yield.

From the above experiments, the polarization of N-oxide group in the phenazine ring seems to be explained by the principal two resonance formulae as shown.



Subsequently, the nitration of chlorophenazines and their N-oxides were successively carried out.

As was reported in the preceding paper[1] on methoxyphenazine and its N-oxide, the nitro substituent was not governed by the polarization of N-oxide but by the effect of methoxyl group. The results obtained from the nitration of chlorophenazine or its N-oxide, however, differed entirely from the case of methoxyl derivatives.

Both 1- and 2-chlorophenazines strongly resist nitration with conc. sulfuric acid and potassium nitrate, and even if the reaction temperature was raised up to 80°,

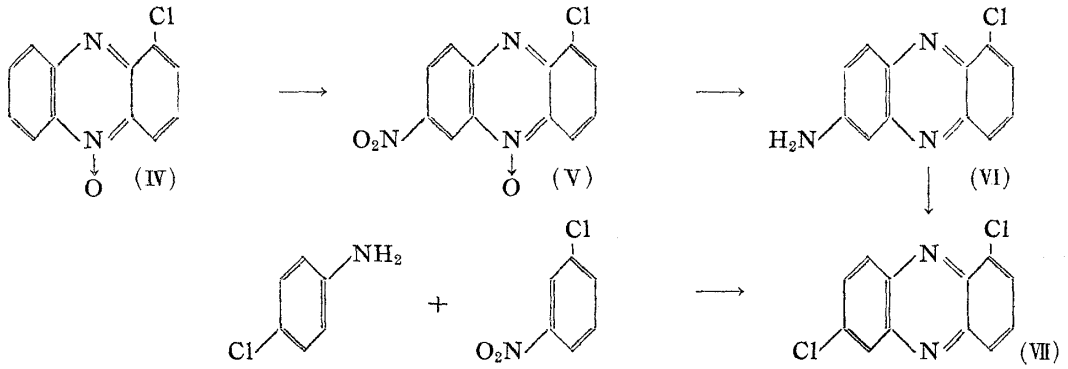
* Part X: J. Pharm. Soc. Japan, **76**, 30(1956). (1) is Part VII.

** 2-Chome, Ebara, Shinagawa-ku, Tokyo (乙益寛隆).

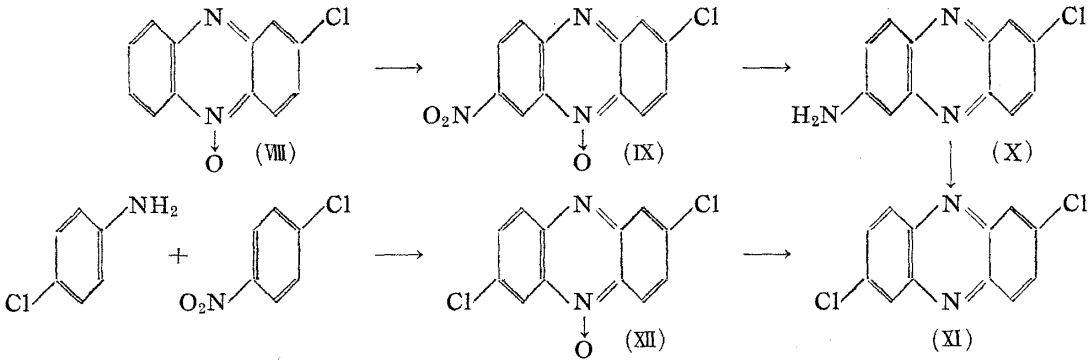
1) H. Otomasu: This Bulletin, **2**, 283(1954).
2) I. Yosioka: J. Pharm. Soc. Japan, **72**, 1128 (1952).
3) I. J. Pachter, M. C. Kloetzel: J. Am. Chem. Soc., **74**, 971(1952).

the reaction does not occur, recovering the starting materials. The nitration was therefore carried out with their N-oxides, the reaction proceeded smoothly, and mononitro compounds were easily obtained.

