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The Preparation of 1- and 2-Aminophenazine Derivatives

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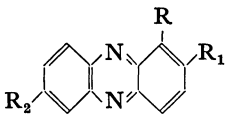
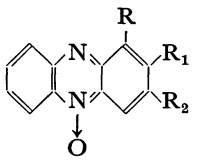
Synopsis. The reactions of chlorophenazines and their *N*-oxides with sodium azide in dimethyl sulfoxide or dimethylformamide yielded the corresponding aminophenazine derivatives.

In previous papers,[1,2] the reactions of halogenophenazines with piperidine, morpholine, sodium carboxymethyl mercaptide, and sodium methyl mercaptide were reported. During the study on the potential biological activities of phenazine derivatives, the preparation of aminophenazine derivatives was required. Pachter *et al.*[3] have reported that 2-aminophenazine (I) was prepared from 2-chlorophenazine (II) with aqueous ammonia by heating in an autoclave. This note describes the application of the transformation of a halogeno group into an amino group by the use of sodium azide.[4]

The reaction of 1-chlorophenazine (III) with sodium azide in dimethyl sulfoxide (DMSO) at 130 °C for 48 h gave 1-aminophenazine (IV).[5] The treatment of 1-chlorophenazine 5-oxide (V) with sodium azide in DMSO at 130 °C for 24 h gave 1-aminophenazine-5-oxide (VI), which was converted into IV by the reduction with zinc dust in acetic acid.

The reaction of II with sodium azide in DMSO or dimethylformamide (DMF) afforded a 2-amino compound (I). The reactions of 2-chloro- (VII) and 3-chlorophenazine 5-oxides (VIII) with sodium azide in DMSO gave the corresponding aminophenazine 5-oxides (IX and X). Both compounds IX and X were converted into I by reduction.





I: $R=R_2=H$; $R_1=NH_2$ V: $R=Cl$; $R_1=R_2=H$
II: $R=R_2=H$; $R_1=Cl$ VI: $R=NH_2$; $R_1=R_2=H$
III: $R=Cl$; $R_1=R_2=H$ VII: $R=R_2=H$; $R_1=Cl$
IV: $R=NH_2$; $R_1=R_2=H$ VIII: $R=R_1=H$; $R_2=Cl$
XI: $R=H$; $R_1=R_2=Cl$ IX: $R=R_2=H$; $R_1=NH_2$
XII: $R=H$; $R_1=NH_2$; $R_2=Cl$ X: $R=R_1=H$; $R_2=NH_2$

The heating of a mixture of VIII and sodium azide in DMF for 1 h under reflux afforded I, II, and X in yields of 3, 28, and 45%, respectively. Prolonged reflux (3 h), however, lead to the formation of I, II, and X in yields of 21, 19, and 20%, respectively. The results suggest that *N*-oxides are partially converted into the parent bases during the course of the displacement of a chlorine atom. This has been well confirmed by heating a solution of VIII in DMF, as shown in Table 1. Such a simple deoxygenation of *N*-oxide by DMF is hitherto unknown.[6]

A similar phenomenon was also observed in the heating of V and VII in DMF.

Table 1. Deoxygenation of 3-chlorophenazine 5-oxide (VIII)

Reflux time in DMF (h)	Deoxygenation product, II (%)	Recovery (%)
10	13	80
20	35	56
40	93	0

The amination of 2,7-dichlorophenazine (XI) gave 2-amino-7-chlorophenazine (XII) which also had been derived from VIII *via* nitration and reduction.[7]

Experimental

All the melting points are uncorrected. Absorption spectra were recorded with a Hitachi Model EPI-S_2 infrared spectrophotometer and a Hitachi Model 124 spectrophotometer.

1-Aminophenazine (IV). From 1-Chlorophenazine (III): To a hot solution of III (2.0 g) in DMSO (20 ml), sodium azide (1.0 g) was added. The mixture was then heated at 130 °C for 48 h, cooled, and poured into water. The crystals thereby separated were analyzed by chromatography on alumina, using benzene as the solvent, and then recrystallized from aqueous methanol to yield IV (520 mg, 29%), mp 176 °C, which showed no decrease in melting point on admixture with an authentic specimen.[5] Unchanged III (800 mg, 40%) was recovered.

