

TABLE I

Compound	Purity by other method (%)	Amount (mg.)	Solvent (cc.)				Purity found (%)		
			AcOH	MeOH	Ethylene glycol	Benzene	Direct titrn.	Back titrn.	Back back titrn.
Na oxalate	99.95	11.95~ 46.65	0~2	10~17	1.8~2	35		100.14 s*=0.56	
Na benzoate	99.69**	23.76~ 83.60	0~7	15~18		35	99.73 s*=0.28		
Na salicylate	99.50**	37.72~ 102.59	0~5	15~17		35	99.50 s=0.05		
Na citrate	99.47**	29.89~ 69.47	5	17		35	99.56 s=0.33		
Pb acetate	102.9**	37.78~ 92.81		15~22	0.2~2	35		103.21 s=0.45	
Ca lactate	98.62**	19.87~ 52.13	5	12~17		35~43		99.29 s=0.72	
Ca gluconate	100.41**	30.24~ 93.79	3~5	17		35		100.25 s=0.68	
K bicarbonate	99.9	21.66~ 81.39	5	17~18		35			99.75 s=0.44
K Na tartrate	97.7**	22.72~ 44.44	3~4	17		35			98.14 s=0.40
	101.1**	22.72~ 88.10	3~5	17		30~35			100.74 s=0.37

$$* \sqrt{\frac{1}{n-1} \sum (x_i - \bar{x})^2}$$

\*\* Determined by the method described in the Japanese Pharmacopoeia VI Ed.

### Summary

Salts of organic acids, mainly Pharmacopoeiae chemicals, were determined by the high frequency titration in non-aqueous solutions, in a mixture of methanol and benzene, and, if necessary, acetic acid and ethylene glycol, with perchloric acid or sodium acetate in acetic acid. Sodium salts were generally titrated directly with perchloric acid, and accuracy was 0.2%. Potassium salts were titrated by back back titration, giving accuracy of 0.4%, while calcium salts were titrated with an accuracy of 0.4~0.7%.

(Received December 16, 1953)

### 15. Itiro Yosioka and Hirotaka Otomasu: Studies on Phenazines. VI.<sup>1)</sup> Synthesis of Iodinine Isomers. (3). Syntheses of 1,3-, 1,4-, and 2,3-Dihydroxyphenazine Di-N-oxides.

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The synthesis of dihydroxyphenazine di-N-oxides, the iodinine isomers, whose hydroxyl

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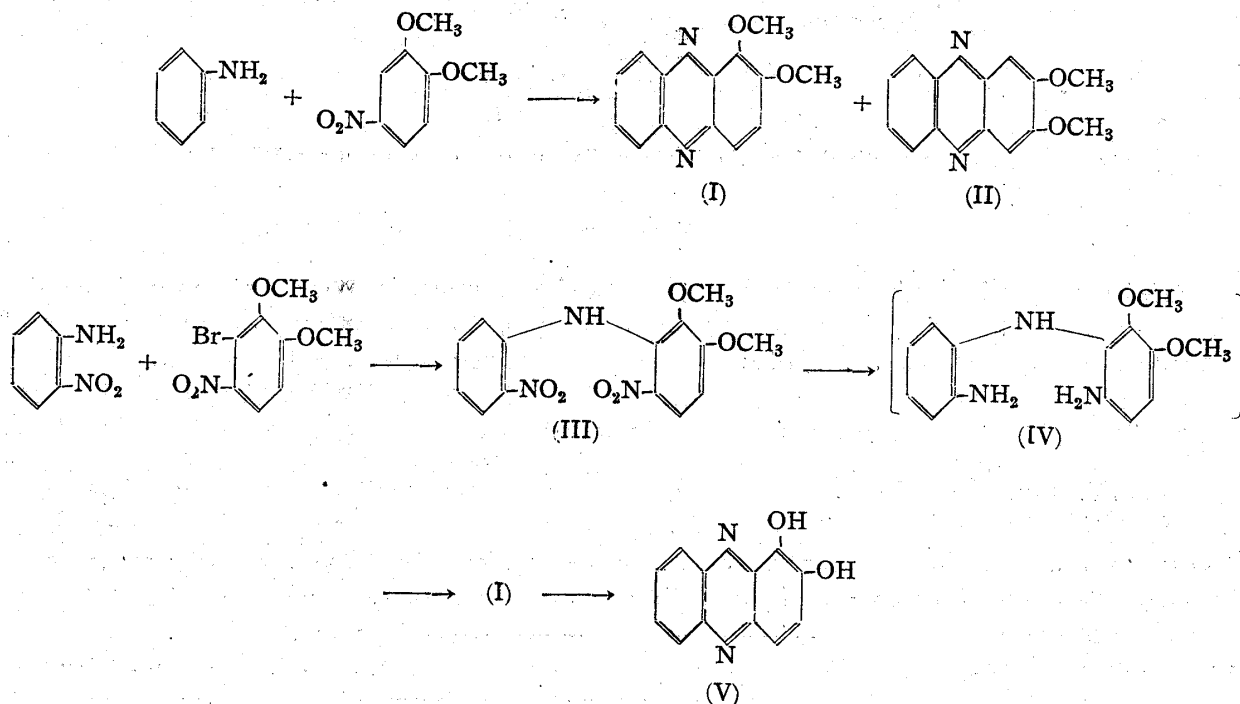
1) Part V: This Bulletin, 2, 25 (1954).

