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FURANIC AND RELATED HETEROCYCLIC DYES
AND COLORED MOLECULES

BY

Marian Weston VanEss

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for the degree of

DOCTOR OF PHILOSOPHY

Major Subject Organic Chemistry

Approved

Signature was redacted for privacy.

In charge of Major work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College

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INTRODUCTION

The formation of highly colored products has been observed in the interaction of aniline (or other amines) and a variety of furan compounds; yet, with the exception of the reactions involving furfural and very closely related types, the chemistry of these transformations is practically unknown.

In a study of 5-nitro-2-furoic acid by Hill and White (1), a curious spontaneous decomposition of the aniline salt of this acid was observed. Even at ordinary temperatures, the aqueous solution of the salt deposited brownish flocks. The addition of more aniline, or better, aniline acetate, accelerated the reaction and a voluminous red precipitate formed with the evolution of carbon dioxide gas. The same product was more conveniently prepared by the action of slightly more than two molecular equivalents of aniline hydrochloride on an aqueous sodium acetate solution of the nitrofuroic acid. This red precipitate on closer examination proved to be two substances; the main portion, a yellow compound, and the smaller fraction, a brilliant red product. A similar pair of substances were obtained by substituting p-toluidine for aniline in the above reaction. All of these colored bodies were analysed; the yellow compound obtained in the aniline run was reduced and the products identified; but no structures were postulated for any of the colored compounds.

(1) Hill and White, Am. Chem. J., 27, 193 (1902).

A further examination of the reaction involving aniline was chosen for this study, since it might furnish a new method for determining the orientation in substituted furans by conversion to known compounds, and also to discover more facts concerning the manner in which the furan ring is opened by amines.

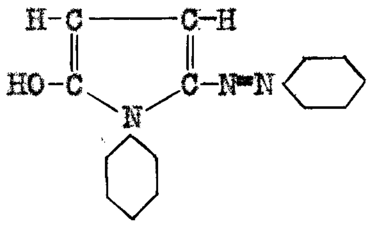
Constitution of the yellow compound.

Approximately 80% of the precipitate deposited in the reaction of aniline and 5-nitro-2-furoic acid was found by Hill and White to be the yellow compound, $C_{16}H_{12}N_2O$, which melted with decomposition at 232° when rapidly heated. They reported that the compound was not sensitive to aqueous acid or alkali, but with alcoholic sodium or potassium hydroxide formed an intense carmine red solution, from which the material was precipitated apparently unchanged. (That the reprecipitated material was truly unchanged was shown later by Vander Wal (2) by means of a mixed melting point determination.) Concentrated sulphuric acid dissolved the compound, producing an orange-yellow solution which became deep greenish blue upon the addition of ferric chloride or potassium dichromate. The greenish tinge was thought to be due to either excess oxidizing agent or the color of the original sulphuric acid solution. Ammonium sulphide reduced the compound, but no definite product was isolated. However, reduction with zinc and hot glacial acetic acid

(2) Vander Wal, R. J., Unpublished work.

yielded ammonia, aniline, and succinanil.

The observations of Hill and White, with the exception of the analyses, were all checked by Vander Wal (2). This investigator also found that the same yellow compound was formed by the reaction of nitrofuran and aniline; hence the carboxyl group of the nitrofuroic acid must be eliminated in the course of the reaction. That carbon dioxide gas is evolved during the reaction had already been observed by Hill and White. On the basis of his studies, Vander Wal, in conference with Wright, suggested the formula:



He also demonstrated the dyeing properties of the compound by immersing samples of wool, silk, acetate rayon, and cotton in the reaction mixture during the period of the reaction. All except the cotton were dyed a clear deep yellow. The cotton was only tinted.

Vander Wal's formula appears to the writer to be in harmony with all of the known properties of the compound. The enolic behavior is accounted for by the phenolic hydroxyl group on the pyrrole ring (3). Reduction may be explained by the following sequence of reactions:

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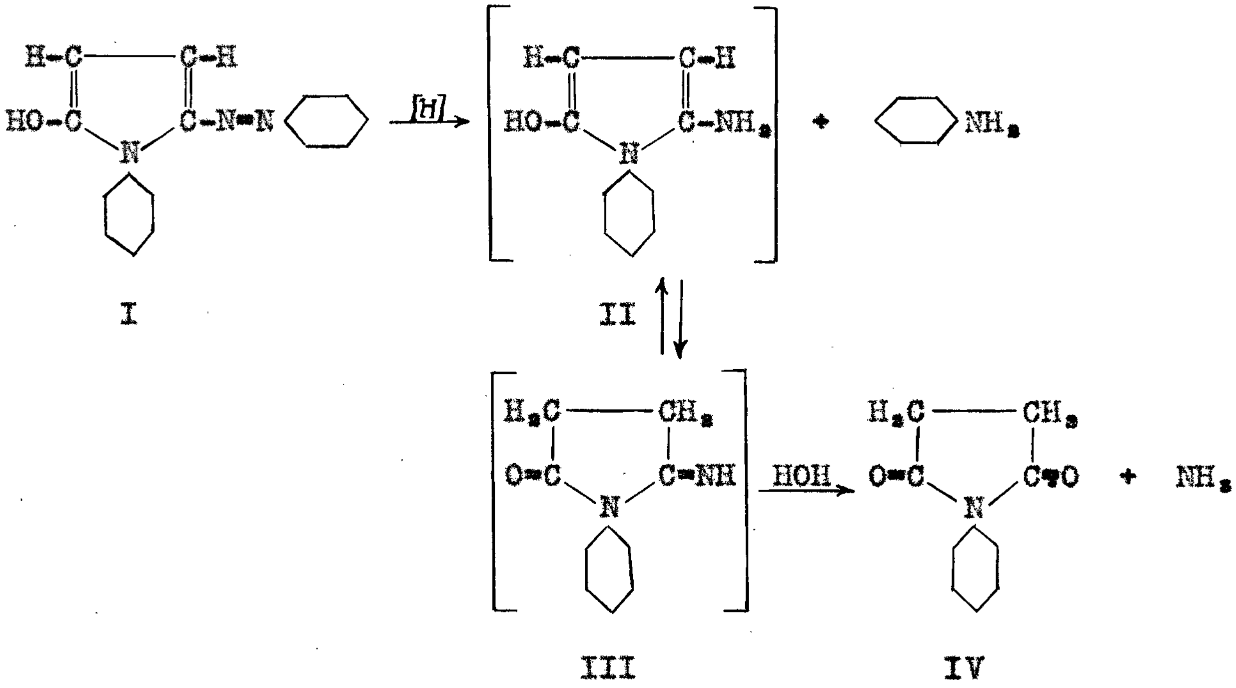
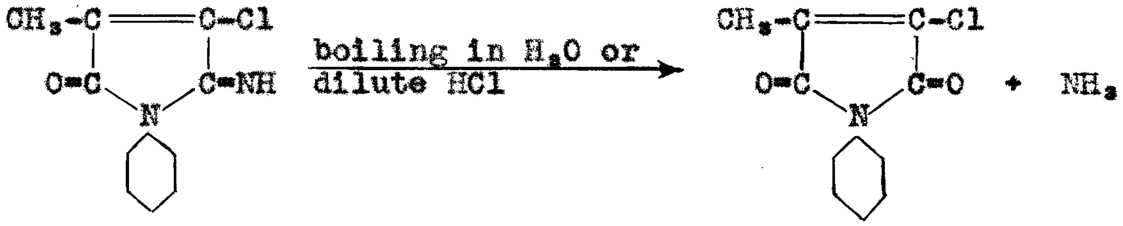
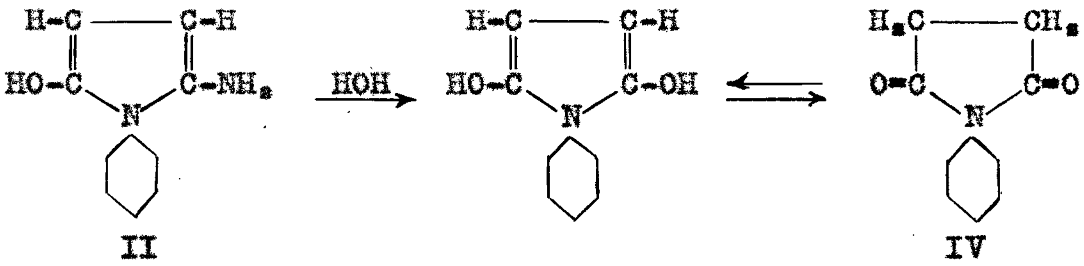
(3) For examples of the enolic properties of pyrrolones see, Thiele, Ann., 306, 246 (1899); Borsche and Fels, Ber., 39, 3877 (1906).



The hydrolysis of the imide group in III is similar to that observed by Anschütz and Meyerfeld (4):

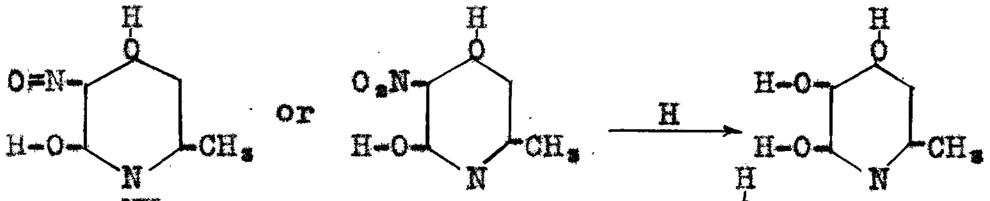


An alternative interpretation of the transformation from II to IV involves the direct hydrolysis of the amino group without shifting first to the imide form as in the previous explanation:



(4) Anschütz and Meyerfeld, Ann., 295, 61 (1897).

