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REACTIONS OF PHENANTHRAQUINONE AND RETENEQUINONE WITH AMINES UNDER PRESSURE

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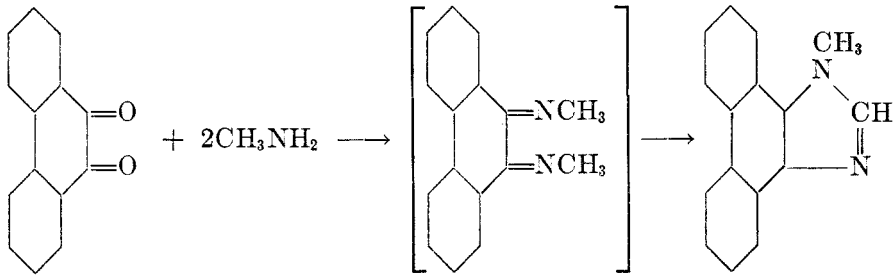
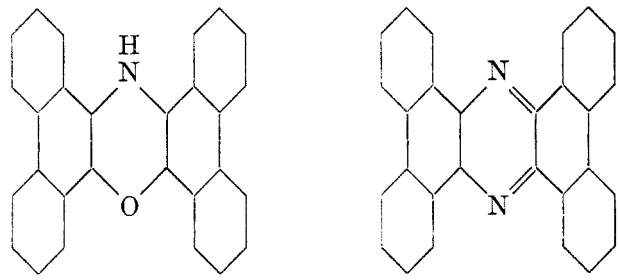
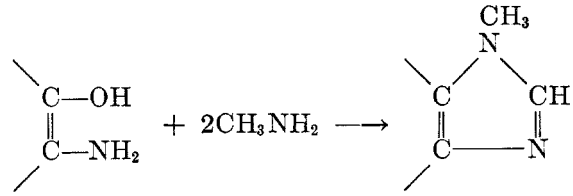
Zincke and Hof (1) first carried out a reaction between phenanthraquinone and methylamine under pressure, but were unable to formulate their products. Later Japp and Davidson (2) studied the same reaction and obtained 1-methylphenanthrimidazole.



However, when benzylamine was used, 2-phenylphenanthroxazole was isolated but no corresponding imidazole was found. In both cases, a mixture of the insoluble phenanthroxazine and phenanthrazine was reported.



Vahlen (3) prepared 1-methylphenanthrimidazole by the action of methylamine on 9,10-aminophenanthrol hydrochloride in the presence of sodium acetate and under pressure.



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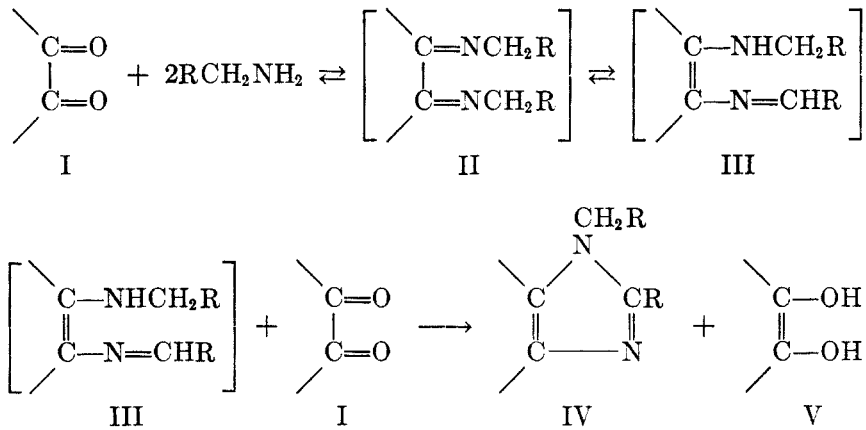
Pschorr (4) made a critical study of Vahlen's work and reported that the first stage of the reaction involved the splitting out of ammonia from the aminophenanthrol to form the hydroquinone. The latter then reacted with two equivalents of methylamine to form the imidazole. This does not appear to be a very logical explanation of the course of reaction.

