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Synthesis of 1- and 2-Piperidinophenazine Derivatives

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A number of new piperidinophenazines have been prepared by the reactions of various halogenophenazines and their oxides, including several new compounds, with piperidine. The halogen-activating effect of the oxide groups in 1- or 2-halogenophenazine oxides, which had previously been known, was also observed in the present piperidination. It has been found that 1-chlorophenazine was considerably less reactive than 2-chlorophenazine in the piperidination, that but the 5-oxide group in 1-chlorophenazine-5-oxide enhanced the reactivity of chlorine.

As a part of our general scheme for the synthetic study of phenazine derivatives and the investigation of their biological activities,[1,2] we have carried out the synthesis of 1- and 2-piperidinophenazine derivatives from halogenophenazines. In the present paper, we shall describe our results in full detail.

Landquist reported that the reaction of 2-chlorophenazine-5,10-dioxide (I) with boiling piperidine gave 2-piperidinophenazine-5,10-dioxide (II) and 2-piperidinophenazine-mono-*N*-oxide as dark red crystals (mp 159°C).[3] Investigating this reaction further, we found that the reaction of I with piperidine under the same conditions yielded II and two piperidinophenazine-mono-*N*-oxides: reddish violet crystals (III) (mp 128°C) and reddish orange crystals (IV) (mp 167°C). In an attempt to decide the position of the *N*-oxide group in III and IV, 2-chlorophenazine-5-oxide (V)[4] and 3-chlorophenazine-5-oxide (VI)[4] were treated with boiling piperidine for 8 hr to give III in a 31% yield and IV in a 43% yield respectively. IV was also obtained in a 41% yield from 3-bromophenazine-5-oxide (VII)[5] under the same conditions. II, III, and IV were heated with zinc powder in acetic acid to yield piperidinophenazine (VIII), which was also derived in a 29% yield from 2-chlorophenazine (IX)[4] by treatment with boiling piperidine for 50 hr. VIII was also obtained in a 31% yield from 2-bromophenazine (X).[5] VIII was heated with diluted sulfuric acid at 200°C for 8 hr in a sealed tube to form 2-hydroxyphenazine (XI), which has already been described by Vivian.[6] From these experiments, it is clear that the structures of III and IV are 2-piperidinophenazine-5-oxide and 3-piperidinophenazine-5-oxide respectively.

The treatment of 2-chloro-9-methylphenazine (XII)[7] with piperidine in the presence of cuprous chloride for 50 hr gave 9-methyl-2-piperidinophenazine (XIII). 2-Chloro-9-methylphenazine-5-oxide (XIV) was prepared by the Wohl-Aue reaction of *p*-chloronitrobenzene with *o*-toluidine or by the oxidation of XII with hydrogen peroxide in acetic acid, and was then submitted to piperidination, thus forming 9-methyl-2-piperidinophenazine-5-oxide (XV). XV was reduced with zinc powder in acetic acid to afford XIII. The same treatment of 2-chloro-7-methoxyphenazine (XVI)[8] and 2-chloro-9-methoxyphenazine (XVII)[9] with piperidine for 50 hr in the presence of cuprous chloride afforded 7-methoxy-2-piperidinophenazine (XVIII) and 9-methoxy-2-piperidinophenazine (XIX) respectively. 2-Chloro-7-methoxyphenazine-5-oxide (XX)[4] was treated with piperidine for 25 hr to give a mixture of XVIII and 7-methoxy-

1) H. Endo, M. Tada and K. Katagiri, *Sci. Rep. Res. Inst. Tohoku Univ. Ser. C*, **12**, 53 (1965); *ibid.*, **13**, 12 (1966); *ibid.*, **13**, 197 (1966).

2) K. Katagiri *et al.*, *Ann. Rept. Shionogi Res. Lab.*, **15**, 84 (1965); *ibid.*, **16**, 52 (1966); *ibid.*, **16**, 58 (1966); *ibid.*, **17**, 127 (1967); *ibid.*, **17**, 133 (1967); *ibid.*, **17**, 137 (1967).

3) J. K. Landquist, *J. Chem. Soc.*, **1956**, 2550.

4) I. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 971 (1952).

