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76. **Yoshinori Kidani** and Hirotaka Otomasu*****: Studies on Phenazines. XII.* Synthesis of Methylphenazines with Sodium Amide.

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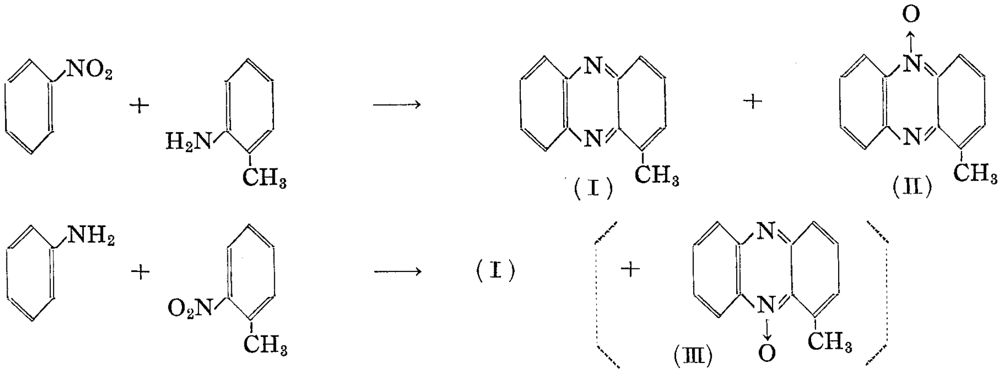
The synthesis of methylphenazines using the Wohl–Aue reaction[1] in the presence of potassium hydroxide has already been reported by Maffei *et al.*,[2,3] Serebryanyi,[4] and others.[5~9] The Wohl–Aue condensation generally gives a very poor yield and an attempt to synthesize methylphenazines by the improved Wohl–Aue method[10] by the present writers failed. It is learned that Pushkareva *et al.*[11] reported the synthesis of 1–methylphenazine mono–N–oxide by condensation with sodium amide instead of potassium hydroxide. No details on the conditions and yield are known but it is supposed to be almost the same as that of the original Wohl–Aue method without a solvent.

They did not obtain 1–methylphenazine (I), m.p. 109°, but obtained only 1–methylphenazine 5–oxide (II), m.p. 142°, by condensation between nitrobenzene and *o*–toluidine. When nitro and amino groups were reversed, that is, aniline and *o*–nitrotoluene were condensed, only 1–methylphenazine 10–oxide (III), m.p. 158°, was obtained and not (I). The same reaction carried out by the present writers afforded (I) and (II) by the former, and only (I) and not (III) by the latter method. At the same time, the m.p. measured by us differed a little from that of Pushkareva *et al.*



Authors, this time, attempted the synthesis of methylphenazines in the presence of sodium amide and the yield was much increased. Therefore, this modified method of the improved Wohl–Aue reaction is recommended for the synthesis of methylphenazine derivatives.