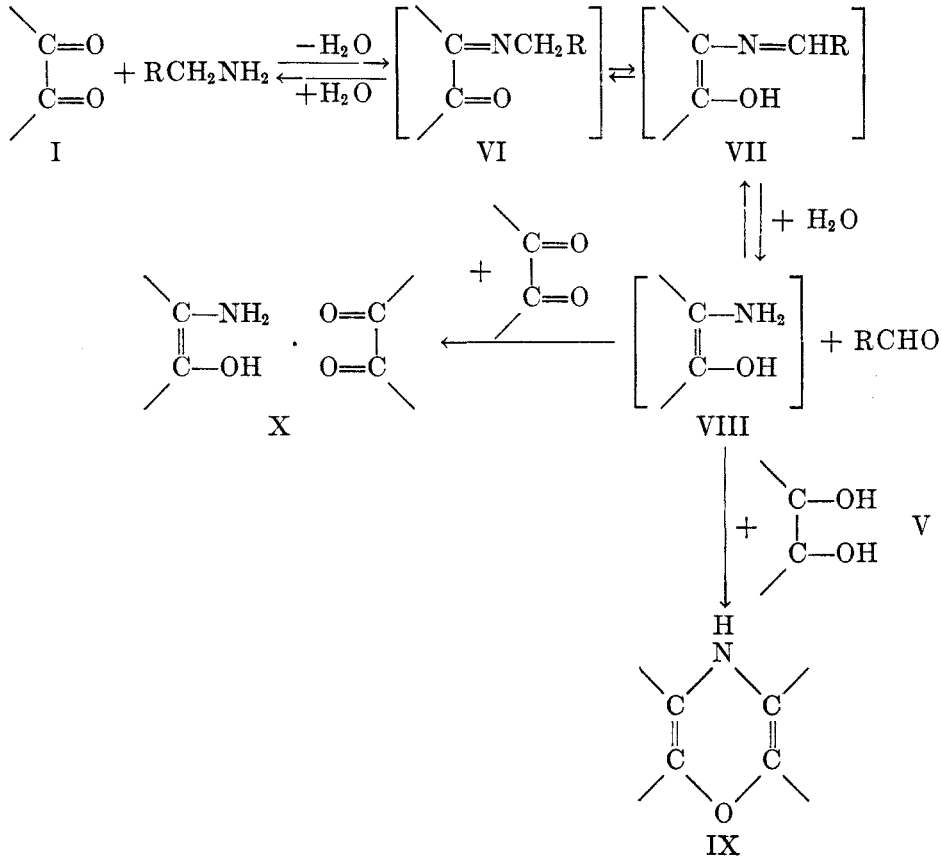
In view of the fact that it has been shown in this laboratory (5) that amines with two hydrogen atoms on the alpha carbon atom react with phenanthraquinone or retenequinone at atmospheric pressure to form the corresponding 2-substituted oxazoles, it appeared desirable to confirm and extend the findings of Japp and Davidson. This study was undertaken primarily to find some correlation between the variety of products formed and the course of reaction.

It has been found that the wholly aliphatic amines, methyl, ethyl, and *n*-butylamines gave similar results. Methylamine yielded 1-methylphenanthrimidazole, ethylamine gave 1-ethyl-2-methylphenanthrimidazole, and *n*-butylamine gave 1-butyl-2-*n*-propylphenanthrimidazole. These imidazoles were obtained in low yields due to the occurrence of side reactions. The imidazoles may be assumed to be formed by steps I–V:



The Schiff's base (III) could result from two hydrogen shifts in the two adjacent triad systems (6) of the N,N′-dialkylphenanthraquinone di-imine (II) formed by the interaction of phenanthraquinone (I) and two equivalents of the amine. The Schiff's base then undergoes an oxidative ring closure to the imidazole. This last step is similar to the reaction reported by Traube and Nithack (7). The latter workers used ferric chloride in the oxidative ring closure of 1,3-dimethyl-4-amino-5-benzalaminouracil to the corresponding imidazole.

Phenanthroxazine and a quinhydrone type of compound, involving 9,10-aminophenanthrol and phenanthraquinone, were isolated from all of the runs using aliphatic amines. These products may be assumed to result from the series of reactions, following.



