[Contribution from the Laboratory of Chemical Pharmacology, National Cancer Institute]

PHENAZINE SYNTHESES. I. HALOGEN-SUBSTITUTED PHENAZINES

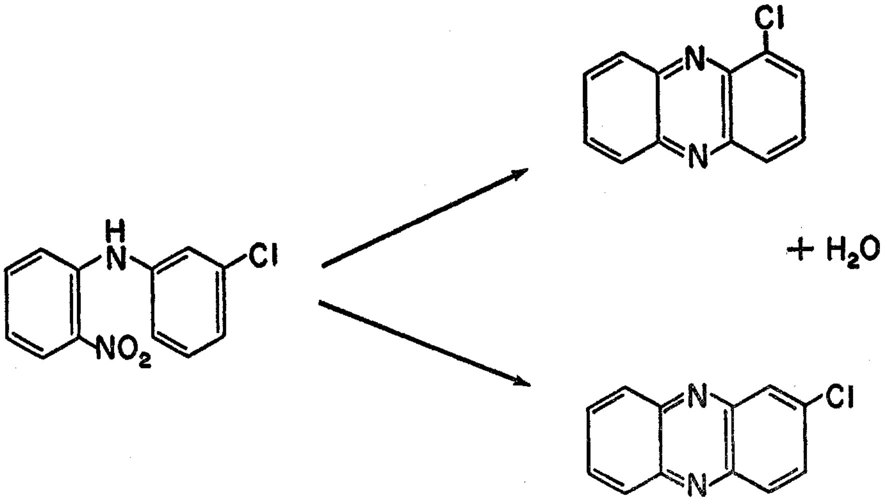
DONALD L. VIVIAN and JONATHAN L. HARTWELL

Received March 6, 1953

The synthesis of phenazines by the reaction of Waterman and Vivian (1, 2) involves heating 2-nitrodiphenylamines with an oxygen-abstracting agent such as metallic iron or ferrous oxide (conveniently obtained from ferrous oxalate by heat decomposition *in situ*). In determining the applicability of this reaction to the synthesis of halogenated phenazines, we have found that 2-nitrodiphenylamines substituted in the 2′ position by chlorine, or in the 2′ or 4′ positions by bromine do not give the expected halogenophenazines only, but instead give mixtures of these with varying proportions of unsubstituted phenazine. Thus there is a loss of part of the halogen, with replacement by hydrogen presumably derived either from break-up of part of the intermediate, or from the action of steam on ferrous oxide or on hot iron.

With 3′-chloro-2-nitrodiphenylamine, on the other hand, there is no such loss of halogen, but instead there are formed both of the two possible isomers, the 1-chloro- and 2-chloro-phenazines, as shown by the formulation given below. This is in accord with the behavior of the 3′-alkoxy-2-nitrodiphenylamines, which likewise gave mixtures of the two isomers (2). Whether 3′-iodo-2-nitrodiphenylamine would lose iodine or not has not been determined, but behavior of the 4-iodo-compound (see below) lends strength to the belief that it would not.

There is also no formation of halogen-free phenazine when halogeno-2-nitrodiphenylamines bearing the halogen in the 4-position of the same ring as the nitro group are subjected to the reaction. This is true even when the halogen is iodine, as shown by the fact that only the 2-halogenophenazines were obtained



when 4-bromo-, 4-chloro-, and 4-iodo-2-nitrodiphenylamine were heated with ferrous oxalate.

Finally, in the one instance where a fluoro-compound was subjected to ring closure, that of 4′-fluoro-2-nitrodiphenylamine, no trace of unsubstituted phenazine could be found, but only 2-fluorophenazine. This result is not surprising, in view of the known great strength of the carbon-fluorine bond.

While all of the isomeric halogeno-2-nitrodiphenylamines have not been investigated, the available evidence allows the drawing of the following tentative conclusions regarding the behavior of monohalogeno-2-nitrodiphenylamines when subjected to ring closure by heating with oxygen-abstracting agents:

1. When the halogen is in the ring not bearing the nitro group.
    a. If the halogen is *ortho-* or *para-* to the imino group, part of the halogen is lost, with concomitant formation of varying amounts of halogen-free phenazine, unless the halogen is fluorine. With this latter halogen no loss occurs.
    b. If the halogen is *meta-* to the imino group, there is no loss of halogen, but mixtures are formed of varying proportions of the 1- and 2-halogenophenazines.
2. When the halogen is in the same ring with the nitro group, no loss of halogen occurs. Thus only the expected halogenophenazine is formed.

