[CONTRIBUTION FROM THE CHEMOTHERAPY SECTION, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

DIRECT RING CLOSURE THROUGH THE NITRO GROUP. ISOMER FORMATION IN THE SYNTHESIS OF UNSYMMETRICAL PHENAZINES, AND SOME GENERAL OBSERVATIONS ON THE PHENAZINE SYNTHESES

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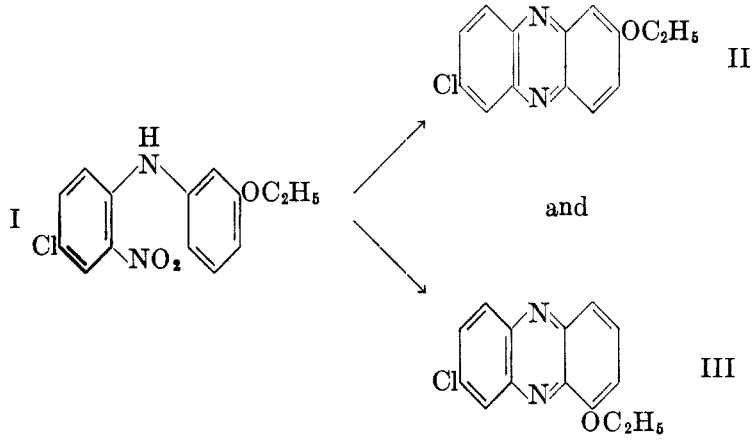
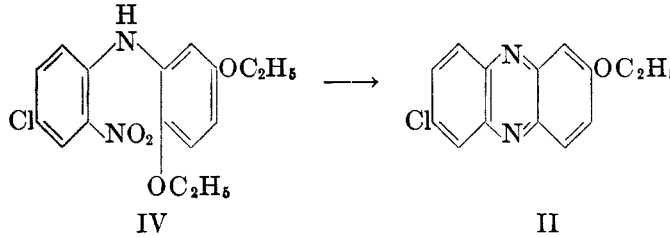
In extending to the preparation of chloro-substituted alkoxyphenazines the reaction of Waterman and Vivian (1), which consists in closing the ring of various nitrogen heterocycles by heating appropriate nitro compounds with reductants which remove oxygen without introducing hydrogen (such as metallic iron or ferrous oxalate), we have been able to show that definite isomer formation may take place where the possibility exists. Thus, when 4-chloro-3′-ethoxy-2-nitrodiphenylamine (I) is heated with ferrous oxalate, both 2-chloro-7-ethoxyphenazine (II) and 8-chloro-1-ethoxyphenazine (III) are formed.

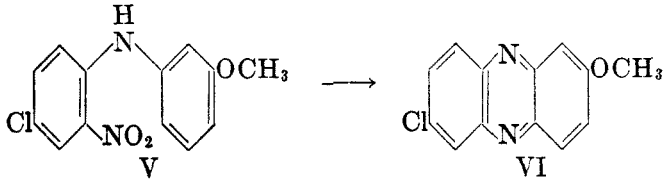


Both isomers have been isolated in pure form, and we have been able to identify them by synthesizing II by an unambiguous method. This latter consists in taking advantage of the fact that an alkoxy group is eliminated, in preference to a hydrogen atom, whenever both are in the appropriate position for reaction (*o*- to the NH group) (1). Thus 4-chloro-2′,5′-diethoxy-2-nitrophenylamine (IV) can form only II:



So prepared, authentic II, m.p. 183–184°,[1] proved to be identical with the isomer (II) separated in the larger quantity from the mixture resulting from ring closure of I. The other isomer, m.p. 149–150°, separated by a rather elaborate series of recrystallizations from different solvents, must therefore be III.

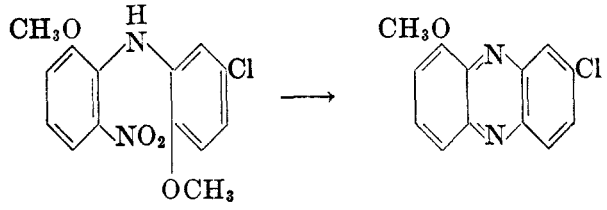
From the mixture of isomers given by 4-chloro-3′-methoxy-2-nitrodiphenylamine (V) we succeeded in obtaining pure only the one present in larger quantity, m.p. 173–174°; comparison with 2-chloro-7-methoxyphenazine (VI) syn-



V VI

thesized by the same unambiguous method as used for its ethoxy homolog (II) proved that the compound isolated had this configuration.

