[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

The Wohl–Aue Reaction. II. Reactivities of the Chlorophenazines and their Oxides[1]

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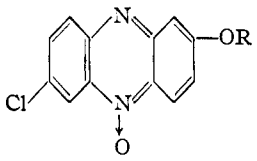
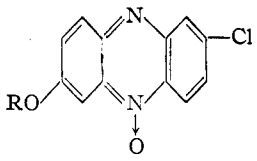
The Wohl–Aue reaction has been used to synthesize several chlorophenazine oxides. These compounds underwent alcoholysis more readily than hydrolysis when treated with aqueous alcoholic alkali, and were reduced to the respective chlorophenazines by means of hot aniline. The halogen-activating effect of amine oxide groups in chlorophenazine oxides has been shown to be primarily one of meta activation. 2-Chlorophenazine itself was found to be reactive toward nucleophilic reagents.

The halogen-activating effect of the oxide groups in chlorophenazine oxides has recently been demonstrated by Vivian.[2] It was presumed that the halogen atoms were activated by para-situated oxide groups and that the product obtained upon hydrolysis of 2,7-dichlorophenazine-5-oxide with aqueous ethanolic potassium hydroxide was 7-chloro-2-hydroxyphenazine-5-oxide (I).

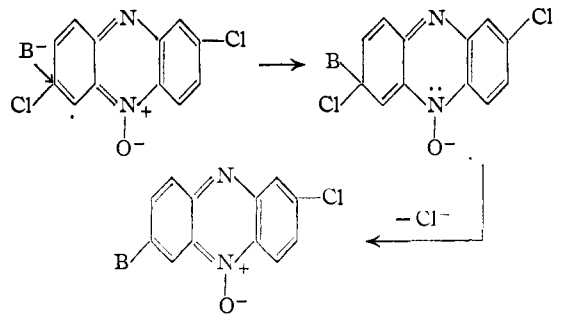


I, R = H
IV, R = CH_3



II, R = H
III, R = CH_3
V, R = CH_2CH_3

Consideration of the mechanism of the reaction of 2,7-dichlorophenazine-5-oxide with a base led us to believe that the reaction might proceed through the following changes



In this event, the halogen atom situated *meta* with respect to the amine oxide group would be activated, and the product obtained upon hydrolysis would be 2-chloro-7-hydroxyphenazine-5-oxide (II).

In a preliminary attempt to investigate the possibility of meta activation, 2-chloro- and 3-chlorophenazine-5-oxide were prepared by the Wohl–Aue reactions of *p*-chloronitrobenzene with aniline and of nitrobenzene with *p*-chloroaniline, respectively,[3] and submitted to the hydrolytic conditions employed by Vivian. It was found that after 24 hours, 3-chlorophenazine-5-oxide had reacted to give a 65% yield of 3-hydroxyphenazine-5-oxide and a 32% yield of an alkali-insoluble product identified as 3-ethoxyphenazine-5-oxide. The latter, when resubjected to the hydrolytic conditions, was readily converted to 3-hydroxyphenazine-5-oxide. It is possible that 3-ethoxyphenazine-5-oxide was an intermediate in the formation of the 3-hydroxyphenazine-5-oxide which arose upon hydrolysis of 3-chlorophenazine-5-oxide.[4] 2-Chlorophenazine-5-oxide gave no hydroxyphenazine oxide under these conditions, but yielded 2-ethoxyphenazine-5-oxide in 91% yield.

It is clear that both isomeric chlorophenazine-5-oxides contain active halogen and that these experiments permit no definite conclusion with regard to which halogen atom is replaced during hydrolysis of 2,7-dichlorophenazine-5-oxide.