Since the use of 2-nitrodiphenylamines halogenated in the ring not bearing the nitro group gives rise to the mixtures mentioned, whose separation is difficult, it is recommended that for preparative purposes 2-nitrodiphenylamines be used which are halogenated in the same ring that bears the nitro group.

EXPERIMENTAL[1]

Cyclization of 2′-chloro-2-nitrodiphenylamine. The starting material was heated with ferrous oxalate and granulated lead in the usual way. There resulted from 10 g. of 2′-chloro-2-nitrodiphenylamine (3) 3.31 g. of orange product, shrinking at 93°, and melting up to 135°. Recrystallized from methyl alcohol, this gave a sulfur-yellow solid melting at 108–140°. Analysis[2] showed it to be richer in carbon than chlorophenazine, but poorer in chlorine.

Anal. Calc'd for chlorophenazine, $C_{12}H_7ClN_2$: C, 67.2; H, 3.27; N, 13.1; Cl, 16.5.
Calc'd for phenazine, $C_{12}H_8N_2$: C, 80.0; H, 4.48; N, 15.5.
Found: C, 70.1; H, 3.77; N, 12.7; Cl, 13.7.

That the product was actually a mixture of 1-chlorophenazine and phenazine was shown by isolation of the pure components. By fractional precipitation from 50% acetic acid, followed by three recrystallizations from methanol, there was obtained from the 3.31 g. original product 0.36 g. sulfur-yellow needles, melting at 121–122°. Wrede and Mühlroth (4) give 122–123° as the m.p. of 1-chlorophenazine.

Anal. Calc'd for $C_{12}H_7ClN_2$: C, 67.2; H, 3.27.
Found: C, 67.1; H, 3.58.

By pouring the mother-liquor from the 50% acetic acid first recrystallization into two volumes of water, there was thrown down 1.8 g. of a product shrinking at 116°, and melting at 125–157°. By another fractionation from 50% acetic acid, followed by three recrystallizations from benzene of the product resulting from dilution of the mother-liquor, as before,

---

[1] All melting-points are corrected.

[2] Microanalyses were performed by the Microanalytical Laboratory of the National Institutes of Health, under the direction of Dr. William C. Alford.

there was finally obtained a small amount of sulfur-yellow needles, m.p. 172.4–174.8°. These, on admixture with a sample of authentic phenazine, m.p. 174.7–176.3°, melted at 172.8–175.1°.

Anal. Calc'd for $C_{12}H_8N_2$: C, 80.0; H, 4.48.
Found: C, 79.4; H, 4.47.

Additional runs of the intermediate gave products with varying analyses, depending on the duration and temperatures of heating, but always falling between the values for chlorophenazine and unsubstituted phenazine. When 20-mesh degreased iron filings were used to effect the reaction instead of ferrous oxalate, a much larger part of the chlorine was lost, as shown by the analysis of the recrystallized product: C, 77.8; H, 4.08; Cl, 3.98. The melting-point range was also more nearly that of the unsubstituted phenazine, being 156–161°.

Cyclization of 2'-bromo-2-nitrodiphenylamine. The intermediate was prepared as follows: A mixture of 79 g. of *o*-chloronitrobenzene, 98 g. of *o*-bromoaniline, and 36 g. of potassium carbonate, together with 0.1 g. of copper bronze (Kahlbaum Naturkupfer C) was heated for 16 hours in an oil-bath maintained at 220–228°. Steam-distillation of the reaction mixture left a coal-black, hard residue weighing 87 g. Ether extraction of this gave only 27 g. of product, which on recrystallization from 95% alcohol (Norit) gave 18 g. of product, still melting poorly (90–102°), but satisfactory for the ring closure, below.

Further recrystallizations from alcohol gave small orange needles, melting at 105–106.5°.

Anal. Calc'd for $C_{12}H_9BrN_2O_2$: Br, 27.2. Found: Br, 27.6.

A 16.5 g.-portion of the 18 g. of partially-purified material was heated 30 minutes with 165 g. of 20-mesh degreased iron filings, in an oil-bath at 280°. Extraction of the reaction mass with ether gave 6.5 g. of light-brown product.

This 6.5 g. was chromatographed from benzene on alumina. Elution of the product yielded 5.2 g. deep yellow material, melting at 104–136°. This, recrystallized from methanol, gave 3 g. of lighter material, but this still melted very poorly, softening and partly melting at 108.6° but still not completely liquid by 135°. Analysis showed this product to have the composition of a mixture of phenazine and bromophenazine. No further attempts were made to separate it into its components.