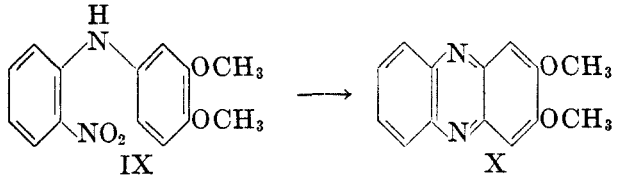
While the other isomer, 8-chloro-1-methoxyphenazine (VII), was not isolated in a pure state, we have, nevertheless, synthesized it unambiguously from 5′-chloro-2′,6-dimethoxy-2-nitrodiphenylamine (VIII):



VIII VII

This isomer melted at 209–211°, and therefore, unlike its ethoxy homolog, considerably higher than the 2,7-isomer. That we did have on hand a mixture of VI and VII from the reaction with V was indicated by the very wide melting range of the mixture after several recrystallizations, together with its analysis, which agreed with figures for chloromethoxyphenazine. Also, a mixture of the pure 2,7- and 8,1-isomers behaved very similarly to that obtained from the reaction, in softening at approximately the same temperature, and having a very similar behavior throughout the wide melting range.

Incidentally, it may be remarked that this isomer formation is contrary to the behavior of 3′,4′-dimethoxy-2-nitrodiphenylamine (IX), which according to Slack and Slack (2) gives only the 2,3-dimethoxyphenazine (X), with no trace of the isomeric 1,2-compound:

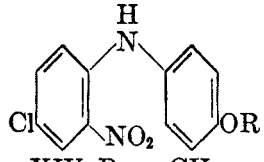


IX X

[1] All our melting points are corrected.

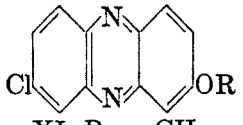
Despite the mixture obtained, preparation of the two 7-alkoxy-2-chlorophenazines (II and VI) through the 3′-alkoxy-4-chloro-2-nitrodiphenylamines (I and V) seems to be about as satisfactory as the syntheses through IV and its methoxy homologue, for the intermediates in the latter instances are somewhat more difficult to purify, while separation of the predominant isomers, II and VI, is not difficult.

In both of the above phenazine syntheses, as well as in the other two described in the experimental part, those of 2-chloro-8-methoxyphenazine (XI) and its ethoxy homolog (XII), it has been found that the original idea expressed by Waterman and Vivian (1), that the proportion of ferrous oxalate can be greatly in excess of any theoretical amount, should be modified. Instead, it has been shown that an optimum quantity for best yields exists, and that this optimum corresponds within fairly narrow limits to the amount satisfying the equation:



XIV, R = CH_3
XV, R = C_2H_5

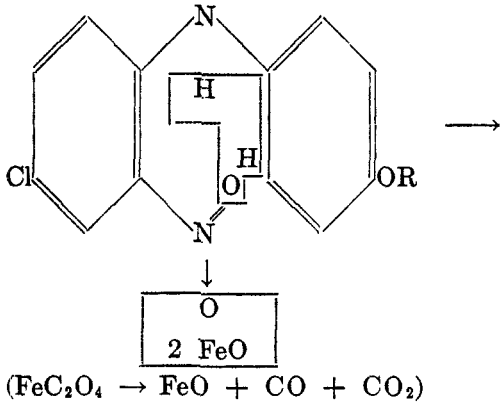
$+ 2\ FeC_2O_4 \longrightarrow$



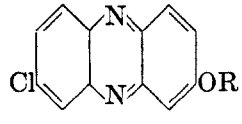
XI, R = CH_3
XII, R = C_2H_5

$+ Fe_2O_3 + 2\ CO + 2\ CO_2 + H_2O$

We have found that varying the amount of oxalate in any substantial proportion from this ratio results in poorer yields. Hence it appears that the reaction may not be as simple as first thought, when it was considered that it could be expressed by showing only one molecule of the *o*-nitrodiphenylamine losing oxygen and H_2O:



($FeC_2O_4 \rightarrow FeO + CO + CO_2$)



$+ H_2O + Fe_2O_3$

Instead, it appears that at least two molecules of the *o*-nitrodiphenylamine may be involved in each interchange of the elements of water, since if the reaction had the mechanism shown immediately above, dilution with larger quantities of oxalate should make very little difference, save for its effect on the temperature attained. Our experimental results do not show any effect that can be ascribed to temperature difference.