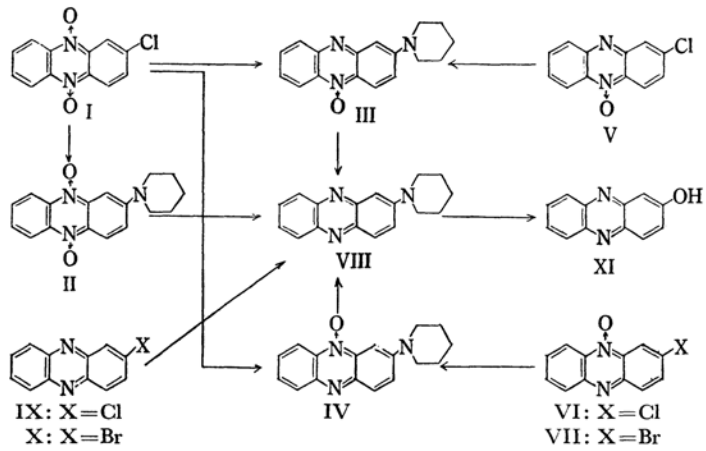
5) V. P. Chernetskii and A. I. Kiprianov, *Zh. Obshch. Khim.*, **26**, 3032 (1956); through *Chem. Abstr.*, **51**, 8762 (1957).

6) D. L. Vivian, *J. Am. Chem. Soc.*, **73**, 457 (1951).

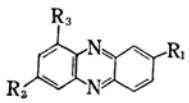
7) S. Maffei, S. Pietra and A. M. Rivolta, *Ann. chim. (Rome)*, **43**, 611 (1953).

8) D. L. Vivian, G. Y. Greenberg and J. L. Hartwell, *J. Org. Chem.*, **16**, 1 (1951).

9) I. Yoshioka and R. Ashikawa, *Yakugaku Zasshi*, **79**, 896 (1959).



2-piperidinophenazine-5-oxide (XXI). By reduction, XXI was converted into XVIII. The piperidination of 2-chloro-9-methoxyphenazine-5-oxide (XXII), which had been derived from XVII by the oxidation, afforded a mixture of XIX and its *N*-oxide derivative (XXIII). XIX was also obtained from XXIII by reduction.



XII: R_1=Cl; R_2=H; R_3=CH_3

XIII: R_1=N⟨ ⟩; R_2=H; R_3=CH_3

XVI: R_1=Cl; R_2=OCH_3; R_3=H

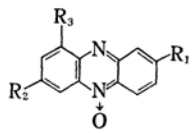
XVII: R_1=Cl; R_2=H; R_3=OCH_3

XVIII: R_1=N⟨ ⟩; R_2=OCH_3; R_3=H

XIX: R_1=N⟨ ⟩; R_2=H; R_3=OCH_3

XXIV: R_1=R_2=H; R_3=Cl

XXV: R_1=R_2=H; R_3=N⟨ ⟩



XIV: R_1=Cl; R_2=H; R_3=CH_3

XV: R_1=N⟨ ⟩; R_2=H; R_3=CH_3

XX: R_1=Cl; R_2=OCH_3; R_3=H

XXI: R_1=N⟨ ⟩; R_2=OCH_3; R_3=H

XXII: R_1=Cl; R_2=H; R_3=OCH_3

XXIII: R_1=N⟨ ⟩; R_2=H; R_3=OCH_3

XXVI: R_1=R_2=H; R_3=Cl

XXVII: R_1=R_2=H; R_3=N⟨ ⟩

The treatment of 1-chlorophenazine (XXIV)[4] with piperidine in the presence of cuprous chloride or cupric chloride for 70 hr gave 1-piperidinophenazine (XXV) in an 8% yield. Thus, although the 1-chloro compound (XXIV) is considerably less reactive to nucleophilic attack than the 2-chloro isomer (IX), it has been found that, in the corresponding 5-oxide (XXVI),[4] the reaction proceeded much more easily. Namely, XXVI was treated with piperidine for 25 hr to give both a 3% yield of XXV and a 28% yield of 1-piperidinophenazine-5-oxide (XXVII), which was then reduced with zinc powder in acetic acid to form XXV.

The halogen-activating effect of the oxide groups in halogenophenazine oxides has already been reported by Pachter and Kloetzel[4] and by Vivian[6] in the case of alcoholysis and hydrolysis. The present experiments reveal that halogens in halogenophenazine oxides, I, V, VI, VII, XIV, XX, XXII, and XXVI, are replaced with piperidine more readily than those of the corresponding phenazines.

