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Synthesis of 1- and 2-Morpholinophenazine Derivatives

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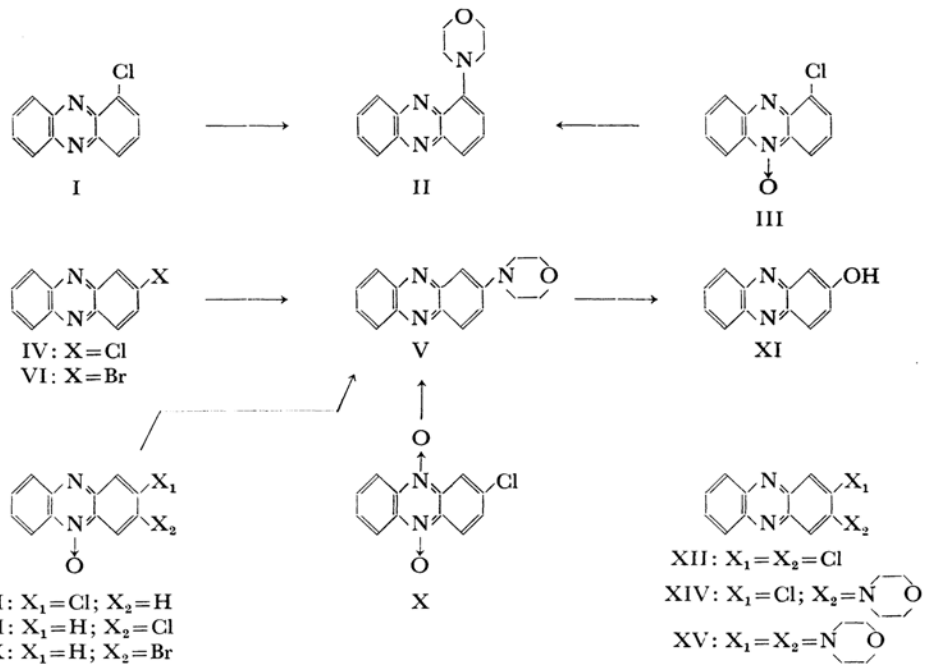
A number of new morpholinophenazines have been prepared by the reactions of various halogenophenazine derivatives with morpholine. It has been found that the replacement of the halogen atom of halogenophenazine-*N*-oxides with morpholine is accompanied by the removal of the oxide group and that no morpholinophenazine-*N*-oxides are formed in these reactions.

In a previous paper,[1] the reactions of halogenophenazine derivatives with piperidine were reported. The present paper will describe the synthesis of morpholinophenazines.

The reaction of morpholine with 1-chlorophenazine (I) in the presence of cuprous chloride or cupric chloride gave a 17% yield of 1-morpholinophenazine (II), which was also obtained from 1-chlorophenazine-5-oxide (III). The treatment of 2-chlorophenazine (IV) with morpholine gave a 59% yield of 2-morpholinophenazine (V), which was also derived from 2-bromophenazine (VI). Either 2-chlorophenazine-5-oxide (VII) or 3-chlorophenazine-5-oxide (VIII) was treated with morpholine to give V, which was also obtained from 3-bromophenazine-5-oxide (IX) or 2-chlorophenazine-5,10-dioxide (X). V was refluxed with diluted sulfuric acid or heated with diluted sulfuric acid at 200°C in a sealed tube to yield 2-hydroxyphenazine (XI), which had been reported by Vivian.[2]

The above series of reactions reveals that the replacement of the halogen atom with morpholine in halogenophenazine-*N*-oxides is accompanied by



1) H. Endo, M. Tada and K. Katagiri. This Bulletin, **42**, 502 (1969).

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

the removal of the oxide group in these phenazine-*N*-oxides, as was found during substitution with piperidine by Landquist[3] and by us.[1] However, the present finding, that no *N*-oxides are produced, is in contrast with the corresponding reaction with piperidine.[1]

The reaction of 2,3-dichlorophenazine (XII)[4] or 2,3-dichlorophenazine-5-oxide (XIII)[4] with morpholine afforded both 2-chloro-3-morpholinophenazine (XIV) in a 44% yield and 2,3-dimorpholinophenazine (XV) in a 3% yield. XV was also obtained from XIV. Brackman *et al.* have reported that the reaction of 4,5-dimorpholino-*o*-benzoquinone with *o*-phenylenediamine gave XV.[5] The treatment of 2-chloro-9-methylphenazine (XVI) or 2-chloro-9-methylphenazine-5-oxide (XVII) with morpholine gave 9-methyl-2-morpholinophenazine (XVIII).

The growth-inhibitory activity of these reaction products against Crocker Sarcoma 180 will be reported on elsewhere.[6]

Experimental[7]

1-Morpholinophenazine (II). *a) From 1-Chlorophenazine (I).* A mixture of I (1.5 g) and cuprous chloride or cupric chloride (0.1 g) in morpholine (15 m*l*) was refluxed for 50 hr and then poured into water (300 m*l*). After the addition of acetic acid (8 m*l*), the resulting precipitate was collected, washed with water, sucked dry, and dissolved in benzene. The benzene solution was then passed through a column of alumina and eluted with benzene. From the effluent, I (0.95 g) was recovered. When the column was then further eluted with chloroform, dark orange crystals were obtained. Recrystallization from cyclohexane gave II (mp 165—166°C; 320 mg) as reddish-orange needles.

