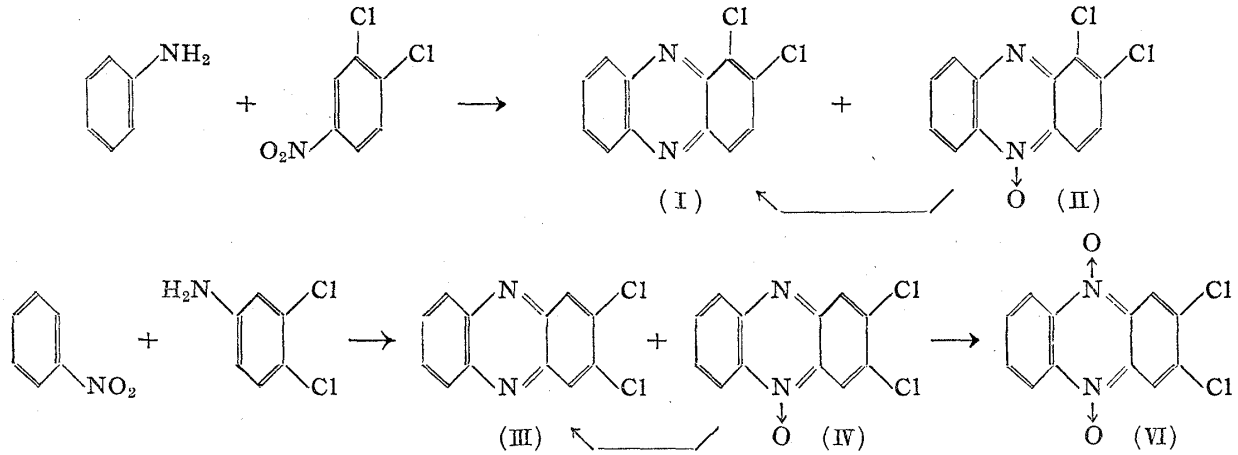
72. **Hirotaka Otomasu**: Studies on Phenazines. IX.* Synthesis of Dichlorophenazines.

(*Hoshi College of Pharmacy***)

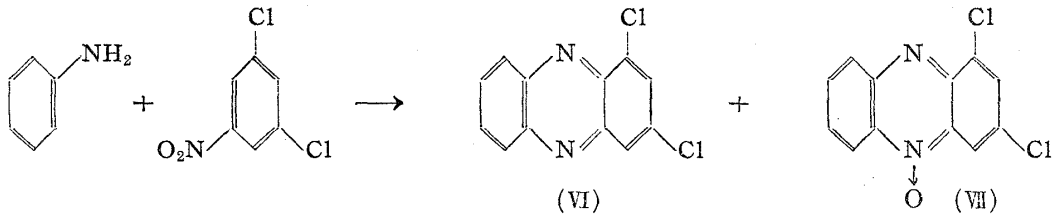
In previous papers of this series, Yosioka and the author reported the synthesis of several kinds of alkoxyphenazines, with a view to examining antibacterial activities. This paper describes the synthesis of dichlorophenazines by the improved Wohl-Aue reaction.[1]

It was learned recently that Chernetzkii and his collaborator[2] obtained all isomers of dichlorophenazine by the same reaction from aromatic amines and nitro compounds. These compounds agree with our results except for differences detailed below.

