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

# PHENAZINE SYNTHESES. II.[1] PHENAZINE ETHERS AND PHENAZINOLS

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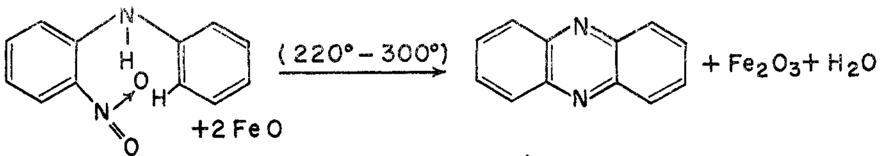
The preparation of the simpler phenazines, as distinguished from the numerous more complex phenazines developed by the dye industry, has hitherto been hampered by cumbersome methods of synthesis and relatively poor yields. The general synthesis of Waterman and Vivian (1) has now, however, made more accessible a wide variety of phenazines (2), as well as a number of other nitrogen heterocycles. The nitro-group ring-closure of "Type A" (1), used in the synthesis of all the phenazine derivatives dealt with in this paper, is most simply represented[3] by:



$$(\text{FeO from: } FeC_2O_4 \cdot 2\,H_2O \xrightarrow{(220°-300°)} FeO + CO_2 + CO + 2\,H_2O)$$

The present series of papers details the preparation of representative examples of these newly available compounds, so that with respect to the phenazine syntheses, the scope, flexibility, and limitations of the reaction may be more clearly delineated.

It is well known that phenazinols may be readily obtained from phenazine ethers by hydrolysis, usually with hydrobromic acid (4) or with aluminum chloride (5). The chief contribution of the present paper, therefore, lies in its presentation of ready means for the preparation of the phenazine ethers, including halogenated derivatives. These last are shown to be likewise converted to the corresponding halogenated phenazinols.

The method given herein for obtaining 2-phenazinol through 2-ethoxyphenazine is an improvement over the synthesis through 2-chlorophenazine-5,10-dioxide reported earlier (6).

## EXPERIMENTAL

*1-Methoxyphenazine. a. 6-Methoxy-2-nitrodiphenylamine.* A mixture of 5.0 g. of 2,3-dinitroanisole (2), 7.2 cc. of aniline, and 35 cc. of absolute alcohol was refluxed about 80

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[1] Paper I: Vivian and Hartwell, *J. Org. Chem.*, **18**, 1065 (1953).

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[3] This formulation is drawn in close accordance with the steric relations indicated by the Hirschfelder-Taylor atom models (3). In the light of more recent work, this monomolecular mechanism is believed to be the predominant one, rather than the bi- or polymolecular mechanism earlier suggested (2).

hours, then steam-distilled to remove excess reactants. Extraction of the residue with ether gave 6.8 g. of a somewhat sticky, dark-red solid. Chromatographic purification of this from benzene on alumina gave 4.6 g. of a bright red solid softening at 61° and melting completely by 75°. Recrystallization from methanol gave red prisms, melting at 86.5–87.5°.[4]

*Anal.*[5] Calc'd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.95.

Found: C, 64.2; H, 5.02.

*b. 1-Methoxyphenazine.* The crude solid 6-methoxy-2-nitrodiphenylamine from the ether extraction was satisfactory for this preparation, although the purified material gave a better yield. When 1.0 g. of the pure intermediate was heated with 1.3 g. of ferrous oxalate dihydrate and 10 g. of granulated lead in a bath at 265°, the internal temperature reached the maximum of about 280° in 7–8 minutes. Vacuum-sublimation from the entire reaction mixture gave 0.54 g. of crude product, which on recrystallization from methanol gave 0.46 g. of 1-methoxyphenazine, melting at 167.4–169.4°. This was converted either by HBr or by $AlCl_3$ to 1-phenazinol, m.p. 152.5–155°. Proof of its identity was given by a mixture melting point with authentic 1-phenazinol, m.p. 153–155°, made from pyocyanine.

When 2.0 g. of the crude 6-methoxy-2-nitrodiphenylamine (as distinct from the chromatographed material) was subjected to ring closure, 0.65 g. of crude 1-methoxyphenazine was obtained, which on recrystallization from methanol gave 0.5 g. of 1-methoxyphenazine with a melting point of about 166°.

