for their curling-motion against *Ascaris lumbricoides* by the Kobayashi-Bando method.

2) The compounds derived from *al*-hydroxytetralin showed a weak but typical curling-motion.

3) The compounds possessing lactone structure but not tetralin ring, showed untypical curling-motion.

4) An assumption of value to the synthesis of santonin analogs was made.

(Received November 5, 1953)

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7. Itiro Yosioka: Studies on Phenazines. V.[1] Synthesis of Iodinin Isomers. (2). Synthesis of 1,7-Dihydroxyphenazine Di-N-oxide.

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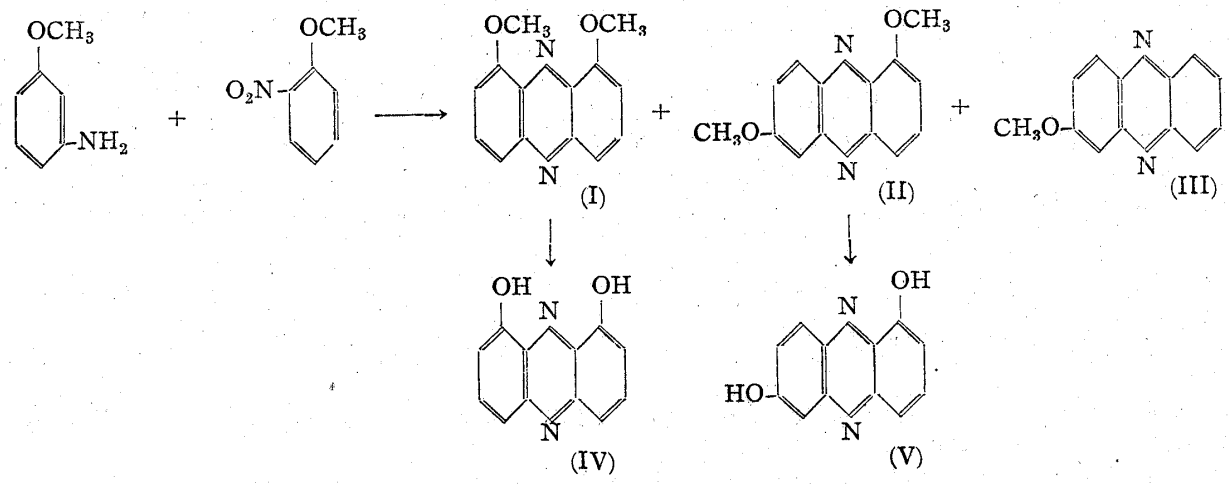
In the previous papers of this series[1,2], the synthesis of iodinin and two of its isomers, 1,8- and 2,7-dihydroxyphenazine di-N-oxides have been reported. In the present paper, the synthesis of another isomer of iodinin, 1,7-dihydroxyphenazine di-N-oxide is reported.

The synthesis of dihydroxyphenazines, the starting materials of di-N-oxides is first described.

Following the improved Wohl-Aue reaction, *o*-nitroanisole was condensed with *m*-anisidine in the presence of potassium hydroxide. In this reaction 1,9- and 1,7-dimethoxyphenazines were expected as the condensation products, which were chromatographed on alumina and separated into three crystalline substances, m.p. 254°, 176° and a small amount of m.p. 122°.

The crystalline product of m.p. 254° showed the same properties and analytical values as that of 1,9-dimethoxyphenazine (I), previously synthesized by Clemo and Daglish[3]. Accordingly, the substance having m.p. 176° must be 1,7-dimethoxyphenazine (II)[4]. The crystals with m.p. 122° were found to be identical with 2-methoxyphenazine (III) by mixed melting point determination with authentic specimen.

(I) and (II) were demethylated with hydrobromic acid in glacial acetic acid to 1,9- (IV) and 1,7-dihydroxyphenazines (V), respectively.



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* Motofuji-cho, Bunkyo-ku, Tokyo (吉岡一郎).