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2) S. Maffei, S. Pietra, *et al.* : Ann. chim.(Rome), **42**, 519(1952).
3) S. Maffei, S. Pietra, *et al.* : *Ibid.*, **43**, 611(1953).
4) S. B. Serebryanyi : J. Gen. Chem. U. S. S. R., **20**, 1692(1950).
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6) V. Merz : *Ibid.*, **19**, 726(1886).
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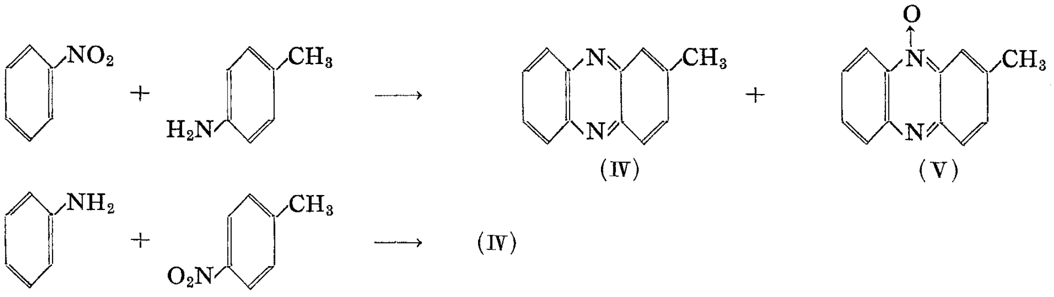
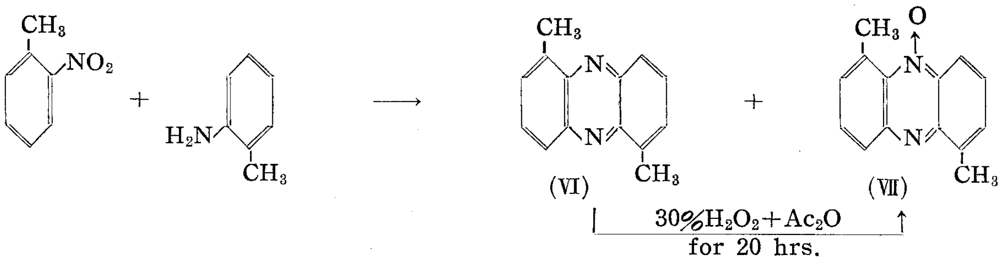
8) H. McCombie, *et al.* : J. Chem. Soc., **1928**, 353.
9) F. Kehrman, C. Mermod : Helv. Chim. Acta, **10**, 63(1927).
10) I. Yosioka, Y. Kidani : J. Pharm. Soc. Japan, **72**, 847(1952).
11) Z. U. Pushkareva, G. I. Agivalova : J. Gen. Chem. U. S. S. R., 8, 151(1938).

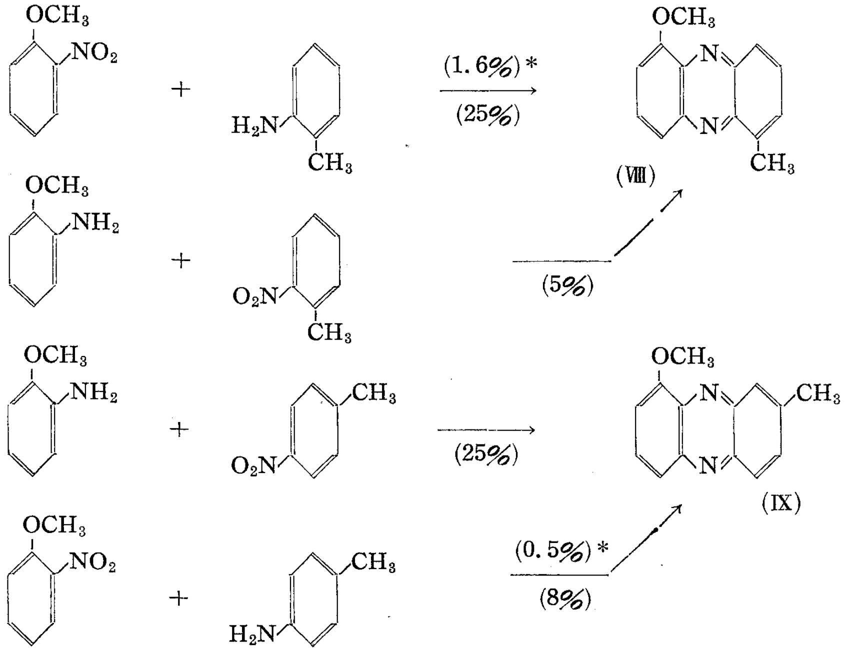
One mole each of aromatic amine and nitro compounds are dissolved in toluene and to this a well-ground sodium amide is added. The reaction occurs as soon as they are mixed together, with an evolution of ammonia gas and a rise of temperature. A few hours' reflux is required to complete the reaction.