*2-Phenazinol. a. 2-Ethoxyphenazine.* 4'-Ethoxy-2-nitrodiphenylamine (7) (5 g.) heated 20 minutes in an oil-bath at 250° with 6.5 g. of ferrous oxalate dihydrate and 50 g. of granulated lead, gave by sublimation 2.5 g. of crude 2-ethoxyphenazine, which on recrystallization from methanol (Norit) yielded 1.5 g. of light yellow needles, melting at 115–116°. Pachter and Kloetzel (8) give 114–115° as the m.p. of 2-ethoxyphenazine.

*Anal.* Calc'd for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.40.

Found: C, 75.1; H, 5.49.

*b. 2-Phenazinol.* In accordance with the method of King, Clark, and Davis (5), 1.8 g. of 2-ethoxyphenazine was refluxed for 16 hours with 100 cc. of thiophene-free benzene and 4 g. of aluminum chloride. The benzene was decanted, the addition product broken up with ice, and the precipitate, separated by centrifuging, was washed once with water. Further purification was effected by dissolving the moist crude phenazinol in 50 cc. of 10% KOH, filtering through fine-porosity fritted glass, and reprecipitating with 1:5 HCl. The product was again separated by centrifuging, and washed to neutrality by the same means. The moist compound was taken up in acetone, and the solvent was allowed to evaporate spontaneously, giving at first a dark red solid, which became a medium yellow on further spontaneous drying at room temperature. The 2-phenazinol so obtained weighed 1.44 g. (91%), darkened beginning at 252°, and was black by 260°, but showed no definite melting point; it was found to be analytically pure.

*Anal.* Calc'd for $C_{12}H_8N_2O$: C, 73.4; H, 4.11.

Found: C, 73.5; H, 4.12.

When 2-methoxyphenazine was subjected to the same process, the yield was lower, hence it is recommended that 2-ethoxyphenazine rather than the methoxy compound be used for the preparation of 2-phenazinol.

*Halogenated phenazinols.* Since the syntheses of these compounds all follow the same general pattern, only one preparation is given in detail, a tabular summary presenting the others.

*7-Bromo-2-phenazinol. a. 4-Bromo-2',5'-dimethoxy-2-nitrodiphenylamine.* A mixture of 70 g. of 2,5-dibromonitrobenzene, 40 g. of 2,5-dimethoxyaniline, and 60 g. of anhydrous sodium acetate was heated for 40 hours in an oil-bath held at 202–208°. After thorough

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[4] All melting points are corrected.

[5] Analyses are by the Microanalytical Laboratory of the National Institutes of Health under the direction of Dr. W. C. Alford.

## TABLE I
### PHENAZINES, PHENAZINOLS, AND INTERMEDIATES

| COMPOUND | CRYSTALLINE FORM AND COLOR[a] | M.P., °C. | YIELD OF CRUDE, % | FORMULA | ANALYSIS | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | | H | |
| | | | | | Calc'd | Found | Calc'd | Found |
| DIPHENYLAMINES | | | | | | | | |
| 4-Bromo-4'-methoxy-2-nitro- | Large red prisms | 131–133 | 90 | $C_{13}H_{11}BrN_2O_3$ | 48.3 | 48.1 | 3.43 | 3.52 |
| 4-Bromo-4'-ethoxy-2-nitro- | Large red prisms | 98–100 | 85 | $C_{14}H_{13}BrN_2O_3$ | 49.9 | 49.8 | 3.89 | 3.63 |
| 4-Bromo-2',5'-dimethoxy-2-nitro- | Very small deep red needles | 127–128 | 73 | $C_{14}H_{13}BrN_2O_4$ | 47.6 | 47.8 | 3.71 | 3.82 |
| 4-Bromo-2',5'-diethoxy-2-nitro- | Very small red-orange needles | 86.5–87.5 | 70 | $C_{16}H_{17}BrN_2O_4$ | 50.4 | 50.5 | 4.49 | 4.78 |
| 4-Chloro-2-nitro-4'-phenoxy- | Yellowish-red plates | 96–97 | 97 | $C_{18}H_{13}ClN_2O_3$ | 63.4 | 63.5 | 3.85 | 3.82 |
| PHENAZINES | | | | | | | | |
| 2-Bromo-7-methoxy- | Yellow needles | 172–174 | [b] | $C_{13}H_9BrN_2O$ | 54.0 | 54.2 | 3.14 | 3.44 |
| 2-Bromo-8-methoxy- | Yellow needles | 155–156 | [b] | $C_{13}H_9BrN_2O$ | 54.0 | 54.0 | 3.14 | 3.33 |
| 2-Bromo-7-ethoxy- | Yellow needles | 164–166 | [b] | $C_{14}H_{11}BrN_2O$ | 55.4 | 55.6 | 3.66 | 3.81 |
| 2-Bromo-8-ethoxy- | Yellow needles | 168–170 | [b] | $C_{14}H_{11}BrN_2O$ | 55.4 | 55.6 | 3.66 | 3.65 |
| 2-Chloro-8-phenoxy- | Small yellow prisms or plates | 176–177 | [b] | $C_{18}H_{11}ClN_2O$ | 70.5 | 70.6 | 3.62 | 4.01 |
| 2-Chloro-7-methoxy (2) | | | | | | | | |
| 2-Chloro-8-methoxy (2) | | | | | | | | |
| HALOGENATED PHENAZINOLS[c] | | | | | | | | |
| 7-Chloro-2-phenazinol | Aggregates of very small yellow needles | 270.5–271.5 (d.) (darkens at 266°) | [d] | $C_{12}H_7ClN_2O$ | 62.5 | 62.8 | 3.06 | 3.08 |
| 8-Chloro-2-phenazinol | Aggregates of very small yellow needles | 277–278.5 (d.) (darkens at 270°) | [d] | $C_{12}H_7ClN_2O$ | 62.5 | 62.3 | 3.06 | 3.31 |
| 7-Bromo-2-phenazinol | Aggregates of very small yellow needles | 256–258° (d.) (darkens at 255°) | [d] | $C_{12}H_7BrN_2O$ | 52.4 | 52.2 | 2.56 | 2.80 |
| 8-Bromo-2-phenazinol | Aggregates of very small yellow needles | 249–251° (d.) | [d] | $C_{12}H_7BrN_2O$ | 52.4 | 51.9 | 2.56 | 2.68 |