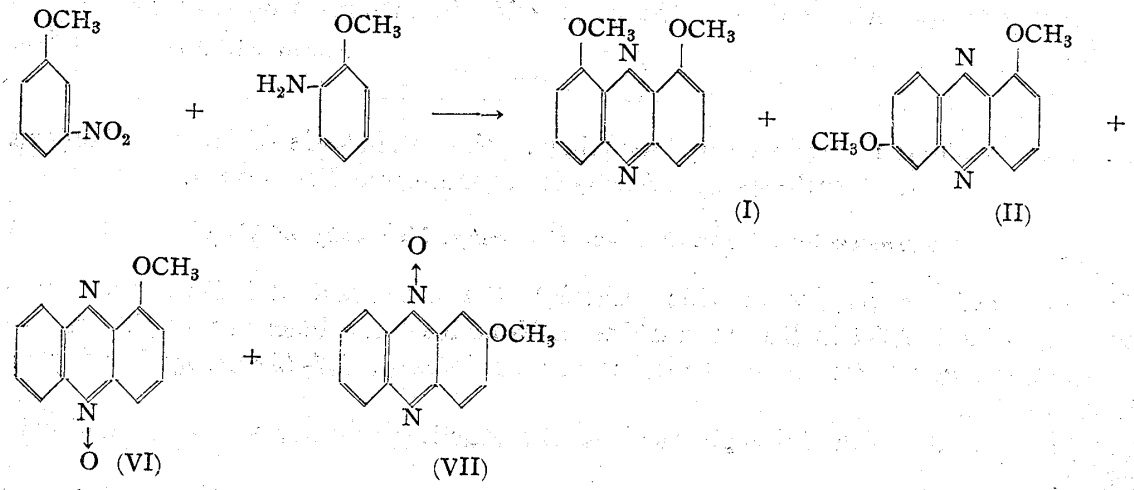
1) Part IV: This Bulletin, 1, 66 (1953).

2) I. Yosioka, Y. Kidani: J. Pharm. Soc. Japan, 72, 1128 (1952).

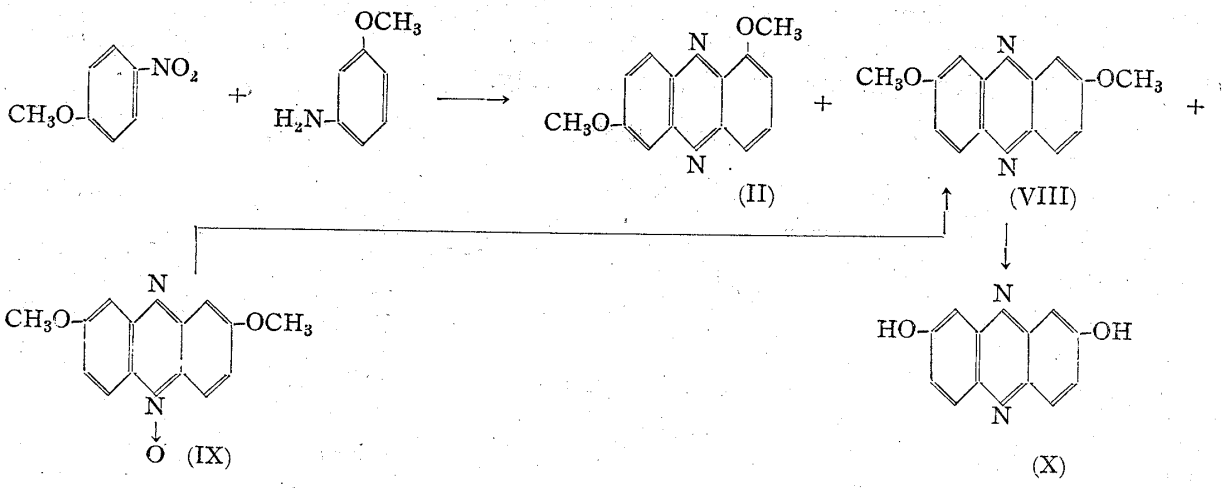
3) G. R. Clemo, A. F. Daglish: J. Chem. Soc., 1950, 1481.

4) Recently it was learned that A. I. Kiprianov and S. B. Serebryani (C. A., 46, 4010 (1952)) carried out the same reaction and obtained 1,9- (m.p. 260°) and 1,7-dimethoxyphenazines (m.p. 174°).

Reversing the nitro and amino groups in the condensation reaction, *m*-nitroanisole and *o*-anisidine were condensed in the presence of potassium hydroxide, yielding 1.9- and 1,7-dimethoxyphenazines together with minute amounts of 1-methoxyphenazine 5-mono-N-oxide (VI) and 2-methoxyphenazine 10-mono-N-oxide (VII). The yield, however, was very poor.