groups are located in each benzene nuclei, have already been reported.<sup>1,2)</sup> In the present paper, the synthesis of dihydroxyphenazine di-N-oxides, whose hydroxyls are located at the same benzene nucleus, is described.

Since iodinin was previously assumed to be 1,2-dihydroxyphenazine di-N-oxide, 1,2-dihydroxyphenazine and its methyl derivative have been synthesized by various authors.<sup>3-5)</sup>

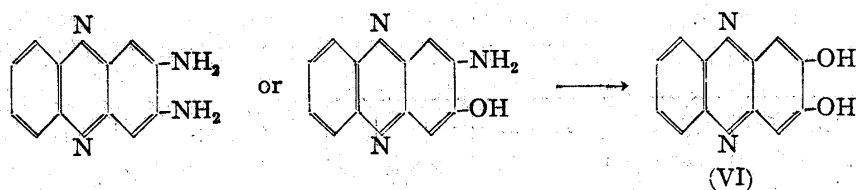
We attempted to prepare 1,2-dimethoxyphenazine (I), together with 2,3-isomer (II), by the improved Wohl-Aue method.<sup>7)</sup> 4-Nitroveratrole was condensed with aniline by means of potassium hydroxide in toluene solution, and 1,2- and 2,3-dimethoxyphenazines were obtained in very small amounts. None of the desired substances were obtained in the condensation of 4-aminoveratrole and nitrobenzene.

The synthesis was therefore carried out in another way. 6-Bromo-5-nitroveratrole<sup>8)</sup> was condensed with *o*-nitroaniline to 2,2'-dinitro-5,6-dimethoxydiphenylamine (III) in the presence of potassium carbonate and copper powder. (III) was then hydrogenated to the diamino compound (IV) catalytically over palladised charcoal and the latter was oxidized with ferric chloride to 1,2-dimethoxyphenazine (I). By refluxing with hydrobromic acid and glacial acetic acid, (I) was demethylated to 1,2-dihydroxyphenazine (V).



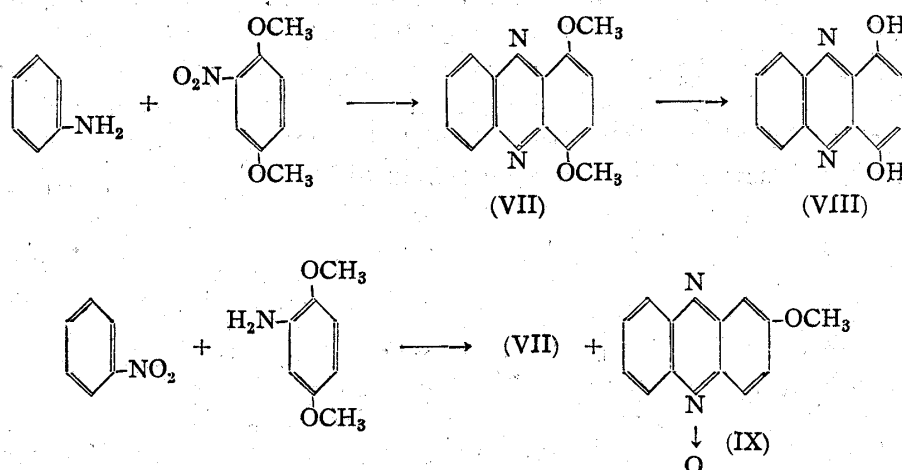
Ullmann and Mauthner<sup>9)</sup> reported that 2,3-dihydroxyphenazine (VI) was synthesized by hydrolysing 2,3-diamino- or 2-amino-3-hydroxyphenazine with sulfuric acid in a sealed tube.

