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105. Itiro Yosioka[*1] and Shizue Arafune[*2]: Studies on Phenazines. XXI.[*3] Bromination of Phenazine Derivatives.

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There are some reports[1] on the nitration of phenazine derivatives, which indicate that phenazine N-oxide is substituted at 1- and 3-positions of phenazine ring. Also 1- and 2-methoxyphenazines were attacked by a nitro group, at the position *para* and *ortho* to the methoxyl.

In this paper bromination of phenazine derivatives, the same electrophilic substitution reaction as nitration, will be described.

Phenazine N-oxide was reacted with bromine in acetic acid solution by standing at 20° over night, but the reaction did not proceed. It was not brominated even at elevated temperature with addition of sulfur as a catalyst, and phenazine, the deoxygenated product, was recovered. However, 1- (I) and 2-methoxyphenazines (VII) were easily brominated in a good yield, affording monobromo compounds of m.p. 153~154° and 179~180°, respectively.

To determine the position of the bromine in phenazine ring, bromo-2-methoxyphenazine (m.p. 179~180°) was boiled for several hours with 5% methanolic sodium hydroxide or sodium methoxide in methanol but only the starting material was recovered. When the bromo compound was boiled with 10% methanolic sodium hydroxide for 6 hours, bromine atom attached to phenazine ring was unexpectedly liberated and 2-methoxyphenazine was obtained. When it was heated with sodium methoxide under pressure at 150° for 3 hours 1,2-dimethoxyphenazine[2] was formed, and therefore, bromination product of 2-methoxyphenazine should be 1-bromo-2-methoxyphenazine (VIII).

The position of bromine in 1-methoxy-bromo compound (m.p. 153~154°) was also determined by the same procedure, as 1,4-dimethoxyphenazine[2] was formed by methanolysis under pressure from 1-methoxy-bromo-phenazine and it was clarified that the position of bromine is at 4.

When 1-methoxyphenazine 5-oxide (IV) was brominated, a monobromo compound was formed in a poor yield. As this bromo compound gave 1-methoxy-4-bromophenazine (II) on reduction, the position of the bromine should be at 4. On the other hand, oxidation product of 1-methoxy-4-bromophenazine (II) with hydrogen peroxide was not identical with 1-methoxy-4-bromophenazine 5-oxide (V) described above, and therefore, this should be the isomer of (V), 1-methoxy-4-bromophenazine 10-oxide (VI).

These results indicate that phenazine derivative, having methoxyl and bromine in α-positions, was oxidized to form N-oxide but in a poor yield at the position adjacent to methoxyl group. On the contrary, 1-methoxyphenazine 5-oxide (IV) was brominated to form 4-bromo compound, i.e. the position adjacent to N-oxide was substituted by bromine.

2-Methoxyphenazine 5-oxide (X) was brominated easily to form a monobromo compound, which on reduction gave 1-bromo-2-methoxyphenazine (VIII). Therefore, this

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bromo compound should be 1-bromo-2-methoxyphenazine 5-oxide (XI). Bromination of 2-methoxyphenazine 10-oxide (XII) did not proceed easily and a monobromo compound was obtained in a poor yield. This bromo N-oxide differed from (XI), and on reduction it gave 1-bromo-2-methoxyphenazine (VIII), the same reduction product as that from bromo 5-oxide, so that it should be 1-bromo-2-methoxyphenazine 10-oxide (XIII). Accordingly, in this reaction bromine entered the sterically hindered 1-position and not in 3-position. This result indicates the strong naphthoid activity of phenazine, and the N-oxide group does not affect the direction of substitution.

