oxazole removed by filtration. It was recrystallized from dioxane and water; yield 7.4 g.; m. p. 175–176°. The yield based on three moles of oxazole per mole of hydrobenzamide was 92.5%.

Reaction of Phenanthraquinonimine with Benzalbispiperidine.—One gram (0.0048 mole) of phenanthraquinonimine and 1.24 g. (0.0048 mole) of benzalbispiperidine were dissolved in 30 cc. of hot, dry alcohol and refluxed for fifteen minutes. After cooling, the 2-phenylphenanthroxazole was removed by filtration; yield 1.37 g. (98%); m. p. 205–206°. A mixed melting point determination with a sample prepared by Stein and Day[3] showed no depression.

Reaction of Phenanthraquinonimine with Methylenebismorpholine.—Two grams (0.0097 mole) of the quinonimine and 1.8 g. (0.0097 mole) of methylenebismorpholine were dissolved in 30 cc. of hot dry alcohol and refluxed for one hour. After dilution with water and cooling, the precipitate was removed and recrystallized from alcohol and water; yield 1.5 g. (51%); m. p. 178–179°. Analysis indicated this compound to be 2-morpholinophenanthroxazole.

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.99; H, 5.30; N, 9.22. Found: C, 75.08; H, 5.46; N, 9.16.

Reaction of Phenanthraquinonimine with Hydrobenzamide.—This reaction was carried out in the manner described for the corresponding reaction with retenequinonimine. The crude 2-phenylphenanthroxazole was recrystallized from alcohol; yield, 86%; m. p. 206–207°. A mixed melting point determination with an authentic sample showed no depression.

Summary

1. It has been shown that retenequinonimine and phenanthraquinonimine react with alkylidenebisamines as well as hydrobenzamide to yield the corresponding retenoxazoles or phenanthroxazoles.

2. The probable mechanisms for these reactions have been formulated.

PHILADELPHIA, PA. RECEIVED MAY 27, 1943

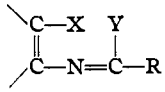
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Ortho Condensations which Lead to Oxazole or Imidazole Formation

BY GEORGE MCCOY[1] AND ALLAN R. DAY

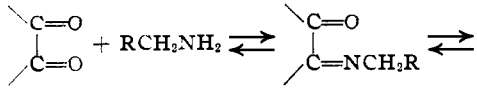
A comprehensive study of the reactions of ortho quinones and ortho quinonimines, which result in the formation of oxazoles and imidazoles, has been carried out in this Laboratory during the past few years. Retenequinone, phenanthraquinone and the corresponding quinonimines were used as examples of ortho quinones and quinonimines. These compounds are much more stable than the corresponding derivatives in the benzene or naphthalene series and are more readily available.

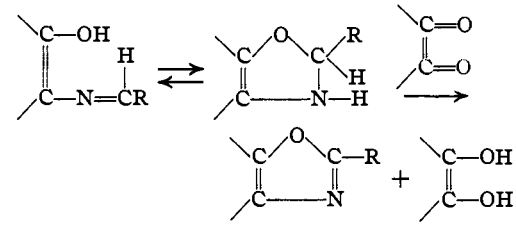
At the conclusion of this work, it was realized that it is possible to represent many if not all ortho condensations which lead to oxazole or imidazole formation by a common intermediate. Whether oxazole or imidazole results is determined by the nature of the groups X and Y



This may clearly be seen from a consideration of the following examples.

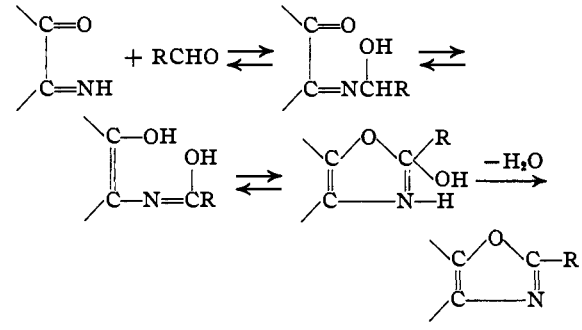
Oxazole Formation. 1. X = OH, Y = H.—It has been shown by McCoy and Day[2] that the interaction of retene- or phenanthraquinone with a primary amine gives this intermediate with the subsequent formation of a 2-substituted oxazole.





This same intermediate is formed in the reaction of aldehydes with *o*-aminophenols. For example, 9, 10-aminophenanthrol reacts rapidly with aldehydes to form 2-substituted phenanthroxazoles.[2]

2. X = OH, Y = OH.—Stein and Day[3] have shown that the interaction of retene- or phenanthraquinonimine with an aldehyde probably proceeds through this intermediate to give 2-substituted oxazoles.