In the case of 1-methylphenazine (I), nitrobenzene and *o*-toluidine were condensed and (I) was obtained in 18% yield, besides its 5-oxide (II), m.p. 147°. When nitro and amino groups were reversed, only (I) was obtained in 10% yield and not (III). In the case of 2-methylphenazine (IV), nitrobenzene and *p*-toluidine were reacted and (IV), m.p. 117°, was obtained in 15% yield, besides 2-methylphenazine 10-oxide (V), m.p. 151°. However, when aniline and *p*-nitrotoluene were condensed, (IV) alone was obtained in 7% yield and not its mono-N-oxide.



In the condensation of *o*-nitrotoluene and *o*-toluidine, 1,6-dimethylphenazine (VI), m.p. 221∼222°, was obtained, besides a substance of m.p. 200°(decomp.). This was ascertained to be 1,6-dimethylphenazine mono-N-oxide (VII) from the derivative which

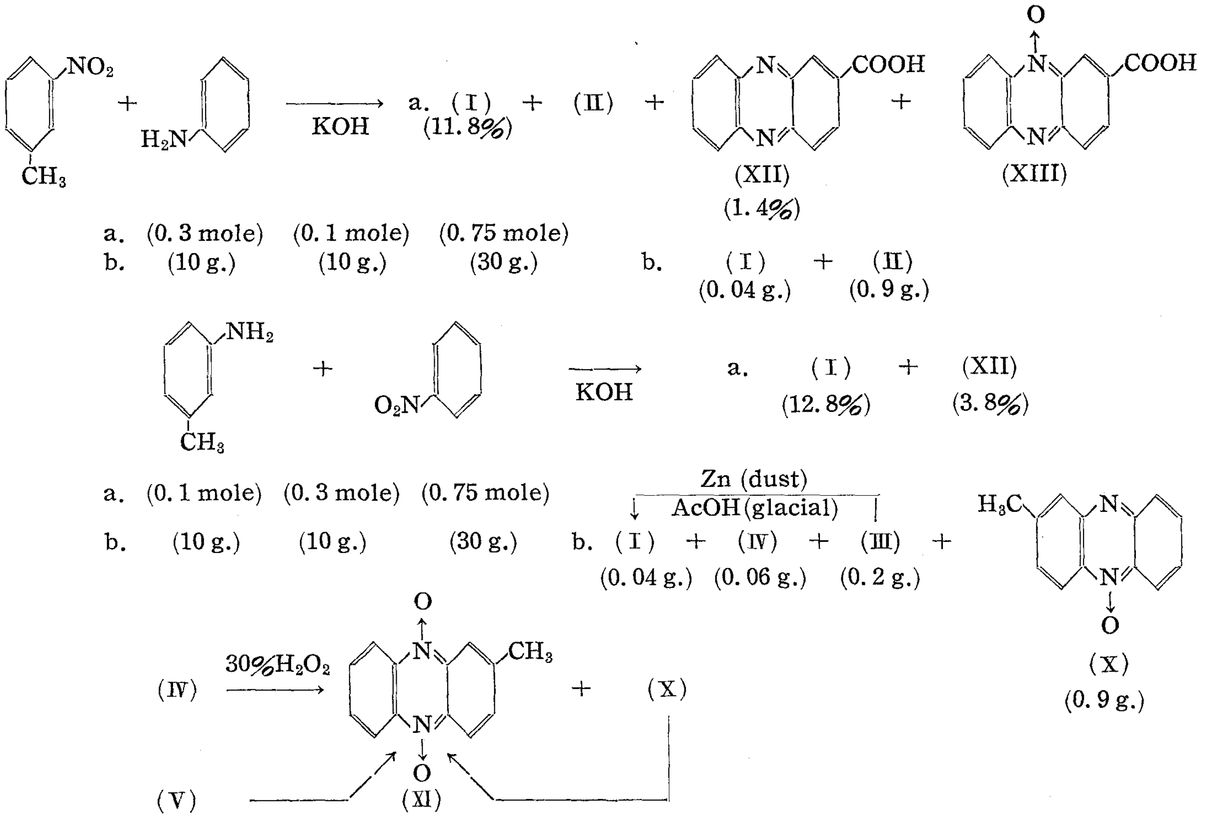


Values in parentheses show the yield. * Yield obtained by Serebryanyi.

was synthesized by the oxidation of (VI) with 30% hydrogen peroxide and acetic anhydride in benzene solution.