It was shown, moreover, that 2-chlorophenazine itself undergoes alcoholysis on treatment with aqueous alcoholic alkali, although a longer reflux period than that required for the oxides is necessary for complete reaction, to give 2-ethoxyphenazine in 88% yield. 2-Chlorophenazine also reacts with ammonium hydroxide at 175° to form 2-aminophenazine. 2-Chlorophenazine is therefore considerably more reactive than the 1-chloro isomer which was reported to be highly resistant to a variety of nucleophilic reagents.[5]

As a more direct experimental approach to the question of meta activation, 2,7-dichlorophenazine-5-oxide was next prepared from *p*-chloronitrobenzene and *p*-chloroaniline, and subjected to the previously described hydrolytic conditions. The alkali-soluble reaction product was methylated to give a compound which was identical with 2-chloro-7-methoxyphenazine-5-oxide (III) prepared from the reaction between *p*-chloronitrobenzene and *p*-anisidine, but which was different from 7-chloro-2-methoxyphenazine-5-oxide (IV) prepared from the reaction between *p*-nitroanisole and *p*-chloroaniline. This confirmed the prediction that the effect of the amine oxide group was primarily one of meta activation.

As Vivian noted,[2] the hydrolysis of 2,7-dichlorophenazine-5-oxide was accompanied by the formation of an alkali-insoluble residue. This was separated chromatographically into 2-chloro-7-ethoxyphenazine-5-oxide (V), 2,7-diethoxyphenazine-5-oxide and traces of a pale yellow compound, m.p. 184° (cor.), which was probably 2-chloro-7-

(1) Abstracted from a portion of the dissertation submitted by Irwin J. Pachter to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) D. L. Vivian, THIS JOURNAL, **73**, 457 (1951).

(3) In the absence of definite knowledge concerning the mechanism of the Wohl–Aue reaction, it is not established beyond all possible doubt which of the two nitrogen atoms bears the oxygen atom in an asymmetrical phenazine N-oxide synthesized by this method. However, in this paper and in the first paper of this series [I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **73**, 4958 (1951)] the very reasonable assumption has been made that it is the nitrogen atom originally in the nitro group which eventually bears the oxygen atom in the N-oxide. The names of the N-oxides in this paper are based upon that assumption.

(4) A. R. Surrey and R. A. Cutler, *ibid.*, **73**, 2623 (1951), demonstrated that an ether is an intermediate in the phenol-catalyzed conversion of 4,7-dichloroquinoline to chloroquine.

(5) F. Wrede and O. Mühlroth, *Ber.*, **63**, 1931 (1930).

TABLE I

WOHL-AUE REACTION PRODUCTS

Phenazine-5-oxide	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1-Chloro-	159–160	14[a]	$C_{12}H_7ClN_2O$	62.48	61.62[b]	3.06	3.08
2-Chloro-	178	35	$C_{12}H_7ClN_2O$	62.48	62.40	3.06	3.17
3-Chloro-	175–176	11	$C_{12}H_7ClN_2O$	62.48	62.68	3.06	3.15
2,7-Dichloro-	236 dec.	17[c]					
2-Chloro-7-methoxy-	207 dec.	24	$C_{13}H_9ClN_2O_2$	59.89	59.81	3.48	3.44
7-Chloro-2-methoxy-	209 dec.	..[d]	$C_{13}H_9ClN_2O_2$	59.89	60.12	3.48	3.67

[a] Raised to 24% when toluene was used as the reaction solvent. [b] Analytical data for several samples of 1-chlorophenazine-5-oxide derived from the Wohl–Aue reaction or from the oxidation of 1-chlorophenazine were consistent, though low in carbon. [c] Previously prepared in 4.5% yield by E. Bamberger and W. Ham, *Ann.*, **382**, 82 (1911), who employed the original Wohl–Aue procedure. [d] Less than 1% yield. Raised to 5% when toluene was used as the reaction solvent. This preparation will be discussed in more detail in a later communication.

ethoxyphenazine.[6] The structure of compound V was confirmed by its preparation from 2-chloro-7-hydroxyphenazine-5-oxide and ethyl sulfate.

The possibility of activation of halogen in the 1-position of phenazine by a suitably situated amine oxide group, as in 1-chlorophenazine-5-oxide, has not been studied previously. 1-Chlorophenazine-5-oxide, prepared by the Wohl–Aue reaction between nitrobenzene and *o*-chloroaniline, proved to be less reactive than either 2-chloro- or 3-chlorophenazine-5-oxide and to be comparable in reactivity to 2-chlorophenazine. Since 1-chlorophenazine itself is considerably less reactive to nucleophilic attack than 2-chlorophenazine, the activation of the former compound by a 5-oxide group is demonstrated. 1-Chlorophenazine-5-oxide was converted into 1-ethoxyphenazine-5-oxide and 1-hydroxyphenazine-5-oxide by prolonged treatment with aqueous alcoholic alkali.