Another point of practical importance for the use of the reaction for preparative purposes is that the use of a smaller proportion of ferrous oxalate than was at first thought necessary makes the use of the hydrated form of the oxalate practicable. Waterman and Vivian (1) had advocated the use of anhydrous FeC_2O_4, but this does not appear to be necessary. It was mentioned by these authors that $FeC_2O_4 \cdot 2H_2O$ from the ordinary commercial sources had frequently proved unsatisfactory, and suggested that the oxalate should perhaps be prepared from ferrous sulfate and oxalic acid. Further experience with commercial samples of the material indicates that some of them, though by no means all, are quite satisfactory. It is hence only necessary to test the $FeC_2O_4 \cdot 2H_2O$ whose use is proposed on a sample of readily available intermediate, such as *o*-nitrodiphenylamine, before using it on less accessible intermediates.

Granulated lead used in conjunction with the oxalate has been stated to give better results than oxalate alone (1). We have found that moderate departures from the ratio found satisfactory (ten parts by weight of lead to one of intermediate) do not markedly affect the yields of the compounds reported herein. A few runs have been made with powdered lead and with degreased iron filings, in place of the granulated lead, but the yields so obtained have been poorer.

One other practical point should be mentioned: no large-scale runs have been made using ferrous oxalate, so that it has not yet been determined if such runs are apt to develop dangerously high temperatures or too violent reactions. Caution would therefore appear advisable if large runs are contemplated.

EXPERIMENTAL PART

4-Chloro-3'-ethoxy-2-nitrodiphenylamine (I). A thorough mixture of 72 g. of *m*-phenetidine, 101 g. of 2,5-dichloronitrobenzene, and 80 g. of anhydrous sodium acetate was heated 40 hours in an oil-bath at 210–220°, with an air-condenser reflux. It was then steam-distilled until no more volatile material passed over. On cooling and thorough washing with water 89 g. (58%) of crude dark red product was obtained, shrinking at 77°; m.p. 83–87°. Several recrystallizations from 95% ethanol (Norit) gave reddish-brown plates, m.p. 91–92°.

Anal.[2] Calc'd for $C_{14}H_{13}ClN_2O_3$: C, 57.4; H, 4.48.
Found: C, 57.4; H, 4.58.

Conversion of I to 2-chloro-7-ethoxyphenazine (II) *and 8-chloro-1-ethoxyphenazine* (III). The crude material was satisfactory for this synthesis; the best yield was obtained when 5.0 g. was heated in an oil-bath at 265–270° with 6.0 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of granulated lead. The internal temperature rose quickly, once the reaction started, to a maximum of 285–300°. The mixture was withdrawn from the bath shortly after this maximum was attained, and transferred after it had cooled to a vacuum sublimation apparatus. Sublimation at about 1 mm. from an oil-bath at approximately 230° gave 2.1 g. of the crude

[2] Microanalyses were performed by Mrs. M. Ledyard and Mrs. E. Peake of the microanalytical laboratory under the direction of Mr. William C. Alford.

mixture of the two phenazines. Recrystallized once from 95% ethanol, there was obtained 1 g. of sulfur-yellow needles, softening at 180°; and m.p. 183–184°. This is shown below to be 2-chloro-7-ethoxyphenazine (II).

From the mother liquor, by an extensive series of fractional crystallizations from methanol, ethanol, and *n*-hexane, there was finally obtained about 0.2 g. of light yellow needles, m.p. 149–150°. These gave a deep green color with conc'd H_2SO_4, whereas the 2,7-isomer, above, gave a deep violet. This lower-melting compound must be 8-chloro-1-ethoxyphenazine (III), since it is the only other phenazine that can be formed from I.

