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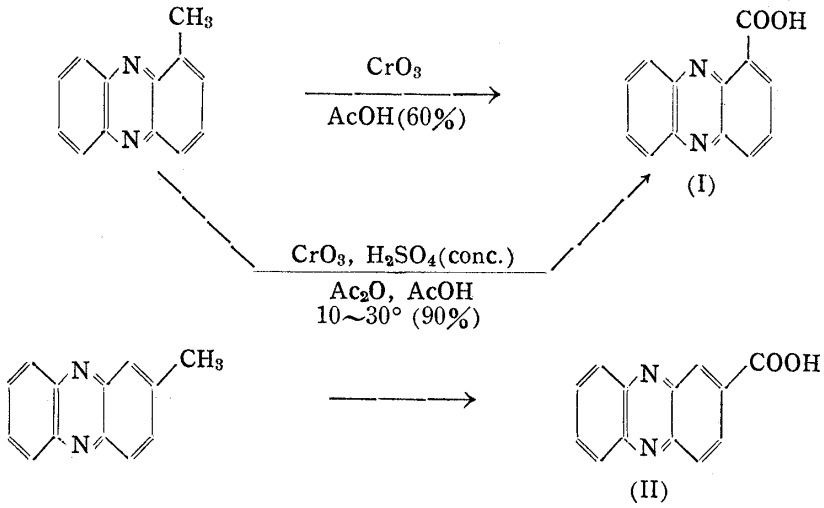
18. **Yoshinori Kidani**: Studies on Phenazines. XIX.* Synthesis of Phenazine-carboxylic Acids.

(*International Christian University***)

There are many reports on the importance of phenazine derivatives from biological aspect, and on phenazine-carboxylic acid derivatives which seem to have a fairly strong antitubercular action. Birkofer,[1] Rozum,[2] and others reported that phenazine-carboxylic acids themselves were much more effective than their homologous amides.

Various synthetic methods for phenazine-carboxylic acids have been reported.[3~6] Among these, Clemo and McIlwain[6] obtained the respective 1-carboxylic acids in about 60% yield by oxidation of 1-methylphenazine with chromium trioxide in warm glacial acetic acid.



The author,[7] together with Otomasu, reported the improved variation of Wohl-Aue method for synthesizing methylphenazine derivatives by sodium amide condensation which resulted in a better yield. In order to obtain phenazine-carboxylic acids, it is only necessary to oxidize methylphenazine derivatives which were primarily condensed by the improved Wohl-Aue variation method in a better yield.

1-Methyl- and 2-methyl-phenazines were each dissolved in a mixture of glacial acetic acid and acetic anhydride (3:1), and oxidized with chromium trioxide at about 10~30° in the presence of conc. sulfuric acid, from which phenazine-1- and -2-carboxylic acids were respectively obtained in a very good yield of about 90%.

Though the Clemo method is available for the oxidation of 1-methyl- and 2-methyl-phenazine to their respective carboxylic acids, it had not been applied for the oxidation of 1-hydroxy-6-methyl- and 1-hydroxy-8-methyl-phenazines to the corresponding carboxylic acid derivatives.