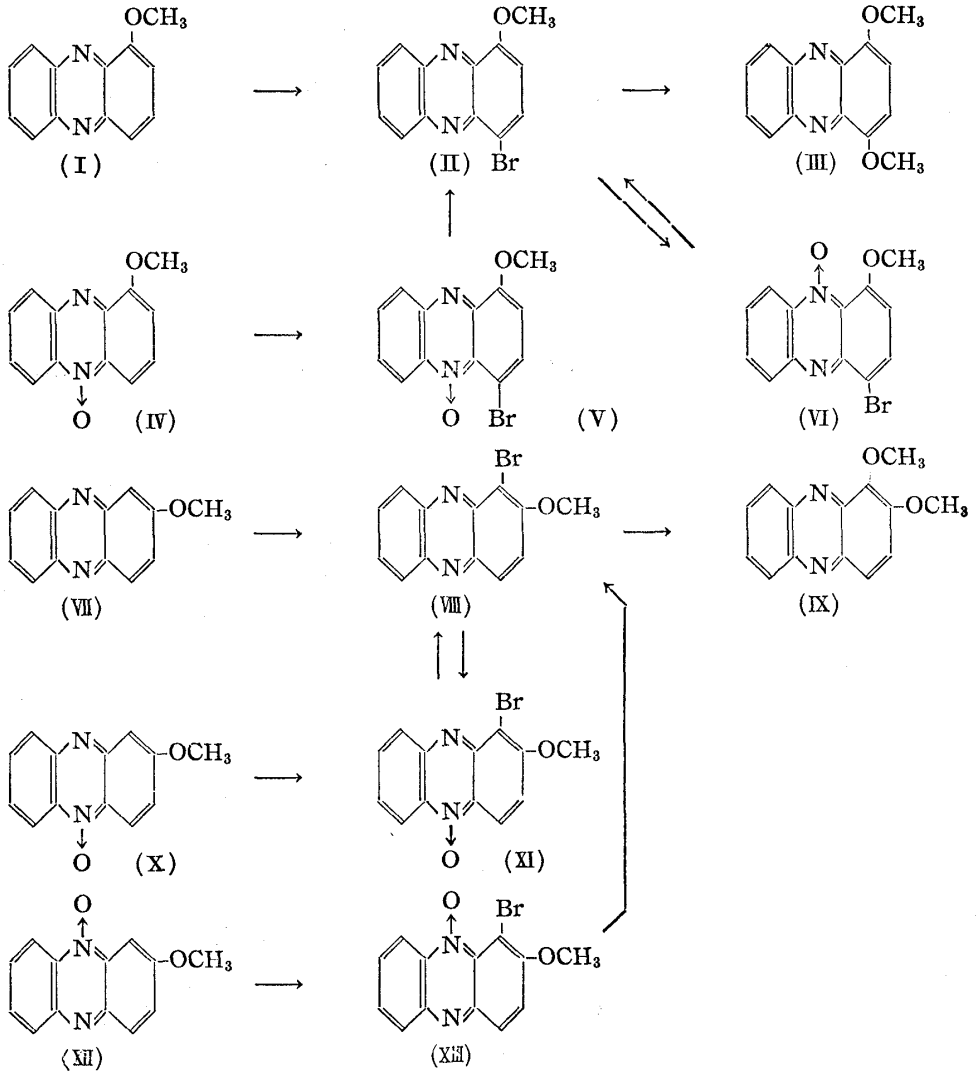

Chart 1.

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Experimental

Bromination of Phenazine N-Oxide—(i) Phenazine 5-oxide (0.3 g.) was dissolved in AcOH (3 cc.) and 1.5 g. of AcOH containing 10% Br_2 was added to this solution. After standing overnight at 20°, this was poured into water, the precipitate that separated out was dissolved in benzene, and purified on alumina column. The starting material, phenazine 5-oxide of m.p. 220° (0.2 g.), was recovered.

(ii) Phenazine 5-oxide (0.3 g.) in AcOH (3 cc.) was mixed with 1.7 g. AcOH containing 10% Br_2 and warmed on a water bath at 50° for 7 hr., but the result was the same as above, recovering the

starting material.

(iii) Phenazine 5-oxide (0.3 g.), sublimed S (0.3 g.), and Br_2 (1.5 g.) were mixed and heated for 3 hr. at 195~205°. In this case phenazine (m.p. 170°) was recovered.

Bromination of 1-Methoxyphenazine (I)—(I) (0.5 g.) was dissolved in AcOH (5 cc.) and 10% Br_2-AcOH (4 g.) was added. After standing overnight at 20°, water was added and the resulting yellow precipitate was chromatographed on alumina in benzene solution. 0.45 g. of yellow needles (from ligroine) of 1-methoxy-4-bromophenazine (II), m.p. 153~154°, was obtained. *Anal.* Calcd. for $C_{13}H_9ON_2Br$: C, 54.00; H, 3.12; N, 9.69. Found : C, 53.95; H, 3.47; N, 9.07.