Ladenburg[4] prepared 2-alkylbenzoxazoles from *o*-aminophenol and aliphatic acids and acid anhy-

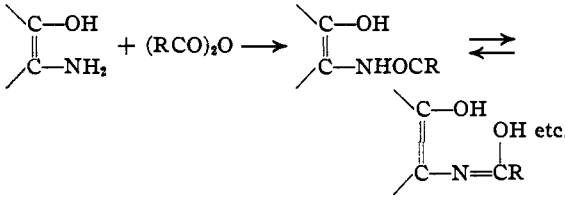
(1) Present address: University of Pennsylvania, Philadelphia, Pa.

(2) McCoy and Day, THIS JOURNAL, **65**, 1956 (1943).

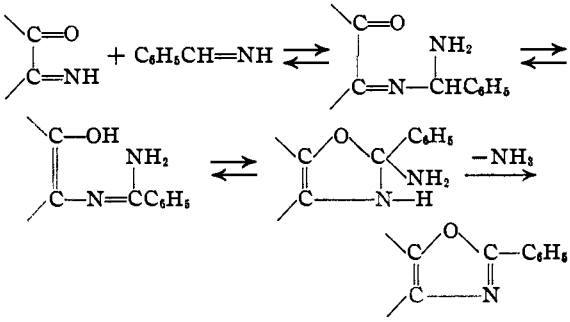
(3) Stein and Day, *ibid.*, **64**, 2567, 2569 (1942).

(4) Ladenburg, *Ber.*, **10**, 1124 (1877).

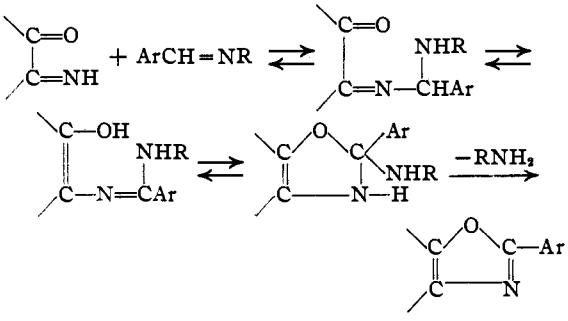
drides. He postulated no intermediates, but the above intermediate could be logically assumed.



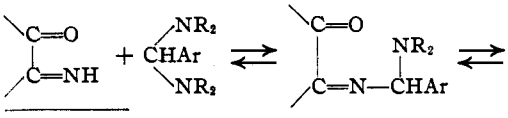
3. X = OH, Y = NH_2.—When retenequinonimine and benzaldimine hydrochloride are dissolved in dry alcohol containing one equivalent of ammonia and refluxed for thirty minutes, an almost quantitative yield of 2-phenylretenoxazole is obtained.[5] Due to the ease with which benzaldimine is converted into hydrobenzamide, it is difficult to say whether the initial aldol-type addition occurs with the aldimine or the hydrobenzamide. The reaction may occur wholly or in part, as



4. X = OH, Y = NHR.—The interaction of retenequinonimine or phenanthraquinonimine and Schiff bases produces 2-substituted oxazoles.[3] It is quite probable that the reaction proceeds through the above type of intermediate.

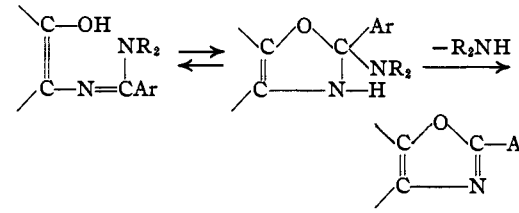


5. C = OH, Y = NR_2.—The formation of 2-substituted oxazoles through the reaction of retenequinonimine or phenanthraquinonimine with alkylidenebisamines has been established by McCoy and Day.[6] Here again the same type of intermediate is undoubtedly formed.

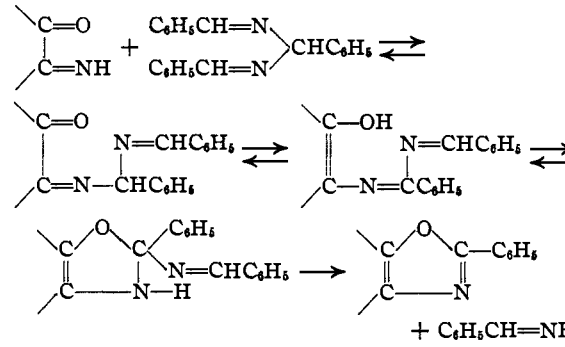


(5) McCoy and Day, unpublished work.