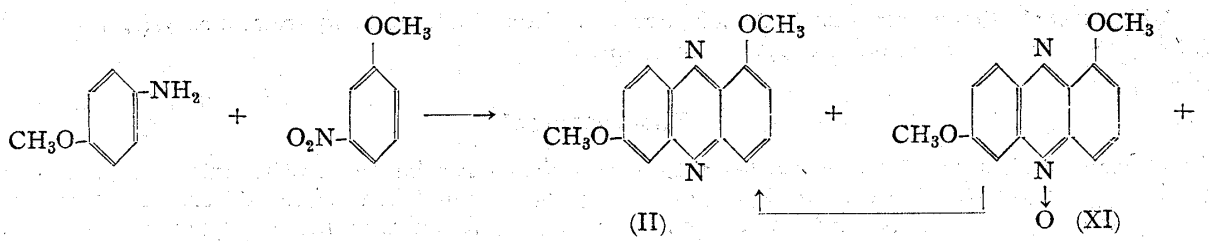


To obtain 2,8- and 1,7-dimethoxyphenazines, the condensation of *p*-nitroanisole and *m*-anisidine was carried out according to the above method. The reaction product was purified by chromatography on alumina and separated into three portions, m.p. 176°, 161°, and 229°. One of these, m.p. 176°, was found to be identical with 1,7-dimethoxyphenazine (II) by mixed melting point determination. Therefore, the substance with m.p. 161°, another dimethoxyphenazine, must be the 2,8-isomer (VIII). The substance having m.p. 229° was assumed to be 2,8-dimethoxyphenazine 5-mono-N-oxide (IX) because it was converted to (VIII) on treating it with acetic anhydride.

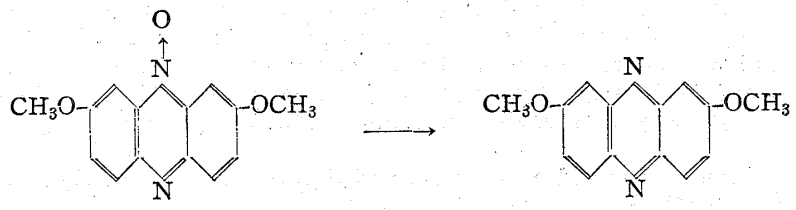


(VIII) was demethylated to 2,8-dihydroxyphenazine (X) by refluxing with hydrobromic acid and glacial acetic acid.

When the condensation was carried out with *m*-nitroanisole and *p*-anisidine, 1,7-dimethoxyphenazine (II) and the two crystalline products, m.p. 211° and 216°, both dimethoxyphenazine mono-N-oxides, were obtained. On heating with acetic anhydride, the substance having m.p. 211° was deoxygenated to 1,7-dimethoxyphenazine (II) and that of m.p. 216° to 2,8-isomer (VIII). Consequently they must be 1,7-dimethoxyphenazine 5-mono-N-oxide (XI) and 2,8-dimethoxyphenazine 10-mono-N-oxide (XII), respectively.



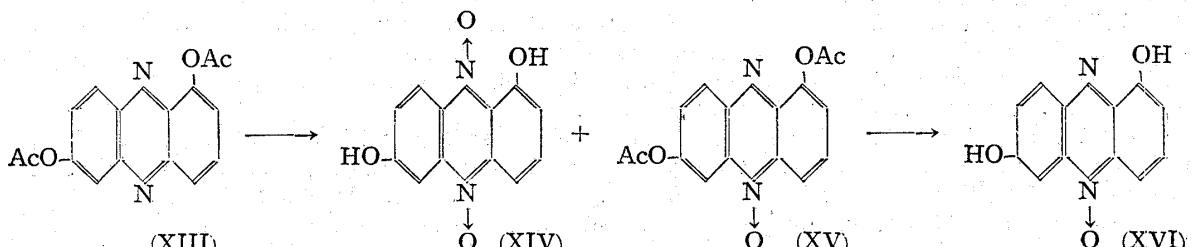
(II) (XI)



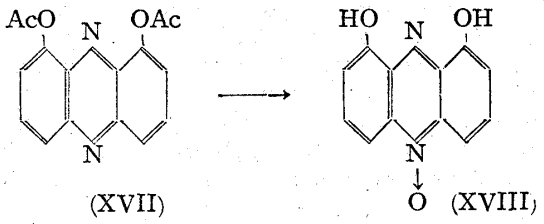
(XII) (VIII)

