17. Itiro Yosioka and Hirotaka Otomasu: Studies on Phenazines. IV. Synthesis of Iodinin Isomers. (1). Syntheses of 2,7- and 1,8-Dihydroxyphenazine Di-N-oxides.

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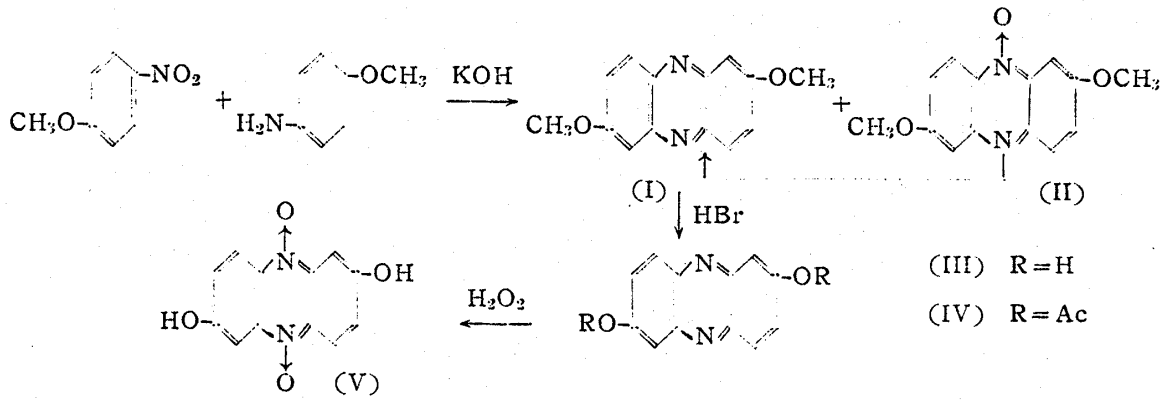
In the previous paper of this series[1], Yosioka and Kidani reported the synthesis of iodinin. Syntheses of iodinin isomers, 2,7- and 1,8-dihydroxyphenazine di-N-oxides, are reported in the present paper, successively.

2,7-Dihydroxyphenazine di-N-oxide was first synthesized by Vivian[2] in 1951, by oxidizing 2,7-dichlorophenazine, the starting material, with hydrogen peroxide and treating the resulting 2,7-dichlorophenazine di-N-oxide with alkali solution.

We synthesized it from 2,7-dihydroxyphenazine by another method which is shown below.

Following the improved Wohl-Aue method of phenazine synthesis, as reported by us[3,4], mixture of *p*-nitroanisole, *p*-anisidine, and potassium hydroxide was heated in toluene for 6 hours and 2,7-dimethoxyphenazine (I) was obtained together with about the same amount of 2,7-dimethoxyphenazine 10-mono-N-oxide (II). The latter (II) was easily deoxygenated by heating with acetic anhydride. When the mixture in this condensation was kept standing at 50~55° for 3 days without the solvent, the yield of both were the same. However, when the reaction temperature was raised to 70~75°, none of the objective compound (I) was obtained but a large amount of azoxy compound was produced, besides the mono-N-oxide (II).

2,7-Dimethoxyphenazine (I) thus obtained was demethylated with hydrobromic acid and acetic acid. As 2,7-dihydroxyphenazine (III) was sparingly soluble in organic solvents and it was difficult to be oxidized, its diacetate (IV) was prepared. This was oxidized with hydrogen peroxide and acetic anhydride in benzene as in the case of iodinin[1] and the objective 2,7-dihydroxyphenazine di-N-oxide (V) was obtained smoothly. In this reaction, acetyl groups were easily saponified by hydrogen peroxide. This substance crystallized as orange microplates, melting at 234~236° with decomposition, and coincided well with that of Vivian's description[2].