(6) McCoy and Day, THIS JOURNAL, **65**, 2157 (1943).

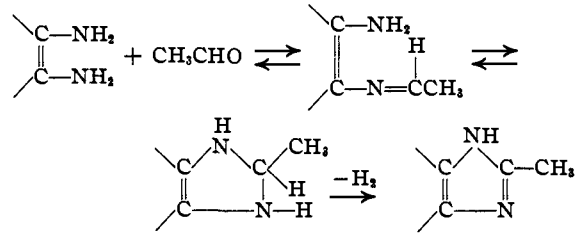


6. X = OH, Y = N = CHAr.—The formation of 2-substituted oxazoles from retenequinonimine or phenanthraquinonimine and hydrobenzamide probably proceeds through such an intermediate.[6]

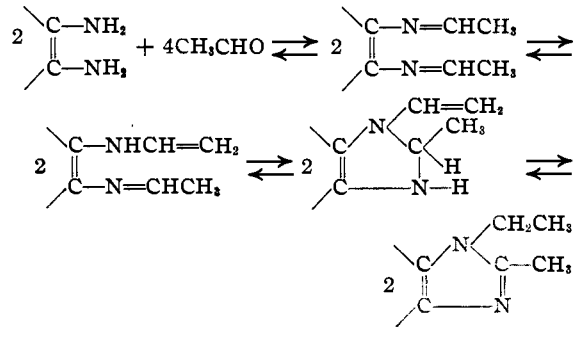


For oxazole formation X must be OH, but Y may be H, OH, NH_2, NHR, NR_2, N=CHAr or related groups.

7. **Imidazole Formation, X = NH_2, Y = H.**—The reaction of *o*-phenylenediamine with acetaldehyde to form 1-ethyl-2-methylbenzimidazole and some 2-methylbenzimidazole[7] may be explained by a similar mechanism.



The formation of 1-ethyl-2-methylbenzimidazole is more complex. However, a somewhat similar mechanism may be written for its formation.

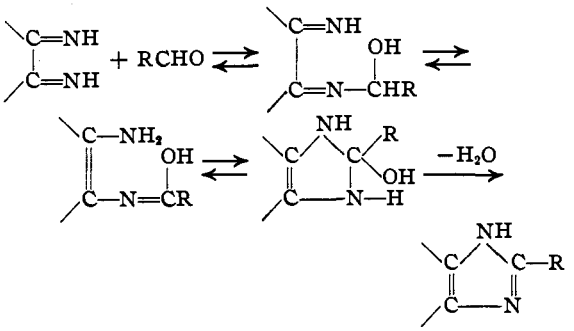


In this case the vinyl side chain may act as the

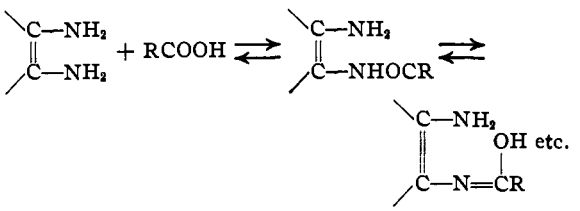
(7) Hinsberg and Funcke, *Ber.*, **27**, 2187 (1894).

hydrogen acceptor necessary for the conversion of the dihydroimidazole to the imidazole.

8. X = NH_2, Y = OH.—Steck and Day[8] prepared 2-substituted phenanthrimidazoles from phenanthraquinone di-imine and aldehydes. Here again the above type of intermediate is indicated.

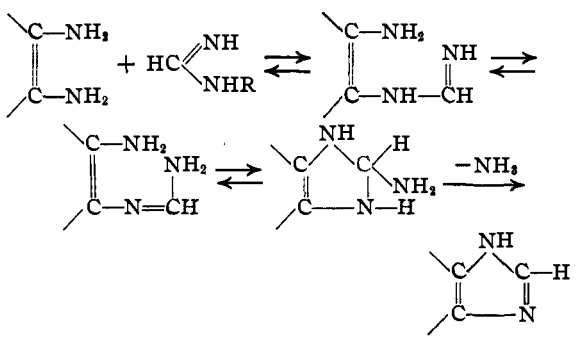


Phillips[9] obtained 2-substituted benzimidazoles from *o*-phenylenediamine and aliphatic acids. Other work[10] has shown that this reaction proceeds through the formation of the monoacyl derivatives. Once more the above type of intermediate may be logically assumed.