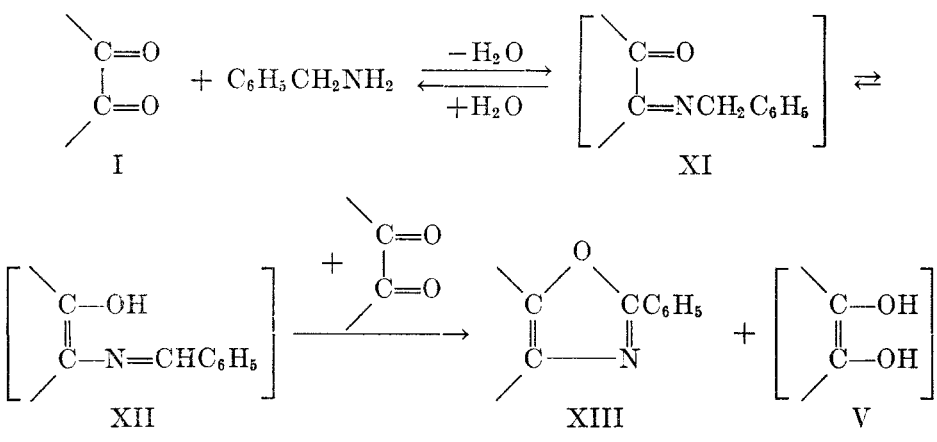
The formation of phenanthroxazine and the quinhydrone type of compound may be explained by the fact that the N-alkylphenanthraquinonimine (VI), the product of phenanthraquinone and one equivalent of amine, rearranges in part to the Schiff's base (VII) before the second equivalent of amine reacts with the other carbonyl group. Subsequent hydrolysis of the Schiff's base would yield 9,10-aminophenanthrol (VIII) and the latter could react with phenanthrahydroquinone (V) to form the oxazine (IX) or with phenanthraquinone (I) to form the quinhydrone compound (X).

In addition to the above reaction products, there was formed in every case a brown, difficultly soluble, amorphous compound which melted above 360°. De and Ghosh (8) reported phenanthroxazole and 2-methylphenanthroxazole to be brown, high-melting, insoluble, amorphous solids. They prepared them from the interaction of 9,10-aminophenanthrol with formic acid and acetic acid respectively. The nitrogen values for the brown compounds obtained in the present work agreed with those calculated for the corresponding 2-alkylphenanthroxazole, but the carbon and hydrogen values did not agree. It is very doubt-

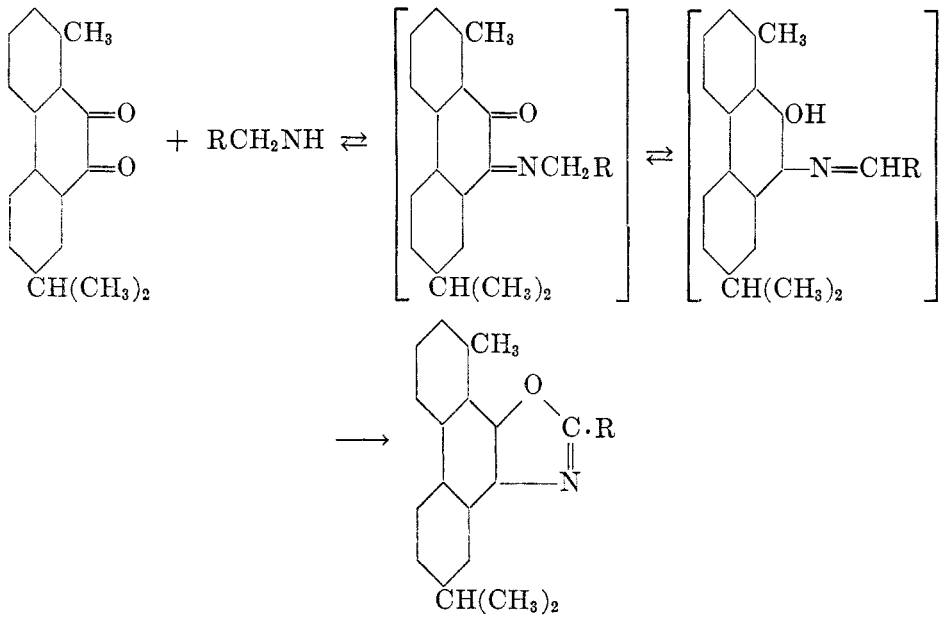
ful that the compounds reported by De and Ghosh were oxazoles, for one would expect 2-alkylphenanthroxazoles to be colorless, crystalline, low-melting solids. 2-*n*-Propylphenanthroxazole has been prepared by Stein and Day (9) and obtained as colorless needles, melting at 84–86°. This product was soluble in most organic solvents. These properties are quite different from those reported by De and Ghosh. It is not possible to assign formulas to these derivatives at the present time.