N-Oxidation of three dihydroxyphenazines was carried out following the method previously reported[1,2]. The acetylated 1,7-dihydroxyphenazine (XIII) was dissolved in benzene and oxidized with hydrogen peroxide in the presence of acetic anhydride. In this reaction acetyl groups were saponified simultaneously and 1,7-dihydroxyphenazine di-N-oxide (XIV) was obtained as purple-red needles with m.p. over 300°. As an intermediate product diacetylated mono-N-oxide (XV) was also obtained. Saponification of diacetyl mono-N-oxide produced 1,7-dihydroxyphenazine 5-mono-N-oxide (XVI) as orange microcrystals, m.p. 310° (decomp.).

When oxidizing 1,9-diacetoxyphenazine (XVII), a red crystalline product precipitated from the solvent and the reaction did not proceed further. The substance thus obtained was 1,9-dihydroxyphenazine mono-N-oxide (XVIII) and no di-N-oxide was produced.



(XIII) (XIV) (XV) (XVI)



(XVII) (XVIII)

2,8-Diacetoxyphenazine was oxidized by the method described above, but no crystalline products were obtained from the alkali soluble portion. However, from the alkali insoluble portion orange-red prisms, m.p. 195~197°, were obtained. This substance was changed by saponification to deep orange-red crystals, m.p. over 310°, whose analytical values agree neither with those of 2,8-dihydroxyphenazine di-N-oxide nor the mono-N-oxide. Absorption maximum of this substance was at 406 mμ. The structure of this substance will be studied in future.

Absorption maxima of 1,7-dihydroxyphenazine di-N-oxide were at 412 mμ and 510 mμ, and those of 1,9-isomer mono-N-oxide, at 470 mμ and 520 mμ in isopropanol solution.

The author's thanks are due to Mr. Kimura and Miss Yamamoto for microanalysis, and to Mr. Takahashi for the absorption spectrum measurement.

Experimental

Condensation of *o*-Nitroanisole and *m*-Anisidine—A mixture of *o*-nitroanisole (7 g.), *m*-anisidine (7 g.) and powdered potassium hydroxide (20 g.) was heated in toluene (110 cc.) under reflux in an oil bath for 7 hours. After the reaction, the toluene solution was filtered from the precipitate and steam-distilled. The crude crystalline substance deposited in the remaining water solution. This was extracted several times with hydrochloric acid (1:1) and the acidic solution was neutralized with ammonia water. The precipitate was filtered, dried, and dissolved in chloroform, and purified on alumina. The eluate was evaporated and recrystallized twice from benzene. 0.5 g. of 1,9-dimethoxyphenazine (I) was obtained as golden yellow needles, m.p. 254°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: N, 11.66. Found: N, 11.89.

The benzene mother liquor was chromatographed on alumina and developed with benzene. The chromatographic procedure is shown in Table I.

Table I.

Eluate	1.	m.p. 118~120°	Eluate	5.	m.p. 165~170°
	2.	m.p. 132~148°		6.	m.p. 166~172°
	3.	m.p. 156~164°		7.	m.p. 246~249°
	4.	m.p. 165~168°			

Eluate 1 yielded pale yellow needles with m.p. 122° (from ligroine), not depressed by admixture with 2-methoxyphenazine (III). Eluates 4, 5, and 6 yielded yellow needles of 1,7-dimethoxyphenazine (II), m.p. 175~176° (from ligroine). *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.00; H, 5.00; N, 11.66. Found: C, 69.84; H, 4.86; N, 11.73. Eluate 7 yielded golden yellow needles of 1,9-dimethoxyphenazine (I), m.p. 254° (from benzene). From eluates 2 and 3 additional (II) was obtained by further chromatography on alumina. Yield of (I) was 0.6 g., and of (II), 0.5 g.

1,9-Dihydroxyphenazine (IV)—(I) (0.5 g.) was refluxed in hydrobromic acid (d=1.48) (7 cc.) and glacial acetic acid (7 cc.) for 17 hours. It was diluted with water, made alkaline with 10% sodium hydroxide solution, and filtered. The filtrate was neutralized with acetic acid, and the precipitate was filtered and recrystallized from benzene. 0.4 g. of orange-red prisms were obtained. m.p. 295° (decomp.)[5]. *Anal.* calcd. for $C_{12}H_8O_2N_2$: N, 13.20. Found: N, 13.49.