Anal. Calc'd for $C_{14}H_{11}ClN_2O$: C, 65.0; H, 4.28.
Found: C, 64.7; H, 4.27.

2-Chloro-7-ethoxyphenazine (II) *by an unambiguous synthesis.* a. *4-Chloro-2',5'-diethoxy-2-nitrodiphenylamine* (IV). A mixture of 10 g. of 2,5-diethoxyaniline, 11 g. of 2,5-dichloronitrobenzene, and 10 g. of sodium acetate was heated 16 hours in an oil-bath at 218–222° with air-condenser reflux. The resulting mixture was steam-distilled until all volatile material had been removed, and the black, viscous residue thoroughly washed with water and air-dried. The very crude material weighed 14 g. Recrystallized several times from absolute alcohol (Norit), it gave scarlet needles, m.p. 92–93°.

Anal. Calc'd for $C_{16}H_{17}ClN_2O_4$: C, 57.1; H, 5.09.
Found: C, 57.2; H, 4.98.

b. *2-Chloro-7-ethoxyphenazine* (II). The ring-closure and sublimation were carried out just as in the case of the 4-chloro-3'-ethoxy-2-nitrodiphenylamine (I), except that partially purified intermediate was necessary, unlike the crude I utilized. A yield of sublimate of about 0.2 g. *per* g. of intermediate was obtained. This, recrystallized from absolute alcohol, gave approximately one-half its weight of very small, pale straw-colored needles, m.p. 183–184° (shrinking at 179°).

Anal. Calc'd for $C_{14}H_{11}ClN_2O$: C, 65.0; H, 4.28.
Found: C, 65.0; H, 4.44.

These needles showed no depression of the melting-point when mixed with an equal quantity of II obtained above from I, and gave the same deep violet color with conc'd sulfuric acid.

4-Chloro-3'-methoxy-2-nitrodiphenylamine (V). *m*-Anisidine (90 g.), 140 g. of 2,5-dichloronitrobenzene, and 100 g. of anhydrous sodium acetate were heated in a flask surmounted by an air-condenser for 44 hours in an oil-bath at 220–230°. The reaction mixture was then steam-distilled to remove unchanged material, and the viscous residue was extracted overnight in a Soxhlet after being washed several times with ether at room temperature to remove semi-liquid products. Evaporation of the ether extract gave 150 g. of black, still partly viscous material. This was heated with 1300 cc. of 95% ethanol and 60 g. of Norit, filtered hot, the filter cake washed with an additional 500 cc. of hot 95% ethanol, in several portions, and the filtrate chilled. Yield, 82 g. (42.5%) of dark red needles, m.p. 92–95° (shrinking 90°). Several recrystallizations from 95% ethanol gave a pure V, m.p. 92–93°.

Anal. Calc'd for $C_{13}H_{11}ClN_2O_3$: C, 56.0; H, 3.96.
Found: C, 55.9; H, 4.01.

Conversion of V to 2-chloro-7-methoxyphenazine (VI) *and 8-chloro-1-methoxyphenazine* (VII). When the once-recrystallized V, m.p. 92–95° (5 g.), was treated with $FeC_2O_4 \cdot 2H_2O$ and granulated lead just as was its ethoxy homolog (I), about 1.6 g. of product was obtained on vacuum sublimation. Treatment of 6.74 g. of this crude product with 450 cc. of hot 95% ethanol gave a clear solution; this, on cooling to room temperature, gave 4.15 g. of pale yellow needles, m.p. 173–174°. These are shown below to be 2-chloro-7-methoxyphenazine (VI).

The mother liquor was evaporated, and the solid remaining was recrystallized from 200 cc. of methanol to give 0.68 g., shrinking at 144°; m.p. 187–205°.

Anal. Calc'd for $C_{13}H_9ClN_2O$: C, 63.8; H, 3.71.
Found: C, 63.6; H, 3.74.

This analysis and the wide melting range show the second product to be a mixture of

the two possible isomers. Repeated recrystallizations from various solvents did not result in separation of 8-chloro-1-methoxyphenazine (VII) in pure form, hence it was prepared, as well as VI already mentioned, as shown below.