In connection with another study, 3-chlorophenazine-5-oxide was refluxed with aniline and sodium acetate for several hours in an attempt to prepare 3-phenylaminophenazine-5-oxide. Actually the reaction mixture afforded a 92% yield of 2-chlorophenazine. When 2-chlorophenazine-5-oxide was refluxed with aniline alone, a similar reduction occurred and 2-chlorophenazine was produced in 96% yield. The reduction of an amine oxide by an aromatic amine has not been reported previously.

When 1-chlorophenazine-5-oxide was reduced with aniline, 1-chlorophenazine was obtained in 88% yield. The properties of the latter and of its chloroaurate derivative were identical with those reported by Wrede and Mühlroth.[5] When warmed with hydrogen peroxide in acetic acid, 1-chlorophenazine was reconverted to 1-chlorophenazine-5-oxide. The fact that a monoxide rather than a dioxide was produced in this reaction is in accord with the observation that 1,6-dichlorophenazine was unaffected by warm peroxide in acetic acid[3] although both phenazine[7] and 2,7-dichlorophenazine[2] yielded dioxides when subjected to these oxidative conditions.

The optimum conditions for the Wohl–Aue reaction have not yet been determined. Serebryanyi[8] recently carried out a number of reactions at room temperature in the absence of a solvent to obtain yields which seem to be generally inferior to those which were obtained in the present study by using the method described by Soule,[9] who prepared phenazine oxide from aniline and nitrobenzene in refluxing benzene as a diluent. Near the conclusion of the present work it was observed that the yields of 1-chlorophenazine-5-oxide and 7-chloro-2-methoxyphenazine-5-oxide were raised by substituting refluxing toluene for benzene. The effects of different solvents and reaction temperatures are receiving further study.

Experimental[10]

The Wohl–Aue Reactions.—Table I summarizes the data for the Wohl–Aue reactions, all of which were run as described here for 2-chlorophenazine-5-oxide. The products crystallized from alcohol or benzene in yellow needles. Phenazine monoxides which melted below 200° generally did so without decomposition.

To 15 g. (0.16 mole) of aniline was added 60 g. (0.38 mole) of *p*-chloronitrobenzene and 150 cc. of benzene. The solution was stirred and 50 g. (0.9 mole) of dry powdered potassium hydroxide was added. The resulting mixture was stirred vigorously under reflux for eight hours and poured into a liter of water. A large portion of the product was obtained at this point by filtration since 2-chlorophenazine-5-oxide is not very soluble in cold benzene. The remainder was extracted from the benzene solution with hydrochloric acid and converted to the free oxide with ammonium hydroxide. The combined product was purified by recrystallization from benzene to give 13.0 g. of yellow needles.

3-Hydroxyphenazine-5-oxide and 3-Ethoxyphenazine-5-oxide from 3-Chlorophenazine-5-oxide.—To 1.00 g. of 3-chlorophenazine-5-oxide was added 40 cc. of 95% ethanol, 25 cc. of water and 5 g. of potassium hydroxide. The mixture was refluxed for 24 hours, diluted with 50 cc. of water, cooled and filtered. The precipitate was washed and dried to give 0.35 g. (32%) of 3-ethoxyphenazine-5-oxide, which crystallized in needles, m.p. 171° or prisms, m.p. 168°. The two crystalline modifications are interconvertible. Solutions of this and other 3(or 7)-alkoxyphenazine-5-oxides reported in this paper exhibit blue fluorescence.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; OEt, 18.75. Found: C, 69.98; H, 5.04; OEt, 18.88.

The deep red mother liquor, on acidification, yielded 0.63 g. (65%) of yellow 3-hydroxyphenazine-5-oxide. After recrystallization from acetic acid, this compound gradually darkens and decomposes without definite m.p. if the m.p. is approached gradually, but melts rather sharply at 258° (dec.) if the sample is introduced at 250° and heated rapidly.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80. Found: C, 67.46; H, 3.98.