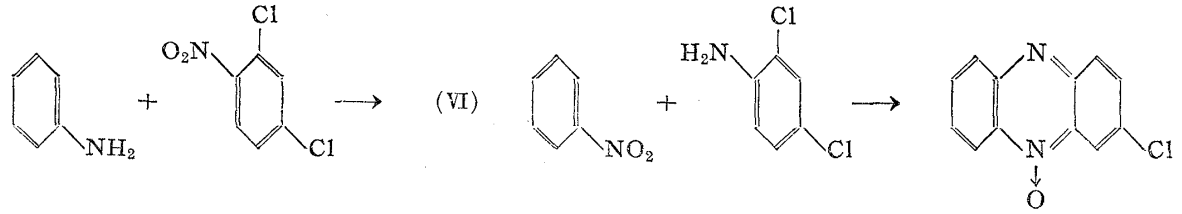
The synthesis of dichlorophenazines with the chlorine on the same benzene ring is first described. 3,4-Dichloro-1-nitrobenzene was condensed with two moles of aniline in the presence of potassium hydroxide in toluene solution. After purifying the reaction products by chromatography on alumina, 1,2-dichlorophenazine 5-oxide (II) was obtained in 20% yield, with 1,2-dichlorophenazine (I). (II) was deoxygenated by heating with dimethylaniline and acetic anhydride to form (I), quantitatively. Reversing the nitro



and amino groups, nitrobenzene and 3,4-dichloroaniline were condensed by the same procedure, and 2,3-dichlorophenazine (III) and its 5-oxide (IV) were obtained in a total yield of 2%. In this case, 1,2-isomer was not produced. (IV) was reduced to (III) with dimethylaniline in acetic anhydride. Both (III) and (IV) were oxidized with hydrogen peroxide in glacial acetic acid to yield 2,3-dichlorophenazine di-N-oxide (V) as deep red crystals.



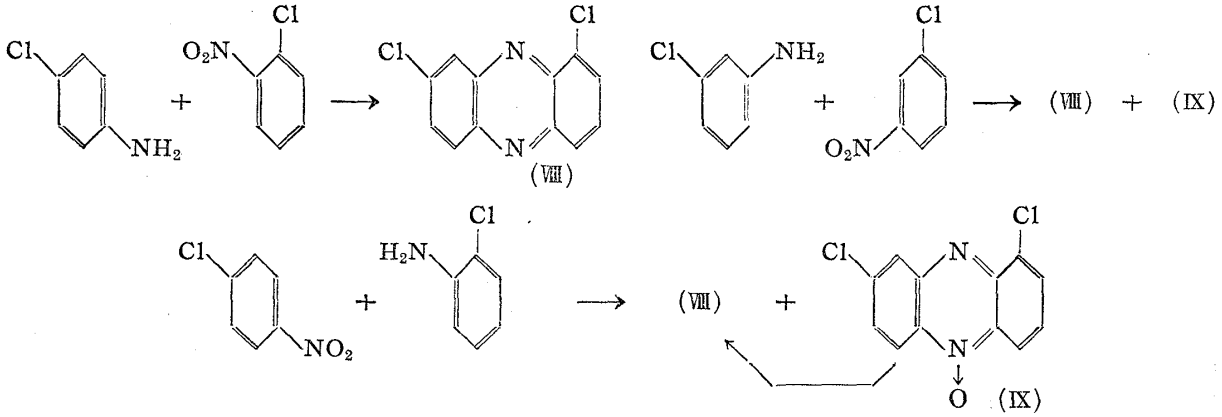
* Part VIII: This Bulletin, **2**, 292(1954).
** 2-Chome Ebara, Shinagawa-ku, Tokyo (乙益寛隆).
1) Wohl, Aue: Ber., **34**, 2442(1901).
2) P. V. Chernetzkii, A. I. Kiprianov: C. A., **48**, 13695(1954); P. V. Chernetzkii, S. B. Serebryani: *Ibid.*, **49**, 1966(1955).



There are two possible ways of obtaining 1,3-dichlorophenazine. One is the condensation of 3,5-dichloro-1-nitrobenzene with aniline, which yielded 1,3-dichlorophenazine (VI) and its 5-oxide (VII). The other is the condensation of 2,4-dichloro-1-nitrobenzene and aniline, from which only 1,3-dichlorophenazine was obtained in 10% yield. Condensation of nitrobenzene with 2,4-dichloroaniline by the same method failed to yield the objective 1,3-isomer and produced 3-chlorophenazine 5-oxide[3] in a poor yield, with a corresponding diphenylamine derivative as a by-product.