2-Chloro-7-methoxyphenazine (VI) *by an unambigouus synthesis.* a. *4-Chloro-2',5'-dimethoxy-2-nitrodiphenylamine* (XIII). A mixture of 15 g. of 2,5-dimethoxyaniline, 18.8 g. of 2,5-dichloronitrobenzene, and 15 g. of anhydrous sodium acetate was heated 40 hours in an oil-bath and the resulting mass was treated in the usual way. Yield, 23.4 g. of a black crude, m.p. 80–95°. Several recrystallizations from ethanol (Norit) gave deep violet-red needles of 4-chloro-2',5'-dimethoxy-2-nitrodiphenylamine (XIII), m.p. 120–121°.

Anal. Calc'd for $C_{14}H_{13}ClN_2O_4$: C, 54.5; H, 4.25.

Found: C, 54.5; H, 4.34.

b. *2-Chloro-7-methoxyphenazine* (VI). Cyclization of XIII to VI was effected by $FeC_2O_4 \cdot 2H_2O$ and granulated lead in the usual way. There resulted pale yellow needles (from ethanol), m.p. 173–174°; not depressed by admixture with an equal quantity of VI isolated, above, from the mixture given by V.

Anal. Calc'd for $C_{13}H_9ClN_2O$: C, 63.8; H, 3.71.

Found: C, 63.7; H, 3.76.

8-Chloro-1-methoxyphenazine (VII). a. *2,3-Dinitroanisole.* The procedure of Wrede and Strack (3), *viz*, addition of 10 g. of *m*-nitroanisole to 30 cc. of nitric acid (sp. gr. 1.48) at 0°, and preservation for 24 hours at 0°, did not yield good results in our hands. Instead, we obtained the desired product by adding 247 g. of *m*-nitroanisole to 1250 cc. of conc'd nitric acid (sp. gr. 1.42), at 76–82°, with stirring. On standing overnight at room temperature, a precipitate formed which was washed once with conc'd nitric acid and then with water to neutrality. This product, weighing 58 g., shrank at 116°, m.p. 119–120°. Wrede and Strack (3) give 119°.

b. *5'-Chloro-2',6-dimethoxy-2-nitrodiphenylamine* (VIII). 2,3-Dinitroanisole (5 g.) and 11.6 g. of 5-chloro-2-anisidine (Eastman Practical 4-chloro-2-aminoanisole, once steam-distilled) were refluxed in 20 cc. of absolute alcohol for 10 days. Steam-distillation of the excess chloroanisidine and washing with water gave 8.2 g. of a black, somewhat tarry product. This, recrystallized several times from 95% ethanol (Norit), yielded crimson needles, m.p. 134–136°.

Anal. Calc'd for $C_{14}H_{13}ClN_2O_4$: C, 54.5; H, 4.25.

Found: C, 54.5; H, 4.32.

c. *8-Chloro-1-methoxyphenazine* (VII). Crude VIII (3 g.) heated with 3.8 g. of $FeC_2O_4 \cdot 2H_2O$ and 30 g. of granulated lead in an oil-bath at 265–267°, gave only 0.15 g. of yellow needles. On recrystallization from methanol these melted at 209–211°.

Anal. Calc'd for $C_{13}H_9ClN_2O$: C, 63.8; H, 3.71.

Found: C, 63.5; H, 4.00.

This compound gave a deep green color with conc'd sulfuric acid, while the 2-chloro-7-methoxy isomer (VI) gave a deep violet, exactly paralleling the behavior of the corresponding ethoxy compounds.

2-Chloro-8-methoxyphenazine (XI). a. *4-Chloro-4'-methoxy-2-nitrodiphenylamine* (XIV) (4). *p*-Anisidine (150 g.), 150 g. of 2,5-dichloronitrobenzene, and 160 g. of anhydrous sodium acetate were heated 40 hours in an oil-bath at 205–215°. Steam-distillation was continued until no more material passed over, then about 150 cc. of conc'd hydrochloric acid was added to hydrolyze the acetyl compound present, and steam-distillation continued until the hydrochloric acid was eliminated. Further treatment of the cooled residue with conc'd hydrochloric acid and washing with water removed the remaining unchanged *p*-anisidine. Yield, 205 g. of a crude black product, which on recrystallization from 95% ethanol (Norit) gave 139.5 g. (64%) of a dark red solid, m.p. 111–117°. On further recrystallization from ethanol, deep red needles, m.p. 120–121°, were obtained.