Bromination of 2-Methoxyphenazine (VII)—(VII) (0.5 g.) was brominated in AcOH as in the case of 1-methoxy compound described above. 0.45 g. of yellow prisms (from ligroine) of 1-bromo-2-methoxyphenazine (VIII), m.p. 179~180°, was obtained. *Anal.* Calcd. for $C_{13}H_9ON_2Br$: C, 54.00; H, 3.12; N, 9.69. Found : C, 53.91; H, 3.52; N, 9.18.

Reaction of 1-Bromo-2-methoxyphenazine (VIII) with Alkali—(i) (VIII) (0.3 g.) was boiled with 5% methanolic KOH in water bath for 20 hr. After cool, water was added to this solution and the precipitate that deposited was recrystallized from ligroine to yellow prisms of m.p. 179~180°, which was found to be identical with the starting material.

(ii) (VIII) (0.3 g.) was boiled with NaOMe in MeOH for 20 hr. on a water bath, but the starting material was recovered unchanged.

(iii) (VIII) (0.3 g.) was boiled with 10% methanolic KOH (60 cc.) for 6 hr. and the resulting product was chromatographed on alumina in benzene. Pale yellow crystals of m.p. 125° (from ligroine) (0.2 g.) were obtained which, on admixture with 2-methoxyphenazine, gave no depression of m.p. Besides, a small amount of (VIII) was recovered.

(iv) Metallic Na (0.1 g.) was dissolved in MeOH (100 cc.), (VIII) (0.5 g.) was added to this solution, and heated in an autoclave at 150° for 3 hr. Reaction product was dissolved in benzene and chromatographed on alumina. From the first eluate, yellow prisms of m.p. 178~180° (0.4 g.) (from ligroine) (the starting material) were obtained. Next eluate, when recrystallized from ligroine, formed deep yellow needles of m.p. 144~145° (0.1 g), which was identical with 1,2-dimethoxyphenazine (IX) by mixed melting point determination. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.00; H, 5.00; N, 11.67. Found : C, 69.62; H, 5.05; N, 11.11.

Reaction of 1-Methoxy-4-bromophenazine (II) with Alkali—A mixture of metallic Na (0.08 g.), MeOH (50 cc.), and (II) (0.5 g.) was heated in an autoclave at 150° for 3 hr. The reaction mixture was treated as above and red needles of m.p. 186~188° (ligroine) (0.1 g.) were obtained, identical with 1,4-dimethoxyphenazine (III). Besides, 0.2 g. of (II) was recoverd. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$ (III) : C, 70.00; H, 5.00; N, 11.67. Found : C, 69.83; H, 4.73; N, 11.81.

Bromination of 1-Methoxyphenazine 5-Oxide (IV) : 1-Methoxy-4-bromophenazine 5-Oxide (V)—(IV) (0.2 g.) was dissolved in AcOH (2 cc.) and 10% Br_2-AcOH (2.0 g.) was added to this solution. After 24 hr.'s standing the mixture was poured into water, the precipitate was dissolved in benzene, and purified by chromatography on alumina. It gave a small amount of orange-yellow needles of m.p. 185° (ligroine). *Anal.* Calcd. for $C_{13}H_9O_2N_2Br$: C, 51.16; H, 2.95; N, 9.18. Found : C, 51.31; H, 3.01; N, 9.61.

Reduction of 1-Methoxy-4-bromophenazine 5-Oxide (V)—To AcOH solution (1 cc.) of (V) (0.1 g.) Zn powder (0.2 g.) was added in small portions and the mixture was heated on a water bath for 5 min. Then water was added to this mixture and extracted with benzene. The solvent was removed and residue was recrystallized from ligroine to yellow needles, m.p. 154°, which was found to be identical with (II) by mixed melting point determination.

Oxidation of 1-Methoxy-4-bromophenazine (II) : 1-Methoxy-4-bromophenazine 10-Oxide (VI)—A mixture of (II) (0.5 g.), AcOH (18 cc.), and 30% H_2O_2 (2 cc.) was warmed for 20 hr. at 45~50° on a water bath. Reaction product was dissolved in benzene and purified on alumina. It gave red crystals (0.1 g.) of m.p. 165°(decomp.) (ligroine). *Anal.* Calcd. for $C_{13}H_9O_2N_2Br$: C, 51.16; H, 2.95; N, 9.18. Found : C, 51.47; H, 2.92; N, 8.96.