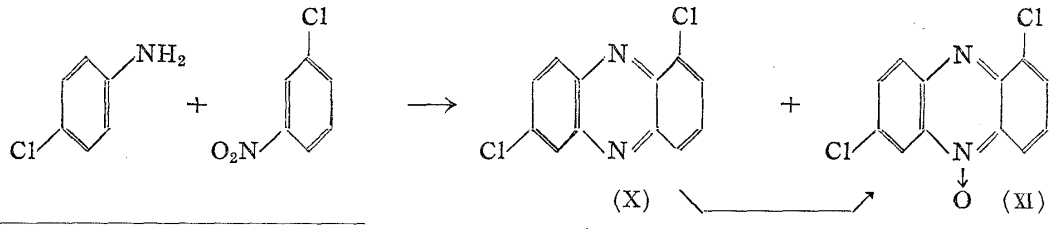
1,4-Dichlorophenazine was synthesized from 2,5-dichloro-1-nitrobenzene and aniline. Maffei *et al.*[4] had obtained this compound using the same method.

The dichlorophenazines in which the chlorine atoms are located separately in each benzene ring, such as 2,7-[3,5] and 1,6-dichlorophenazine[6] were synthesized in the following manner.

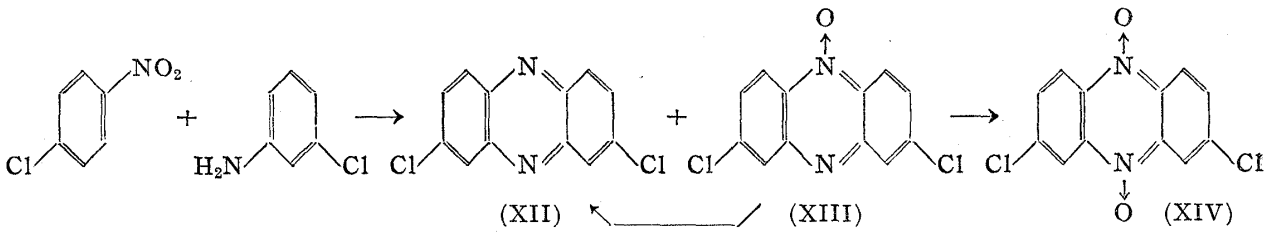


1,8-Dichlorophenazine (VIII) was obtained in 25% yield by the condensation of *o*-chloronitrobenzene and *p*-chloroaniline. The reverse of this reaction, changing the position of the nitro and amino groups, i.e. condensation of *p*-chloronitrobenzene and *o*-chloroaniline, afforded a small amount of (VIII) along with 5-oxide (IX) in 12% yield. The same compounds, (VIII) and (IX), were also obtained by the reaction between *m*-chloronitrobenzene and *m*-chloroaniline, in respective yields of 14% and 30%. (IX) was reduced to (VIII) by the same method.

Similarly, from the condensation of *p*-chloroaniline and *m*-chloronitrobenzene, 1,7-dichlorophenazine (X) and its 5-oxide (XI) were obtained in 10% and 13% yield, respectively. (X) was oxidized to (XI) with hydrogen peroxide in glacial acetic acid.