Anal. Calc'd for $C_{13}H_{11}ClN_2O_3$: C, 56.0; H, 3.96.

Found: C, 56.2; H, 4.47.

b. *2-Chloro-8-methoxyphenazine* (XI). When 5 g. of the once-recrystallized intermediate (XIV), m.p. 111–117°, was heated with 6.5 g. of $FeC_2O_4 \cdot 2H$ O and 50 g. of lead, the subli-

mate weighed 3.3 g. Recrystallized from methanol, the yield was 2.9 g. of small, sulfur-yellow needles, m.p. 151–152°.

Anal. Calc'd for $C_{13}H_9ClN_2O$: C, 63.8; H, 3.71.

Found: C, 63.6; H, 3.81.

2-Chloro-8-ethoxyphenazine (XII). a. *4-Chloro-4′-ethoxy-2-nitrodiphenylamine* (XV) (5) was prepared similarly to the methoxy homolog (XIV), giving an almost quantitative yield of a crude deep red product. One recrystallization from 95% ethanol gave 77% of thick red needles, softening at 82°, m.p. 90–95°. These were satisfactory for ring closure, but further recrystallizations gave thick, yellowish-red needles, m.p. 94–95°.

Anal. Calc'd for $C_{14}H_{13}ClN_2O_3$: C, 57.4; H, 4.48.

Found: C, 57.3; H, 4.43.

b. *2-Chloro-8-ethoxyphenazine* (XII). From 5 g. of the crude intermediate (XV), heated with 6 g. of $FeC_2O_4 \cdot 2H_2O$ and 50 g. of lead, there was obtained 2.9 g. of sublimate, which on recrystallization from 95% ethanol gave 2.2 g. of light yellow needles, m.p. 171–172°.

Anal. Calc'd for $C_{14}H_{11}ClN_2O$: C, 65.0; H, 4.29.

Found: C, 65.2; H, 4.41.

Variations of yield of phenazines with different ratios of oxalate to intermediate. A number of runs were made with each of the four most accessible of the intermediates described above (I, V, XIV, and XV), varying the ratio of $FeC_2O_4 \cdot 2H_2O$ to the intermediate. It was found that with all four there was an optimum ratio of about 6 to 6.5 g. of $FeC_2O_4 \cdot 2H_2O$ *per* 5 g. of intermediate, as shown by the following illustrative examples of the yield of 2-chloro-8-methoxyphenazine (XI) from 4-chloro-4′-methoxy-2-nitrodiphenylamine:

INTERMEDIATE, G.	$FeC_2O_4 \cdot 2H_2O$, G.	LEAD, G.	YIELD OF PHENAZINE, G.
5	10	50	2.0
5	7.5	50	2.6
5	6.5	50	3.3
5	5	50	2.4

Changing the relative amount of granulated lead did not seem to make much difference within fairly wide limits, but substitution of powdered lead or of 20-mesh degreased iron filings for the granulated lead gave poorer results.

Acknowledgment. We are indebted to Mr. Lee F. Merriam for assistance with laboratory operations.

SUMMARY

1. Six new phenazines and a number of new intermediates have been prepared.

2. In the instances studied, isomer formation has been shown to occur whenever such is possible in the unsymmetrical phenazine syntheses.

3. A ratio of approximately two moles of oxalate *per* mole of nitro compound is optimum in the ring-closure reaction: this moderate proportion makes dehydration of the oxalate before use unnecessary. Some grades of commercial $FeC_2O_4 \cdot 2H_2O$ are satisfactory.

BETHESDA 14, MD.

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(3) WREDE AND STRACK, *Ber.*, **62**, 2055 (1929).
(4) BRITISH CELANESE LTD. AND ELLIS, British Patent 237,943 (August 28, 1925); no analysis or m.p. given.
(5) BRITISH CELANESE LTD. AND ELLIS, British Patent 284,376 (February 23, 1928); no analysis or m.p. given.