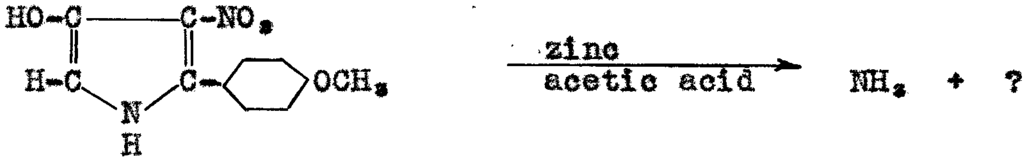
Such direct replacement of an amino group by an hydroxyl group has been found in certain hydroxypyridines:



(See 5,6)

(See 7)

The only case in the pyrrole series is not at all clear out. (8).



Since reduction with zinc and acetic acid may or may not open the pyrrole ring, depending on the concentration of the acid and the duration of the reaction (9), it is not certain that the ammonia was generated by the removal of the amino group formed by the reduction of the nitro group.

Though Hill and White reported that the yellow compound was not attacked by acid or alkali, it was found in the present study that by prolonged refluxing (six hours or more) with 20% hydrochloric acid solution, the compound was finally dissolved.

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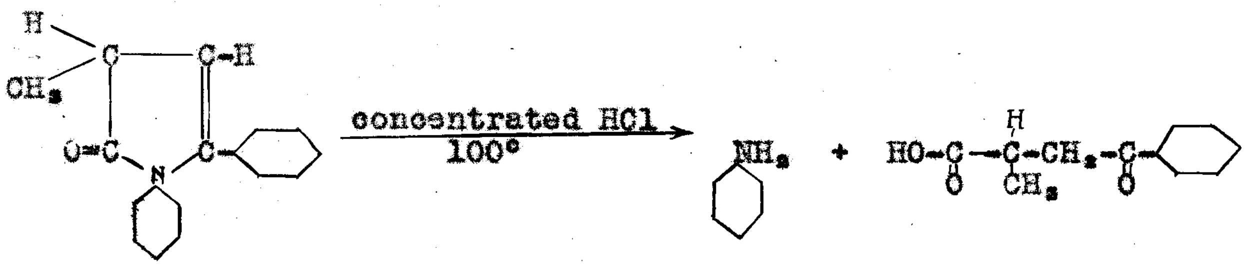
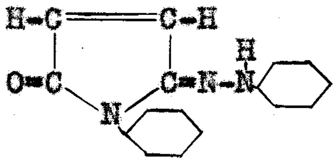
(5) Hess, Ber., 32, 1985 (1899).
(6) Lapworth and Collie, J. Chem. Soc., 71, 844 (1897).
(7) Stokes and von Pechmann, Ber., 19, 2701 (1886).
(8) Wieland and Bloch, Ann., 340, 79 (1905).
(9) Ciamician and Dennstedt, Ber., 16, 1536 (1883); Ciamician, Ber., 34, 3952 (1901).

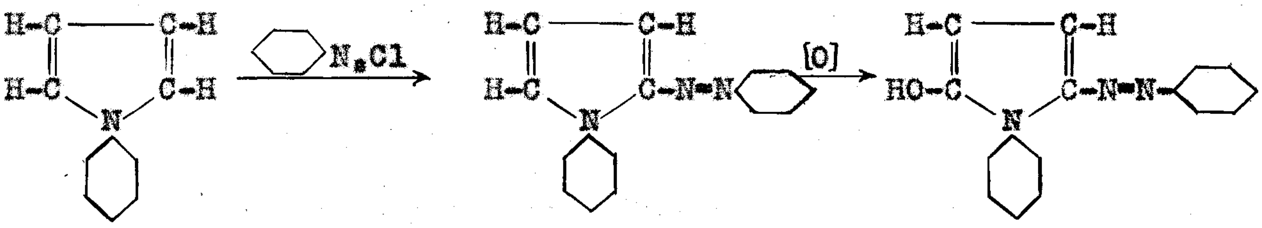
Only one product, aniline, could be isolated. Refluxing five hours with 10% sodium hydroxide solution had little effect though there was a distinct odor of aniline. The aniline is in each case probably formed by ring scission, a reaction observed with other α-pyrrolone derivatives (10):



In the hydrolysis of the yellow compound a similar cleavage appears to take place; 50% of one equivalent of aniline was isolated, but the other fragment decomposed to a tar. Since no phenylhydrazine could be identified among the products, one of the tautomeric formulas for the yellow compound seems to be excluded (11):



Following the above indications of the proposed formula, a synthesis of the yellow compound was undertaken involving the following steps:



(10) Klobb, Bull. soc. chim., (3), 19, 395 (1898).

(11) For evidence of such tautomerism of α-benzeneazopyrrole, see Plancher and Soncini, Gazz. chim. ital., 32, II, 447 (1902); Atti Accad. Lincei, (5), 10, I, 299 (1901).

The N-phenylpyrrole was coupled with benzenediazonium chloride by the method of Plancher and Ghigi (12) to obtain the known N-phenyl-α-benzeneazopyrrole. The oxidation was accomplished by means of perbenzoic acid, which had been used successfully by Böeseken in the oxidation of furan (13). The structure of the oxidation product is based on the fact that the oxidation of pyrrole compounds appears to always involve hydroxylation in the α-positions as the first step (14). The final step of proving the identity of the synthetic product and the yellow compound was established by a mixed melting point determination.

The only derivative which was successfully prepared from the yellow compound was a yellow monoacetyl derivative melting at 197°. This derivative did not prove to be very useful since the yield was poor and the product rather difficult to purify. Consequently it was not possible to prepare this derivative from the extremely small amount of the yellow compound obtained in the synthesis from N-phenyl-α-benzeneazopyrrole. Several attempts were made to prepare the methoxy derivative by reaction with diazomethane, but the compound was so very slightly soluble in the suitable solvents that no reaction occurred even on long standing.

Constitution of the red compound.

The minor product of the Hill and White reaction is the

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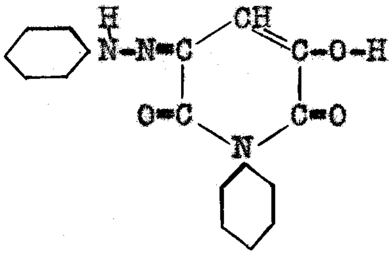
(12) Plancher and Ghigi, Gazz. chim. ital., 55, 49 (1925).
(13) Böeseken, Vermij, Bunge, and Van Meeuwen, Rec. trav. chim., 50, 1023 (1931).
(14) Ciamician and Silber, Ber., 45, 1842 (1912); Plancher and Cattadori, Atti Accad. Lincei, (5), 13, I, 489 (1904).

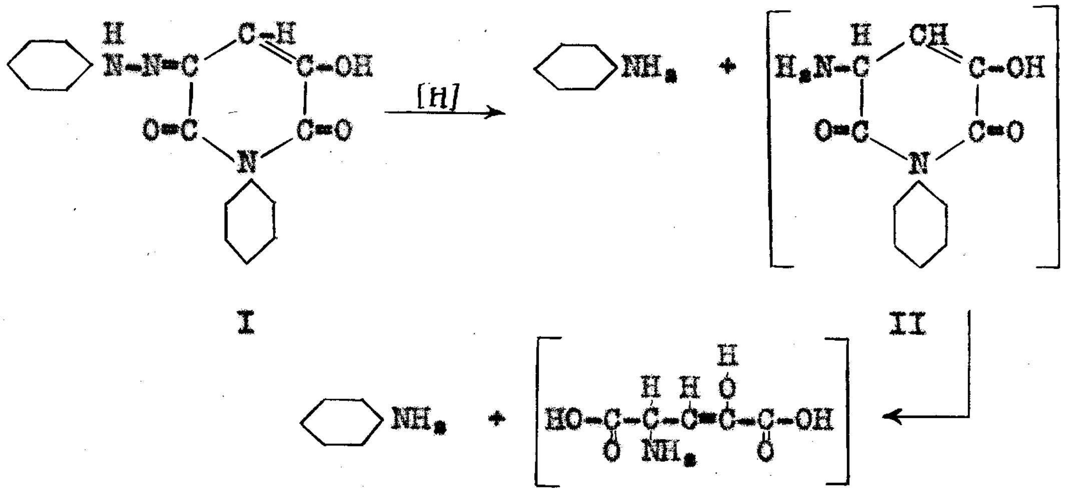
red compound, $C_{17}H_{13}N_3O_3$, which melts at 218° with decomposition. No degradation reactions or derivatives of this compound were found by Hill and White. The compound was not studied by Vander Wal.

On the basis of the properties of the compound, and the study of the mechanism of the reaction, the following formula (or a tautomer of it) was found by the writer to be the most probable:



Since the difference between the yellow and the red compound is one molecule of carbon dioxide, one's first thought is that the red compound may differ from the yellow only by a carboxyl group. It was soon discovered, however, that although the compound dissolves in alkaline solutions slowly, it does so with decomposition hence it is not acidic. The compound is readily soluble in alcoholic potassium hydroxide with a red color, but the solution rapidly becomes light brown. Cold aqueous 10% sodium hydroxide dissolves the compound very slowly to form a similar solution; in warm alkali the same result is obtained more rapidly. Acidification does not precipitate the compound unchanged.