1,9-Diacetoxyphenazine (XVII)—(IV) (0.2 g.) was acetylated with acetic anhydride (4 cc.) and anhydrosu sodium acetate (0.3 g.). Pale yellow plates (from benzene), m.p. 256~257°[5]. *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.05; N, 9.50. Found: C, 65.11; H, 3.77; N, 9.08.

1,7-Dihydroxyphenazine (V)—(II) (0.5 g.) was demethylated with hydrobromic acid (20 cc.) and glacial acetic acid (10 cc.). 1,7-Dihydroxyphenazine was obtained as brown needles of m.p. 320° (decomp.)[5] (from hydrated methanol). Yield: 0.3 g. *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.77; N, 13.21. Found: C, 67.86; H, 3.92; N, 12.64.

1,7-Diacetoxyphenazine (XIII)—(V) (0.3 g.) was acetylated with acetic anhydride (5 cc.) and anhydrous sodium acetate (0.4 g.). Pale yellow needles (from ligroine), m.p. 152~153°[5]. *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.05; N, 9.05. Found: C, 65.09; H, 4.07; N, 9.55.

Condensation of *m*-Nitroanisole and *o*-Anisidine—A mixture of *m*-nitroanisole (10 g.), *o*-anisidine (10 g.), and powdered potassium hydroxide (30 g.) was refluxed in toluene (150 cc.) for 7 hours. The reaction mixture was treated in the ordinary manner and the crude product obtained was purified into four portions by chromatography on alumina. The first eluate (0.3 g.) yielded yellow needles, m.p. 176° (from ligroine), not depressed by admixture with 1,7-dimethoxyphenazine. The second eluate (0.3 g.), yellow needles, m.p. 254° (from benzene), was found to be identical with 1,9-dimethoxyphenazine. The third and the fourth yielded a small amount of yellow crystals, m.p. 204° and 176°. The former was not depressed by admixture with 1-methoxyphenazine 5-mono-N-oxide (VI) and the latter was found to be identical with 2-methoxyphenazine 10-mono-N-oxide (VII) by mixed melting point determination.

Condensation of *p*-Nitroanisole and *m*-Anisidine—A mixture of *p*-nitroanisole (9.5 g.), *m*-anisidine (8 g.), and powdered potassium hydroxide (30 g.) was refluxed in toluene (140 cc.) for 6 hours. The reaction product was treated by the ordinary method and crude

Table II.

Eluate	1.	m.p. 158~161°	Eluate	5.	m.p. 169~173°
	2.	m.p. 144~150°		6.	m.p. 180~190°
	3.	m.p. 135~150°		7.	m.p. 227°
	4.	m.p. 152~162°			

5) Recently S. B. Serebryani reported the synthesis of 1,9- and 1,7-dihydroxyphenazines and their diacetates. He recorded m.p. 296~297° and 305~306° for 1,9- and 1,7-dihydroxyphenazines, and 257~258° and 148~149° for their diacetates, respectively.

crystals were obtained, which were dissolved in benzene and purified on alumina by chromatography. The procedure is shown in Table II. Eluate 1 yielded yellow needles, m.p. 161° (from ligroine), of 2,8-dimethoxyphenazine (VIII). *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.00; H, 5.00; N, 11.68. Found: C, 69.73; H, 4.73; N, 11.46. Eluate 5 yielded yellow needles with m.p. 175~176° (from ligroine), which were found to be identical with 1,7-dimethoxyphenazine (II). Eluate 7 yielded yellow needles, m.p 229° (from benzene), which were assumed to be 2,8-dimethoxyphenazine 5-mono-N-oxide (IX). *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.68; N, 10.93. Found: C, 65.61; H, 4.57; N, 10.63. Eluates 2, 3, and 4 were collected, rechromatographed on alumina and isolated into (VIII) and (II), respectively. Eluate 6 was also separated into (II) and (IX). Yield: (II), 0.8 g. (VIII), 0.4 g. (IX), 0.2 g.

Deoxygenation of 2,8-Dimethoxyphenazine 5-Mono-N-oxide—Mono-N-oxide of m.p. 229° (0.15 g.) was dissolved in acetic anhydride (2 cc.), refluxed for 1 hour, and the reaction mixture was poured into water. It was then extracted with benzene, dried, and purified on alumina. It yielded yellow needles of m.p. 161° (from ligroine), not depressed by admixture with 2,8-dimethoxyphenazine.