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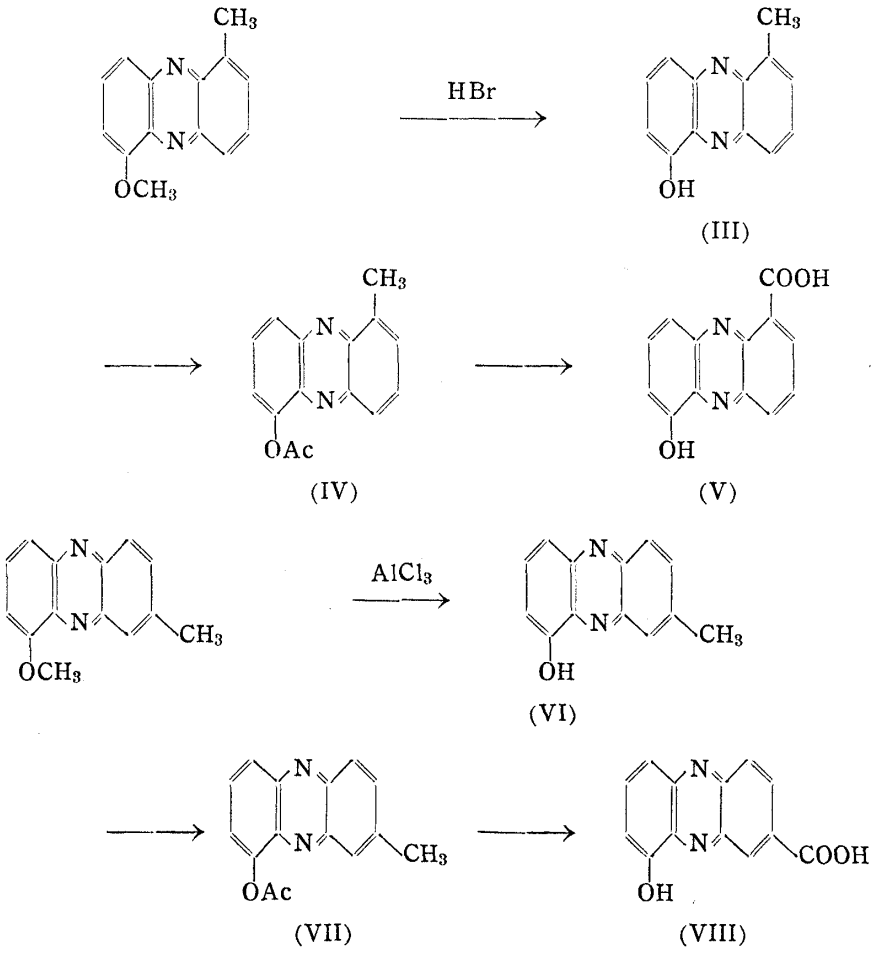
** 1500 Osawa, Mitaka-shi, Tokyo (喜谷喜徳).

1) L. Birkofer, A. Widmann: Ber., **86**, 1295(1953).
2) Yu S. Rozum: Ukrain. Khim. Zhur., **20**, 661(1954); **21**, 361(1955).
3) F. Kögl, J. J. Postowsky: Ann., **480**, 293(1930).
4) D. L. Vivian, J. L. Hartnell, H. C. Waterman: J. Org. Chem., **20**, 797(1955).
5) S. Pietra, S. Maffei, A. Rivolta: Ann. chim. (Rome), **43**, 227(1953).
6) G. R. Clemo, H. McIlwain: J. Chem. Soc., **1934**, 1991.
7) Y. Kidani, H. Otomasu: This Bulletin, **4**, 391(1956).



In the case of 1-hydroxy-6-methylphenazine, the corresponding 6-hydroxyphenazine-1-carboxylic acid was obtained by oxidizing its acetate under the similar conditions as mentioned above, but 9-hydroxyphenazine-2-carboxylic acid was obtained by oxidizing 1-acetoxy-8-methylphenazine in glacial acetic acid alone, without the use of acetic anhydride.

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Experimental

Phenazine-1-carboxylic Acid (I)—1-Methylphenazine (1 g.) was dissolved in a mixture of glacial AcOH (15 cc.) and Ac_2O (5 cc.), and conc. H_2SO_4 (2 cc.) was added drop by drop, keeping its temperature at 10~30° under agitation. Then, CrO_3 (2 g.) was added in small portions. After about 1 hr.'s agitation, the reaction mixture, which assumed a green color, was poured onto cracked ice, the unreacted 1-methylphenazine was removed by extraction with benzene in alkaline solution and then the mixture was extracted with benzene in AcOH acidity. After the extract was washed with water, dried, and filtered, benzene was removed. The residue was recrystallized from 40% AcOH to yellow needles, m.p. 239°. Yield, ca. 90%. This compound showed no m.p. depression on admixture with the authentic specimen, synthesized by the Clemo's method.

Phenazine-2-carboxylic Acid (II)—2-Methylphenazine (1 g.) was dissolved in a mixture of glacial AcOH (15 cc.) and Ac_2O (5 cc.), and under agitation with cooling, keeping its temperature at 5~30°, conc. H_2SO_4 (2 cc.) was added, followed by CrO_3 (2 g.) in small portions. After completion of the reaction, the mixture was poured onto cracked ice and diluted with water, from which phenazine-2-carboxylic acid deposited as yellow precipitate. As this substance is scarcely soluble in various organic solvents, it was purified by washing with benzene to remove 2-methylphenazine, the starting material, and sub-

limed or recrystallized from acetone to yellow crystalline powder, m.p. 292°. Yield, 0.9 g.