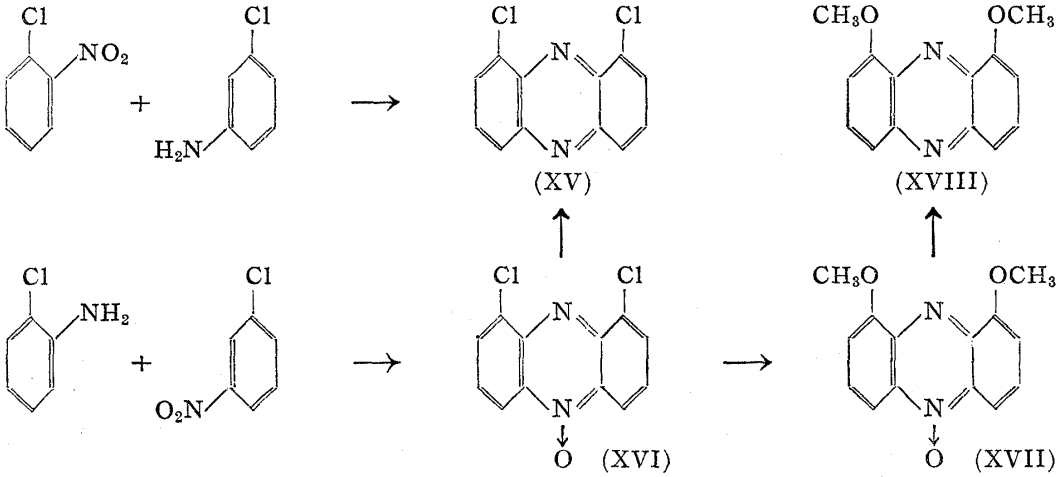


3) I. J. Pachter, M. C. Kloetzel: J. Am. Chem. Soc., 74, 971(1952).
4) S. Maffei, S. Pietra, A. Gattaeno: C. A., 48, 12123(1954).
5) Eng. Bamberger, W. Ham: Ann., 382, 93(1911).



When the nitro and amino groups were reversed, the result differed entirely from that of previously case. When *p*-chloronitrobenzene and *m*-chloroaniline were condensed, 2,8-dichlorophenazine 5-oxide (XIII) was obtained in 17% yield. In this reaction, 2,8-dichlorophenazine (XII) was produced along with (XIII) by the use of 2 moles of *m*-chloroaniline, as described by Chernetzkii.[2] (XIII) was reduced to (XII) by deoxygenation and oxidized to 2,8-dichlorophenazine di-N-oxide (XIV) by the same method.

To obtain 1,9-dichloro isomer, the condensation of *m*-chloroaniline and *o*-chloronitrobenzene was conducted in the same way, and pale yellow needles (XV) of m.p. 208~209° were obtained in 32% yield. On the other hand, the condensation of *m*-chloronitrobenzene and *o*-chloroaniline produced yellow needles (XVI), m.p. 223°(decomp.), in 13%



yield. (XVI) was converted to (XV) by deoxygenation and was changed to dimethoxyphenazine mono-N-oxide (XVII), m.p. 261°(decomp.), by methanolysis. This compound was proved to be 1,9-dimethoxyphenazine 5-oxide, because the deoxygenation product of (XVII) was found to be identical with 1,9-dimethoxyphenazine (XVIII), m.p. 254°,[7] by admixture. The substance (XV) having m.p. 208~209° must therefore be 1,9-dichlorophenazine.

The properties of the compounds thus obtained are summarized in the accompanying table.

No.	Phenazines	Appearance (Recrystn. solvt.)	m.p., °C*	Anal. values C%	H%
(I)	1,2-Dichloro-	Pale yellow needles (ligroine)	170~171	a) 57.76	2.32
(II)	1,2-Dichloro 5-oxide	Yellow needles (MeOH)	217(decomp.)	b) 54.74	2.57
(III)	2,3-Dichloro-	Pale yellow plates (benzene)	241~242	a) 58.08	2.38
(IV)	2,3-Dichloro 5-oxide	Yellow needles (MeOH)	220(decomp.)	b) 54.55	2.11

6) I. J. Pachter, M. C. Kloetzel: J. Am. Chem. Soc., **73**, 4958(1951).
7) I. Yosioka: This Bulletin, **2**, 25(1954).

