[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE]

Phenazine Syntheses. V.[1] Amines

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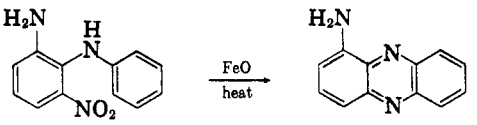
A practical method is given for the preparation of 1-aminophenazine. Several substituted 2-halogenated phenazines have been prepared from which the corresponding 2-aminophenazines have been made. One of the aminophenazines has the structure attributed to the color base of Neutral Red, and another that of the color base of "Neutral Violet."

An aminophenazinol is described, which is potentially of interest as a vital stain because of its amphoteric nature.

This paper continues the demonstration of the general applicability of ring closure through the nitro group to the synthesis of a wide variety of phenazines.[2]

Direct ring closure to the amine was employed in the instance of 1-aminophenazine. Albert and Duewell[3] have summarized the difficulty of obtaining 1-aminophenazine, and have put forward a synthesis of this compound from 2'-amino-2,6-dinitrodiphenylamine-4-carboxylic acid. In our hands this method did not give as satisfactory results as did the preparation through 6-amino-2-nitrodiphenylamine described herein:



The method of preparation of all of the 2-aminophenazines given here has been the replacement of the halogen in 2-halogenophenazines by bomb-tube reaction with ammonia.[4]

Details are given of the preparation of 2-amino-8-N,N-dimethylamino-3-methylphenazine, which has the structure accepted for the color base of Neutral Red. This is the first time it has been synthesized by an unambiguous method. Work to be reported elsewhere (infrared spectra, etc.) has shown that this structure is correct with regard to the position of the substituent groups; additional considerations must be taken into account, however, for the compound prepared as detailed herein will not produce vital staining when put into solution by HCl, but must first undergo modification. The same considerations apply to 2-amino-8-N,N-dimethylaminophenazine, the color base of "Neutral Violet" (German usage)[4a], and to 8-amino-2-phenazinol, both of these having their preparation likewise described in this paper. This latter compound possesses additional interest as a vital stain because of its amphoteric nature.

As indicated, details of the conversion of these phenazines to vital stains will be reported elsewhere.

EXPERIMENTAL[5]

1-Aminophenazine. One g. of crude 6-amino-2-nitrodiphenylamine[6] was thoroughly mixed with 1.3 g. of ferrous oxalate dihydrate and 10 g. of granulated lead, and the mixture was heated for 10 minutes in an open vessel in an oil-bath at 250–260°. Vacuum sublimation from the whole reaction mixture gave 0.25 g. (30%) of crude product, melting at 160–175°. This was purified by solution in conc'd H_2SO_4, dilution, and precipitation by NH_4OH, giving red microneedles, m.p. 183–185° (lit.[3a] m.p. 179–181°).

Anal.[7] Calc'd for $C_{12}H_9N_3$: N, 21.5. Found: N, 21.2.

2-AMINO-7-N,N-DIMETHYLAMINOPHENAZINE

(*a*) *2-Chloro-7-N,N-dimethylaminophenazine.* A thorough mixture of 2.0 g. of 5-chloro-4'-N,N-dimethylamino-2-nitrodiphenylamine,[8] 2.6 g. of ferrous oxalate dihydrate, and 20 g. of granulated lead was heated for 8–10 minutes in an open flask immersed in an oil-bath at 255–265°, until the inner temperature had risen to the maximum of 280–290°. Vacuum sublimation from the whole reaction mixture gave 0.8 g. of a translucent red product, darkening on exposure to air. Recrystallization from ethanol gave brownish-red short needles, m.p. 209–210°. These fluoresced a brilliant crimson under U-V illumination.

Anal. Calc'd for $C_{14}H_{12}ClN_3$: C, 65.3; H, 4.67. Found: C, 65.2; H, 4.81.

(*b*) *2-Amino-7-N,N-dimethylaminophenazine.* When 1.2 g. of 2-chloro-7-N,N-dimethylaminophenazine was heated for 14 hours in a bomb-tube with 30 cc. of conc'd NH_4OH and a little Cu_2Cl_2, the dark, water-insoluble material from filtration of the bomb contents weighed 0.65 g. Vacuum sublimation of this gave bright-red microneedles, darkening to a deeper red, but not melting, by 310°.

Anal. Calc'd for $C_{14}H_{14}N_4$: C, 70.6; H, 5.91. Found: C, 70.7; H, 5.70.

2-AMINO-8-N,N-DIMETHYLAMINOPHENAZINE (COLOR BASE OF "NEUTRAL VIOLET")

(*a*) *4-Bromo-4'-N,N-dimethylamino-2-nitrodiphenylamine.* A mixture of 39.4 g. of 2,5-dibromonitrobenzene, 20 g. of

(1) Paper IV: *J. Org. Chem.*, **20**, 797 (1955).

(2) Waterman and Vivian, *J. Org. Chem.*, **14**, 289 (1949).

(3) Albert and Duewell, *J. Soc. Chem. Ind. (London)*, **66**, 11 (1947).

(3a) Hegedüs, *Helv. Chim. Acta*, **33**, 766 (1950).

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

(4a) Witt, German Patent 15,272; Beil., [4] **25**, 394.

(5) All melting points reported by us are corrected.

(6) Borsche and Rantscheff, *Ann.*, **379**, 167 (1911).

(7) Microanalyses by the Microanalytical Laboratory of the National Institutes of Health, under the supervision of Dr. W. C. Alford.

(8) Jacobson, *Ann.*, **427**, 192 (1922).