[a] Recrystallizations from alcohol, except as noted. [b] Yields of phenazines from crude intermediates, 40–60%. [c] Made from corresponding halogeno-methoxyphenazines. [d] Yield, 70–90%.

steam-distillation, the dark residue was allowed to dry, then broken up and extracted with ether, giving 60 g. of a dark red solid, which was satisfactory for the phenazine preparation. Three recrystallizations from alcohol (Norit) gave deep red, very small needles, melting at 127–128°.

*Anal.* Calc'd for $C_{14}H_{13}BrN_2O_4$: C, 47.6; H, 3.71.

Found: C, 47.8; H, 3.82.

*b. 2-Bromo-7-methoxyphenazine.* Heating 5 g. of the crude 4-bromo-2′,5′-dimethoxy-2-nitrodiphenylamine with 6.5 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of granulated lead in a bath at 252–255° for about 18 minutes (during which there was very little heat effect noticeable in the reaction mixture) gave on sublimation 1.65 g. of crude 2-bromo-7-methoxyphenazine. This, on recrystallization from alcohol, yielded 1.3 g. of yellow needles, melting at 174–175°.

*Anal.* Calc'd for $C_{13}H_9BrN_2O$: C, 54.0; H, 3.14.

Found: C, 54.2; H, 3.44.

*c. 7-Bromo-2-phenazinol.* The preparation of this compound was analogous to that of the 2-phenazinol, already detailed. From 2.0 g. of 2-bromo-7-methoxyphenazine there was obtained 1.50 g. of crude product. This, recrystallized from methanol and then sublimed at 3–4 mm. from an oil-bath at about 240°, gave aggregates of very small yellow needles, which melted to a black viscous liquid at 256–258°.

*Anal.* Calc'd for $C_{12}H_7BrN_2O$: C, 52.4; H, 2.56.

Found: C, 52.2; H, 2.80.

Table I which follows gives other compounds formed by the same general methods.

In precipitating the halogenated phenazinols from alkaline solution by dilute hydrochloric acid, it was noted that both the 8-chloro- and the 8-bromo-2-phenazinols exhibited a change from a yellowish-red in alkaline solution to a lemon-yellow in acid. This change was not shown by the 7-halogeno-2-phenazinols. Another difference was noted between the two pairs in their behavior with concentrated sulfuric acid: the 8-halogeno-2-phenazinols gave a reddish-brown color, while their isomers gave a deep violet, almost black.

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## SUMMARY

1. A number of new 2-nitrodiphenylamines and phenazines derived therefrom have been synthesized.

2. The synthesis of 1- and of 2-phenazinol has been simplified by new methods of obtaining their ethers.

3. Four halogenated 2-phenazinols have been made.

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