(V)	2,3-Dichloro di-N-oxide	Deep red needles (MeOH)	206(decomp.)	c) 51.32	2.31
(VI)	1,3-Dichloro-	Pale yellow needles (ligroine)	190~191	a) 58.00	2.40
(VII)	1,3-Dichloro 5-oxide	Yellow needles (MeOH)	235(decomp.)	b) 54.59	2.16
(VIII)	1,8-Dichloro-	Pale yellow needles (benzene)	216~218	a) 58.41	2.71
(IX)	1,8-Dichloro 5-oxide	Yellow needles (MeOH)	215(decomp.)	b) 54.37	2.33
(X)	1,7-Dichloro-	Pale yellow needles (ligroine)	191~195	a) 58.09	2.54
(XI)	1,7-Dichloro 5-oxide	Yellow needles (MeOH)	197~198	b) 54.40	2.54
(XII)	2,8-Dichloro-	Pale yellow needles (benzene)	224~225	a) 58.01	2.08
(XIII)	2,8-Dichloro 5-oxide	Yellow needles (MeOH)	232(decomp.)	b) 54.64	2.22
(XIV)	2,8-Dichloro di-N-oxide	Red needles (MeOH)	211(decomp.)	c) 51.50	2.46
(XV)	1,9-Dichloro-	Pale yellow needles (MeOH)	208~209	a) 58.17	2.44
(XVI)	1,9-Dichloro 5-oxide	Yellow needles (MeOH)	223(decomp.)	b) 54.80	2.55

* All melting points are uncorrected.
a) Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.83; H, 2.41.
b) Calcd. for $C_{12}H_6ON_2Cl_2$: C, 54.37; H, 2.26.
c) Calcd. for $C_{12}H_6O_2N_2Cl_2$: C, 51.25; H, 2.15.

The author is very grateful to Prof. Dr. Ishidate for his encouragement. His thanks are also due to Mr. Kimura for the microanalyses.

Experimental

General Procedure of the Improved Wohl-Aue Reaction. Condensation of 3,4-Dichloronitrobenzene with Aniline: 1,2-Dichlorophenazine 5-Oxide (II)—A mixture of 3,4-dichloronitrobenzene (10 g.) and aniline (5 g.) was refluxed gently for 2 hrs. in toluene (150 cc.) with powdered KOH (30 g.). The toluene solution was filtered from the residue while hot and steam distilled. The crude product deposited in the remaining aqueous solution was collected and washed with MeOH. Yield, 2.8 g. This was dissolved in benzene and purified by chromatography on alumina to yield yellow needles, m.p. 217°(decomp.)(from MeOH).

Deoxygenation of 1,2-Dichlorophenazine 5-Oxide—Mono-N-oxide (0.5 g.) was refluxed gently with dimethylaniline (5 cc.) and Ac_2O (10 cc.) for 2 hrs. Dimethylaniline and Ac_2O were removed under reduced pressure and the residue was washed with cold MeOH. The product in benzene solution was purified by chromatography on alumina and pale yellow needles (0.42 g.), m.p. 170~171°(from ligroine), were obtained.

Oxidation of 2,3-Dichlorophenazine—To a solution of 2,3-dichlorophenazine (0.1 g.) dissolved in glacial AcOH (60 cc.), 30% H_2O_2 (6 cc.) was added. It was warmed on a water bath for 20 hrs. at 55°, and the reaction mixture was poured into several volumes of water. The product deposited was filtered and recrystallized from MeOH yielding red needles, m.p. 206°(decomp.).

Methanolysis of 1,9-Dichlorophenazine 5-Oxide: 1,9-Dimethoxyphenazine 5-Oxide (XVII)—Following the method of Pachter *et al.*,[4] 1,9-dichlorophenazine 5-oxide (0.8 g.) was dissolved in MeOH (300 cc.) and KOH (50 g.) in water (100 cc.) was added. The mixture was boiled for 12 hrs., MeOH was evaporated, and the crystals that deposited were collected and washed with water. This was recrystallized from EtOH to golden yellow needles (0.6 g.), m.p. 261°(decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.68; N, 10.93. Found: C, 66.01; H, 4.57; N, 10.81.

1,9-Dimethoxyphenazine (XVIII)—This was obtained by the deoxygenation of 1,9-dimethoxyphenazine 5-oxide (XVII) with dimethylaniline in Ac_2O. Yellow needles, m.p. 254°(from benzene), undepressed by admixture with the authentic specimen.