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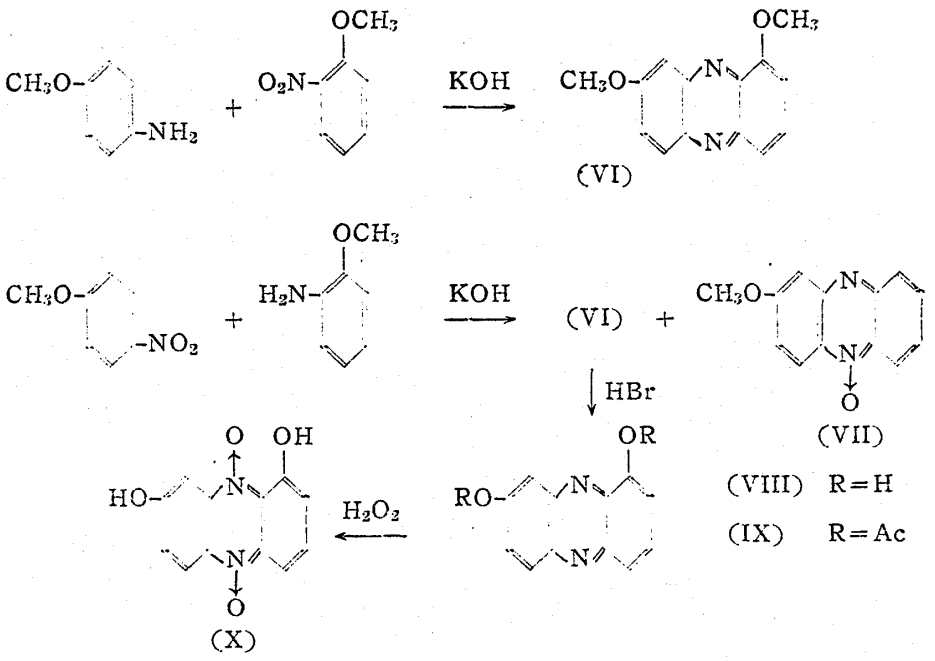
1) Yosioka, Kidani: J. Pharm. Soc. Japan, **72**, 1301 (1952).
2) Vivian: J. Am. Chem. Soc., **73**, 457 (1951).
3) Yosioka: J. Pharm. Soc. Japan, **72**, 1128 (1952).
4) Yosioka, Kidani: *Ibid.*, **72**, 847 (1952).

The synthesis of 1,8-dihydroxyphenazine di-N-oxide was achieved as in the case of the 2,7-isomer. A mixture of *p*-anisidine, *o*-nitroanisole, and potassium hydroxide was heated in toluene for 6 hours and 1,8-dimethoxyphenazine (VI) was obtained. When the mixture was kept standing at 50~55° without the solvent, the same result was observed with less yield.



When the condensation was carried out with *p*-nitroanisole, *o*-anisidine, and potassium hydroxide in toluene, minute amount of 1,8-dimethoxyphenazine (VI) and a large amount of 2-methoxyphenazine 5-mono-N-oxide (VII), which is the demethoxylated product in α-position of 1,8-dimethoxyphenazine mono-N-oxide, were produced.

1,8-Dimethoxyphenazine (VI) was demethylated to 1,8-dihydroxyphenazine (VIII) by heating with hydrobromic acid and acetic acid. The required 1,8-dihydroxyphenazine was acetylated to 1,8-diacetoxyphenazine (IX), and the latter was oxidized with hydrogen peroxide and acetic anhydride in benzene. 1,8-Dihydroxyphenazine di-N-oxide was obtained as violet brown needles, m.p. 235° (decomp.).

Fig. 1 shows the absorption spectra of 2,7-dihydroxyphenazine di-N-oxide (V) and 1,8-dihydroxyphenazine di-N-oxide (X). (V) was measured in alcohol and (X) in chloroform by the Beckman spectrophotometer. Absorption maximum of (V) was 476 mμ, and of (X), 524 mμ.

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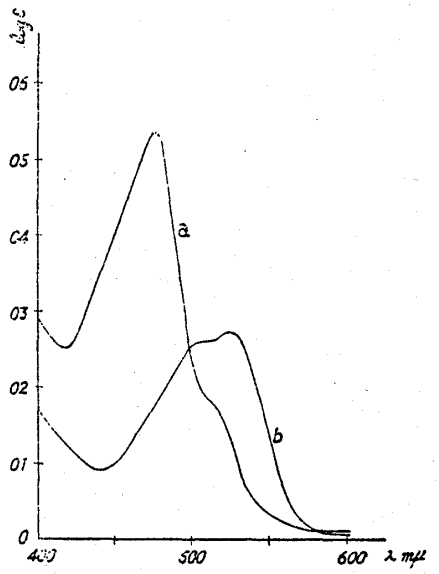

a: 2,7-Dihydroxyphenazine di-N-oxide 476 mμ (max.) (0.540)
b: 1,8-Dihydroxyphenazine di-N-oxide 524 mμ (max.) (0.275)