We shall report elsewhere on the growth-inhibitory activity of the compounds described above against Crocker Sarcoma 180.[10]

Experimental[11]

The Reaction of 2-Chlorophenazine-5,10-dioxide (I) and Piperidine. A mixture of I (3.0 g) and piperidine (30 m*l*) was submitted to the reaction conditions employed by Landquist[3]: when the mixture was refluxed for 1.5 hr, 2-piperidinophenazine-5,10-dioxide (II) (mp 173—174°C; 1.25 g) was obtained as violet-black needles (from a mixture of benzene and petroleum ether). From the benzene - petroleum ether mother liquor, red crystals (1.0 g) were obtained after the evaporation of the solvent. The crystals were dissolved in benzene, and the solution was then passed through a column of alumina and eluted with benzene. From the first effluent, a mixture of 2- (V) and 3-chlorophenazine-5-oxide (VI) (0.2 g) was obtained. The column was then further eluted with chloroform, yielding crude crystals. Recrystallization from a mixture of benzene and ligroin gave 3-piperidinophenazine-5-oxide (IV) (mp 166—167°C; 210 mg) as reddish-orange needles.

Found: C, 73.37; H, 6.04; N, 14.91%. Calcd for

10) H. Endo, M. Tada and K. Katagiri, *Sci. Rep. Res. Inst. Tohoku Univ. Ser. C*, to be published.

11) All melting points are uncorrected.

$C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04%.

The mother liquor was evaporated to dryness, and the residue was recrystallized from diluted methanol to yield 2-piperidinophenazine-5-oxide (III) (mp 127—128°C; 200 mg) as reddish-violet needles.

Found: C, 73.29; H, 6.05; N, 14.90%. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04%.

2-Piperidinophenazine-5-oxide (III). A mixture of V (1.5 g) and piperidine (15 m*l*) was refluxed for 8 hr. After the addition of water (0.5 *l*) and acetic acid (8 m*l*), the resulting precipitate was filtered, washed with water, dried, and dissolved in chloroform. The chloroform solution was then passed through a column of alumina and eluted with chloroform. From the first effluent, V (0.4 g) was recovered, while from the second effluent III (560 mg) was obtained.

3-Piperidinophenazine-5-oxide (IV). *a) From VI.* A mixture of VI (1.5 g) and piperidine (15 m*l*) was refluxed for 8 hr; the reaction mixture was then treated as in the case of III to give IV (780 mg).

b) From VII. A mixture of VII (500 mg) and piperidine (5 m*l*) was refluxed for 8 hr; then the reaction mixture was treated as in the case of III to yield IV (210 mg).

2-Piperidinophenazine (VIII). *a) From IX.* A solution of IX (1.5 g) in piperidine (15 m*l*) was refluxed for 50 hr and then poured into water (0.5 *l*). The crystals thereby separated were dissolved in chloroform. The solution was passed through a column of alumina and eluted with chloroform. From the effluent, orange crystals were obtained; they were recrystallized from methanol to yield VIII (mp 129—130°C; 540 mg) as orange needles.

Found: C, 77.38; H, 6.59; N, 15.98%. Calcd for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96%.

b) From X. A solution of X (0.5 g) in piperidine (5 m*l*) was treated as in the case of a) above to afford VIII (160 mg).

c) From II. To a solution of II (200 mg) in acetic acid (10 m*l*), zinc powder (0.4 g) was added in small portions. The reaction mixture was then warmed on a water bath for 30 min and filtered. The filtrate was diluted with water and made slightly alkaline with diluted ammonium hydroxide. The crystals precipitated were collected, washed with water, dried, and dissolved in chloroform. The solution was passed through a column of alumina and eluted with chloroform. From the effluent, VIII (90 mg) was obtained.

d) From III or IV. To a solution of III or IV (200 mg) in acetic acid (10 m*l*), zinc powder (0.5 g) was added. The mixture was treated as in the case of the reduction mentioned above to give VIII (100 mg).

2-Hydroxyphenazine (XI). A solution of VIII (200 mg) in 20% sulfuric acid (3 m*l*) was heated at 200°C for 8 hr in a sealed tube. After cooling, the reaction mixture was diluted with water, made slightly alkaline with diluted sodium hydroxide, and filtered by suction. The filtrate was acidified weakly with diluted acetic acid. The crystals thereby yielded were recrystallized from diluted ethanol to yield red needles (mp 248—250°C (decomp.); 70 mg), which were identified as XI[6] by a comparison of their infrared spectra.