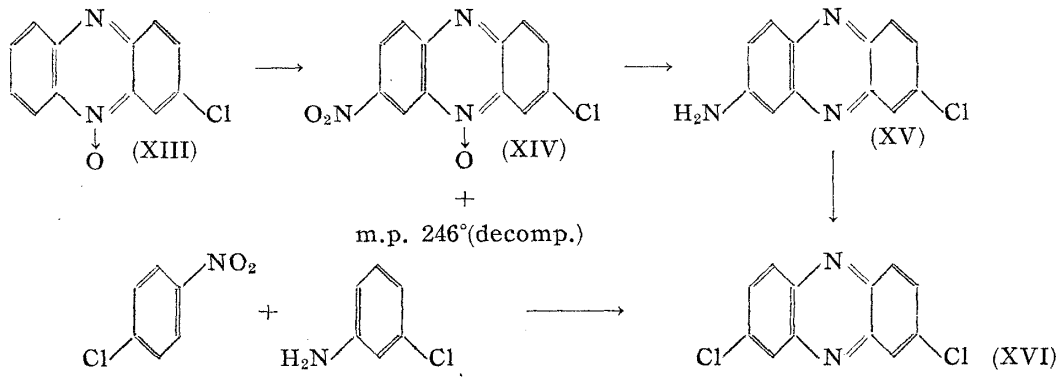
When 1-chlorophenazine 5-oxide (IV) was nitrated with conc. sulfuric acid and potassium nitrate at 0°, and a mononitro compound of m.p. 240°(decomp.) (V) was produced in a good yield. This was reduced to the amino derivative (VI) with stannous chloride, followed by diazotation and treatment with cuprous chloride to 1,7-dichlorophenazine (VII) previously prepared.[4]



From 2-chlorophenazine 5-oxide (VIII), mononitro compound (IX) was obtained in 90% yield. This was converted into the dichloro derivative (XI) of m.p. 266° by way of aminophenazine (X) in a poor yield. This was found to be identical with 2,7-dichlorophenazine[3,5] prepared from Wohl-Aue condensation of *p*-chloronitrobenzene with *p*-chloroaniline.



Nitration of 3(2)-chlorophenazine 5(10)-oxide (XIII) gave two kinds of mononitro isomers, m.p. 266°(decomp.) (XIV) and m.p. 246°(decomp.), in a good yield, which were separated by fractional recrystallization from acetic anhydride.



4) H. Otomasu : This Bulletin, **3**, 365(1955).
5) Eng. Bamberger, W. Ham : Ann., **382**, 93(1911).

The structure of the mononitro compound, m.p. 266°(decomp), the main product, which was obtained in 85% yield, was determined by its conversion into the dichloro derivative of m.p. 224~225° and was identified as 3,7(2,8)-dichlorophenazine (XVI) by comparison with a specimen previously synthesized.[4] The structure of the other yellow compound of m.p. 246°(decomp.) has not been examined yet.

Consequently, in these cases of 1-, 2-, and 3-chlorophenazine 5-oxides, the same 7-position of the phenazine ring was substituted with the nitro group.

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Experimental

Changing Reaction of 3-Nitrophenazin 5-Oxide (I) : 3(2)-Methoxyphenazine 5(10)-Oxide (II)—To the solution of 3-nitrophenazine 5-oxide (0.4 g.) in MeOH (80 cc.) was added KOH (0.5 g.) and water (10 cc.). The mixture was refluxed on a water bath for 12 hrs., MeOH was removed, and the residue was washed with water. The solid reaction product in benzene solution was chromatographed on Al_2O_3, and yellow needles (0.18 g.) were obtained, m.p. 175~176°(from ligroine), not depressed by admixture with the authentic specimen of 3(2)-methoxyphenazine 5(10)-oxide.[2]

In an analogous procedure, 2-methoxyphenazine (20 mg., m.p. 123~124°[2]) was obtained from 2-nitrophenazine (0.4 g.). The water-soluble mothor liquor was neutralized with AcOH and extracted with AcOEt. The residue from AcOEt solution was recrystallized from benzene to brownish yellow powder, m.p. 248~250°(decomp.)[2], of 2-hydroxyphenazine (60 mg.).

3-Ethoxyphenazine 5-Oxide (III)—According to the same method as described above, 3-ethoxyphenazine 5-oxide[3] was obtained from (I). Yield : 10%. Yellow needles, m.p. 171°(from MeOH).