Condensation of *m*-Nitroanisole and *p*-Anisidine—A mixture of *m*-nitroanisole (10 g.), *p*-anisidine (10 g.), and powdered potassium hydroxide (30 g.) was heated in toluene (150 cc.) under reflux for 6 hours. After the reaction, toluene was filtered and left standing over night. The crystalline product, deposited from the solution, was recrystallized from benzene. 0.4 g. of yellow needles (m.p. 211°), 1,7-dimethoxyphenazine 5-mono-N-oxide (XI), was obtained. *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.68; N, 10.93. Found: C, 65.42; H, 4.91; N, 10.77.

The toluene mother liquor was treated by the ordinary method and the crude product obtained was dissolved in benzene and purified on alumina by chromatography. 1,7-Dimethoxyphenazine (II) (m.p. 175~176°) was easily isolated from the first eluate, but the crystals from successive eluates were not pure. Finally a small amount of yellow needles, m.p. 211° and 216°, were isolated by recrystallization from ligroine. The greater part of the mixture was deoxygenated with acetic anhydride and recovered and found to be 1,7- and 2,8-dimethoxyphenazine, respectively. The substance of m.p. 216° was an isomer of 2,8-dimethoxyphenazine 5-mono-N-oxide (m.p. 229°) and assumed to be 10-mono-N-oxide (XII). *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.68; N, 10.93. Found: C, 65.71; H, 4.82; N, 10.76.

Deoxygenation of 1,7-Dimethoxyphenazine 5-Mono-N-oxide (XI)—Mono-N-oxide (m.p. 211°) (0.1 g.) was refluxed with acetic anhydride for 1 hour. After purifying by chromatography, yellow needles, m.p. 176° (1,7-dimethoxyphenazine), were obtained.

Deoxygenation of 2,8-Dimethoxyphenazine 10-Mono-N-oxide (XII)—Mono-N-oxide (m.p. 216°) (0.1 g.) was deoxygenated by heating with acetic anhydride (2 cc.) for 2 hours. Yellow needles with m.p. 161° (from ligroine), not depressed by admixture with (VIII), were obtained.

2,8-Dihydroxyphenazine (X)—(VIII) (0.3 g.) was demethylated by refluxing with hydrobromic acid (12 cc.) and acetic acid (6 cc.) for 17 hours. Yellow brown microcrystals of m.p. over 320° (from hydrated ethanol) were obtained. Yield: 0.1 g. *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.77; N, 13.21. Found: C, 68.15; H, 4.02; N, 13.02.

2,8-Diacetoxyphenazine—(X) (0.2 g.) was acetylated by the usual method. Faint brown plates of m.p. 225~227° (from benzene) were obtained. Yield: 0.2 g. *Anal.* Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.05; N, 9.50. Found: C, 65.18; H, 3.93; N, 9.33.

N-Oxidation of 1,7-Diacetoxyphenazine—1,7-Diacetoxyphenazine (0.3 g.) was dissolved in benzene (100 cc.), to which were added acetic anhydride (3 cc.) and 30% hydrogen peroxide (3.5 cc.). The mixture was warmed on water bath for 12 hours and turned deep purple red. After the reaction ceased, the mixture was washed with water, extracted with 10% sodium hydroxide solution, which was neutralized with acetic acid and the precipitate obtained. This was collected, dried, and recrystallized from larger amounts of chloroform. Deep purple-red needles, m.p. over 330° (darkened from 260°), were obtained in 0.1 g. yield. It gave dark green coloration when dissolved in sodium hydroxide solution. *Anal.* Calcd. for $C_{12}H_8O_4N_2$: C, 59.01; H, 3.27; N, 11.11. Found: C, 59.26; H, 3.32; N, 11.23.

After extracting the di-N-oxide, the benzene layer was evaporated and the residue recrystallized from ligroine. 1,7-Diacetoxyphenazine 5-mono-N-oxide (XV) was obtained as golden yellow needles having m.p. 177~178°. *Anal.* Calcd. for $C_{16}H_{12}O_5N_2$: C, 61.53; H, 3.84; N, 8.97. Found: C, 61.30; H, 3.84; N, 8.73.