- I. Yosioka, H. Otomasu: *This Bulletin*, 1, 66 (1953).
- G. R. Clemo, A. F. Daglish: *Nature*, 160, 752 (1947) (*C. A.*, 42, 1595 (1948)).
- P. Z. Slack, R. Slack: *Nature*, 160, 437 (1947) (*C. A.*, 42, 4591 (1948)).
- S. Maffei: *Gazz. chim. ital.*, 80, 651 (1950) (*C. A.*, 45, 9063 (1951)).
- B. Hegedüs: *Jubilee Vol. Emil Barelle*, 1946, 388 (*C. A.*, 41, 6262 (1947)).
- I. Yosioka: *J. Pharm. Soc. Japan*, 72, 1128 (1952).
- T. Girbert, H. Jones, R. Robinson: *J. Chem. Soc.*, 1917, 903.
- F. Ullman, F. Mauthner: *Ber.*, 35, 4302 (1902).

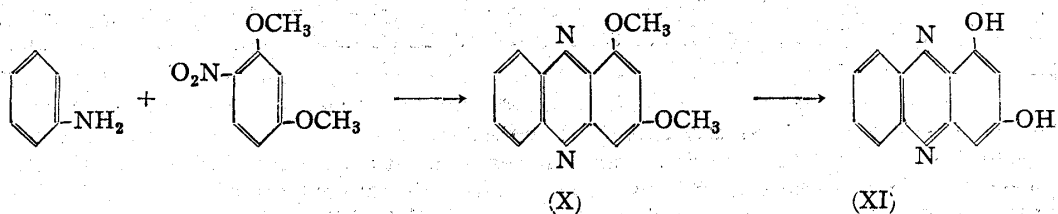


To obtain 1,4-dihydroxyphenazine, the condensation of aniline and 2-nitrohydroquinone dimethyl ether was carried out following the improved Wohl-Aue method. After purifying the reaction products by chromatography on alumina, 1,4-dimethoxyphenazine (VII) was obtained as orange red needles, m.p. 185°, which coincided well with the description of King, *et al.*<sup>10)</sup> and that of Slack and Slack<sup>4)</sup>.

Reversing the nitro and amino groups, *i.e.* nitrobenzene and 2-aminohydroquinone dimethyl ether were condensed by the method described above, and both 1,4-dimethoxyphenazine (VII) and 2-methoxyphenazine 5-mono-N-oxide (IX) were obtained. (VII) was demethylated in the usual way to 1,4-dihydroxyphenazine (VIII).