Anal. Calc'd for $C_{12}H_7BrN_2$: C, 55.6; H, 2.75; Br, 30.8; N, 10.8.
Calc'd for $C_{12}H_8N_2$: C, 80.0; H, 4.48; N, 15.5.
Found: C, 69.7; H, 3.69; Br, 14.1; N, 12.8.

Cyclization of 4'-bromo-2-nitrodiphenylamine. When 50 g. of 4'-bromo-2-nitrodiphenylamine (5) was heated with 500 g. of 20-mesh degreased iron filings, the original color of the intermediate became a very pale yellow after about 20 minutes in an oil-bath at 290°. Extraction of the reaction mixture with ether gave 10 g. of crude greenish-gray product. On sublimation at about 1 mm., this gave 5 g. of a light yellow product melting at 155.7–160.3°. All attempts to obtain a pure compound from this material proved fruitless: Chromatography on alumina from benzene solution, two recrystallizations from methanol, and steam-distillation, in which the mixture proved unexpectedly volatile, gave 1.4 g. of a sulfur-yellow product, melting at 155–162°. Analysis showed that this material had the composition of a mixture of phenazine and bromophenazine, similarly to the preceding one.

Anal. Calc'd for $C_{12}H_7BrN_2$: C, 55.6; H, 2.75; Br, 30.8; N, 10.8.
Calc'd for $C_{12}H_8N_2$: C, 80.0; H, 4.48; N, 15.5.
Found: C, 76.1; H, 4.05; Br, 5.35; N, 14.5.

Cyclization of 3'-chloro-2-nitrodiphenylamine. The 3'-chloro-2-nitrodiphenylamine was prepared by heating for 16 hours in an oil-bath at 234–237° a mixture of 220 g. of *o*-chloronitrobenzene, 250 g. of *m*-chloroaniline, and 97 g. of K_2CO_3. Steam-distillation was used to remove unreacted starting material, and the dark residue was recrystallized several times with alcohol (Norit). Thus there was obtained a poor yield (about 40 g.) of the crude compound as short orange needles, shrinking at 77.6°, and melting at 78.8–81.2°. These were satisfactory for the ring closure, below.

On further recrystallizations from alcohol the compound melted at 90–91°.

Anal. Calc'd for $C_{12}H_9ClN_2O_2$: C, 58.0; H, 3.65.
Found: C, 58.0; H, 3.69.

Heating 7.5 g. of the partially purified 3′-chloro-2-nitrodiphenylamine with 10 g. of ferrous oxalate dihydrate and 75 g. of granulated lead in the usual way gave 4 g. of crude sublimate. This, by a long series of fractionations from methanol was separated into 1-chlorophenazine and 2-chlorophenazine, both identified by mixture melting points with authentic specimens. From the 4 g. of crude substance 0.37 g. of the 1-chloro- and 0.16 g. of the 2-chloro- isomer were obtained, but no idea of the relative proportions present in the crude mixture can be obtained from these figures, because of the obvious very large losses in the fractional precipitations.

SYNTHESIS OF 2-HALOGENOPHENAZINES BY PRACTICAL METHODS

1. *2-Fluorophenazine.* The intermediate was prepared as follows: A mixture of 18 g. of *p*-fluoroaniline, 25 g. of *o*-chloronitrobenzene, and 27 g. of anhydrous sodium acetate was heated 22 hours (air-condenser) in an oil-bath held at 213–219°, and the reaction mixture then was steam-distilled until all unchanged starting material was removed. Then 20 cc. of conc'd HCl was added, and the distillation was continued until the HCl was eliminated. After the mixture was cooled, washed with cold water, and dried, it gave 20.1 g. of a reddish-black crude, which was satisfactory for ring-closure. Two recrystallizations from alcohol gave small, thick orange needles, melting at 84–85°.

Anal. Calc'd for $C_{12}H_9FN_2O_2$: C, 62.1; H, 3.90.
Found: C, 62.3; H, 3.82.

Heating 5 g. of the 4′-fluoro-2-nitrodiphenylamine with 6.5 g. of ferrous oxalate dihydrate and 50 g. of granulated lead in an oil-bath at 255–258° resulted in the maximum internal temperature of 262°. The reaction was complete in 10 minutes. Sublimation at about 3 mm. from a bath at 250° gave 2.1 g. shrinking at 148°, and melting to a clear amber at 169–172.5°. Three recrystallizations from methanol gave very pale yellow needles, melting at 180.8–181.2°.