Mono-N-oxides of 1-methoxy-6-methylphenazine (VIII), m.p. 188~189°, and 1-methoxy-8-methylphenazine (IX), m.p. 184°, were not obtained. In these condensations, the refluxing period depends upon the location of the methyl group in phenazine ring. In the case of α-methylphenazine derivatives, such as (VIII), refluxing for 2 to 3 hours is enough to complete the reaction, but at least 7 hours was required in the case of β-methylphenazine derivatives, such as (IX).

In the condensation between *o*-nitroanisole and *o*-toluidine, (VIII) was obtained in 25% yield, but when *o*-anisidine and *o*-nitrotoluene were condensed, (VIII) was obtained in only 5% yield. The yield was also 25% in the condensation of *o*-anisidine and *p*-nitrotoluene, and when *o*-nitroanisole and *p*-toluidine were reacted, the yield was only 8%.



a) Results obtained by Maffei *et al.*
b) Present writers'.

In order to examine the results obtained by Pushkareva *et al.*, the following experiments were carried out and the results obtained differed widely from that of Maffei *et al.* As 1-methylphenazine 10-oxide (III) was not obtained by the sodium amide condensation, the improved Wohl-Aue method was applied in this reaction. One mole each of *m*-nitrotoluene and aniline were condensed in the presence of powdered potassium hydroxide and (I) and its 5-oxide (II) were obtained. When *m*-toluidine and nitrobenzene were condensed in the presence of potassium hydroxide, followed by purification through alumina column, the first eluate was (I), the second (IV), the third (III), m.p. 136°, and the last was 2-methylphenazine 5-oxide (X), m.p. 122°. (III) was deoxygenated with zinc dust in glacial acetic acid to (I)(picrate, m.p. 182°), identified with that obtained by the sodium amide method. At the same time, (IV) was oxidized with 30% hydrogen peroxide to 2-methylphenazine di-N-oxide (XI), m.p. 180°(decomp.), and (X) was also obtained. (X) was oxidized to (XI) by the same method with hydrogen peroxide. Maffei *et al.* used three times of nitro compound as amino compound in the presence of excess potassium hydroxide. *m*-Toluidine and nitrobenzene were condensed with potassium hydroxide, and (I) was obtained in 12.8% yield and 2-phenazinecarboxylic acid (XII), m.p. 292°, in 3.8% yield. When aniline and *m*-nitrotoluene were reacted with potassium hydroxide, they obtained (I) in 11.8% yield, together with (XII) in 1.4%, (II), m.p. 263°, and 2-phenazinecarboxylic acid 10-oxide (XIII), m.p. 129°. In this condedsation, they obtained carboxylic acid derivatives and it may have resulted by the use of an excess of nitro compounds. As for 1-methylphenazine 5-oxide (II), every author showed a different m.p.; Pushkareva reported 142°, Maffei 263°, and 147° by us.

The modified Wohl-Aue method in the presence of sodium amide is recommended for the synthesis of methylphenazine derivatives and sodium amide is so reactive that the yield of methoxy- and halophenazines were rather poor.