Preparation of (III)—A mixture of *p*-phenetidine (10 g.) and nitrobenzene (10 g.) was refluxed for 4 hrs. in toluene (150 cc.), in the presence of powdered KOH (30 g.). The mixture was treated as usual and amorphous product in benzene solution was purified by chromatography on Al_2O_3. The first eluate gave 0.04 g. of 2-ethoxyphenazine as pale yellow needles, m.p. 114~115°[3](from ligroine). *Anal.* Calcd. for $C_{14}H_{12}ON_2$: N, 12.50. Found : N, 12.56.

The last eluate gave 1.2 g. of 3-ethoxyphenazine 5-oxide as yellow needles, m.p. 171°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: N, 11.66. Found : N, 11.80.

Niration of 1-Chlorophenazine 5-Oxide (IV) : 1-Chloro-7-nitro-phenazine 5-Oxide (V)—1-Chlorophenazine 5-oxide (3 g.) was dissolved in conc. H_2SO_4(30 cc.) and cooled to 0°. To the solution was added powdered KNO_3(1.6 g.) in small portions, and the mixture was stirred at below 5°. After the addition was completed, the solution was allowed to stand for 6 hrs. at room temp. Then the reaction mixture was poured into water, whereupon orange precipitate separated. It weighed 2.8 g. This was recrystallized from Ac_2O to yield 1-chloro-7-nitrophenazine 5-oxide as orange yellow needles, m.p. ca. 240°(decomp.). *Anal.* Calcd. for $C_{12}H_6O_3N_3Cl$: C, 52.26; H, 2.17; N, 15.24. Found : C, 52.66; H, 2.70; N, 14.97.

Reduction of (V) : 1-Chloro-7-aminophenazine (VI)—To the suspension of (V)(0.5 g.) in MeOH (4 cc.) was added $SnCl_2$(1.5 g. in 8 cc. conc. HCl) in small portions with shaking. The reaction mixture was warmed on a water bath for a while, the amino salt that separated was collected, and dissolved in dil. HCl solution with heating. The acid solution was filtered and neutralized with NH_4OH, to separate the free amino derivative. The dark red precipitate obtained was recrystallized from MeOH to deep red needles, m.p. 210°. *Anal.* Calcd. for $C_{12}H_8N_3Cl$: C, 62.75; H, 3.49; N, 18.30. Found : C, 62.97; H, 3.49; N, 17.75.

1-Chloro-7-acetylaminophenazine—This was obtained by the acetylation of (VI) with Ac_2O. Yellow needles, m.p. 269°(from MeOH). *Anal.* Calcd. for $C_{14}H_{10}ON_3Cl$: C, 61.88; H, 3.65; N, 15.46. Found : C, 62.07; H, 3.57; N, 15.00.

Sandmeyer Reaction of (VI) : 1,7-Dichlorophenazine (VII)—To the solution of (VI)(0.4 g.) in conc. HCl (10 cc.), $NaNO_2$ solution (0.21 g. in 2 cc. H_2O) was added at 0°. To the mixture, freshly prepared Cu_2Cl_2(0.8 g.) was added in small portions. After standing for 30 min., the reaction mixture was warmed on a water bath for a while. This was neutralized with ammonia water, the precipitate was dissolved in benzene, and run through the column of Al_2O_3. The eluate gave a small amount of pale yellow needles, m.p. 191~195°, which was not depressed by the authentic specimen of 1,7-dichlorophenazine.[4]

2-Chloro-7-nitrophenazine 5-Oxide (IX)—(VIII)(1 g.) in conc. H_2SO_4(10 cc.) with KNO_3(0.6 g.) was nitrated by the usual method. The reaction product was recrystallized from Ac_2O to yield 2-chloro-7-nitrophenazine 5-oxide, as orange yellow needles, m.p. 266°(decomp.). Yield, 90%. *Anal.* Calcd. for $C_{12}H_6O_3N_3Cl$: C, 52.26; H, 2.17; N, 15.24. Found : C, 52.19; H, 2.51; N, 15.01.