It may be noted at this point that no phenanthrazine was isolated from any of the experiments. This is contrary to the work of Japp and Davidson and it may be that the formation of the azine in their work was due to the presence of ammonia as an impurity in the amines used. This supposition is based on the work of Bamberger and Grob (10) and Foresti (11) who reported the formation of the azine by the action of ammonia on the corresponding oxazine.

The behavior of benzylamine with phenanthraquinone differed from that of the wholly aliphatic amines, for 2-phenylphenanthroxazole (XIII) was formed but no corresponding imidazole. The formation of the oxazole probably follows the same course of reaction as that suggested first by McCoy and Day (5):



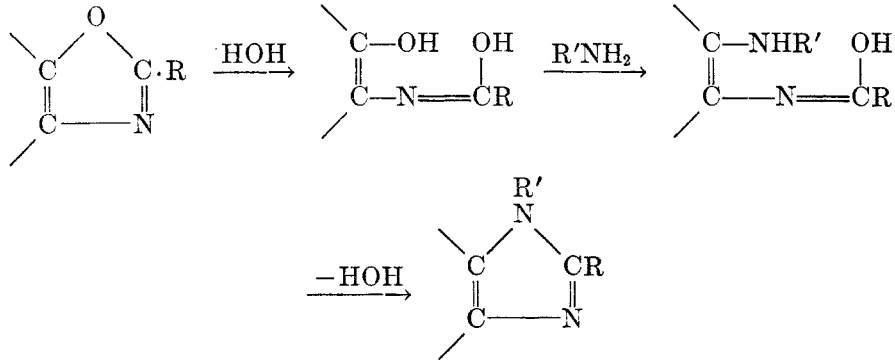
Apparently in this reaction there is a more rapid shift of the methylene hydrogen in XI due to the activating influence of the phenyl group, thus preventing the reaction between the second molecule of amine and the other carbonyl group. As a result, compound XII is rapidly oxidized to the oxazole by the phenanthraquinone. In these runs the second equivalent of amine was recovered almost quantitatively from the reaction mixtures. Phenanthroxazine (IX) and the quinhydrone (X) type of compound were also formed in this reaction. A course of reaction explaining the formation of these two products was suggested earlier in the paper. Evidence for this mechanism was obtained by the isolation and identification of benzaldehyde from the reaction mixture.



When retenequinone was used in place of the phenanthraquinone somewhat different results were obtained. Reactions were carried out under pressure using the same five amines but in no case could any imidazole be isolated, only oxazoles being obtained.

These results indicate steric hindrance in the retene molecule. This effect may be caused by the proximity of the methyl group to the 9 and 10 positions, which prevents a second molecule of the amine from reacting with the second carbonyl group. This hindrance is also indicated by the non-formation of retenoxazine and the corresponding quinhydrone type of compound.

The fact that the wholly aliphatic amines yield imidazoles with phenanthraquinone under pressure, but give only the corresponding oxazoles at atmospheric pressure (5), suggested another course of reaction for imidazole formation. For example, the oxazole may be formed first and then undergo an aminolysis, at the temperature and pressure used, to form the imidazoles.



Hence it became necessary to eliminate this possibility in order to establish the validity of the course of reaction previously suggested.

The investigations of Sircar and his associates (12) indicated that the course of the reaction with phenanthraquinone or acenaphthoquinone, aromatic aldehydes, and ammonia depended primarily on the temperature at which the reactions were carried out. At higher temperatures, imidazole formations usually predominated and at lower temperatures, oxazole formation predominated. The assumption that oxazoles were formed first and imidazoles resulted from the ammonolysis of the oxazoles, however, was not experimentally demonstrated by these workers.