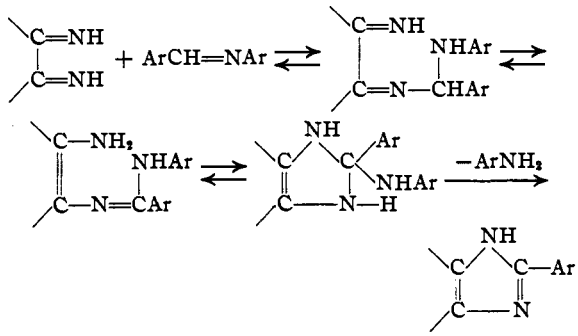


Esters, amides and other acid derivatives have also been used in place of the carboxylic acids.

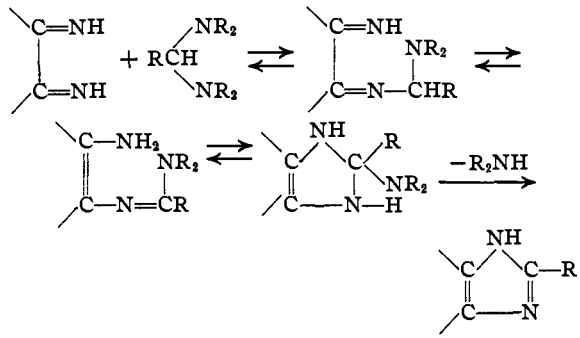
9. X = NH_2, Y = NH_2.—Dains[11] prepared benzimidazole from *o*-phenylenediamine and a formamidine. He postulated no intermediate, but the type suggested above appears quite probable.



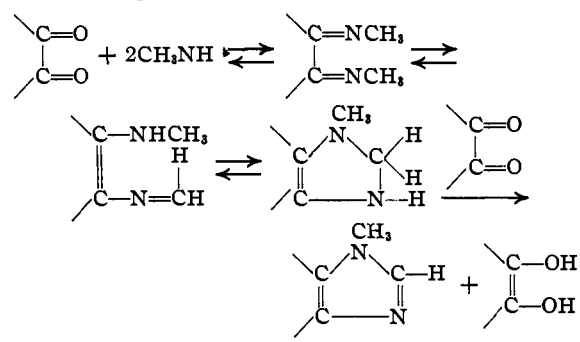
10. X = NH_2, Y = NHR.—The reaction of phenanthraquinone di-imine with a Schiff base has been shown recently[12] to yield a 2-substituted phenanthrimidazole.



11. X = NH_2, Y = NR_2.—There are no examples known at present. Since a similar intermediate produced oxazoles,[6] the following may be predicted



12. X = NHR, Y = H.—The reaction of phenanthraquinone with methylamine under pressure to form 1-methylphenanthrimidazole, which was investigated by Jaffe and Day,[13] must proceed through a similar intermediate.



For imidazole formation X must be NH_2 or NHR and Y may be OH, NH_2, NHR, NR_2, H or related groups.

It will be noted that all of these reactions have one thing in common, namely, the addition of OH, NH_2 or RNH across a Schiff base linkage. Such an addition is not surprising for it is a well established fact that active hydrogen compounds readily add to Schiff bases under suitable conditions.[14] In general, the final step in the formation of an oxazole or imidazole involves the splitting out of

(8) Steck and Day, THIS JOURNAL, **65**, 452 (1943).

(9) Phillips, *J. Chem. Soc.*, 2393 (1928).

(10) Roeder and Day, *J. Org. Chem.*, **6**, 25 (1941); Green and Day, THIS JOURNAL, **64**, 1167 (1942).

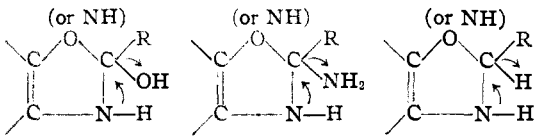
(11) Dains, *Ber.*, **35**, 2496 (1902).

(12) Hassler and Day, unpublished work.

(13) Jaffe and Day, *J. Org. Chem.*, **8**, 43 (1943).

(14) Knoevenagel, *Ber.*, **31**, 2596 (1898); Mayer, *Bull. Soc. Chim.*, **33**, 157, 395, 498 (1905).

water, ammonia, some derivative of ammonia, or hydrogen. This may be shown as



Such cleavages would be facilitated by the presence of acids or bases and the reactions noted 1 to 12 are actually carried out under the influence of acids or bases.