2-Chloro-7-aminophenazine (X)—The suspension of (IX)(0.5 g.) in MeOH (20 cc.) was reduced with $SnCl_2$(1.5 g. in conc. HCl 6 cc.). The amino salt was treated as for (VI) and red needles, m.p. 250°(from MeOH), were obtained. *Anal.* Calcd. for $C_{12}H_8N_3Cl$: C, 62.75; H, 3.49; N, 18.30. Found : C, 62.75; H, 3.36; N, 17.86.

2-Chloro-7-acetylaminophenazine—Yellow needles, m.p. 266°(from MeOH). *Anal.* Calcd. for $C_{14}H_{10}ON_3Cl$: C, 61.88; H, 3.65; N, 15.46. Found : C, 61.89; H, 3.45; N, 14.95.

2,7-Dichlorophenazine (XI)—The diazotized solution of (X) was added with freshly prepared Cu_2Cl_2 in small portions. The reaction mixture was treated as in the case of (VII), and 2,7-dichlorophenazine (XI) was obtained as pale yellow needles, m.p. 266°(from benzene), which was not depressed by admixture with the sample from the next process.

Preparation of (XI) by Wohl-Aue Condensation—According to the method of Pachter *et al.*,[3] a mixture of *p*-chloroaniline (10 g.) and *p*-chloronitrobenzene (10 g.) was refluxed for 2 hrs. in toluene (150 cc.) in the presence of powdered KOH (30 g.). The reaction product was treated as usual, and yellow needles, m.p. 235°(decomp.), of 2,7-dichlorophenazine 5-oxide (XII), were obtained in 18% yield. *Anal.* Calcd. for $C_{12}H_6ON_2Cl_2$: N, 11.20. Found : N, 10.98. This was refluxed gently with excess of aniline and 2,7-dichlorophenazine was obtained in theoretical yield. *Anal.* Calcd. for $C_{12}H_6N_2Cl_2$: N, 12.44. Found : N, 12.12.

3(2)-Chloro-7(8)-nitrophenazine 5(10)-Oxide(XIV)—(XIII)(1.5 g.)was nitrated by the same method as described above and an orange product was obtained in 85% yield. This was recrystallized from Ac_2O to (XIV) as orange yellow needles, m.p. 266°(decomp.). *Anal.* Calcd. for $C_{12}H_6O_3N_3Cl$: C, 52.26; H, 2.17; N, 15.24. Found : C, 52.14; H, 2.19; N, 15.03.

From the Ac_2O mothor liquor of recrystallization, 0.06 g. of isomeric mononitro compound was obtained as yellow needles, m.p. 246°(decomp.). *Anal.* Calcd. for $C_{12}H_6O_3N_3Cl$: C, 52.26; H, 2.17; N, 15.24. Found : C, 52.64; H, 2.52; N, 15.03.

3(2)-Chloro-7(8)-aminophenazine (XV)—Red needles, m.p. 251°(from MeOH). *Anal.* Calcd. for $C_{12}H_8N_3Cl$: C, 62.74; H, 3.49; N, 18.30. Found : C, 62.54; H, 3.72; N, 18.06.

3(2)-Chloro-7(8)-acetylaminophenazine—Yellow needles, m.p. 255°(from MeOH). *Anal.* Calcd. for $C_{14}H_{10}ON_3Cl$: C, 61.88; H, 3.65; N, 15.46. Found : C, 61.56; H, 3.26; N, 15.05.

3,7(2,8)-Dichlorophenazine (XVI)—This was obtained by the Sandmeyer reaction of (XV), as in the case of (VII). Pale yellow needles, m.p. 224~225°, which was undepressed by a sample of 3,7(2,8)-dichlorophenazine.[4]

Summary

1) The main product of m.p. 204°, which was previously obtained by the nitration of phenazine N-oxide, was converted into 3-methoxyphenazine 5-oxide by refluxing with methanolic solution of potassium hydroxide.

2) 1- and 2-Chlorophenazine were not nitrated with conc. sulfuric acid and potassium nitrate, even when the temperature was raised to 80°.

3) 1-, 2-, and 3-Chlorophenazine 5-oxides were substituted at the same 7- position by the nitro group.

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