The assumption that imidazoles may be formed through the ammonolysis of oxazoles was tested by Kreps and Day (13). They subjected 2-phenylretenoxazole and concentrated aqueous ammonia to a temperature of 170–180° and a pressure of five hundred pounds for forty-nine hours, but observed no conversion to the corresponding imidazole. Similar results were obtained with 2-(2′-hydroxyphenyl)retenoxazole. However, this work can not be assumed to apply to the unsubstituted phenanthrene series, for it has been shown in the course of the present work that where phenanthraquinone reacted to form 1,2-disubstituted phenanthrimidazoles, retenequinone formed only oxazoles. Consequently, if oxazoles can be converted into imidazoles it would not be expected in the retene series, because of a probable steric hindrance effect which prevents the formation of imidazoles.

Similar results were obtained in the present study when attempts were made to convert 2-phenylphenanthroxazole and 2-(2′-hydroxyphenyl)phenanthroxazole to imidazoles. The oxazoles were treated with ammonia or methylamine, under various conditions of temperature and pressure, but no conversion to imidazole was noted. Even the addition of sodium hydroxide to these mixtures failed to cleave the oxazole ring. It would appear, therefore, that oxazoles can not be regarded as intermediates in the formation of imidazoles, in the phenanthrene and retene series. This conclusion can not be applied to benzoxazoles and naphthoxazoles, for there is evidence (14) that the oxazole ring in these compounds may be readily cleaved.

EXPERIMENTAL

Analysis and melting points. The semi-micro Kjeldahl method was used for the nitrogen determinations and the semi-micro combustion method was used for carbon and hydrogen. The recorded melting points are corrected values.

Molecular weights. The Rast method of determining molecular weights by the depression of the m.p. of *d*-camphor, triphenylmethane, or naphthalene was used according to the directions of Shriner and Fuson (15).

Phenanthraquinone. It was prepared by the chromic acid oxidation of phenanthrene (technical grade) in glacial acetic acid (16). The crude product was purified by the bisulfite method of Courtot (17) and finally recrystallized from 50% acetic acid, yield 60%, m.p. 208–209.5°.

Retenequinone. Retenequinone was prepared by the method of Kreps and Day (13). It was recrystallized from chloroform, yield 50%, m.p. 197–199°.

Reactions of phenanthraquinone with amines. Preliminary work showed that where these reactions were carried out at temperatures higher than 100°, the imidazoles were formed in lower yields, and larger amounts of intractable gums were obtained.

I. With methylamine. Eight grams (0.0385 mole) of phenanthraquinone, 3.1 g. (0.1 mole) of methylamine and 25 cc. of benzene were heated under pressure for 6 hours at 100°. The reaction mixture was extracted with hot benzene, leaving 0.30 g. of a brown solid. The latter on recrystallization from nitrobenzene gave green, micro crystals of phenanthroxazine, m.p. above 360°.

Anal. Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.86.

The benzene extract was evaporated and the residue extracted with hydrochloric acid. The brown, gummy solid, left after the acid extraction, was washed thoroughly with alcohol and refluxed with ethyl acetate. The hot mixture was filtered to remove a small amount of brown powder. The addition of alcohol to the filtrate precipitated 0.5 g. of yellow, micro crystals of the quinhydrone type of compound, formed from 9,10-aminophenanthrol and phenanthraquinone. The product melts with decomposition over a wide range, 150–214°. On oxidation with chromic acid, phenanthraquinone was obtained as the sole product.

Anal. Calc'd for $C_{28}H_{19}NO_3$: C, 80.57; H, 4.55; N, 3.36, Mol. wt., 417.
Found: C, 80.82; H, 4.74; N, 3.53, Mol. wt., 407.

The brown residue remaining after the ethyl acetate extraction could not be identified. The analytical values for carbon, hydrogen, and nitrogen did not agree with any probable formula.

The hydrochloric acid extract, from above, on neutralization with sodium bicarbonate yielded 5.65 g. (63%) of crude 1-methylphenanthrimidazole. It was recrystallized from alcohol with the aid of Darco, m.p. 196°, picrate m.p. 288–289°.