N,N-dimethyl-*p*-phenylenediamine, 20 g. of sodium acetate trihydrate, and 520 cc. of 95% ethanol was refluxed for 134 hours. Allowing the solution to cool to room temperature, filtering, and washing the precipitate once with ethanol gave 24.6 g. of sparkling dark red crystals. Three recrystallizations from absolute ethanol gave deep-red microcrystals, melting to a deep brown liquid at 147–148°.

Anal. Calc'd for $C_{14}H_{14}BrN_3O_2$: C, 50.0; H, 4.20. Found: C, 50.1; H, 4.25.

(*b*) *2-Bromo-8-N,N-dimethylaminophenazine.* When 2.0 g. of 4-bromo-4′-dimethylamino-2-nitrodiphenylamine was heated in an open flask with 2.5 g. of ferrous oxalate dihydrate and 20 g. of granulated lead in an oil-bath at 260–265°, the internal temperature rose to a maximum of 281° in $5^1/_2$ minutes. The flask was withdrawn from the bath when the inside temperature began to fall, and the contents were allowed to cool. Grinding the whole reaction mixture in a mortar, and subjecting it to vacuum sublimation at about 0.2 mm. from a bath at 250° gave 0.7 g. of a red, glass-like solid. Recrystallization from ethanol gave dull-red needles, melting gradually at 199–207°.

Anal. Calc'd for $C_{14}H_{12}BrN_3$: N, 13.9. Found: N, 14.1.

(*c*) *2-Amino-8-N,N-dimethylaminophenazine.* When 1.0 g. of 2-bromo-8-N,N-dimethylaminophenazine was heated 14 hours at 225° in a bomb-tube with 20 cc. of conc'd NH_4OH and 0.2 g. of Cu_2Cl_2, filtration of the bomb contents gave 0.4 g. of nearly black solid. Sublimation at about 0.2 mm. and 225° gave dull red microcrystals darkening beginning at 183°, and gradually melting to a dark brown liquid beginning at 232.5°.

Anal. Calc'd for $C_{14}H_{14}N_4$: N, 23.5. Found: N, 23.2.

2-AMINO-8-N,N-DIMETHYLAMINO-3-METHYLPHENAZINE (COLOR BASE OF NEUTRAL RED)

(*a*) *4-Bromo-4′-N,N-dimethylamino-5-methyl-2-nitrodiphenylamine.* A mixture of 170 g. of 2,5-dibromo-4-nitrotoluene,[9] 87.5 g. of sodium acetate trihydrate, 87.5 g. of N,N-dimethyl-*p*-phenylenediamine, and 2300 cc. of 95% ethanol was refluxed for four weeks. Allowing the mixture to cool to room temperature, filtering, and washing the precipitate twice with 100-cc. portions of absolute alcohol, gave on air-drying 160.5 g. of black sparkling crystals with a greenish reflex. Recrystallized three times from absolute alcohol (Norit) these gave brown needles, shrinking and darkening at 197–198°, m.p. 198–199°.

Anal. Calc'd for $C_{15}H_{16}BrN_3O_2$: C, 51.4; H, 4.61. Found: C, 51.4; H, 4.73.

(9) Cohen and Dakin, *J. Chem. Soc.*, **79**, 1130 (1901).

(*b*) *2-Bromo-8-N,N-dimethylamino-3-methylphenazine.* A 2-g. portion of the crude, unrecrystallized diphenylamine, above, was mixed with 2.6 g. of ferrous oxalate dihydrate and 20 g. of granulated lead, and the mixture was put in an open flask and heated for 25–30 min. in an oil-bath at 225–235°. There was very little evidence of heat of reaction; the internal temperature did not go above 225°. The yield of crude phenazine was 1.3 g. on vacuum sublimation from the whole reaction mass. Two recrystallizations from ethyl acetate gave scarlet micro-crystals, darkening at 202°, m.p. 203–205° (d).

Anal. Calc'd for $C_{15}H_{14}BrN_3$: C, 57.0; H, 4.46. Found: C, 56.9; H, 4.67.

(*c*) *2-Amino-8-N,N-dimethylamino-3-methylphenazine.* One gram of the preceding phenazine, once-recrystallized from ethyl acetate, was heated for 16 hours at 225° in a bomb-tube with 0.2 g. of Cu_2Cl_2 and 10 cc. of NH_4OH. There resulted 0.84 g. of black, water-insoluble material on opening the bomb and filtering off the product. From this, by vacuum sublimation for 10 hours at 155–160° and 0.2 mm. there was obtained 0.3 g. of red micro-needles. These began to darken at 168°, started to melt at 171°, by which temperature they were quite black, and by 187° had completely melted and decomposed. Their yellow solution in ether exhibited a strong green fluorescence.

Anal. Calc'd for $C_{15}H_{16}N_4$: C, 71.4; H, 6.39. Found: C, 71.3; H, 6.14.

Although this compound has the correct structure for the color base of Neutral Red, as previously mentioned, it is also repeated here that its solution in dilute HCl does not act as a vital stain, and that it only does so when subjected to certain modification, which will be reported elsewhere.

8-AMINO-2-PHENAZINOL.[10]

One gram of 8-chloro-2-phenazinol[11] was heated with 0.1 g. of Cu_2Cl_2 and 12 cc. of conc'd NH_4OH for 16 hours at 225° in a bomb-tube. There resulted 0.89 g. of water-insoluble dark solid on filtration and air-drying, from which 0.2 g. of red micro-needles was obtained by sublimation at 165° and 0.15 mm. These did not melt by 350°.

Anal. Calc'd for $C_{12}H_9N_3O$: C, 68.2; H, 4.29. Found: C, 68.7; H, 4.75.

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(10) Ullmann and Gnaedinger, *Ber.*, **45**, 3442 (1912).

(11) Vivian, Hartwell, and Waterman, *J. Org. Chem.*, **19**, 1138 (1954).