Reduction of the red compound with zinc and boiling glacial acetic acid was not successful. Stannous chloride and hydrochloric acid in hot acetic acid gave 67% of one equivalent of aniline, but no significant amount of any other product. The reduction does not aid greatly in the proof of structure, since the aniline could be formed not only by reduction of the azo group but also by the hydrolysis of the anil fragment, II.



I

II

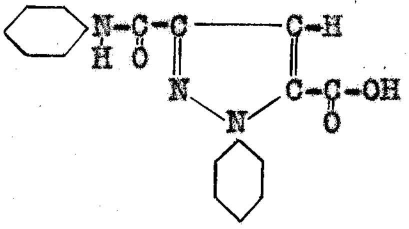
Numerous attempts were made to prepare a quinoxaline derivative of the red compound by reaction with *o*-phenylenediamine, but none was successful. Due to the anil type of structure, the typical carbonyl properties are probably lacking in the α-position.

An orange monoacetyl derivative was prepared in a manner similar to that employed for the yellow compound. The melting point was 195°. The mixed melting point with the acetyl derivative of the yellow compound showed a large depression. The two compounds also differ in their composition, as revealed by analysis.

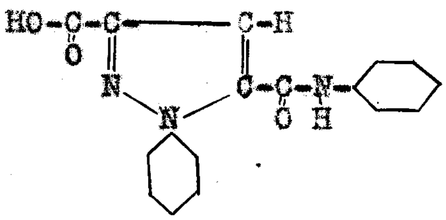
When the red compound was refluxed with 0.1 N sodium hydroxide, hydrolysis proceeded smoothly and both fragments of the molecule were isolated. Aniline and 1-phenyl-3,5-dicarboxypyrazole were obtained in yields of 77% and 81% respectively.

The aniline was converted to benzanilide, and the identification of the acid was checked by mixed melting point determinations of both the acid and its dimethyl ester with authentic specimens.

It is obvious that the simplest compound which could give these products would be the monoanilide of the dicarboxypyrazole compound:



or



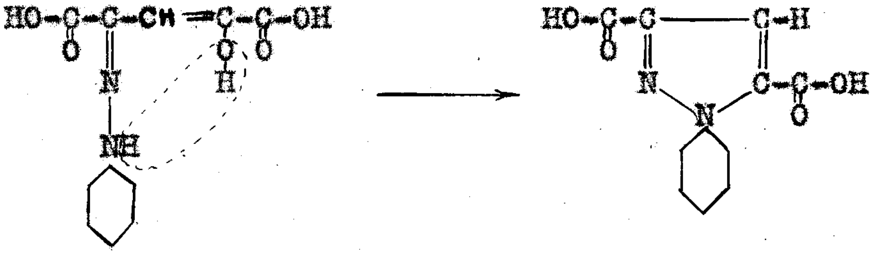
On closer inspection, it is evident that both of these possibilities are barred by the presence of a free carboxyl group and the lack of a chromophore. The anilides of some of the pyrazole acids are also hydrolysed with much more difficulty (15) than was encountered with the red compound.

The dicarboxypyrazole must then be formed by a secondary reaction from one of the products of the hydrolysis. Judging by the methods of preparing pyrazole derivatives, (16), this intermediate must be the following phenylhydrazone which produces the dicarboxypyrozole in the manner indicated:

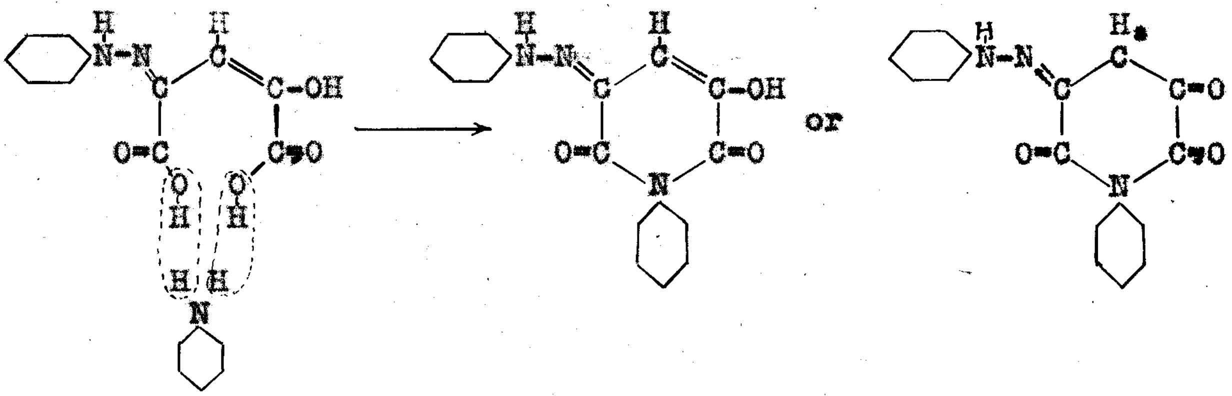
---

(15) Dains and Harger, J. Am. Chem. Soc., 40, 562 (1918); Dains and Long, Ibid., 43, 1200 (1921).

(16) Meyer and Jacobson, "Lehrbuch der organischen Chemie," Vol. 2, part 3, 1920, p. 355.



If the red compound breaks down into the above aliphatic derivative and one molecule of aniline, and yet has no carboxyl groups, it must be the anil of the acid (or some tautomeric form) as shown below:

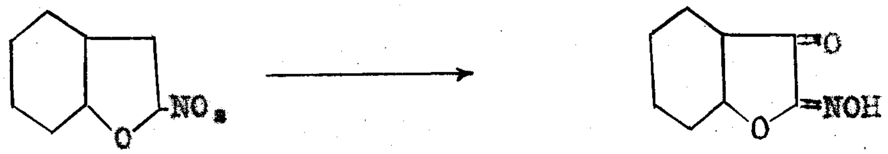


Mechanism of the reaction.

If one compares the structure of the red and yellow products with that of the initial compound, nitrofuroic acid, it is obvious that the reaction must be rather complex. For this reason it was planned to halt the reaction at various stages to isolate intermediate compounds. It was first necessary to find which of the two reactants, aniline or sodium acetate, initiated the reaction with nitrofuroic acid.

If one recalls that the reaction was first observed when the aqueous solution of the aniline salt of nitrofuroic acid was allowed to stand, it is obvious that the alkaline medium, as provided by the sodium acetate, is not a necessity. In addition, it was reported by Hill and White that this gradual reaction was hastened by adding aniline acetate. In this study it was found that though the reaction proceeded well in the presence of a weak acid as indicated, a small amount of strong acid inhibited the completion of the reaction.

Owing to the sensitivity of nitrofuran derivatives to strong alkali, it was thought by Wright (17) that this reaction would involve, in its first phase, the replacement of the nitro group by an hydroxyl group. Nitrocoumarone (18) has been shown to undergo a reaction in the presence of sodium alcoholate which involves the nitrogroup:

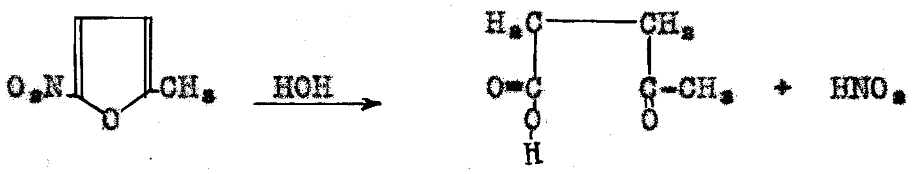


Nitrothiophene derivatives form colored products when treated with alkali or sodium alcoholate. Steinkopf (19) has isolated a series of such compounds in which sodium methoxide has added to the nitro group. Acetic acid regenerated the original nitro compound. The nitro group in certain polysubstituted benzene compounds may be replaced by hydroxy or methoxy groups by the use of sodium hydroxide or methoxide respectively (20).

(17) Wright, George, Private communication.
(18) Kahlert, Dissertation, Rostock, 1902.
(19) Steinkopf, Ann., 513, 285 (1934).
(20) Clark and Carter, Trans. Roy. Soc. Canada, (3), 21, part 1, 323 (1927).

In the furan series, Hill and White (1) have reported the hydrolysis of 2,5-dinitrofuran and 5-nitro-2-furoic acid with boiling barium hydroxide. In the first instance a deep red color developed which faded to yellow on continued boiling with the formation of a little ammonia. Barium maleate and barium nitrite were identified in the solution. The nitro-acid under the same treatment developed a reddish yellow color, and finally a brown precipitate. Barium nitrite was detected, but the brown precipitate was not identified. The nitro-acid was found to be sufficiently sensitive to alkali that it acted as its own indicator when it was titrated with a strong base. Marquis (21) also noted the effect of alkali on nitro-furans. He found that alkali nitrite was always among the products, but he did not identify any other products, a failure which he attributed to the resinification of the aldehydic compound formed on ring scission. Support of the aldehydic nature of the products was drawn from the reduction of Fehling's solution or ammoniacal silver nitrate by nitrofuran. Reduction did not take place in the cold, only on heating. This behavior appeared to be general for all furan compounds except furan itself. Ethyl nitrofuroate was found to be particularly sensitive to alkali, whereas dinitrofuran was not attacked in the cold. More recently, it has been shown that nitrosylvan is converted to levulinic acid by prolonged refluxing (13 hours) with water (22).