Fig. 1 Absorption Spectrum (Beckman)

Experimental

Condensation of *p*-nitroanisole and *p*-anisidine: 2,7-Dimethoxyphenazine (I) and 2,7-dimethoxyphenazine mono-N-oxide (II)—A mixture of *p*-nitroanisole (10 g.), *p*-anisidine (10 g.), and well-powdered potassium hydroxide (30 g.) was heated in toluene (150 cc.) under a reflux in an oil bath for 6 hours. After the reaction, toluene was distilled off under a reduced pressure, and 300 cc. of water was added. Unreacted substance was removed by steam distillation and the residue was extracted with benzene. The solution was extracted once with dil. hydrochloric acid (10 %) and the acid layer was neutralized with ammonia water, then filtered, leaving a yellowish brown substance. It weighed 1.35 g. in 7.1% yield. The products was dissolved in benzene and purified on alumina. The chromatogram was developed with benzene, and a yellow band containing the two substances was gradually eluted. The first eluate gave 0.5 g. of 2,7-dimethoxyphenazine (I) as yellow needles, m.p. 246°, which was recrystallized from ligroine. It showed yellow coloration with dil. hydrochloric acid. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.00; H, 5.00; N, 11.68. Found: C, 69.96; H, 4.95; N, 11.62.

The last eluate gave 0.55 g. of 2,7-dimethoxyphenazine mono-N-oxide (II), m.p. 236° (decomp.), as orange yellow needles, which was recrystallized from chloroform. It showed red coloration with hydrochloric acid. *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.69; N, 10.89. Found; C, 65.84; H, 4.50; N, 11.12.

The same products were obtained in 7.4% yield when the mixture was kept standing for 3 days without the solvent at 50~55°. When the temperature was kept at 70~75°, 1.5 g. of (II) and 5 g. of azoxy compound were obtained.

Deoxygenation of 2,7-dimethoxyphenazine mono-N-oxide (II)—The mono-N-oxide (0.3 g.) was heated with acetic anhydride (6 cc.) for one hour. The cooled mixture was poured into water and extracted with benzene. The solution was dried and chromatographed on alumina; the eluate gave yellow needles (from ligroine), m.p. 246°, not depressed by admixture with 2,7-dimethoxyphenazine.

2,7-Dihydroxyphenazine (III)—2,7-Dimethoxyphenazine (0.3 g.) was heated with hydrobromic acid (6 cc.) (d=1.48) and glacial acetic acid (3 cc.) for 17 hours. This was diluted with water, alkalized with sodium hydroxide, and the unreacted substance was removed with chloroform. Then it was neutralized with acetic acid, the precipitate filtered, and recrystallized from absolute alcohol. 0.2 g. of yellowish brown fine microneedles were obtained. It did not melt below 300°. *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.77; N, 13.21. Found: C, 67.75; H, 4.07; N, 12.93.

2,7-Diacetoxyphenazine (IV)—2,7-Dihydroxyphenazine (0.4 g.) and anhydrous sodium acetate were heated with acetic anhydride for 2 hours. 0.41 g. of pale rose needles (from benzene), m.p. 266~267° (decomp.), were obtained. *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$; C, 64.86; H, 4.05; N, 9.50. Found: C, 64.63; H, 4.06; N, 9.23.

2,7-Dihydroxyphenazine di-N-oxide (V)—2,7-Diacetoxyphenazine (0.2 g.) was dissolved in 80 cc. of benzene, and 30% hydrogen peroxide (3 cc.) and acetic anhydride (3 cc.) were added. This mixture was warmed on a water bath for 6 hours. After the reaction, the solution became deep reddish orange. The unreacted substance was removed with hydrochloric acid, extracted with 10% NaOH solution, and neutralized with acetic acid. The precipitate produced was collected, and recrystallized, after being dried, from a large amount of absolute alcohol. Reddish orange microplates obtained melted at 234~236° with decomposition. Yield: 0.1 g. It gives violet coloration with sodium hydroxide solution. It is slightly soluble in hot water, alcohol, and glacial acetic acid. *Anal.* Calcd. for $C_{12}H_8O_4N_2$: C, 59.01; H, 3.27; N, 11.47. Found: C, 59.09; H, 3.64; N, 11.34.