1-Hydroxy-6-methylphenazine (III)—1-Methoxy-6-methylphenazine (0.5 g.) was refluxed with 10 cc. of HBr (d: 1.48) and glacial AcOH (5 cc.) in an oil bath for about 16 hrs. The reaction mixture was basified, extracted with benzene to remove unreacted substance, and acidified with AcOH. This was extracted with benzene and purified by chromatography on Al_2O_3. Recrystallization from ligroine gave yellow needles, m.p. 173°, which assumed a red tinge in dil. HCl and cherry-red in NaOH solution. Yield, 0.38 g. *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.3; H, 4.8; N, 13.3. Found: C, 73.61; H, 4.66; N, 13.56.

1-Acetoxy-6-methylphenazine (IV)—1-Hydroxy-6-methylphenazine (0.5 g.) was dissolved in Ac_2O (5 cc.), and AcONa (1 g.) was added to this solution. After heating in an oil bath for 1 hr., it was diluted with water and an oily substance separated which solidified to greyish precipitate by vigorous shaking. It was collected and recrystallized from EtOH to yellow needles, m.p. 162°, in 95% yield. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 70.38; H, 4.76; N, 10.65.

6-Hydroxyphenazine-1-carboxylic Acid (V)—1-Acetoxy-6-methylphenazine (1 g.) was dissolved in a mixture of glacial AcOH (15 cc.) and Ac_2O (5 cc.), and conc. H_2SO_4 (2 cc.) was added drop by drop, keeping the temperature at 5~15° with cooling under agitation. Then CrO_3 (2 g.) was added in small portions and the reaction was completed upon assuming a green coloration. The reaction mixture was poured onto cracked ice, the deposited yellow precipitate was collected by filtration, and dissolved in NaOH solution to effect deacetylation. The solution was acidified again with AcOH, the deposited precipitate was extracted with $CHCl_3$, and purified over Al_2O_3 by chromatography. The product was recrystallized from EtOH to orange needles, m.p. 245° (decomp.); yield, 0.4 g. *Anal.* Calcd. for $C_{13}H_8O_3N_2$: C, 65.0; H, 3.3; N, 11.7. Found: C, 64.81; H, 2.90; N, 11.54.

1-Hydroxy-8-methylphenazine (VI)—1-Methoxy-8-methylphenazine (0.4 g.) was dissolved in benzene (15 cc.) and refluxed with anhyd. $AlCl_3$ (1 g.) for about 16 hrs. on a water bath. After the reaction, benzene layer was separated and water was added to the residue. This was extracted with benzene which was combined with the former benzene layer. By purification through Al_2O_3 and recrystallization from ligroine, yellow needles, m.p. 152°, were obtained in 0.3 g. yield. *Anal.* Calcd. for $C_{13}H_{10}ON_2$: C, 74.3; H, 4.8; N, 13.3. Found: C, 73.59; H, 4.42; N, 13.29.

1-Acetoxy-8-methylphenazine (VII)—1-Hydroxy-8-methylphenazine (0.5 g.) was refluxed with Ac_2O (10 cc.) and anhyd. AcONa (0.6 g.) in an oil bath for about 1 hr. The reaction mixture was poured onto cracked ice and diluted with water, by which an oily layer separated and deposited as greyish precipitate by vigorous shaking. This was collected and recrystallized from hydr. EtOH to faint yellow leaflet crystals, m.p. 146°, in 95% yield. *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: N, 11.11. Found: N, 11.01.

9-Hydroxyphenazine-2-carboxylic Acid (VIII)—1-Acetoxy-8-methylphenazine (1 g.) was dissolved in glacial AcOH (20 cc.) and conc. H_2SO_4 (2 cc.) was added to this drop by drop, keeping the temperature at 5~15° with cooling under agitation. Then, CrO_3 (2 g.) was added in small portions, and the reaction was completed by a green coloration in 1.5 hrs. The reaction mixture was poured onto cracked ice and diluted with water. The yellow precipitate that deposited was collected, dissolved in alkali, and acidified with AcOH, followed by extraction with $CHCl_3$. Recrystallization from hydr. EtOH gave yellowish orange needles, m.p. 830° (decomp.), in 0.8 g. yield. *Anal.* Calcd. for $C_{13}H_8O_3N_2$: C, 65.0; H, 3.3; N, 11.68. Found: C, 65.52; H, 3.64; N, 11.65.

Summary

By oxidation with chromium trioxide in the presence of conc. sulfuric acid at about 5~15°, 6-hydroxyphenazine-1- and 9-hydroxyphenazine-2-carboxylic acids were obtained from their respective methylphenazine derivatives.

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