1,7-Dihydroxyphenazine 5-Mono-N-oxide (XVI)—(XV) was saponified with sodium hydroxide solution to 1,7-dihydroxyphenazine 5-mono-N-oxide (XVI). Orange microneedles were obtained (from chloroform), m.p. 310° (decomp.). *Anal.* Calcd. for $C_{12}H_8O_3N_2$: C, 63.15; H, 3.50; N, 12.28. Found: C, 62.88; H, 3.73; N, 12.00.

N-Oxidation of 1,9-Diacetoxyphenazine—(XVII) (0.35 g.) was dissolved in benzene (150 cc.) and to this acetic anhydride (3 cc.) and 30% hydrogen peroxide (5 cc.) were added. The mixture was warmed on water bath for 10 hours. Red crystalline precipitate gradually deposited from the

reaction solution. After the reaction ceased the precipitate was filtered, recrystallized from larger amounts of chloroform, and 1,9-dihydroxyphenazine 5-mono-N-oxide (XVIII) was obtained as red plates of m.p. 258° (decomp.). The filtrate was washed with water, shaken with sodium hydroxide, and the alkaline solution was neutralized with acetic acid. From the precipitate thus obtained only 1,9-dihydroxyphenazine 5-mono-N-oxide was purified. Prolonged oxidation produced a smaller yield. Mono-N-oxide dissolved in alkaline solution with violet coloration. *Anal.* Calcd. for $C_{12}H_8O_3N_2$; C, 63.15; H, 3.50; N, 12.28. Found: C, 63.00; H, 3.54; N, 11.96.

N-Oxidation of 2,8-Diacetoxyphenazine—2,8-Diacetoxyphenazine (0.2 g.) was dissolved in benzene (130 cc.) and oxidized with hydrogen peroxide (3.5 cc.) and acetic anhydride (3 cc.) for 7 hours on water bath. After the reaction ceased, the benzene solution was shaken with 10% sodium hydroxide. From the benzene layer, orange-red prisms (from benzene), m.p. 195~197°, were obtained, which were saponified with sodium hydroxide solution, and after neutralizing with acetic acid, orange-red microcrystals (from a large amount of ethanol), m.p. over 310°, were obtained. Red coloration was produced in sodium hydroxide solution. *Anal.* Found: C, 63.36; H, 3.75.

Summary

1,7-, 1,9-, and 2,8-dihydroxyphenazines were synthesized by the improved Wohl-Aue method. From 1,7-dihydroxyphenazine, 1,7-dihydroxyphenazine di-N-oxide was obtained by oxidation with hydrogen peroxide and acetic anhydride in benzene solution.

In the case of the 1,9-isomer, only its mono-N-oxide was obtained by the same oxidation condition employed for the 1,7-isomer.

The oxidation product of 2,8-dihydroxyphenazine, however, agreed neither with the di-N-oxide nor with mono-N-oxide.

(Received November 7, 1954)

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8. Torizo Takahashi, Juichiro Shibasaki, and Masao Uchibayashi: Syntheses of Heterocyclic Compounds of Nitrogen. LXXXVIII*. Phenyl Pyridyl Ethers. (8)**.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo****)

In the previous papers of this series, we reported on the syntheses of several kinds of phenyl pyridyl ethers, with a view to examining their antitubercular activities. The present paper describes the synthesis of derivatives possessing a thioether linkage in the γ-position of pyridine.

For the preparation of the starting material, γ-thiopyridone, the method described by Koenigs and his co-worker[1] appeared inconvenient as it gave this compound in poor yield by the treatment of unstable γ-chloropyridine in ethanol as solvent with potassium hydrogen sulfide in a sealed tube. For this reason, the method of King and his co-worker[2] was followed converting chelidonic acid[3] into γ-pyridone and treating the latter with phosphorus pentasulfide. In the present case, however, the reaction temperature in the latter step was required to be raised up to approximately 150°, while the temperature range reported by King was 60~70°.

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* Part LXXXVII: J. Pharm. Soc. Japan, 73, 1078 (1953).
** Part (7): This Bulletin, 1, 70 (1953).
*** Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 柴崎寿一郎, 内林政夫).
1) Koenigs, Kinne: Ber., 54, 1357 (1921).
2) King, Ware: J. Chem. Soc., 1939, 873.
3) Gilman: Org. Syntheses, 17, 40 (1937).