Anal. Calc'd for $C_{16}H_{12}N_2$: N, 12.07. Found: N, 11.87.

II. With ethylamine. A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 2.93 g. (0.065 mole) of ethylamine, and 33.5 g. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was worked up by the method described under methylamine. The following products were isolated: phenanthroxazine, m.p. above 360° (*Anal.* Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.82); quinhydrone type compound (*Anal.* Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: N, 3.28); and a 5.4% yield of 1-ethyl-2-methylphenanthrimidazole. The latter was purified by recrystallization from alcohol, with the aid of Darco, m.p. 193.5–194.5°, picrate m.p. 222–242° (decomp.).

Anal. Calc'd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.77.
Found: C, 82.70; H, 6.13; N, 10.72.

III. With n-butylamine. A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 4.95 g. (0.065 mole) of *n*-butylamine and 35 cc. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was worked up by the procedure described previously and the following products isolated: phenanthroxazine (0.31 g.); quinhydrone type compound 0.11 g. (*Anal.* Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: 3.25); and a 2% yield of 1-*n*-butyl-2-*n*-propylphenanthrimidazole. The latter was recrystallized from alcohol, with the aid of Darco, m.p. 59–62°, picrate m.p. 199–200°.

Anal. Calc'd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.68.
Found: C, 83.33; H, 7.75; N, 8.67.

IV. With benzylamine. A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 6.42 g. (0.06 mole) of benzylamine and 25 cc. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was extracted with boiling benzene, leaving 2 g. of a dark yellow powder, consisting of a mixture of phenanthroxazine and the quinhydrone type compound. The quinhydrone was removed by extraction with dioxane, and the residue on recrystallization from nitrobenzene yielded 1.25 g. of the oxazine, m.p. above 360°.

Anal. Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.96.

The dioxane extract was concentrated and a little alcohol added to precipitate the yellow, micro crystals of the quinhydrone type compound, yield 0.5 g., m.p. 150–192° (decomp.).

Anal. Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: 3.11.

The benzene extract from above was evaporated until crystals of 2-phenylphenanthroxazole began to separate. After cooling, the crude oxazole was removed by filtration, yield 4.5 g. (51%). It was purified by recrystallization from a mixture of dry alcohol and benzene (3:1), with the aid of Darco, m.p. 206.5–207°. The pure product gave no depression in a mixed melting point determination with an authentic sample.

The benzene filtrate from the oxazole was evaporated to dryness and the gummy residue extracted with hydrochloric acid. The acid extract on evaporation yielded only benzylamine hydrochloride. The residue from the acid extraction was dissolved in alcohol and treated with semicarbazide hydrochloride and sodium acetate. The precipitate obtained from this reaction proved to be benzaldehyde semicarbazone, m.p. 217–218°.

Reactions of retenequinone with amines. I. With methylamine. A mixture of 2.64 g. (0.01 mole) of retenequinone, 0.80 g. (0.026 mole) of methylamine and 35 cc. of benzene was heated under pressure at 100° for 3 hours. The reaction mixture was extracted with hot benzene and filtered to remove a trace of a gummy solid. The benzene extract was evaporated to dryness and the residue extracted with methyl alcohol. Evaporation of the alcohol gave 0.92 g. (33% yield) of 2-methylretenoxazole. It was recrystallized from methyl alcohol with the aid of Darco, colorless needles, m.p. 108°. No imidazole could be isolated.

Anal. Calc'd for $C_{19}H_{17}NO$: C, 82.95; H, 6.23; N, 5.09.
Found: C, 82.78; H, 6.37; N, 4.91.

II. With ethylamine. The above procedure, using ethylamine in place of methylamine, gave 2.15 g. (74.5% yield) of 2-ethylretenoxazole. The crude product was recrystallized from ethyl alcohol, with the aid of Darco, colorless needles, m.p. 127.5–128.5°.

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.08; H, 6.63; N, 4.82.
Found: C, 82.87; H, 6.73; N, 4.88.