(21) Marquis, Ann. chim. phys., (8), 4, 229 (1905).
(22) Van Ess, Paul R., Unpublished work.



It appears to be established, however, that in the reaction of 5-nitro-2-furoic acid with aniline in 10% sodium acetate solution, the replacement of the nitro group by hydroxyl as a preliminary step does not take place. This is not entirely surprising when it is considered that cold 10% sodium acetate is a much weaker base than dilute sodium hydroxide or boiling barium hydroxide solution. In all of the cases just described in which the nitro group has been removed, strong bases or higher temperatures have been employed. It has been observed by the writer that 5-nitro-2-furoic acid does not even on standing in 10% sodium acetate solution develop the characteristic red brown color produced by stronger alkalis.

It is also true that when 5-nitro-2-furoic acid reacts with aniline in the presence of stronger bases such as sodium carbonate, dark red tars are formed which yield almost none of the usual red and yellow compounds. However, if the nitrofuroic acid is first treated with standard sodium hydroxide until almost neutralized and this solution added to the usual reaction mixture, the relative proportion of the red compound in the product is greatly increased. By the original procedure, the ratio of red to yellow compound was approximately 1:13, but with the modification, 1:2. The combined yield is decreased considerably by the modification, owing to the formation of more tar.

A final proof of the unimportance of the sodium acetate for the initial steps of the reaction was obtained by allowing an aqueous sodium acetate solution of nitrofuroic acid to stand for the usual period of the reaction. Not until eight hours have elapsed, may a faint test for nitrite ion be noted, whereas in the usual reaction, a strong test for nitrite is observed in less than one hour (23). Eighty five percent of the nitrofuroic acid was recovered.

If the sodium acetate is not necessary for the initial steps of the reaction, the aniline must then be involved. The first action is apparently the formation of the aniline salt of the nitrofuroic acid, since some of this salt separates out if the reaction mixture is too concentrated. This salt also reacts with more aniline acetate to give the normal yields of red and yellow compound.

The probable second step of the reaction is suggested by the known reactions of aniline with other furan compounds, of which furfural has been the principal one studied. Furfural combines with both aliphatic and aromatic amines. With aromatic amines, the reaction may be one of three types depending on the amine used and the conditions of the reaction. (1) With

(23) Nitrite ion was detected by acidifying a drop of the solution with dilute sulphuric acid and testing with potassium iodide-starch paper.

tertiary amines, as dimethylaniline, dyes of the diphenylfurylmethane type are formed (24); (2) primary and secondary amines react in 1:1 ratio by condensation of one molecule of amine with the aldehyde group; and (3) in 2:1 ratio by condensation of one molecule of amine with the aldehyde group and with the second molecule by ring scission. The latter type of reaction is the basis of the aniline acetate test for furfural (25). Since the Hill and White reaction seems almost certain to involve ring opening, the reaction of type (3) only will be discussed in detail. Because the mechanism of this reaction, the constitution of the product, and the chemical properties of the product have long been the subject of investigation and have not yet been entirely explained, an historical review is here included.

The color reaction of furfural with aniline has long been known, having been first observed in 1850 by Stenhouse (26). The use of acid to deepen the color was discovered by Persoz (27) and a decade later the dye salts were isolated and analysed by Stenhouse (28). Schiff (29) became interested in the problem,

(24) Fischer, Ber., 10, 1623 (1877); Ann., 206, 141 (1881); Renshaw and Naylor, J. Am. Chem. Soc., 44, 862 (1922); Mahood and Aldrich, J. Am. Chem. Soc., 52, 4477 (1930). The 5-bromofuryl and 5-chlorofuryl analogs were prepared by Hewlett, Doctoral Dissertation, Iowa State College, 1930.

(25) Gilman and Wright, Chem. Rev., 11, 346 (1932).

(26) Stenhouse, Ann., 74, 282 (1850).

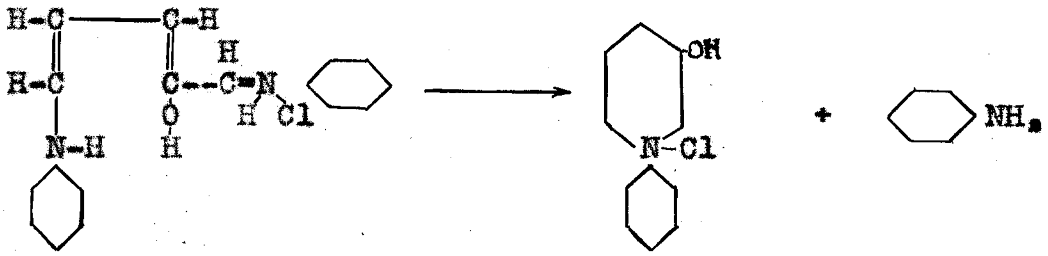
(27) Persoz, Rep. chim. appl., 1860, 220 (1860). Original not seen. See Teunissen, Dissertation, Leiden, 1929.

(28) Stenhouse, Ann., 156, 197 (1870).

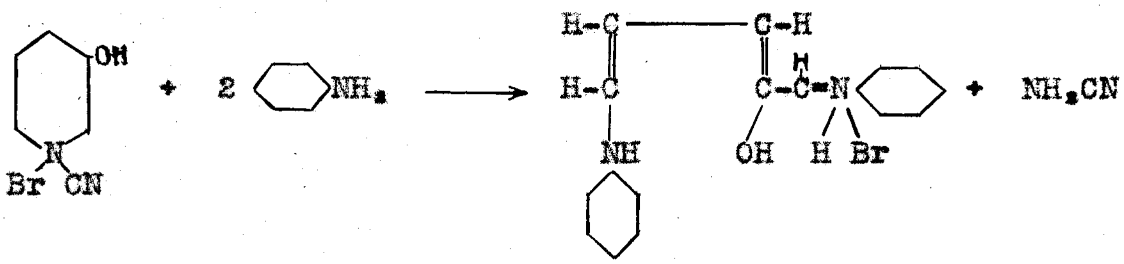
(29) Schiff, Ber., 10, 773 (1877); 19, 847, 2153 (1886); Ann., 201, 355 (1880); 239, 349 (1887).

and reported in 1877 that the reaction was rather general for aromatic amines, including primary and secondary amines, diamines, and even amino acids.

Twenty years later the structure of the dye salt was finally proven by Zincke and Mühlhausen (30), who demonstrated that the Stenhouse salts were transformed into pyridinium salts by heating, and who also succeeded in preparing one of the Stenhouse salts from the appropriate β-hydroxypyridine derivative.



Stenhouse salt



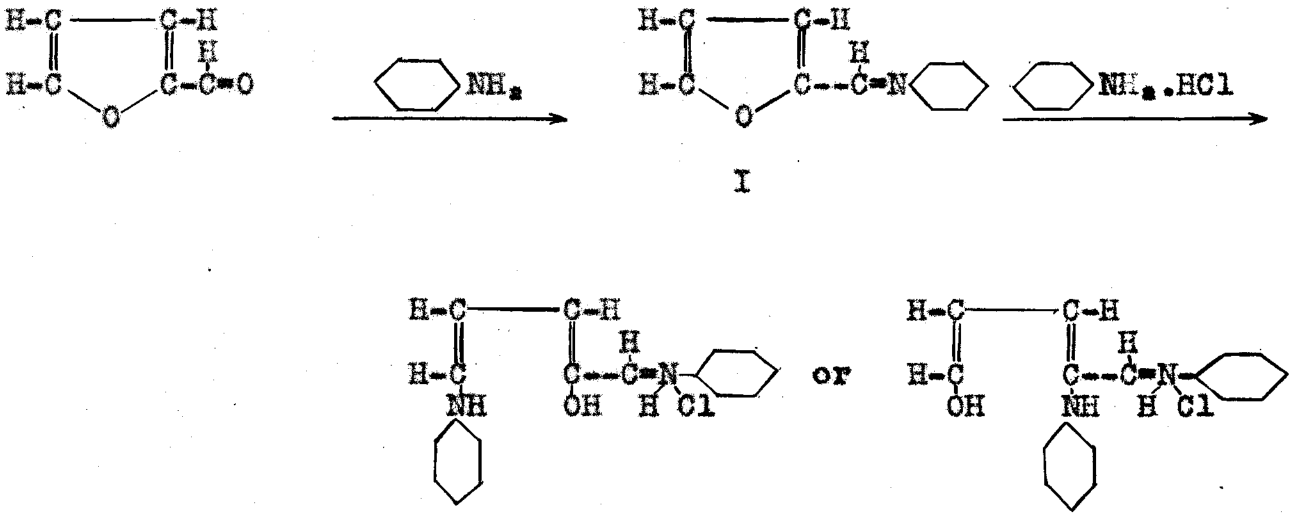
Stenhouse salt

These reactions proved the opening of the furan ring, a possibility which had apparently been overlooked by Schiff.

The steps of the reaction according to Zincke and

(30) Zincke and Mühlhausen, Ber., 38, 3824 (1905).