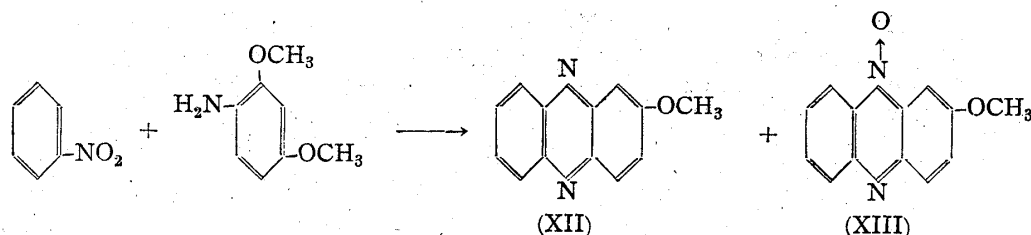


1,3-Dimethoxyphenazine (X) was synthesized from aniline and 4-nitroresorcinol dimethyl ether by the same method as the 1,4-isomer. Condensing nitrobenzene with 4-aminoresorcinol dimethyl ether by the same method, no objective 1,3-isomer was obtained except 2-methoxyphenazine (XII) and its 10-mono-N-oxide (XIII). 1,3-Dimethoxyphenazine was demethylated to 1,3-dihydroxyphenazine (XI), which gave brown yellow needles, and did not melt below 280°. Its diacetate gave pale yellow needles, m.p. 263~264°. There is a wide discrepancy between the melting points of these compounds and those of Clemo, *et al.* The reason has not yet been elucidated.



10) F. E. King, N. G. Clark, P. M. H. Davis: J. Chem. Soc., 1949, 3012.

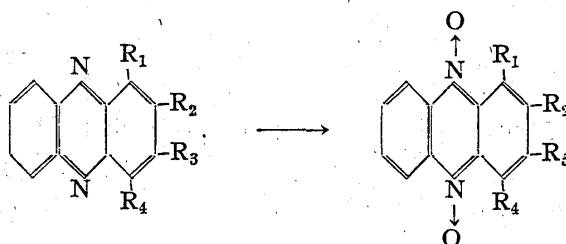
11) G. R. Clemo and A. F. Daglish (J. Chem. Soc., 1948, 2318) reported m.p. 275° for 1,3-dihydroxyphenazine and m.p. 163° for its acetate.



N-Oxidation of dihydroxyphenazines, except 1,4-isomer, was carried out on their acetates by the same method previously reported<sup>2,12</sup>. 2,3-Diacetoxyphenazine (XIV) and 1,3-isomer (XVII) were dissolved in benzene and oxidized with 30% hydrogen peroxide in the presence of acetic anhydride. In these reactions acetyl groups were also hydrolyzed simultaneously and 2,3-dihydroxyphenazine di-N-oxide (XV), dark purplish brown needles which did not melt below 340°, and the 1,3-isomer (XVIII), red needles which did not melt below 280°, were obtained, respectively.

In the case of the 1,2-isomer, however, the objective di-N-oxide was not obtained. Since 1,4-dihydroxyphenazine (VIII) was soluble in benzene, it was oxidized directly by the same method described above, and 1,4-dihydroxyphenazine di-N-oxide (XVI), pale brown-yellow needles which did not melt below 340°, was obtained.

This di-N-oxide differed from the other isomers by its color, color reaction with alkaline solution, and the absorption spectrum in the visible region, but its analytical value agreed well with that of the theoretical. It may therefore be concluded that the product obtained was 1,4-dihydroxyphenazine di-N-oxide.



(XIV) R<sub>2</sub>=R<sub>3</sub>=OAc, R<sub>1</sub>=R<sub>4</sub>=H

(VIII) R<sub>1</sub>=R<sub>4</sub>=OH, R<sub>2</sub>=R<sub>3</sub>=H

(XVII) R<sub>1</sub>=R<sub>3</sub>=OAc, R<sub>2</sub>=R<sub>4</sub>=H

(XV) R<sub>2</sub>=R<sub>3</sub>=OH, R<sub>1</sub>=R<sub>4</sub>=H

(XVI) R<sub>1</sub>=R<sub>4</sub>=OH, R<sub>2</sub>=R<sub>3</sub>=H

(XVIII) R<sub>1</sub>=R<sub>3</sub>=OH, R<sub>2</sub>=R<sub>4</sub>=H

Absorption maxima of 1,3-dihydroxyphenazine di-N-oxide are 400 m $\mu$  and 510 m $\mu$ , and those of the 2,3-isomer, 435 m $\mu$  and 482 m $\mu$ , but the 1,4-isomer has no absorption in the visible region in isopropanol solution.