Hydrolysis of 3-Ethoxyphenazine-5-oxide.—To 0.100 g. of 3-ethoxyphenazine-5-oxide was added 8 cc. of ethanol, 5 cc. of water and 1 g. of potassium hydroxide. The mixture was refluxed for 24 hours. The red solution was concen-

(6) D. L. Vivian, G. Y. Greenberg and J. L. Hartwell, *J. Org. Chem.*, **16**, 1 (1951).

(7) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).

(8) S. B. Serebryanyi, *J. Gen. Chem. (U. S. S. R.)*, **20**, 1629 (1950); [*C. A.*, **45**, 2009 (1951)].

(9) E. C. Soule, U. S. Patent 2,332,179.

(10) Microanalyses are by Mr. J. Pirie. Melting points are uncorrected unless otherwise specified.

trated by evaporation of the alcohol and was filtered after addition of 30 cc. of water to yield 0.016 g. (16%) of unreacted 3-ethoxyphenazine-5-oxide. Upon acidification, the red mother liquor yielded 0.071 g. (80%) of 3-hydroxyphenazine-5-oxide.

Alcoholysis of 2-Chlorophenazine-5-oxide.—Under the conditions previously described for the reaction of 3-chlorophenazine-5-oxide, 1.00 g. of 2-chlorophenazine-5-oxide underwent alcoholysis to yield 0.98 g. (91%) of 2-ethoxyphenazine-5-oxide, yellow needles, m.p. 155–155.5°. The red mother liquor upon acidification became slightly turbid with loss of red color, but no hydroxyphenazine oxide separated.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; OEt, 18.75. Found: C, 69.85; H, 4.85; OEt, 18.90.

Alcoholysis of 2-Chlorophenazine.—A mixture of 1.00 g. of 2-chlorophenazine, 49 cc. of 95% ethanol, 25 cc. of water and 10 g. of potassium hydroxide was refluxed for three days. Concentration and dilution with 50 cc. of water precipitated 2-ethoxyphenazine which was recrystallized from methanol to give 0.91 g. (88%) of small yellow needles, m.p. 114–115°. After 24 hours, this reaction was only partially complete.

Anal. Calcd. for $C_{14}H_{12}N_2O$: OEt, 20.09. Found: OEt, 19.78.

2-Aminophenazine.—A mixture of 0.50 g. of 2-chlorophenazine and 50 cc. of concentrated ammonium hydroxide was heated at 175° in a rocking bomb for 24 hours. The solid reaction product in benzene solution was chromatographed on alumina to yield 0.065 g. (13%) of red 2-aminophenazine. Recrystallization from methanol–water yielded red needles, m.p. 265–267°. Fischer and Hepp[11] reported a m.p. of 265°.

Reaction of 2,7-Dichlorophenazine-5-oxide with Aqueous Alcoholic Alkali.—A 0.500-g. sample of 2,7-dichlorophenazine-5-oxide was treated for 17 hours as described by Vivian.[2] The alkali-insoluble residue yielded 0.282 g. of yellow substance, m.p. 192–201°. Acidification of the mother liquor gave 0.212 g. of 2-chloro-7-hydroxyphenazine-5-oxide (II) which had the properties reported by Vivian[2] for 7-chloro-2-hydroxyphenazine-5(?)-oxide.

The alkali-insoluble residue was dissolved in benzene and chromatographed on alumina. A few mg. of pale yellow compound, m.p. 181°, rapidly passed through the column. This was followed by a fraction which yielded 2-chloro-7-ethoxyphenazine-5-oxide, m.p. 213–214° (dec.).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_2$: OEt, 16.40. Found: OEt, 16.70.

The final fraction yielded 2,7-diethoxyphenazine-5-oxide, m.p. 225° (dec.).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: OEt, 31.70. Found: OEt, 31.77.