Mühlhausen are: (1) condensation of the aldehyde group and aniline, and (2) the opening of the ring by the aniline salt.



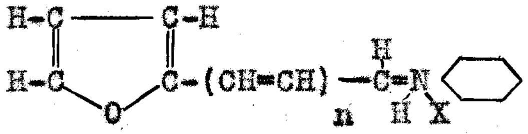
I

II

III

That the product had configuration II rather than III, was shown by ring closure to N-phenyl-β-hydroxypyridinium chloride, since III could not possibly close to this compound. The same mechanism was almost simultaneously advanced by Dieckmann and Beck (31) and König (32).

König (33) recently has again confirmed the above mechanism of reaction, and also prepared the vinylene homologs of compounds of type I and II:



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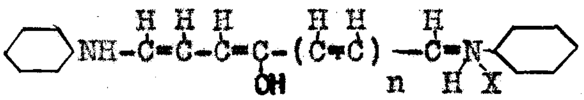

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(31) Dieckmann and Beck, Ber., 38, 4122 (1905).
(32) König, J. prakt. Chem. (2), 72, 555 (1905); 88, 193 (1913).
(33) König, Hey, Schulze, Silberweit, and Trautmann, Ber., 67, 1274 (1934).

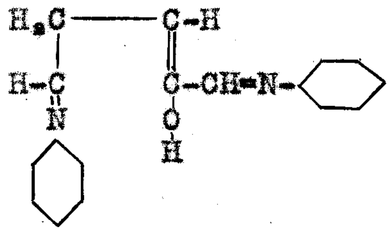
These higher homologs (n=1,2) are more stable than the corresponding furfural derivatives of type I, but less stable than the derivatives of type II. Secondary amines form the more stable derivatives of type II, whereas dyes of type I are more stable when prepared from primary amines. This is not surprising since one would normally not expect to prepare Schiff bases from secondary amines. However, König prepared compounds which on the basis of analyses and properties appear to have the same general formula as the primary amine derivatives and were so designated by König. It will be remembered that Schiff (29) had also observed that secondary amines appeared to react with furfural in the same fashion as primary amines.

Oddly enough, at the time the mechanism of the reaction was established no one had yet been successful in isolating the free color base. Fifteen years later, Otto Fischer and co-workers (34) had rather meager success in obtaining the free color bases with nitroanilines. An aniline base was finally obtained by Boehm (35). It then appeared that some of the bases had been isolated earlier by König and Schiff, but they had not recognized their compounds as such. There was now considerable confusion, since there was not much agreement among these various reports. Lowenstein (36) harmonized all the discordant facts by showing that the base exists in two isomeric forms.

(34) Fischer, Balling and Aldinger, J. prakt. Chem., 100, 105 (1920).
(35) Boehm, Private Communication, Lowenstein, Dissertation, Berlin, 1931.
(36) Lowenstein, Dissertation, Berlin, 1931.

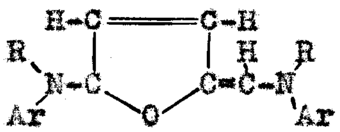
The low melting easily soluble type prepared by Schiff and König is the true base of the Stenhouse salts, and may be formed by the condensation of the amine and furfural in the absence of a solvent. The isomeric compound is higher melting, forms no salts, is insoluble in most media, and dissolves in sulphuric acid with a yellow rather than a violet or red color. The inert isomer, the pseudo base, agreed in properties with Fischer's and Boehm's compounds, and is formed by carrying out the condensation in ethyl acetate in the presence of acetic acid. Lowenstein was able to prepare both isomers with all three of the nitroanilines, but aniline, p-toluidine, p-phenetidine, and p-chloroaniline formed the pseudo base even when reacted in the absence of solvent. The pseudo bases may also be obtained by allowing the true base to stand or to be warmed in pyridine. The reverse transformation may take place to a very limited extent, but is accompanied by much decomposition. The pseudo bases are rather resistant to acids and hence must not contain the furan ring. They have no properties indicating a carbonyl group, but appear to have an hydroxyl group since esters are obtained upon treatment with p-nitrobenzoyl chloride, maleic acid or maleic anhydride.

Lowenstein gave the pseudo bases the formula:



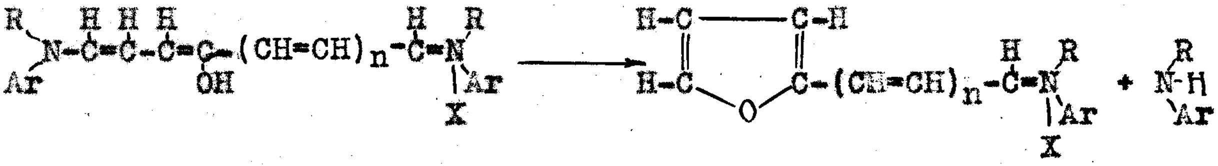
He seems a little inconsistent, since he explains that the absence of salt forming properties is due to both nitrogen atoms being present in -CH=N-Ar groups, yet in his formula for the dye salts he has (like all of the other investigators) represented this very group as salt forming.

In more recent work of König (24), mention is made of ψ-bases which are formed along with the true bases, or by treating the true color bases with cold concentrated alkali, sodium ethoxide, or potassium cyanide. He does not make it clear whether these ψ-bases are by-products also in the preparation of the bases of the higher vinylene homologs, but mentions specifically that only the furfural bases are subject to the action of the alkaline reagents, and further gives no account of the direct synthesis of the ψ-bases of the higher homologs. The ψ-bases form no salts, are higher melting than the true bases and seem to correspond to what Lowenstein called "pseudo bases", but König does not make it clear whether they are the same or not, and does not even mention the work of Lowenstein. König did not use primary amines for these compounds, but cyclic secondary amines, as tetrahydro-p-methyl quinoline, and dihydromethylindole. He suggests the following formula:

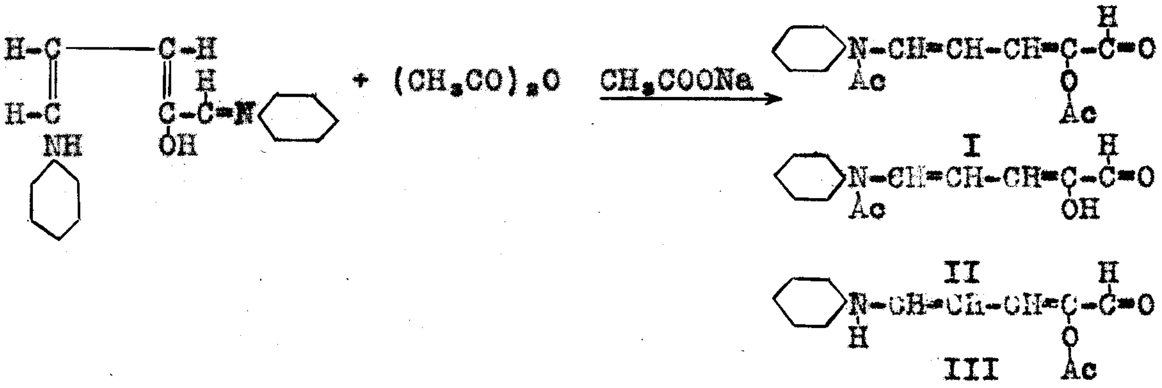


He offers no other evidence for this structure and does not explain why such a molecule is not salt forming.

König also observed another kind of ring closure when the true dye salts from the higher vinylene homologs are heated. It will be recalled that the primary amine derivatives of furfural on heating lose one molecule of amine to form pyridinium salts(30). The higher vinylene homologs from secondary amines on heating also lose a molecule of amine and the remainder closes to a furan compound.

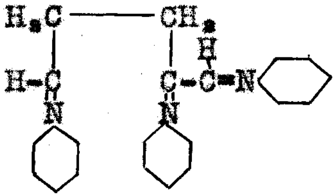


The reversion to the furan derivative is greatly diminished by acylation of the enol with acetic anhydride, acetyl chloride, or benzoyl chloride. Acylation is rather difficult, since other reactions occur simultaneously. Aschan and Schwalbe (37) obtained three different products when the aniline color base was acetylated with acetic anhydride in the presence of sodium acetate. The acetylation was accompanied by the loss of one molecule of amine:



(37) Aschan and Schwalbe, Ber., 67, 1830 (1934).

Lowenstein noted that when furfural was dropped into three equivalents of aniline, there was formed, beside the pseudo base, a compound melting at 127°, which was rather unstable and went over to the pseudo base with ease. Analysis indicated the formula $C_{23}H_{21}N_3$, for which the following structure was suggested.