9-Methyl-2-piperidinophenazine (XIII). *a) From XII. i)* A mixture of XII (1.4 g), piperidine (15 m*l*), and cuprous chloride (0.1 g) was refluxed for 50 hr and then poured into water (1 *l*). The crystals thereby formed were collected by filtration, washed with water, dried, and dissolved in benzene. The benzene solution was passed through a column of alumina and eluted with benzene. From the effluent, XII (0.5 g) was recovered. When the column was further eluted with chloroform, dark red crystals were obtained. Recrystallization from a mixture of cyclohexane and petroleum ether afforded XIII (mp 76—77°C; 190 mg) as fine, reddish-orange crystals.

Found: C, 77.95; H, 6.95; N, 15.32%. Calcd for $C_{18}H_{19}N_3$: C, 77.94; H, 6.91; N, 15.15%.

ii) A mixture of XII (1.4 g) and piperidine (15 m*l*) was treated as in the case of i) to give XIII (140 mg). XII (0.8 g) was also recovered.

b) From XV. To a solution of XV (200 mg) in acetic acid (6 m*l*), zinc powder (0.5 g) was added in small portions. The resulting mixture was treated as in the procedure c) used in the preparation of VIII to afford XIII (50 mg).

2-Chloro-9-methylphenazine-5-oxide (XIV). *a) By the Wohl-Aue Reaction.* To a solution of *p*-nitrochlorobenzene (45 g) and *o*-toluidine (25 g) in toluene (300 m*l*), powdered potassium hydroxide (60 g) was added, and the resulting mixture was refluxed gently for 5 hr. The toluene solution was filtered while hot and then steam-distilled. The crude product deposited in the remaining aqueous solution was collected, washed with water, dried, and dissolved in chloroform. The solution was then passed through a column of alumina and eluted with chloroform. From the effluent, crystals were obtained. These were recrystallized from benzene to afford XIV (mp 173—174°C; 5 g) as bright yellow needles.

Found: C, 63.59; H, 3.70; N, 11.40%. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45%.

A mixture of XIV (1 g) and zinc powder (1 g) in acetic acid (20 m*l*) was treated as in the case of the procedure c) used in the preparation of VIII to give crude crystals. Recrystallization from a mixture of benzene and ethanol afforded yellow needles (mp 152—153°C; 750 mg), which showed no depression of melting point upon admixture with XII.[7] The infrared spectrum was identical with that of XII.

b) By Oxidation. To a solution of XII (1 g) in acetic acid (50 m*l*), 30% hydrogen peroxide (5 m*l*) was added. The reaction mixture was warmed at 55°C for 3 hr and then poured into water (1 *l*). The crystals thus formed were collected by filtration and recrystallized from benzene to give XIV (850 mg).

9-Methyl-2-piperidinophenazine-5-oxide (XV). A mixture of XIV (2 g) and piperidine (10 m*l*) was refluxed for 16 hr and then poured into water (300 m*l*) and acetic acid (5 m*l*). The crystals thereby separated were collected, washed with water, and dried. The product was dissolved in benzene, and the solution was passed through a column of alumina and eluted with benzene. From the first effluent, XII (320 mg) was obtained, while XIV (620 mg) was recovered from the second effluent. When the column was then further eluted with chloroform, dark violet crystals were obtained from the effluent. The recrystallization of these from a mixture of benzene and methanol gave XV (mp 165—166°C; 750 mg) as reddish-violet needles.

Found: C, 73.54; H, 6.63; N, 14.03%. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33%.

7-Methoxy-2-piperidinophenazine (XVIII). *a)* A

mixture of XVI (1.5 g), piperidine (15 ml), and cuprous chloride (0.1 g) was refluxed for 50 hr and then treated as in the case of XV to give XVIII (mp 146—147°C; 160 mg) as bright reddish-orange needles (from a mixture of cyclohexane and benzene); XVI (0.9 g) was also recovered.

Found: C, 73.78; H, 6.45; N, 14.31%. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33%.

b) A mixture of XVI (1.5 g) and piperidine (15 ml) was refluxed for 100 hr; the resulting mixture gave XVIII (200 mg). XVI (1.1 g) was also recovered.

9-Methoxy-2-piperidinophenazine (XIX). A mixture of XVII (1.5 g), piperidine (15 ml), and cuprous chloride (0.2 g) was refluxed for 50 hr and then treated as in the case of XV to give dark orange crystals. Recrystallization from diluted methanol yielded XIX (mp 124—125°C; 310 mg) as deep reddish-orange needles. XVII (120 mg) was also recovered.

Found: C, 73.55; H, 6.38; N, 14.06%. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33%.