Alkylations of 2-Chloro-7-hydroxyphenazine-5-oxide (II).—A solution of 0.100 g. of 2-chloro-7-hydroxyphenazine-5-oxide in 20 cc. of 10% sodium hydroxide was warmed to 70° and stirred with 3 cc. of methyl sulfate. When the reaction subsided, an additional 3 cc. of methyl sulfate and 10 cc. of 10% sodium hydroxide were added. The addition of methyl sulfate and sodium hydroxide was repeated three times until no further 2-chloro-7-methoxyphenazine-5-oxide separated. The filtered product was chromatographed to remove 5 mg. of readily eluted pale yellow substance, m.p. 152–154°, and traces of strongly adsorbed red material, and gave 0.066 g. (62%) of yellow needles of III, m.p. 207° (dec.). The product gave no depression of melting point upon admixture with 2-chloro-7-methoxyphenazine-5-oxide prepared by the reaction between *p*-chloronitrobenzene and *p*-anisidine, but upon admixture with 7-chloro-2-methoxyphenazine-5-oxide prepared by the reaction between *p*-nitroanisole and *p*-chloroaniline, the m.p. was depressed to 182–190°. The 7-chloro-2-methoxyphenazine-5-oxide also differed from the samples of 2-chloro-7-methoxyphenazine-5-oxide in that its solutions were not fluorescent.

Similar treatment of 2-chloro-7-hydroxyphenazine-5-oxide with ethyl sulfate converted it into 2-chloro-7-ethoxyphenazine-5-oxide (V); m.p. and m.p. on admixture with the compound from alcoholysis of 2,7-dichlorophenazine-5-oxide, 213–214° (dec.).

Alcoholysis and Hydrolysis of 1-Chlorophenazine-5-oxide.—A 0.500-g. sample of 1-chlorophenazine-5-oxide was refluxed for three days with 20 cc. of 95% ethanol, 13 cc. of water and 5 g. of potassium hydroxide. Concentration, addition of 30 cc. of water and cooling precipitated a product which was chromatographed to yield 0.090 g. (18%) of unreacted material and 0.373 g. (72%) of 1-ethoxyphenazine-5-oxide, fine yellow needles from methanol which soften near 180° and melt slowly and incompletely at 184–186°, then resolidify and melt sharply at 192°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: OEt, 18.75. Found: OEt, 18.77.

Upon neutralization, the deep blue-violet mother liquor became red and, after standing for a day, yielded several mg. of 1-hydroxyphenazine-5-oxide. Recrystallization from aqueous methanol yielded orange needles which became yellow when dried *in vacuo*, m.p. 190° (dec.).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.91; H, 3.80. Found: C, 67.72; H, 4.06.

After 24 hours under the conditions used for 2- and 3-chlorophenazine-5-oxide, only 20–30% of the starting material had reacted.

Reduction of 2-Chlorophenazine-5-oxide with Aniline.—To 2.00 g. of 2-chlorophenazine-5-oxide was added 20 cc. of aniline. The mixture was refluxed gently for three hours and the aniline removed with steam. The residue was dissolved in benzene and chromatographed to remove black aniline oxidation products. The eluate yielded 1.78 g. (96%) of 2-chlorophenazine, m.p. 138–139°. McCombie, Scarborough and Waters[12] previously reported a m.p. of 139° for this compound.

Reduction of 1-Chlorophenazine-5-oxide and Oxidation of 1-Chlorophenazine.—In the manner described for reduction of 2-chlorophenazine-5-oxide, 1-chlorophenazine-5-oxide was reduced to 1-chlorophenazine, m.p. 122–123°, in 88% yield. The orange chloroaurate derivative, m.p. 232–234° (dec.), was prepared. Wrede and Mühlroth[1] previously reported a m.p. of 122–123° for 1-chlorophenazine and *ca.* 232° (dec.) for the chloroaurate.

To 7.5 cc. of glacial acetic acid and 1 cc. of superoxol was added 0.240 g. of 1-chlorophenazine. The mixture was heated at 50° for 20 hours, diluted with 25 cc. of water and cooled. The yellow product which separated at this point was filtered and the filtrate was extracted with 20 cc. of benzene. The filtered product was dissolved in the benzene extract and, after drying over potassium carbonate, the benzene solution was chromatographed on alumina. The yellow eluate was evaporated and the residue was crystallized from methanol to give 0.222 g. (86%) of 1-chlorophenazine-5-oxide, m.p. 159–160°, which gave no depression of m.p. on admixture with a sample derived directly from the Wohl–Aue reaction. No band of dioxide separated during the chromatographic procedure.

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(11) O. Fischer and E. Hepp, *Ber.*, **22**, 355 (1889).

(12) H. McCombie, H. A. Scarborough and W. A. Waters, *J. Chem. Soc.*, 353 (1928).