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Experimental

Condensation of *o*-Toluidine with Nitrobenzene : 1-Methylphenazine (I) and its 5-Oxide (II)—To a solution of *o*-toluidine (10 g.) and nitrobenzene (10 g.) in toluene (150 cc.), well-ground $NaNH_2$(10 g.) was added in small portions with shaking. The mixture was warmed on a water bath for 1∼2 hrs. and steam distilled. The tarry substance deposited in the remaining aqueous solution was extracted with dil. HCl. To the acidic solution, a small amount of fuming HNO_3 was added, filtered, and alkalized with NH_4OH. The crude product that separated in benzene was purified by chromatography over Al_2O_3. 1.7 g. of (I), yellow needles (from ligroine), m.p. 109°(picrate, yellow needles, m.p. 182°), and its 5-oxide (II), (0.1 g., from MeOH), were obtained. *Anal.* Calcd. for $C_{13}H_{10}N_2$ (I): N, 14.43. Found : N, 14.56. *Anal.* Calcd. for $C_{19}H_{12}O_7N_5$(picrate of (I)) : N, 16.54. Found : N, 16.67.

Condensation of *o*-Nitrotoluene with Aniline : 1-Methylphenazine (I)—To a mixture of *o*-nitrotoluene (14 g.) and aniline (9.3 g.) in toluene (150 cc.), well-ground $NaNH_2$ (10 g.) was added and the mixture was refluxed on a water bath. By the same after-treatment, 1.7 g. of (I) was obtained.

Condensation of *p*-Toluidine with Nitrobenzene : 2-Methylphenazine (IV) and its 10-Oxide (V)—From the reaction of *p*-toluidine (10 g.) and nitrobenzene (10 g.) in toluene (150 cc.) with $NaNH_2$ (10 g.), 2 g. of (IV) as yellow needles (from ligroine), m.p. 117°, and 0.08 g. of (V) as yellow needles (from MeOH), m.p. 151°, were obtained. *Anal.* Calcd. for $C_{13}H_{10}N_2$ (IV) : N, 14,43. Found : N, 14.09. *Anal.* Calcd. for $C_{13}H_{10}ON_2$ (V) : C, 74.24; H, 4.76; N, 13.33. Found : C, 74.74; H, 4.99; N, 13.12.

Condensation of *p*-Nitrotoluene with Aniline : 2-Methylphenazine (IV)—From the condensation between *p*-nitrotoluene (20 g.) and aniline (20 g.) in toluene (300 cc.) with $NaNH_2$ (20 g.), 1 g. of (IV) was obtained.

Oxidation of 2-Methylphenazine (IV) and its Oxide (V)—To a solution of (IV) (1.2 g.) dissolved in glacial AcOH (20 cc.), 30% H_2O_2 was added, the solution was warmed on a water bath for 20 hrs. at 55°, diluted with water, and neutralized with NaOH solution. The product that separated was collected and purified over Al_2O_3 from benzene. The eluate gave (V). The strongly adsorbed upper zone was extracted with MeOH and evaporated to dryness. This was recrystallized from benzene to 2-methylphenazine di-N-oxide (XI) as red needles of m.p. 180°(decomp.). This was also obtained by the analogous treament from (X). *Anal.* Calcd. for $C_{13}H_{10}O_2N_2$ (XI) : C, 69.03; H, 4.42; N, 12.39. Found : C, 69.25; H, 4.40; N, 12.09.

1,6-Dimethylphenazine (VI) and its Mono-N-Oxide (VII)—From the condensation of *o*-nitrotoluene (20 g.) and *o*-toluidine (20 g.) in toluene (300 cc.) with $NaNH_2$ (20 g.), (VI) was obtained as yellow needles, m.p. 221∼222°(from benzene), in 1.4 g. yield and (VII) as yellow needles (from MeOH), m.p. 200°(decomp.) in a yield of 0.1 g. *Anal.* Calcd. for $C_{14}H_{12}N_2$(VI) : C, 80.77; H, 5.77; N, 13.46. Found: C, 80.68; H, 5.47; N, 13.60. *Anal.* Calcd. for $C_{14}H_{12}ON_2$ (VII) : C, 70.54; H, 5.36; N, 12.5. Found: C, 74.99; H, 5.66; N, 12.13.