7-Methoxy-2-piperidinophenazine-5-oxide (XXI). *a*) A mixture of XX (1.5 g) and piperidine (15 ml) was refluxed for 25 hr and then poured into water (1 *l*). After the usual work-up, the crystals obtained were dissolved in benzene. The solution was passed through a column of alumina and eluted with benzene. From the first effluent, XVI (0.7 g) was obtained. XX (200 mg) was recovered from the second effluent. When the column was further eluted with chloroform, XVIII (55 mg) and dark red crystals were obtained. The recrystallization of the crystals from diluted methanol afforded XXI (mp 171—172°C; 150 mg) as fine, red crystals.

Found: C, 69.59; H, 6.14; N, 13.87%. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58%.

b) A mixture of XX (1.5 g) and piperidine (15 ml) was refluxed for 16 hr and then treated as in the case of a) above to give XVI (400 mg), XX (350 mg), and XXI (100 mg).

To a solution of XXI (200 mg) in acetic acid (10 ml), zinc powder (0.5 g) was added; the mixture was then treated as in the case of the procedure c) used in the preparation of VIII to afford XVIII (110 mg).

2-Chloro-9-methoxyphenazine-5-oxide (XXII). To a solution of XVII (1.4 g) in acetic acid (50 ml), 30% hydrogen peroxide (10 ml) was added. The resulting solution was warmed at 55°C for 3 hr and then poured into water (2 *l*). The deep yellow crystals which separated were collected and washed with water. The recrystallization of the crystals from a mixture of benzene and ligroin gave XXII (mp 217—218°C (decomp.); 1.2 g) as orange-yellow needles.

Found: C, 60.02; H, 3.49; N, 10.49%. Calcd for $C_{13}H_9ClN_2O_2$: C, 59.90; H, 3.48; N, 10.75%.

XXII was treated with zinc powder in acetic acid to give XVII.

9-Methoxy-2-piperidinophenazine-5-oxide (XXIII). A mixture of XXII (1.5 g) and piperidine (15 ml) was refluxed for 24 hr and then treated as in the case of the procedure a) used in the preparation of XXI to give XVII (450 mg), XIX (500 mg), and dark violet crystals. The crystals were recrystallized from diluted methanol to yield XXIII (mp 153—154°C; 250 mg) as deep reddish-violet micro-prisms.

Found: C, 69.73; H, 6.24; N, 13.26%. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58%.

To a solution of XXIII (100 mg) in acetic acid (5 ml), zinc powder (0.3 g) was added; the mixture was then treated as in the case of the procedure c) used in the preparation of VIII to afford XIX (50 mg).

1-Piperidinophenazine (XXV). *a*) To a solution of XXIV (1.5 g) in piperidine (15 ml), cuprous chloride or cupric chloride (0.2 g) was added. The mixture was refluxed for 70 hr and then poured into water (1 *l*). The resulting precipitate was washed with water, dried, and dissolved in benzene. The benzene solution was passed through a column of alumina and eluted with benzene. From the first effluent, XXIV (500 mg) was recovered, while crude crystals were obtained from the second effluent. Recrystallization from a mixture of cyclohexane and petroleum ether gave XXV (mp 130—131°C; 150 mg) as orange-red needles.

Found: C, 77.25; H, 6.60; N, 15.70%. Calcd for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96%.

b) A solution of XXIV (1.5 g) in piperidine (15 ml) was refluxed for 60 hr and then treated as in a) above to give XXV (50 mg). XXIV (0.9 g) was also recovered.

1-Piperidinophenazine-5-oxide (XXVII). *a*) A mixture of XXVI (1.5 g) and piperidine (15 ml) was refluxed for 25 hr and then treated as in the case of XXV to give XXIV (60 mg), XXV (50 mg), XXVI (50 mg), and dark red crystals (500 mg). The crystals were recrystallized from cyclohexane to afford XXVII (mp 161—162°C) as fine, reddish-violet needles.

Found: C, 72.98; H, 6.18; N, 14.90%. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04%.

b) A mixture of XXVI (1.0 g) and piperidine (10 ml) was refluxed for 10 hr and then treated as in the case of a) above to afford XXIV (50 mg), XXVI (650 mg), and XXVII (120 mg).

To a solution of XXVII (100 mg) in acetic acid (5 ml), zinc powder (0.3 g) was added; the mixture was then treated as in the case of the procedure c) used in the preparation of VIII to give XXV (25 mg).