Found: C, 72.11; H, 5.74; N, 15.73%. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%.

b) From 1-Chlorophenazine-5-oxide (III). A solution of III (1.5 g) in morpholine (15 m*l*) was refluxed for 24 hr and then treated as in the case of a) to give both I (1.1 g) and II (100 mg).

2-Morpholinophenazine (V) *a) From 2-Chlorophenazine (IV).* A solution of IV (1.5 g) in morpholine (15 m*l*) was refluxed for 70 hr and then treated as in the case of the procedure a) used in the preparation of II to give dark orange crystals (1.1 g). Recrystallization from benzene afforded V (mp 172—173°C) as yellowish orange needles. IV (0.1 g) was also recovered.

Found: C, 72.22; H, 5.68; N, 16.04%. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%.

b) From 2-Bromophenazine (VI). A solution of VI (150 mg) in morpholine (5 m*l*) was refluxed for 50 hr and then treated as in the case of the a) used in the preparation of II to give V (80 mg). VI (20 mg) was also recovered.

c) From 2-Chlorophenazine-5-oxide (VII). A mixture of VII (1.5 g) and morpholine (15 m*l*) was refluxed for 12 hr and then treated as in the case of the a) used in the preparation of II to give both IV (600 mg) and V (450 mg).

d) From 5-Chlorophenazine-5-oxide (VIII). A mixture of VIII (1.5 g) and morpholine (15 m*l*) was refluxed for 12 hr and then treated as in the case of the a) used in the preparation of II to give both IV (150 mg) and V (500 mg).

e) From 3-Bromophenazine-5-oxide (IX). A mixture of IX (150 mg) and morpholine (5 m*l*) was refluxed for 12 hr and then treated as in the case of the a) used in the preparation of II to give V (40 mg).

f) From 2-Chlorophenazine-5,10-dioxide (X). *i)* A mixture of X (1.5 g) and morpholine (15 m*l*) was refluxed for 3 hr and then treated as in the case of the a) used in the preparation of II to give crude crystals (1.1 g), which contained IV (850 mg), V(20 mg), and a mixture (15 mg) of VII and VIII.

ii) A mixture of X (1.5 g) and morpholine (15 m*l*) was refluxed for 12 hr and then treated as in the case of the a) used in the preparation of II to give IV (530 mg) and V (580 mg).

The Reaction of 2,3-Dichlorophenazine (XII) or 2,3-Dichlorophenazine-5-oxide (XIII) with Morpholine. A mixture of XII or XIII (1.5 g), morpholine (15 m*l*), and cupric chloride (0.2 g) was refluxed for 70 hr and then poured into water (1.5 *l*). The crystals thereby separated were collected, washed with water, sucked dry, and dissolved in benzene. The solution was passed through a column of alumina and eluted with benzene. From the first effluent, yellow crystals were obtained. Recrystallization from ethanol gave 2-chloro-3-morpholinophenazine (XIV) (mp 131—132°C; 800 mg) as bright yellow needles.

Found: C, 64.08; H, 4.69; N, 13.87%. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02%.

From the second effluent, dark orange crystals (60mg) were obtained; they were recrystallized from ethanol to form yellow needles (mp 218—219°C; 35 mg), which showed no depression of melting point on admixture with 2,3-dimorpholinophenazine (XV).[5] The infrared spectrum was identical with that of XV. By refluxing XIV (100 mg) in morpholine (5 m*l*) for 70 hr, XV (10 mg) was also obtained.

9-Methyl-2-morpholinophenazine (XVIII). *a) From XVI.* A mixture of XVI (1.5 g), morpholine (15 m*l*), and cupric chloride (0.2 g) was refluxed for 70 hr and then treated as in the case of the a) used in the preparation of II to give orange crystals. Recrystallization from a mixture of benzene and cyclohexane afforded XVIII (mp 185—186°C; 650 mg) as brilliant yellowish-orange needles. XVI (250 mg) was also recovered.

Found: C, 73.00; H, 6.05; N, 15.01%. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04%.

b) From XVII. A mixture of XVII (1.5 g), morpholine (15 m*l*), and cupric chloride (0.2 g) was refluxed for 70 hr and then treated as in the case of the a) used in the preparation of II to give both XVI (110 mg) and XVIII (850 mg).

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

4) V. P. Chernetskii and A. I. Kiprianov, *Zh. Obshch. Khim.*, **23**, 1743 (1953); through *Chem. Abstr.* **48**, 13695 (1954).

5) W. Brackman and E. Havinga, *Rec. Trav. Chim.*, **74**, 937 (1955).

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

7) All melting points are uncorrected.