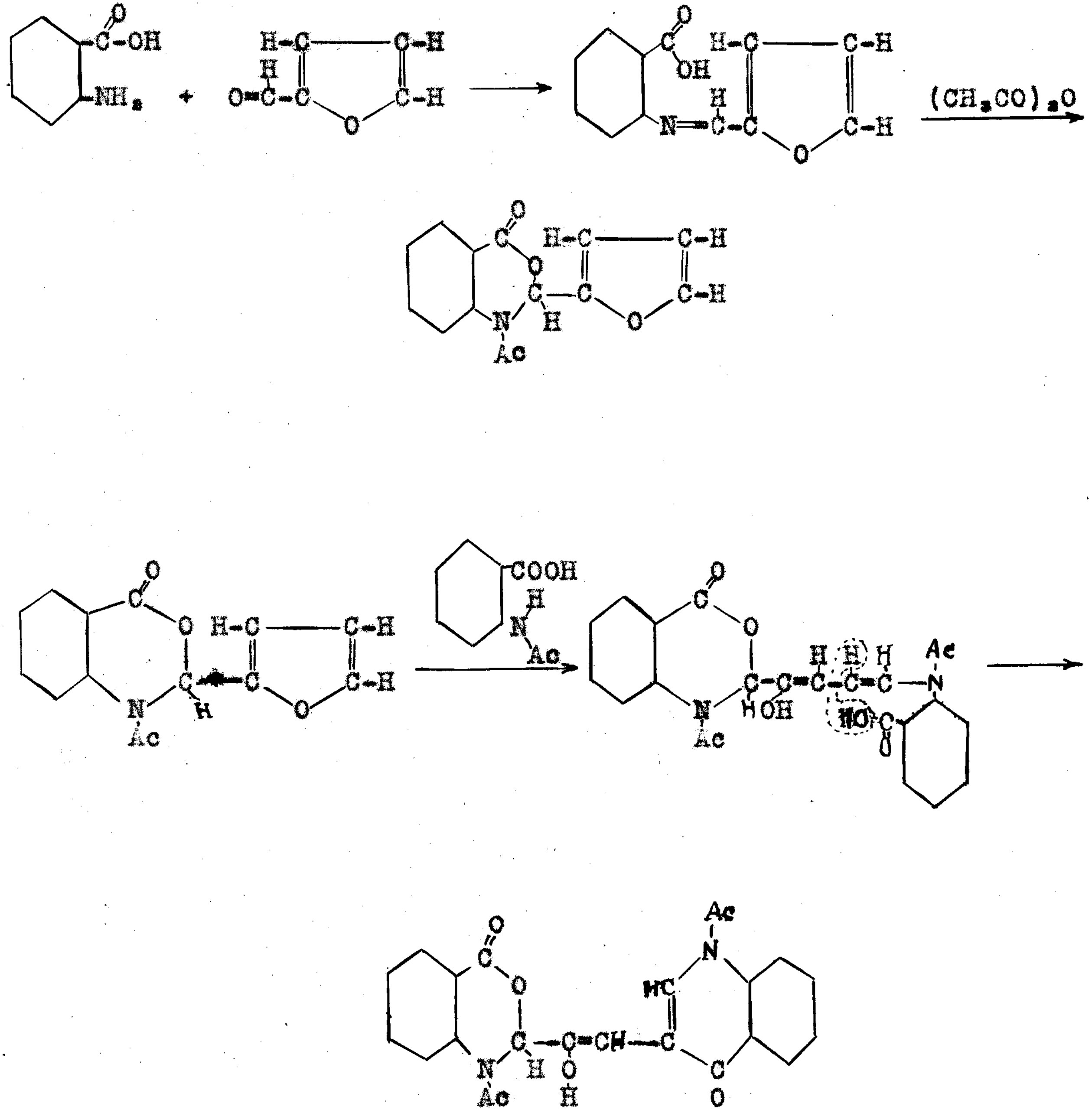
A close relationship to the pseudo base is indicated by this formula; but the new compound could not be obtained from the reaction of aniline with the pseudo base. A compound which appears to be an acetyl derivative of the 127° product was obtained from the prolonged reaction of aniline and furfural in a mixture of glacial acetic acid and ethyl acetate. The compound is not formed except in the presence of ethyl acetate, and other acids may be substituted for the acetic acid.

Reports of the reaction of other furan compounds with aniline are not abundant. Levene (38) investigated the color reaction of some twenty seven different furan derivatives with Shear's reagent (13 volumes of aniline and 1 volume of hydrochloric acid); but found the results far from uniform. Some compounds gave no color whatever, and among those which formed colored products there was no uniformity of hue. The chemistry of these reactions was not examined. Burtner (39)

(38) Levene and Seaman, Biochem. J., 27, 2047 (1933).
(39) Burtner, R.R., Unpublished work.

found that a number of nitrofuran derivatives gave colored products with aniline, but again the products were not individually studied.

A rather complex case of ring scission has been observed by Ekeley and Rogers (40). The mechanism is, by analogy, thought to be the following:



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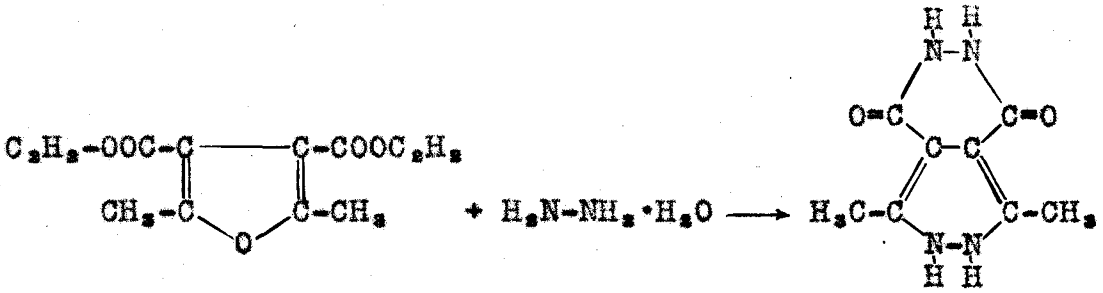
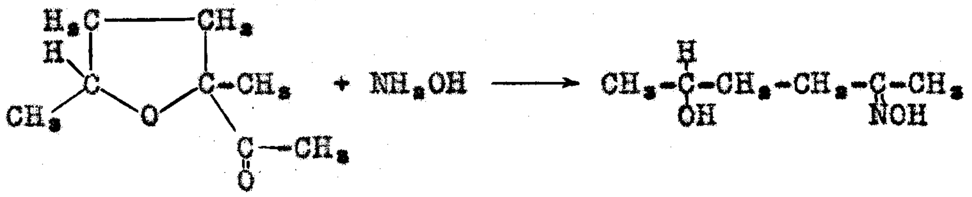
(40) Ekeley and Rogers, J. Am. Chem. Soc., 44, 2655 (1922).

Similar ring opening reactions have been observed with hydrazine, hydroxylamine, and ammonia, though many of these occurred under more drastic conditions. Seka and Preiszecker (41) observed that when 2,5-dimethyl-3,4-dicarboethoxyfuran was treated with hydrazine hydrate in ether (sealed tube) the following reaction took place:



Saunders (42) obtained an unidentified highly colored compound when furamide was reacted first with one mole of bromine and then treated with phenylhydrazine. The compound has the formula $C_{11}H_{11}N_3O_2$.

A tetrahydrofuran derivative has been reported to undergo ring scission with hydroxyl amine (43).



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(41) Seka and Preiszecker, Monatsh., 57, 81 (1931).
(42) Saunders, Am. Chem. J., 15, 130 (1893).
(43) Lipp and Scheller, Ber., 42, 1966 (1909).

With ammonia, 2-methyl-3-carboxy-5-furylacetic acid at 320° in a sealed tube reacts to form 2,5-dimethylpyrrole (44). 2,5-Dimethyl-3-acetylfuran (or 2,5-dimethyl-3-acetyl-4-carboxyfuran) and ammonia at 100° yields 2,5-dimethyl-3-acetylpyrrole (45). 2,5-Dihydrodehydromucic acid reacts with ammonium hydroxide and ammonium bromide at 160° to form 2-hydroxy-6-carboxypyridine (46). Furan itself when treated with ammonia in the presence of a catalyst (alumina) at 450° produces pyrrole (47). Sylvan under the same conditions is converted to α-methylpyrrole (48).

Another one of the furfural color reactions has been very recently shown to involve ring splitting by means of amines. Hueck (49) observed that when the alcoholic solution of furfuralmalonitrile was treated with potassium hydroxide or alcoholic ammonia, a deep red color developed. Boehm and Grohnwald (50) have recently reported that hydrofuramide behaves similarly. Their research, however, was primarily concerned with furfuralmalonitrile. They found that whereas various amines could be used in the reaction, benzyl amine leads to the greatest yield. The following mechanism of reaction appears to be reasonably well established:

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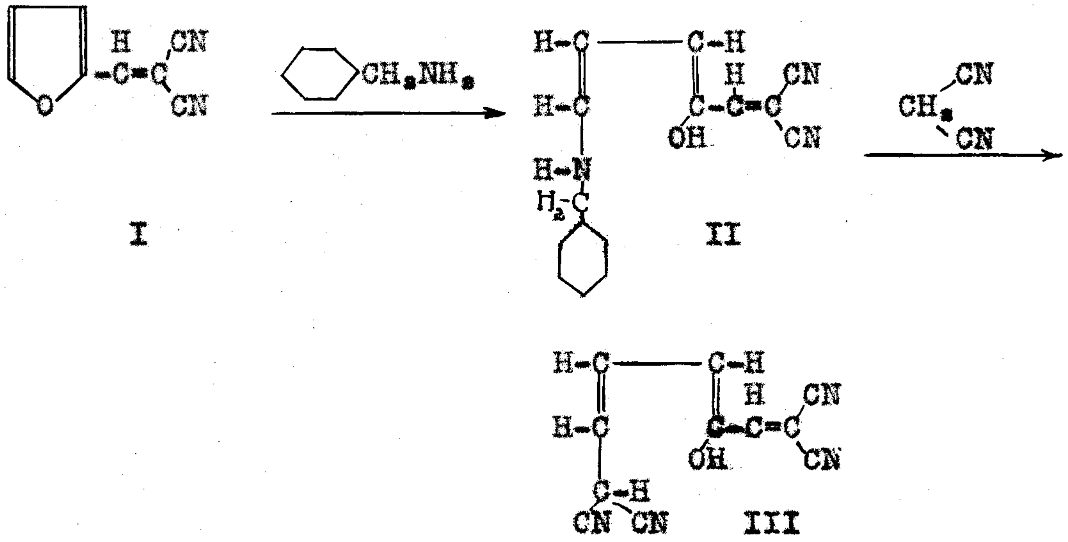
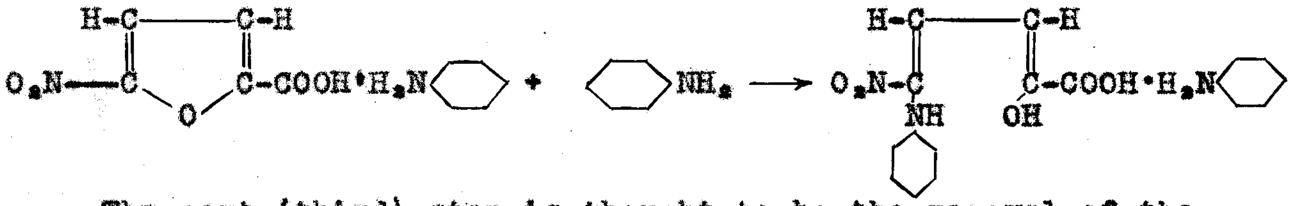
(44) Trephilieff, *Ber.*, 41, 2845 (1908).
(45) Magnanini and Bentivoglio, *Gazz. chim. ital.*, *24*, *I*, 433 (1894); Magnanini, *ibid.*, *23*, *I*, 462 (1893).
(46) Fischer, Hess, and Stahlschmidt, *Ber.*, *45*, 2456 (1912).
(47) Jurjew, Ber., *69*, 440 (1936).
(48) Jurjew, *Ber.*, *69*, 1002 (1936).
(49) Hueck, *Ber.*, *28*, 2251 (1895).
(50) Boehm and Grohnwald, *Arch. Pharm.*, *5*, 318 (1936).

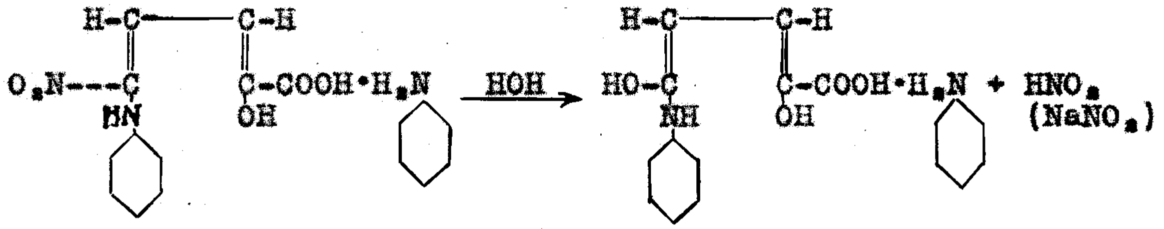


The intermediate blue dye, II, was isolated. When treated with malonitrile it gave dye III previously obtained by the uninterrupted reaction of furfuralmalonitrile and benzylamine. Dye III forms an acetyl derivative indicating the presence of an hydroxyl group. Cyanacetamide may be substituted for malonitrile to give a dye corresponding to III.

It is evident from these numerous examples of ring scission by amines that there is considerable basis for postulating ring scission by aniline as the second step in the Hill and White reaction, for it is seen that not only is this type of reaction the only one observed with amines (other than reaction with functional groups), but also in many cases the ring opening takes place under conditions which are very mild indeed. This step in the Hill and White reaction may then be represented as follows:



The next (third) step is thought to be the removal of the nitro group by hydrolysis:



It is probably at this point that the mildly alkaline medium hastens the reaction by its hydrolytic action.

The nitro group is probably particularly sensitive to hydrolysis when the ring has been opened due to the presence of this very negative nitro group on a carbon atom now holding the very positive anilino group. This explanation may also apply to the loss of halogen in the reaction of 5-chloro-and 5-bromofurfural with aniline (51).

In observing the effect of substituents on the opening of the furan ring with aniline, a number of curious paradoxes were discovered. Since the reaction of aniline and furfural had been fairly well established, it was thought desirable to try this same reaction with 5-nitro-2-furfural. This was disappointing for 5-nitro-2-furfural condensed with one molecule of aniline easily, but resisted even forced attempts at ring opening with

(51) Hewlett, A. P., Doctoral Dissertation, Iowa State College, 1930. See also page 34 of this thesis.

a second molecule of aniline in the absence of acid. The use of aniline hydrochloride in sodium acetate solution was also unavailing. In the presence of acid, as when aniline and aniline hydrobromide are reacted with the aldehyde in alcohol solution, Hewlett (51) found that the reaction was vigorous and exothermic. He was not able to isolate any pure products from the green tar which formed along with considerable gas. It is possible that it is the acid which actually accomplishes the ring opening in Hewlett's reaction, since acid appears to be essential for the reaction and is known to have a pronounced influence toward ring opening (52). The fact remains that the nitro group in furfural greatly decreases the sensitivity of the ring to aniline, for it was found in this study that furfural is easily cleaved by aniline even in the absence of acid, whereas nitrofurfural is not cleaved in the absence of acid. A most striking anomaly is that whereas the nitro group reduces the sensitivity of the ring in furfural to aniline, it greatly increases the sensitivity of the ring in the acid series. 2-Furoic acid itself is not attacked at the ring by aniline under the conditions in which 5-nitro-2-furoic acid is rapidly cleaved. A further contradiction is that although 5-nitro-2-furoic acid readily undergoes ring scission with aniline, the anilide of this acid does not. One of the difficulties in this case may be that of the solvent. The nitrofuroic acid itself did not undergo ring opening in

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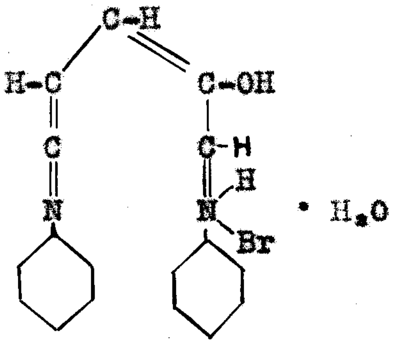
(52) Teunissen, Doctoral Dissertation, Leiden, 1929, or see <u>Rec. trav. chim., 49</u>, 784 (1930).

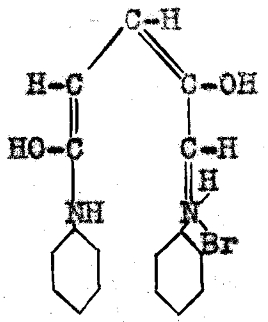
alcohol solution, but did in aqueous solution. The anilide of the acid is of course not soluble in aqueous media of any kind. Teunissen (52) found that the solvent has considerable influence on the ring opening of hydroxymethylfurfural by hydrochloric acid. Furfural itself is apparently opened by amines under a variety of conditions.

With 5-chloro- or 5-bromofurfural and the corresponding acids, the results are also somewhat paradoxical, though the evidence is not entirely conclusive, since the two types of compounds were reacted under different conditions. The halogenofurfural derivatives react in the presence of acid (51), and it may be that here, as in the case of 5-nitro-2-furfural, the ring splitting is due primarily to the acid. The acids were treated in aqueous sodium acetate solution, but were not attacked. When either 5-chloro- or 5-bromofurfural react with aniline in alcohol in the presence of hydrogen bromide, the halogen groups are thereby removed (38). Hewlett suggested the following formula for the product:



He was not able to remove the water of crystallization, nor was he successful in closing the ring to a pyridinium salt.

The removal of halogen during this reaction is remindful of the loss of the nitro group in the Hill and White reaction, and it seems very possible that both are the result of a similar process. In each case the negative chloro, bromo, or nitro group finds itself upon ring opening attached to a carbon atom now holding the positive anilino group and hence is readily removed by hydrolysis. According to this view, Hewlett's compound is not formed by the elimination of halogen acid, but rather by the replacement of the halogen by hydroxyl, and the product probably is:



(or a tautomeric form)

This interpretation accounts for the difficulties experienced by Hewlett in trying to remove a molecule of water from his assumed hydrate.

The failure of 5-chloro- and 5-bromo-2-furoic acids to react with aniline in sodium acetate solution is rather surprising for one would expect them to resemble the corresponding nitro-acid rather closely, since the halogen and nitro groups are all negative substituents.

Other substituted furfurals have been subjected to the aniline acetate color test. Teunissen, (52,53) reported that that both methylfurfural and hydroxymethylfurfural give colored products with aniline acetate. 4,5-Dibromofurfural also gives a positive test (54). 3-Furaldehyde and 2,5-dimethyl-3-furaldehyde (55,56) give no color with this reagent. Furfuryl alcohol, a close relative of furfural but lacking the aldehyde group, is also negative to this test when a pure sample is tested (57). It would appear that the aldehyde group in the 2-position is essential for a positive result(25).