The splitting out of hydrogen presents a more complicated situation. In the examples given above, where hydrogen is eliminated, it is believed that a so-called hydrogen acceptor must be present to aid in the elimination of hydrogen. In one case (reaction 1) the hydrogen acceptor has been shown to be a quinone and a mechanism has been proposed to account for the reaction.[2] In the other cases mentioned, suitable hydrogen acceptors were present and so similar mechanisms may be assumed for them.

Summary

1. It has been shown that *ortho* condensations leading to oxazole or imidazole formation may be represented by a common intermediate. The ring closure of the intermediate involves the addition of OH, NH_2 or RNH across a Schiff base linkage, —N=C—, with subsequent aromatization of the resulting dihydroöxazole or dihydroimidazole to the corresponding oxazole or imidazole.

PHILADELPHIA, PA. RECEIVED MAY 27, 1943

[CONTRIBUTION FROM THE MOSCOW TEXTILE INSTITUTE, THE ALL-UNION INSTITUTE OF EXPERIMENTAL MEDICINE]

Studies in the Vitamin K Group. I. Synthesis of Potassium 2-Methyl-1,4-naphthoquinone-3-sulfonate[1]

BY D. A. BOCHVAR, L. A. SCHUKINA, A. S. CHERNYSHEV, N. G. SEMENOV AND M. M. SHEMIAKIN

Since the discovery of the high antihemorrhagic activity of 2-methyl-1,4-naphthoquinone (I), exceeding that of the naturally occurring vitamins K_1 and K_2, considerable interest has been drawn to the compounds of the 1,4-naphthoquinone series and to kindred substances. The relationship between structure and antihemorrhagic activity of these compounds has been studied in many laboratories, and the results have established that certain groupings are essential for antihemorrhagic action.[2]

One of the most serious disadvantages of both natural K_1 and K_2 vitamins and of most of their biologically active synthetic analogs (including 2-methyl-1,4-naphthoquinone) is their insolubility in water, which not only limits their application in medicine, but greatly prolongs the onset of the maximum antihemorrhagic effect within the organism (eventually up to one and one-half to two days in the case of 2-methyl-1,4-naphthoquinone). Hence, numerous attempts have been made to obtain highly active water-soluble analogs of vitamins K_1 and K_2.[2]

In connection with a study of water soluble antihemorrhagic agents in the Laboratory headed by one of the authors (M. M. S.), the potassium salt of 2-methyl-1,4-naphthoquinone-3-sulfonate, V, was prepared at the beginning of 1941 by K. G. Packendorf and E. N. Lazareva. As the antihemorrhagic activity of this compound was found to be only slightly less than 2-methyl-1,4-naphthoquinone,[3] its preparation and properties seemed worthy of greater study.

The compound was first synthesized by a method resembling that developed by Fieser and Fieser[4] for converting 1,4-naphthoquinone to potassium 1,4-naphthoquinone-2-sulfonate in 80% yield which consists of treatment of the quinone with sodium bisulfite followed by oxidation with potassium dichromate. This procedure, however, was not suited to 2-methyl-1,4-naphthoquinone; our yields under similar conditions of sulfonation and oxidation did not exceed 9%. It was found that the yield depends not on the conditions of oxidation but rather on the manner in which the sulfonation of the quinone is carried out.

This investigation was interrupted in the autumn of 1941 and was resumed in the beginning of 1942. In the meantime, Moore[5] reported the

(1) The original versions of the manuscript of this article and of the following article, "Studies in the Vitamin K Group. II. The Mechanism of Biological Action of Vitamin K and of its Synthetic Analogs," by Shemiakin, Schukina and Shvezov, were received from the Soviet Embassy in Washington for publication in the JOURNAL. While their subject matter for the most part was acceptable for publication, a revision of the presentation to meet the requirements of the JOURNAL was necessary, and, in view of the inaccessibility of the authors, this revision was made at our request by an expert familiar with this special field, for whose assistance we are very grateful. With minor exceptions the revision involved only alterations in form and deletions. The revised manuscripts, therefore, with the approval of the Soviet Embassy, are being published without submission to the authors.—*The Editor.*

(2) For a complete bibliography, *cf.* L. F. Fieser, M. Tishler and W. L. Sampson, *J. Biol. Chem.*, **137**, 659 (1941).

(3) B. A. Kudriashev, *Bull. Exptl. Biol. Med.*, 510 (1941) (Russ.) Sov. Zdravookhranenie Turkmenii No. 1 (1942) (Russ.). It is of interest to note that the biological action of this derivative sets in more promptly than 2-methyl-1,4-naphthoquinone although its duration is shorter.

(4) L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 491 (1935).

(5) M. B. Moore, *ibid.*, **63**, 2049 (1941).