It was not identical with 1-methoxy-4-bromophenazine 5-oxide (V) described above. Besides, 0.05 g. of the starting material was recovered.

Oxidation of 1-Bromo-2-methoxyphenazine (VIII) : 1-Bromo-2-methoxyphenazine 5-Oxide (XI)—(VIII) (0.5 g.) was dissolved in benzene (50 cc.), Ac_2O (3 cc.) and 30% H_2O_2 (3 cc.) were added and heated on a water bath for 7 hr. Then benzene layer was shaken with water several times, dried, concentrated, and purified through alumina column. 0.45 g. of orange needles, m.p. 209~210° (benzene), was obtained. *Anal.* Calcd. for $C_{13}H_9O_2N_2Br$: C, 51.16; H, 2.95; N, 9.18. Found: C, 51.12; H, 2.97; N, 9.11.

Bromination of 2-Methoxyphenazine 5-Oxide (X)—A mixture of (X) (0.2 g.), AcOH (3 cc.), and 10% Br_2-AcOH (2 g.) were treated as described above. It gave 0.2 g. of orange-yellow needles, m.p. 208~210°(ligroine), which were identical with (XI), obtained from 1-bromo-2-methoxyphenazine by oxidation.

Reduction of 1-Bromo-2-methoxyphenazine 5-Oxide (XI)—0.3.g of (XI) was reduced with Zn

powder in AcOH. It gave 0.2 g. of yellow needles, m.p. 179~180° (ligroine), which was found to be identical with 1-bromo-2-methoxyphenazine.

Bromination of 2-Methoxyphenazine 10-Oxide (XII) : 1-Bromo-2-methoxyphenazine 10-Oxide (XIII)—(XII) (0.2 g.) was brominated as described above. It gave a small amount of deep yellow crystals, m.p. 185~188° (ligroine), which showed mixed m.p. depression with 1-bromo-2-methoxyphenazine 5-oxide. *Anal.* Calcd. for $C_{13}H_9O_2N_2Br$: C, 51.16; H, 2.95; N, 9.18. Found : C, 51.48; H, 3.11; N, 8.77. A fair amount of the starting material was recovered.

Reduction of 1-Bromo-2-methoxyphenazine 10-Oxide (XIII)—(XIII) (0.1 g.) was reduced with Zn powder and AcOH. Yellow crystals of m.p. 180° (ligroine) were formed, which were identical with 1-bromo-2-methoxyphenazine by mixed m.p.

Summary

Bromination of phenazine N-oxide, and 1- and 2-methoxyphenazine was carried out and 1-methoxy-4-bromo- and 1-bromo-2-methoxy-phenazines were obtained, but bromo derivative of phenazine N-oxide was not formed. Bromination of 1-methoxyphenazine 5-oxide and 2-methoxyphenazine 5- and 10-oxides was also carried out and each of their bromo derivatives was prepared.

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106. Haruo Saikachi*1 and Keizo Suzuki*2 : Synthesis of Furan Derivatives. XIX. 2-Methyl-3-(5-nitro-2-furyl)acrylamides.

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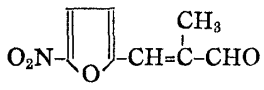
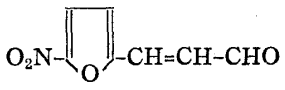
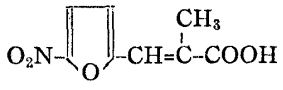
In a previous paper,[1] relationship between antibacterial activity and chemical structure of 3-(5-nitro-2-furyl)acrylamides was described. These experimental results showed that 3-(5-nitro-2-furyl)acrylamide of this series is especially highly active and shows a broad spectrum against microörganisms. It had also been suggested[2] that 2-methyl-3-(5-nitro-2-furyl)acrolein (I) is generally more active than unsubstituted 3-(5-nitro-2-furyl)acrolein (II) as antibacterial compound.



(I)



(II)



(III)

Therefore, it was deduced from above facts that although the functional end group in the side chain is different from either (I) or (II), 2-methyl-3-(5-nitro-2-furyl)acrylic acid (III) would be a new antiauxobacterial compound. It is of interest that the methyl in α-position of (5-nitro-2-furyl)acrylic acid is associated with that of tuberculous metabolic substances, such as C_{27}-phthienoic acid,[3] mycolipenic acid,[4] and 1,2,15-trimethyldocosanoic acid.[5]

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