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

### Experimental

**Condensation of 4-Nitroveratrole and Aniline: 1,2- (I) and 2,3-Dimethoxyphenazines (II)**—A mixture of 4-nitroveratrole (10 g.), aniline (10 g.), and powdered potassium hydroxide (30 g.) was refluxed in toluene (150 cc.) for 6 hours. After the reaction, toluene was distilled off under reduced pressure, and to it 300 cc. of water was added. Unreacted substances were removed by steam distillation and the residue was extracted with benzene. This solution was extracted with dild. hydrochloric acid (10%) and the acidic layer was neutralized with ammonia water. The precipitate produced was dissolved in benzene and chromatographed on alumina. The first eluate yielded 0.09 g. of 2,3-dimethoxyphenazine (II), pale yellow blades, m.p. 226° (from ligroine). (Slack and Slack<sup>11</sup> reported the synthesis of (II), but no m.p. was recorded). *Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 70.00; H, 5.00; N, 11.68. Found: C, 70.32; H, 4.84; N, 11.78.

12) I. Yosioka, Y. Kidani: *J. Pharm. Soc. Japan*, 72, 1310 (1952)..

The next eluate yielded 0.03 g. of 1,2-dimethoxyphenazine (I), orange yellow needles, m.p. 145~146° (from ligroine). (Clemo and Daglish,<sup>3)</sup> Slack<sup>4)</sup> and Maffei<sup>5)</sup> recorded m.p. 138~139°, and Hegedüs<sup>6)</sup> m.p. 145~146° for (I). *Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 70.00; H, 5.00; N, 11.68. Found: C, 70.29; H, 5.23; N, 11.43.

The same products were obtained in similar yields when the condensation mixture was kept standing for 3 days without a solvent at 55°.

Condensation of 4-aminoveratrole and nitrobenzene was carried out by the same procedure as described above, but none of the desired compounds were obtained.

**2,2'-Dintro-5,6-dimethoxydiphenylamine (III)**—A mixture of 3-bromo-4-nitroveratrole<sup>8)</sup> (1.31 g.), *o*-nitraniline (0.7 g.), anhydrous potassium carbonate (1.1 g.), copper powder (0.2 g.), and nitrobenzene (4 cc.) were stirred and heated at 205~210° for 1 hour. The cooled reaction mixture was filtered and washed with benzene. The solvent was removed and the residue was dissolved in boiling benzene (20 cc.) and to it light petroleum was added. From the mixture an orange red solid was deposited. It yielded 0.35 g. of (III), orange brown needles, m.p. 145~147° (from ethanol). *Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>O<sub>6</sub>N<sub>3</sub>: C, 52.66; H, 4.07; N, 13.16. Found: C, 52.46; H, 3.87; N, 13.09.

**1,2-Dimethoxyphenazine (I)**—A suspension of (III) (0.2 g.) and palladised charcoal (0.05 g.) in ethanol (15 cc.) was shaken with hydrogen at room temperature. The reaction mixture was acidified with hydrochloric acid and filtered. Then ethanol was removed and the residue was dissolved in water (10 cc.), which was oxidized with ferric chloride solution (1 g. in 2 cc. water). After 12 hours, water (40 cc.) was added and neutralized with ammonia water. The precipitate thus produced was dissolved in benzene and purified by chromatography on alumina. 1,2-Dimethoxyphenazine was obtained as orange yellow needles (0.08 g., 53%), m.p. 145~146° (from ligroine). *Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 70.00; H, 5.00. Found: C, 70.32; H, 5.19.

**1,2-Dihydroxyphenazine (V)**—1,2-Dimethoxyphenazine (0.3 g.) was demethylated with hydrobromic acid (6 cc.) in glacial acetic acid (3 cc.) by refluxing for 16 hours. 1,2-Dihydroxyphenazine (V) (0.25 g.) was obtained as fine orange red needles (from chloroform), m.p. 250° (Maffei<sup>9)</sup> recorded m.p. 261°, and Hegedüs,<sup>6)</sup> 270~275° for (V). *Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>O<sub>2</sub>N<sub>2</sub>: C, 67.92; H, 3.77; N, 13.21. Found: C, 68.13; H, 4.08; N, 13.01.

**1,2-Diacetoxyphenazine**—1,2-Dihydroxyphenazine was acetylated with acetic anhydride and anhydrous sodium acetate. It yielded pale fine yellow needles (from xylene), m.p. 175°. (For this compound, Hegedüs<sup>6)</sup> recorded m.p. 168°). *Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>O<sub>4</sub>N<sub>2</sub>: C, 64.86; H, 4.05; N, 9.50. Found: C, 65.11; H, 4.30; N, 9.21.