III. With n-*butylamine.* The above procedure, using *n*-butylamine in place of methylamine, gave 2.1 g. (66% yield) of 2-propylretenoxazole. It was recrystallized from ethyl alcohol with the aid of Darco, m.p. 100–101.5°. This value agrees with the m.p. reported by Stein and Day (9). A mixed m.p. determination gave no depression.

IV. With benzylamine. Five grams (0.019 mole) of retenequinone, 4.10 g. (0.038 mole) of benzylamine, and 15 cc. of dry alcohol were heated at 100° for 6 hours under pressure. The reaction mixture was digested with dry alcohol and filtered. Concentration of the filtrate yielded 2.66 g. (40%) of 2-phenylretenoxazole. It was recrystallized from ethyl alcohol, m.p. 172°. The m.p. agrees with the value reported by Kreps and Day (13).

Attempts to convert phenanthroxazoles to phenanthrimidazoles by aminolysis. I. 2-Phenylphenanthroxazole. (a) In boiling p-*cymene.* One gram of the oxazole was dissolved in *p*-cymene and ammonia passed through the refluxing solution for 4 hours. Evaporation of the solution gave a quantitative recovery of the starting compound, m.p. 206.5–207°.

(*b*) *In the presence of sodium hydroxide.* A solution containing 1.48 g. of 2-phenylphenanthroxazole and 0.25 g. of sodium hydroxide in 100 cc. of alcohol was refluxed for 7 hours while ammonia was passed through the solution. Evaporation of the solution gave a quantitative recovery of the oxazole, m.p. 206.5–207°.

(*c*) *With methylamine under pressure.* Two grams (0.00678 mole) of 2-phenylphenanthroxazole, 0.25 g. (0.00807 mole) of methylamine, and 30 cc. of absolute alcohol were heated at 100° for 6 hours under pressure. The starting material was recovered almost quantitatively, m.p. 205–206°.

II. 2-(2′-Hydroxyphenyl)phenanthroxazole. This compound was prepared by the method of Stein and Day (9). It was recrystallized from pyridine, m.p. 243–243.5°. (*a*) *In alcoholic solution.* A sample (0.50 g.) of 2-(2′-hydroxyphenyl)phenanthroxazole was refluxed in 100 cc. of dry alcohol for 2.5 hours while ammonia was passed through the suspension. On cooling, the starting material was recovered quantitatively, m.p. 243–243.5°.

(*b*) *In the presence of sodium hydroxide.* A solution of 0.50 g. (0.00161 mole) of 2-(2′-hydroxyphenyl)phenanthroxazole and 0.13 g. (0.00322 mole) of sodium hydroxide in 100 cc. of alcohol and 10 cc. of water was refluxed for 4 hours while ammonia was passed through the

solution. Neutralization of the solution with dilute hydrochloric acid yielded 0.48 g. of the starting oxazole, m.p. 243–243.5°.

(*c*) *With ammonium hydroxide under pressure.* A mixture of 0.78 g. of 2-(2′-hydroxyphenyl)phenanthroxazole and 25 cc. of concentrated ammonium hydroxide was heated at 100° for 5 hours under a pressure of 130 lbs. At the end of this period, the solid was washed with water and recrystallized from pyridine, m.p. 243–243.5°. The recovery of starting material was quantitative.

A similar run was carried out at 200° and 550 lbs. pressure. Some oxazole was recovered together with decomposition products, but no conversion to imidazole was noted.

SUMMARY

1. The interaction of primary amines with phenanthraquinone under pressure has been studied. The wholly aliphatic amines gave 1,2-disubstituted phenanthrimidazoles, whereas benzylamine yielded only 2-phenylphenanthroxazole. By-products of each reaction were phenanthroxazine and a quinhydrone type compound of 9,10-aminophenanthrol and phenanthraquinone. A mechanism has been postulated for the formation of these compounds.

2. The reaction of retenequinone and primary amines under pressure has been studied. The only product isolated in each case was the corresponding 2-substituted retenoxazole.

3. 2-Arylphenanthroxazoles were subjected to aminolysis and simultaneous hydrolysis and aminolysis. No conversion to imidazole was obtained, thus eliminating the possibility of intermediate oxazole formation in the preparation of imidazoles.

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