From 1-Aminophenazine 5-Oxide (VI): Into a solution of VI (210 mg) in acetic acid (5 ml), zinc dust (1.5 g) was added. The mixture was then warmed in a water bath for 10 min, and filtered while hot. After usual treatment, recrystallization of the product from aqueous methanol afforded IV (150 mg, 77%), mp 176 °C.

1-Aminophenazine 5-Oxide (VI). A mixture of V (1.15 g) and sodium azide (450 mg) in DMSO (12 ml) was heated at 130 °C for 24 h, and treated as described above to afford crystals. Recrystallization from a mixture of chloroform and methanol (1: 1) gave VI (mp 226—227 °C (dec.), 400 mg) as reddish-violet micro-prisms in a 38% yield. Found: C, 67.98; H, 4.29; N, 19.98%. Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90%. IR (KBr): 3440 and 3330 cm^{-1}. UV: λ_{max}^{MeOH} 252 (log ε=4.49), 289 (4.61), 367 (3.75), 384 (3.72), and 515 (3.60) nm.

2-Aminophenazine (I). In DMSO: A mixture of II (2.6 g) and sodium azide (1.1 g) in DMSO (30 ml) was heated at 130 °C for 10 h, and then diluted with water. The precipitate was dissolved in ethyl acetate. The solution was then passed through a column of alumina and eluted with ethyl acetate. From the effluent, reddish-orange crystals were obtained. Recrystallization from chloroform gave fine red crystals (900 mg, 38%), mp 267—268 °C (dec), which were identified with I[3] by a comparison of their infrared spectra.

In DMF: A suspension of II (1.2 g) and sodium azide (450 mg) in DMF (20 ml) was gently refluxed for 5 h, and then treated in a similar way to yield I (550 mg, 56%), mp 267—268 °C (dec).

2-Aminophenazine 5-Oxide (IX). A suspension of VII

(1.2 g) and sodium azide (450 mg) in DMSO (12 ml) was heated at 130 °C for 4 h, and then treated as in the procedure used in the preparation of I to give crystals, which were recrystallized from ethanol to afford IX (mp 260—261 °C (dec), 500 mg) as deep-violet micro-crystals in a 47% yield. Found: C, 68.34; H, 4.19; N, 19.72%. Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90%. IR (KBr): 3400 and 3320 cm^{-1}. UV: λ_{max}^{MeOH} 279 (log ε=4.81), 333 (3.75), 350 (3.84), 371 (3.98), 391 (4.22), and 500 (3.82) nm.

IX (210 mg) was treated with zinc dust (0.5 g) in acetic acid (5 ml) to yield I (120 mg, 62%), mp 267—268 °C (dec).

3-Aminophenazine 5-Oxide (X). *In DMSO*: A mixture of VIII (1.16 g) and sodium azide (0.3 g) in DMSO (20 ml) was heated at 130 °C for 3 h, and then treated as in the above experiment to afford crystals. Recrystallization of the product from ethanol gave X (mp 253—254 °C (dec), 700 mg) as red micro-prisms in a 66% yield. Found: C, 68.45; H, 4.29; N, 20.10%. Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90%. IR (KBr): 3400 and 3320 cm^{-1}. UV: λ_{max}^{MeOH} 241 (log ε= 4.22), 285 (4.75), 366 (3.79), 384 (4.08), and 500 (4.00) nm.

In DMF: A suspension of VIII (2.31 g) and sodium azide (0.6 g) in DMF (25 ml) was refluxed for 1 h to give I (50 mg, 3%), II (600 mg, 28%), and X (950 mg, 45%).

X (210 mg) was treated with zinc dust (0.5 g) in acetic acid (5 ml) to yield I (110 mg, 56%).

Deoxygenation of Chlorophenazine 5-Oxides. A solution of chlorophenazine 5-oxide (1.16 g) in DMF (20 ml) was refluxed, and then diluted with water. The crystals thereby separated were dissolved in benzene. The benzene solution was passed through a column of alumina, and eluted with benzene. From the first effluent, a deoxygenation product was obtained, and 5-oxide was recovered from the second effluent.

2-Amino-7-chlorophenazine (XII). A suspension of XI (1.25 g) and sodium azide (390 mg) in DMSO (30 ml) was heated at 130 °C for 4 h, and then treated as in the case of I to give red needles (450 mg, 39%), mp 252 °C, which showed no decrease in melting point on admixture with an authentic specimen.[7]

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