Anal. Calc'd for $C_{12}H_7FN_2$: C, 72.7; H, 3.56.
Found: C, 72.4; H, 3.62.

2. *2-Chlorophenazine.* This preparation has already been reported (1). Better yields than that described have been obtained by the use of 6.5 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of granulated lead with 5 g. of 4-chloro-2-nitrodiphenylamine, (5).

3. *2-Bromophenazine. a.* 4-Bromo-2-nitrodiphenylamine was synthesized by heating 56.2 g. of 2,5-dibromonitrobenzene with 60 g. of aniline and 35 g. of anhydrous sodium acetate for 23 hours in an oil-bath at 205–210° (air-condenser). Steam-distillation was used to remove unreacted starting material, then 50 cc. of conc'd HCl was added to the residue, and further steam-distillation was employed, to hydrolyze and remove any acetanilide derivative formed.

The residue on cooling gave a hard, almost black cake, which on trituration with water and air-drying weighed 57.2 g. This crude material could be used for the formation of 2-bromophenazine, below, although the yields were better if a purified preparation was used. Recrystallized several times from alcohol, the compound formed small, stout, red-orange prisms, melting at 65–66°.

Anal. Calc'd for $C_{12}H_9BrN_2O_2$: C, 49.2; H, 3.09.
Found: C, 49.3; H, 3.23.

b. 2-Bromophenazine was synthesized in the usual way by heating 5.0 g. of crude 4-bromo-2-nitrodiphenylamine with 6.5 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of granulated lead in an oil-bath at 270°. The internal temperature reached the maximum of 281° within 11 minutes after the reaction mixture had been placed in the hot oil, and the flask was then withdrawn from the bath, allowed to cool, and the entire reaction mixture was broken up and subjected to sublimation at about 3–4 mm. from the bath at 250°. Thus there was obtained 1.5 g. of crude material. This on recrystallization from methanol gave 1.1 g., shrinking at 148.4°, and melting at 149–150°, lit. (5) m.p. 150°.

Anal. Calc'd for $C_{12}H_7BrN_2$: C, 55.6; H, 2.72; Br, 30.9.
Found: C, 55.8; H, 3.02; Br, 30.5.

4. *2-Iodophenazine.* The method of Jacobson, Fertsch, and Heubach (6) was used to prepare 5-iodo-2-nitrodiphenylamine. When 6.0 g. of this intermediate was heated in an oil-bath at 270–280° with 7.8 g. of $FeC_2O_4 \cdot 2H_2O$ and 60 g. of granulated lead, the internal temperature reached a maximum of 290° in a period of about 10 minutes. The yield on vacuum sublimation was 1.8 g. crude 2-iodophenazine. This, on recrystallization from methanol, gave about 1.2 g. melting at 168–169°. Further recrystallization gave light yellow needles melting at 169.5–170°.

Anal. Calc'd for $C_{12}H_7IN_2$: C, 47.1; H, 2.30.
Found: C, 47.1; H, 2.20.

Acknowledgment. We are indebted to Mr. G. W. Cogan for assistance with laboratory operations.

SUMMARY

1. It has been shown that in all instances studied, except that of the fluoro compound, mixtures of varying proportions of phenazine and halogenated phenazines arise when 2′ or 4′-halogeno-2-nitrodiphenylamines are subjected to direct ring closure.

2. In no instance were mixtures formed when 4-halogeno-2-nitrodiphenylamines were likewise cyclized.

3. Two new phenazines and several new intermediates have been prepared.

BETHESDA 14, MARYLAND

REFERENCES

(1) WATERMAN AND VIVIAN, *J. Org. Chem.*, **14**, 289 (1949).
(2) VIVIAN, GREENBERG, AND HARTWELL, *J. Org. Chem.*, **16**, 1 (1951).
(3) CAMPBELL AND MACLEAN, *J. Chem. Soc.*, 505 (1942).
(4) WREDE AND MÜHLROTH, *Ber.*, **63**, 1931 (1930).
(5) MCCOMBIE, SCARBOROUGH, AND WATERS, *J. Chem. Soc.*, 353 (1928).
(6) JACOBSON, FERTSCH, AND HEUBACH, *Ann.*, **303**, 339 (1898).