Summary

Dichlorophenazines and their N-oxides except the 1,4-, 1,6-, and 2,7-isomers were

prepared by using the improved Wohl–Aue reaction from aromatic amines and nitro compounds. Oxidation of 2,3- and 2,8-dichlorophenazine with hydrogen peroxide in glacial acetic acid afforded their di-N-oxides.

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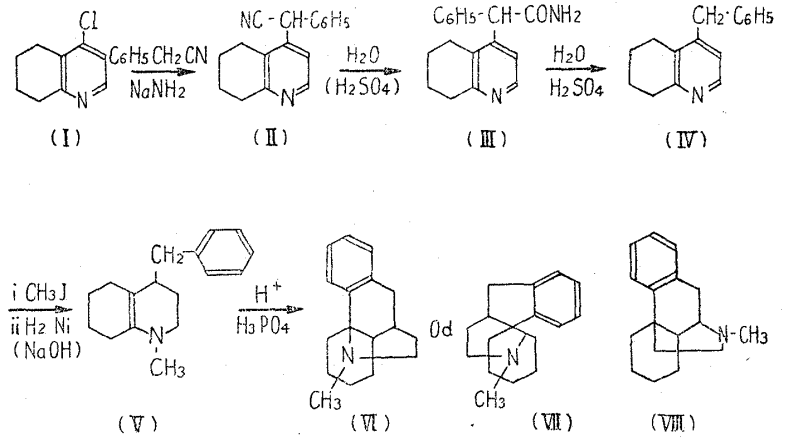
73. Eiji Ochiai und Kenji Harasawa*: Polarisation der heterozyklischen Ringe mit aromatischem Charakter. CXIII.[1] Synthese eines Chinolin-Analogens des N-Methylmorphinans.

(*Pharm. Institut d. Mediz. Fakultät d. Universität Tokyo**)

Vor kurzem hat Ikehara[1] eine neue Synthese von N-Methylmorphinan aus 1-Chlor-*Bz*-tetrahydroisochinolin veröffentlicht. Führt man eine analoge Synthese mit 4-Chlor-*Bz*-tetrahydrochinolin (I) als das Ausgangsmaterial durch, so könnte man nach den unten angegebenen Reaktionsstufen zu einer Verbindung gelangen, deren Konstitution der Formel (VI) oder (VII) entspricht. Da uns das 4-Oxy-*Bz*-tetrahydrochinolin durch die katalytische Reduktion von 4-Oxychinolin-N-oxyd ziemlich leicht zugänglich geworden ist,[2] haben wir das erstere in (I) übergeführt und diesen synthetischen Versuch ausgeführt. Die Reaktionen verliefen dabei meistens wie erwartet und führten tatsächlich zu einer Verbindung, deren Konstitution als (VI) nachgewiesen wurde. Das Grundskelett von (VI) kann man aus Morphinan (VIII) durch Austausch seines Dekahydroisochinolin-Ringes mit dem Dekahydrochinolin-Ring ableiten, sodass wir ihm den Namen Allomorphinan vorschlagen.



Die Kondensation von (I) und Benzylcyanid mit pulverisiertem Natriumamid verlief ziemlich glatt in wasserfreiem Äther. Die in ca. 65%iger Ausbeute erhaltene 4-(α-Cyanobenzyl)-*Bz*-tetrahydrochinolin (II) wurde durch Behandlung mit konz. H_2SO_4 bei Zimmertemperatur in praktisch theoretischer Ausbeute in das gut kristallisierbare Säureamid (III) übergeführt. Andererseits ging (II) sowie (III) mit etwa 85~90%iger Ausbeute in 4-Benzyl-*Bz*-tetrahydrochinolin (IV) über, wenn man dasselbe mit 50~60 %iger H_2SO_4 unter Rückfluss erhitzte. (IV) stellt eine flüssige Base dar, lässt sich

* Hongo, Tokyo (落合英二, 原沢堅治).
1) CXII. Mitt.: dieses Bulletin, **3**, 316(1955).
2) dieses Bulletin, **2**, 109(1954).
3) T. Ishii: J. Pharm. Soc. Japan, **72**, 1318(1952).