Condensation of *p*-anisidine and *p*-nitroanisole: 1,8-Dimethoxyphenazine (VI)—A mixture of *p*-anisidine (10 g.), *o*-nitroanisole (10 g.), and well-powdered potassium hydroxide (30 g.) was heated in toluene (150 cc.) under a reflux for 6 hours. The reaction mixture was treated as in the case of the condensation of *p*-nitroanisole and *p*-anisidine, and a dark greenish yellow product was obtained. It weighed 5.4 g. in 26.3% yield. This was dissolved in benzene and purified by chromatography on alumina. Yellow needles, m.p. 154~156°[5] (from ligroine). It gives a red coloration with dil. hydrochloric acid. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.00; H, 5.00; N, 11.68. Found: C, 69.84; H, 5.22; N, 11.76. Picrate: Red needles, m.p. 198°[5]. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2 \cdot C_6H_2O_7N_3$: N, 14.95. Found: N, 14.54.

The same product was obtained in 13% yield when the mixture was kept standing for 3 days at 50~55° in the absence of a solvent.

Condensation of *p*-nitroanisole and *o*-anisidine: 1,8-Dimethoxyphenazine (VI) and 2-methoxyphenazine 5-mono-N-oxide (VII)—Condensation was carried out by the same procedure as described above. The products obtained were separated into two portions by chromatography

5) Selebryani [C.A., 45, 2009 (1951).] described the m.p. of 1,8-dimethoxyphenazine as 158° and of its picrate as 209°.

on alumina. The first eluate gave 0.3 g. of yellow needles, m.p. 154° (from ligroine), not depressed by admixture with 1,8-dimethoxyphenazine. The next eluate gave 3 g. of yellow needles, m.p. 177° (from ligroine), not depressed by admixture with an authentic specimen of 2-methoxyphenazine 5-mono-N-oxide. *Anal* Calcd. for $C_{13}H_{10}O_2N_2$; N, 11.38, Found; N, 11.24.

1,8-Dihydroxyphenazine (VIII)—1,8-Dimethoxyphenazine was demethylated with hydrobromic acid and acetic acid, and the demethylated 1,8-dihydroxyphenazine was obtained as yellowish brown needles (from chloroform), m.p. 247~248°(decomp.). *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.77; N, 13.21. Found: C, 68.20; H, 4.02; N, 13.04.

1,8-Diacetoxyphenazine (IX)—This was obtained by the acetylation of 1,8-dihydroxyphenazine with acetic anhydride and anhydrous sodium acetate. Pale yellow plates, m.p. 181°. *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.05; N, 9.50. Found: C, 64.79; H, 4.20; N, 9.60.

1,8-Dihydroxyphenazine di-N-oxide (X)—1,8-Diacetoxyphenazine (0.2 g.) was dissolved in 40 cc. of benzene, and 30% hydrogen peroxide (3 cc.) and acetic anhydride (3 cc.) were added. This mixture was warmed on a water bath for 4 hours. After the reaction, the solution became deep red, and the unreacted substance was removed by dil. hydrochloric acid (10%), then extracted with 10% sodium hydroxide solution. It was neutralized with acetic acid and the preciptate was collected. Purplish brown fine needles, m.p. 235°(decomp.), were produced. Yield: 0.1 g. It gives greenish blue coloration with sodium hydroxide solution, and is readily soluble in alcohol, acetone, and less soluble in hot water, ether, and chloroform. *Anal.* Calcd. for $C_{12}H_8O_4N_2$: C, 59.01; H, 3.27; N, 11.47. Found: C, 59.31; H, 3.59; N, 11.11.

Summary

By using the improved Wohl-Aue method of phenazine synthesis, 2,7- and 1,8-dihydroxyphenazines were synthesized. From these, 2,7- and 1,8-dihydroxyphenazine di-N-oxides, the isomers of iodinin, were obtained by oxidation with hydrogen peroxide and acetic anhydride in benzene solution.

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