**2,3-Dihydroxyphenazine (VI)**—Following the method of Ullmann and Mauthner<sup>9)</sup>, 2,3-diaminophenazine (0.6 g.) was heated with 3*N* sulfuric acid (12 cc.) in a sealed tube at 200° for 8 hours. 2,3-Dihydroxyphenazine (VI) was obtained as brown crystals (from ethanol), which did not melt below 340°. Yield: 0.4 g. *Anal.* Calcd. for C<sub>12</sub>H<sub>8</sub>O<sub>2</sub>N<sub>2</sub>: C, 67.92; H, 3.77; N, 13.21. Found: C, 67.62; H, 4.05; N, 12.81.

**2,3-Diacetoxyphenazine (XIV)**—(VI) was acetylated by the ordinary method. It gave pale yellow needles (from xylene), m.p. 236°. (For this compound, Ullmann, *et al.* recorded m.p. 226° and O. Fischer *et al.*<sup>13)</sup>, 230°.) *Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>O<sub>4</sub>N<sub>2</sub>: C, 64.86; H, 4.05; N, 9.50. Found: C, 65.12; H, 4.21; N, 9.48.

**Condensation of 2-Nitrohydroquinone Dimethyl Ether and Aniline: 1,4-Dimethoxyphenazine (VII)**—A mixture of 2-nitrohydroquinone dimethyl ether (10 g.), aniline (6 g.), and powdered potassium hydroxide (30 g.) was refluxed in toluene (150 cc.) for 6 hours. The reaction mixture was treated in the ordinary method and 5.2 g. (40%) of crude crystals were obtained. They were dissolved in benzene, and purified by chromatography on alumina. It gave orange red needles of 1,4-dimethoxyphenazine (VII), m.p. 185° (from ligroine). *Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 70.00; H, 5.00; N, 11.68. Found: C, 69.81; H, 5.12; N, 11.51.

The same compound was obtained in 32% yield, when the mixture was kept standing for 3 days without a solvent at 55°.

**Condensation of 2-Aminohydroquinone Dimethyl Ether and Nitrobenzene: (VII) and 2-Methoxyphenazine 5-Mono-N-oxide (IX)**—A mixture of 2-aminohydroquinone dimethyl ether (4 g.), nitrobenzene (3 g.), and powdered potassium hydroxide (13 g.) was refluxed in toluene (65 cc.) for 6 hours. The crude crystals obtained was dissolved in benzene, and purified on alumina. The first eluate yielded 1.2 g. of yellow needles, m.p. 177° (from ligroine), which were found to be identical with 2-methoxyphenazine 5-mono-N-oxide (IX) by mixed fusion with authentic specimen. *Anal.* Calcd. for C<sub>13</sub>H<sub>10</sub>O<sub>2</sub>N<sub>2</sub>: N, 12.38. Found: N, 12.10.

The next eluate yielded 1.0 g. of orange red needles, m.p. 185°, not depressed by admixture with 1,4-dimethoxyphenazine (VII).

**1,4-Dihydroxyphenazine (VIII)**—1,4-Dimethoxyphenazine was demethylated with hydrobrom-

13) O. Fischer, E. Hepp: Ber., 23, 841 (1890).

ic acid and acetic acid to 1,4-dihydroxyphenazine (VIII). It gave deep red needles, m.p. 232~234° (from chloroform). (King *et al.*<sup>10</sup>) recorded m.p. 230° for (VIII). *Anal.* Calcd. for  $C_{12}H_8O_2N_2$ : C, 67.92; H, 3.77; N, 13.21. Found: C, 67.98; H, 3.93; N, 12.92.

**1,4-Diacetoxyphenazine**—(VIII) was acetylated to 1,4-diacetoxyphenazine with acetic anhydride and anhydrous sodium acetate. It yielded tarnish yellow prisms, m.p. 195° (from ethanol). *Anal.* Calcd. for  $C_{16}H_{12}O_4N_2$ : C, 64.86; H, 4.05; N, 9.50. Found: C, 65.17; H, 4.17; N, 9.13.