Oxidation of 1,6-Dimethylphenazine (VI)—0.5 g. of (VI) was dissolved in benzene (60 cc.), and 30% H_2O_2 (4 cc.) and Ac_2O (4 cc.) were added. The mixture was refluxed for 20 hrs. on a water bath. After the reaction, the benzene layer was washed with a mixture of acetone and MeOH and run through a column of Al_2O_3 after drying. Yellow needles of 1,6-dimethylphenazine mono-N-oxide (VII) (0.2 g.) were obtained together with the starting substance.

1-Methoxy-6-methylphenazine (VIII)—(i) To a mixture of *o*-nitroanisole (15 g.) and *o*-toluidine

(10 g.) in toluene (150 cc.), $NaNH_2$ (8 g.) was added and the faint yellow solution turned tarry brown immediately after mixing. This mixture was refluxed for about 3.5 hrs. at 120°, and after steam distillation, it was extracted with benzene, followed by extraction with HCl and alkalized with NH_4OH. The deposited precipitate was extracted with benzene again and purified over Al_2O_3. 5.4 g. of (VIII), yellow needles, m.p. 188～189°(from ligroine), was obtained. *Anal.* Calcd. for $C_{14}H_{12}ON_2$(VIII): N, 12.50. Found: N, 12.14.

(ii) From the condensation of *o*-anisidine (12 g.) and *o*-nitrotoluene (13 g.) for 2 hrs.,(VIII) was obtained in a yield of 0.3 g.

1-Methoxy-8-Methylphenazine (IX)—(i) A mixture of *o*-anisidine (12 g.) and *p*-nitrotoluene (13 g.) was refluxed for 7 hrs. in the presence of $NaNH_2$ (8 g.) and 4 g. of (IX), yellow needles, m.p. 184° (from ligroine), was obtained. *Anal.* Calcd. for $C_{14}H_{12}ON_8$ (IX): N, 12.50. Found: N, 12.19.

(ii) From the condensation of *o*-nitroanisole (15 g.) and *p*-toluidine (10 g.), (IX) was obtained in a yield of 0.6 g.

Condensation of *m*-Nitrotoluene with Aniline: 1-Methylphenazine (I) and its 5-Oxide (II)—A mixture of *m*-nitrotoluene (10 g.) and aniline (10 g.) was refluxed gently for 4 hrs. in toluene (150 cc.) with well-powdered KOH (30 g.). The reaction mixture was treated as described above and (I) (0.04 g.) and (II) (0.9 g.) as yellow needles (from MeOH), m.p. 147°, were separated chromatographically. *Anal.* Calcd. for $C_{13}H_{10}ON_2$ (II): N, 13.33. Found: N, 13.48.

Condensation of *m*-Toluidine with Nitrobenzene—A mixture of *m*-toluidine (10 g.), nitrobenzene (10 g.), and KOH (30 g.) was refluxed in toluene, the reaction product was treated by the ordinary method, and chromatographic procedure afforded the following fractions:

Eluate	1	Pale yellow needles (I)	m.p.	109°	0.04 g.
〃	2	Pale yellow needles (IV)	〃	117°	0.06 g.
〃	3	Yellow needles (III)	〃	136°	0.2 g.
〃	4	Yellow needles (X)	〃	122°	0.9 g.

Deoxygenation of 1-Methylphenazine 10-Oxide (II)—To a solution of (III) (0.1 g.) in glacial AcOH (2 cc.), Zn dust (0.5 g.) was added in small portions, the reaction mixture was warmed on a water bath for a while, alkalized with dil. NaOH solution, and extracted with benzene. The extract was dried and chromatographed over Al_2O_3, and 1-methylphenazine (I), m.p. 109°(picrate, m.p. 182°), was obtained. This was not depressed on admixture with the authentic specimen.

Summary

Though the synthesis of methylphenazine derivatives has been reported, the yield was generally very poor. A variation of the improved Wohl-Aue reaction, carried out in the presence of sodium amide, gave better yield. The syntheses of 1- and 2-methyl- and 1,6-dimethylphenazines and their oxides, as well as that of 1-methoxy-6-methyl- and 1-methoxy-8-methylphenazines are described.

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