**Condensation of 4-Nitroresorcinol Dimethyl Ether and Aniline: 1,3-Dimethoxyphenazine (X)**—A mixture of 4-nitroresorcinol dimethyl ether (10 g.), aniline (6 g.), and powdered potassium hydroxide (30 g.) was refluxed in toluene (150 cc.) for 6 hours. The reaction mixture was treated ordinarily, and the crude material thus obtained was purified on alumina in benzene. The eluate gave 0.4 g. of 1,3-dimethoxyphenazine (X), yellow needles, m.p. 228° (from ligroine). *Anal.* Calcd. for  $C_{14}H_{12}O_2N_2$ : C, 70.00; H, 5.00; N, 11.68. Found: C, 70.27; H, 5.06; N, 11.64.

The same product was obtained in 1.5% yield when the mixture was kept standing for 3 days without a solvent at 55°.

**Condensation of 4-Aminoresorcinol Dimethyl Ether and Nitrobenzene: 2-Methoxyphenazine (XII) and 2-Methoxyphenazine 10-Mono-N-oxide (XIII)**—A mixture of 4-aminoresorcinol dimethyl ether (4.3 g.), nitrobenzene (3.2 g.), and powdered potassium hydroxide (13 g.) was refluxed in toluene (65 cc.) for 6 hours. The reaction mixture was treated as described above and the crude product (2.7 g.) was obtained in 41% yield. This was dissolved in benzene and purified on alumina. The first eluate yielded 0.6 g. of 2-methoxyphenazine (XII), pale yellow needles, m.p. 123° (from ligroine), not depressed by mixed fusion with authentic specimen. *Anal.* Calcd. for  $C_{13}H_{10}ON_2$ : N, 13.33. Found: 13.14.

The next eluate yielded 1.4 g. of yellow needles, m.p. 175~176° (from ligroine), not depressed by admixture with 2-methoxyphenazine 10-mono-N-oxide (XIII). *Anal.* Calcd. for  $C_{13}H_{10}O_2N_2$ : N, 12.38. Found: N, 12.23.

**1,3-Dihydroxyphenazine (XI)**—Brown yellow microneedles (from ethanol), did not melt below 280°. *Anal.* Calcd. for  $C_{12}H_8O_2N_2$ : C, 67.92; H, 3.77; N, 13.21. Found: C, 67.50; H, 4.13; N, 12.84.

**1,3-Diacetoxyphenazine (XVII)**—Pale yellow needles, m.p. 263~264° (from benzene). *Anal.* Calcd. for  $C_{16}H_{12}O_4N_2$ : C, 64.86; H, 4.05; N, 9.50. Found: C, 64.92; H, 4.35; N, 9.40.

**2,3-Dihydroxyphenazine Di-N-oxide (XV)**—2,3-Diacetoxyphenazine (0.2 g.) was dissolved in benzene (40 cc.) and 30% hydrogen peroxide (3 cc.) and acetic anhydride (3 cc.) were added. The mixture was warmed on a water bath for 4 hours. The reaction solution was washed with dild. hydrochloric acid, extracted with 10% caustic soda, and the alkaline layer neutralized with acetic acid. The precipitate produced was collected and crystallized from ethanol. It gave dark purplish brown microneedles, which did not melt below 340°. Yield: 0.14 g. It dissolves in alkaline solution with orange red coloration. *Anal.* Calcd. for  $C_{12}H_8O_4N_2$ : C, 59.01; H, 3.27; N, 11.47. Found: C, 59.24; H, 3.74; N, 11.35.

**1,4-Dihydroxyphenazine Di-N-oxide (XVI)**—1,4-Dihydroxyphenazine (0.3 g.) was dissolved in benzene (80 cc.), 30% hydrogen peroxide (3 cc.), and acetic anhydride (3 cc.) were added, and warmed on water bath for 6 hours. The solvent was evaporated and the crystals deposited were recrystallized from ethanol. It gave pale brown yellow needles, which did not melt below 340°. Yield: 0.1 g. It dissolves in alkaline solution without coloring. *Anal.* Calcd. for  $C_{12}H_8O_4N_2$ : C, 59.01; H, 3.27; N, 11.47. Found: C, 59.27; H, 3.39; N, 11.12.

**1,3-Dihydroxyphenazine Di-N-oxide (XVIII)**—1,3-Diacetoxyphenazine (0.1 g.) was dissolved in benzene (80 cc.), 30% hydrogen peroxide (1.5 cc.) and acetic anhydride (1.5 cc.) were added, and warmed on water bath for 5 hours. The reaction solution was treated ordinarily, and red microneedles (from ethanol), m.p. 280°, were obtained. It gave a violet coloration with dild. sodium hydroxide. *Anal.* Calcd. for  $C_{12}H_8O_4N_2$ : C, 59.01; H, 3.27; N, 11.47. Found: C, 58.82; H, 3.36; N, 11.27.

**N-Oxidation of 1,2-Diacetoxyphenazine**—1,2-Diacetoxyphenazine was oxidized with hydrogen peroxide and acetic anhydride in benzene as described above but no crystalline substances were obtained.

### Summary

1,2-Dihydroxyphenazine was prepared by oxidizing 2,2'-dinitro-5,6-dimethoxydiphenylamine with ferric chloride solution and the resultant product was demethylated with hydrobromic acid. 2,3-Dihydroxyphenazine was prepared by hydrolyzing 2,3-diaminophenazine with sulfuric acid in a sealed tube. 1,3- and 1,4-dihydroxyphenazines

were prepared by using the improved Wohl-Aue method.

These four dihydroxyphenazines, i.e. 1,2-, 1,3-, 1,4-, and 2,3-dihydroxyphenazines were oxidized with hydrogen peroxide in the presence of acetic anhydride in benzene, and 1,3-, 1,4-, and 2,3-dihydroxyphenazine di-N-oxides were obtained, respectively. In the case of the 1,2-isomer, its di-N-oxide was not obtained.

(Received December 17, 1953)

16. **Shun'ichi Yamada, Ichiro Chibata, and Ryoya Tsurui:** Application of Ion Exchangers in Organic Reactions. III<sup>1)</sup>. Application to the Rearrangement of Hydrazobenzene Derivatives\*.

(Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.\*\*)

In the previous paper<sup>2)</sup> on the application of ion exchangers in organic reactions, it was shown that the cation exchangers afford an effective and convenient condensing agent for the Fischer indole synthesis. This result induced the authors to carry out the present experiments of the application of cation exchangers for the rearrangement reaction of hydrazobenzene derivatives, as the Fischer indole synthesis is considered to proceed through the *o*-benzidine type rearrangement.

The rearrangement reaction of the hydrazobenzene derivatives has been investigated in greater detail than any of the others because of its exceptional theoretical interest. Since the publication of the famous general review by Jacobson<sup>3)</sup> many reports on the matter have been made.

As catalytic agents for this rearrangement, mineral acids such as sulfuric acid and hydrochloric acid have been employed, especially the latter with stannous chloride have been used as effective agents for the reaction. However, the yields of the reaction are low except in the case of the rearrangement of hydrazobenzene to benzidine. Furthermore, because of the mixed presence of the rearranged product with unreacted material, azo compound and split amine produced during the reaction, the troublesome procedures of separating and purifying the desired products cannot be avoided. It was hoped to simplify the procedure of separation by employing the cation exchangers instead of mineral acids as catalytic agents. Four different type rearrangements of hydrazobenzene derivatives were carried out. When the hydrazobenzenes were heated with the previously activated hydrogen form<sup>2)</sup> of the cation exchangers of nuclear sulfonic acid-type resin, such as Amberlite IR-120 and Dowex-50, in water or aqueous alcohol, the unreacted material and azo compound produced during the reaction were recovered from the filtrate of the reaction mixture by concentration and/or by the extraction of the insoluble substances as they were not adsorbed on the resins. The rearranged product was obtained by the elution of the resins with alkaline solution. By this

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1) S. Yamada, I. Chibata, R. Tsurui: *J. Pharm. Soc. Japan*, **73**, 123 (1952).

2) S. Yamada, I. Chibata, R. Tsurui: *This Bulletin*, **1**, 14 (1953).

3) Jacobson: *Ann.*, **428**, 76 (1922).