From the above discussion, it seems fair to conclude that the opening of the furan ring by aniline is not a general reaction, but is rather profoundly influenced by the substituents already present in the ring.

The fourth step in the Hill and White reaction is probably the diazotization of the unreacted aniline by the sodium nitrite formed in step three. The presence of benzenediazonium hydroxide in the reaction mixture was demonstrated by adding β-naphthol to the usual reaction and isolating the known Sudan I (1-benzeneazo-2-hydroxynaphthalene), among the products. The identity of the Sudan I obtained was established

(53) For other reports on the reaction of hydroxymethylfurfural and aniline acetate see: Middendorp, Rec. trav. chim., 38, 63 (1919); van Ekenstein and Blanksma, Chem. Weekblad, 6, 217 (1909).

(54) Vander Wal, R. J., Unpublished work.

(55) Burtner, R. R., Doctoral Dissertation, Iowa State College, 1933

(56) Gilman and Burtner, J. Am. Chem. Soc., 54, 3014 (1932).

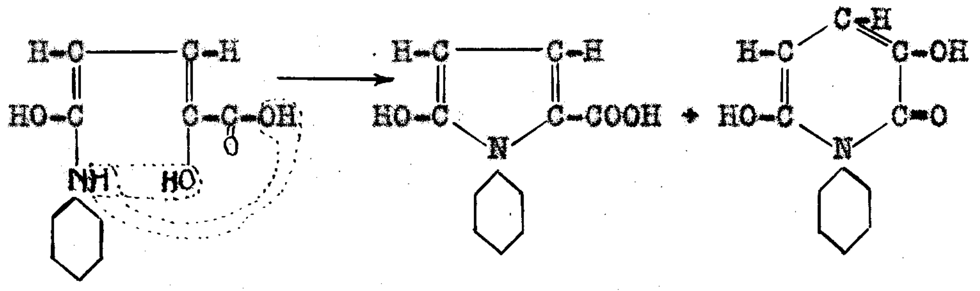
(57) Wissel and Tollens, Ann., 272, 293 (1893).

by a mixed melting point determination with an authentic specimen. Sudan I was also obtained in the reaction of 2,5-dimethyl-3-nitrofuran with aniline hydrochloride in the presence of β-naphthol in a dilute alcoholic solution of sodium acetate.

If some means could be found to prevent the diazotization of the aniline and the subsequent ring closure reaction, it should be possible to isolate a straight chain intermediate. It was hoped that by using a secondary amine such as methylaniline, the nitrosoamine could be separated from the ring cleavage product. An oily tarry mass was obtained from which the desired product could not be separated.

Previously, attempts had been made to halt the reaction at some point by chilling, but little success was realized. After allowing the reaction mixture to stand four hours at 0°, the clear solution was quickly acidified with cold acid and filtered. A very small amount of precipitate was obtained which was principally the yellow compound. Ether extraction of the filtrate yielded nitrofuroic acid. Apparently the very first steps in the reaction are the slower reactions, and once these are completed the rest of the series of reactions proceeds with very great speed. Since the reaction in its later steps involves such processes as diazotization and coupling of the diazonium compound, it is understandable why chilling would not halt these steps at least.

The fifth step is probably ring closure, which takes place in two different fashions and thus brings about the formation of the two different compounds:



precursor of yellow compound　　precursor of red compound

It will be recalled that in some of the reactions already described, it was shown that the furan ring once opened by amines closes again to a heterocycle containing nitrogen (58). There it was noted, among others, that 2,5-dimethyl-3-acetyl-4-carboxyfuran (2,5-dimethyl-3-acetylfuran) and 2-methyl-3-carboxy-5-furyl acetic acid give pyrrole derivatives. These are in a sense only modifications of a frequently used method of synthesizing pyrroles, namely, the reaction of amines with γ-diketones, or keto acids (59). Lactones of crotonic and butyric acid derivatives or maleic anhydride derivatives (60) may be easily opened by amines and closed again to form compounds which are generally regarded (61) as pyrrole derivatives.

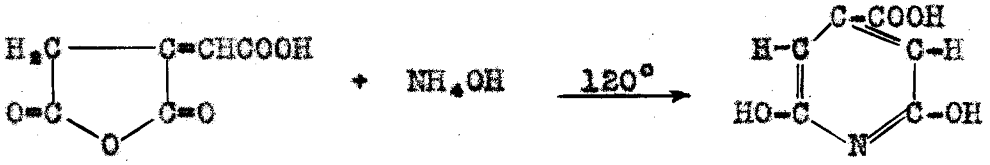
(58) See page 30 of this thesis.

(59) Meyer and Jacobson, "Lehrbuch der organischen Chemie," Vol. 2, part 3, 1920, p. 210. For more recent uses of this synthesis, see: Almstrom, Ann., 400, 131 (1913); Carriere, Ann. chim. phys., (9) 17, 38 (1922); and Fischer and Adler, Z. physiol. Chem., 197, 237 (1931).

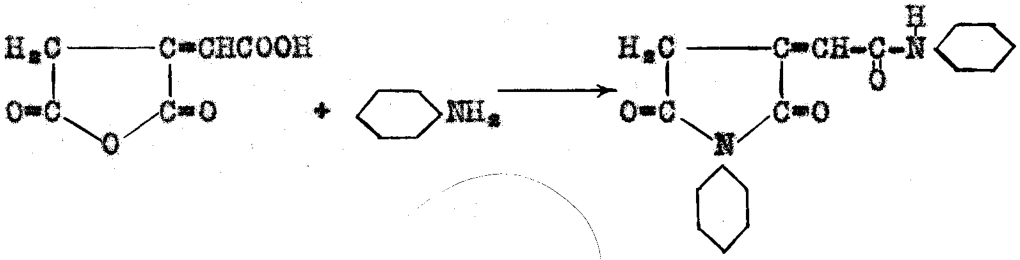
(60) Klingemann, Ann., 269, 131 (1892); Gysae, Ber., 26, 2478 (1893); Japp and Maitland, J. Chem. Soc., 85, 1496 (1904); Meyer, Kissin, and Pfotenhauer, Ber., 42, 2837 (1909).

(61) Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m.b.H., Leipzig. 1934, p. 124.

Ring closure to the six membered pyridine ring has also been observed under conditions similar to those just indicated for pyrrole derivatives. The case of 2,5-dihydrodehydromucic acid (46) which forms 2-carboxy-6-hydroxypyridine is particularly interesting since it is quite similar to the ring closure postulated for the precursor of the red compound. In both of these cases an α-carboxyfuran undergoes ring scission, and closes again through the carboxyl group to give a pyridine derivative. Another somewhat similar instance was reported by Easterfield and Sell (62):

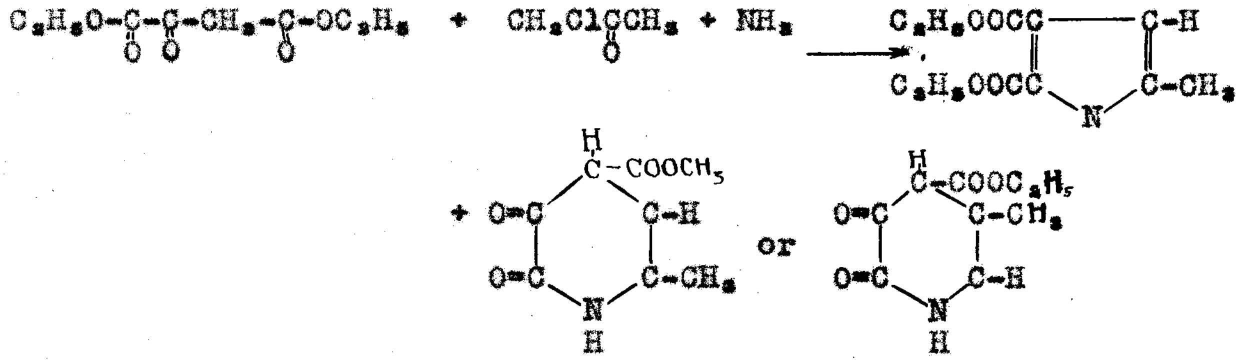


The same compound with aniline, however, closes to the five membered pyrrole ring instead of the six membered ring (63):



Feist and co-workers (64) observed in the reaction of ammonia, ethyl oxalacetate, and chloroacetone, in ether solution, ring closure to both five and six membered rings. The mechanism of the reaction has not been proven.

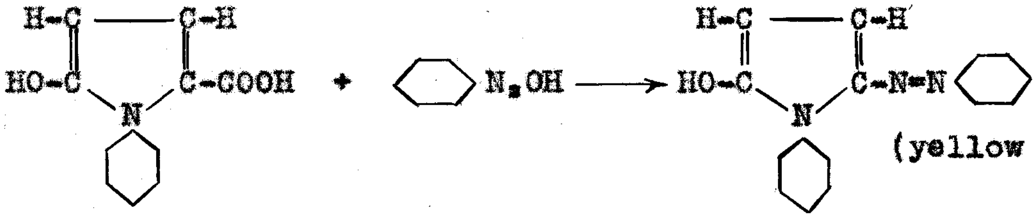
(62) Easterfield and Sell, *J. Chem. Soc.*, *61*, 1003 (1892).
(63) Bertram, *Ber.*, *38*, 1619 (1905).
(64) Feist, Widmer, and Dubosc, *Ber.*, *35*, 1545 (1902).



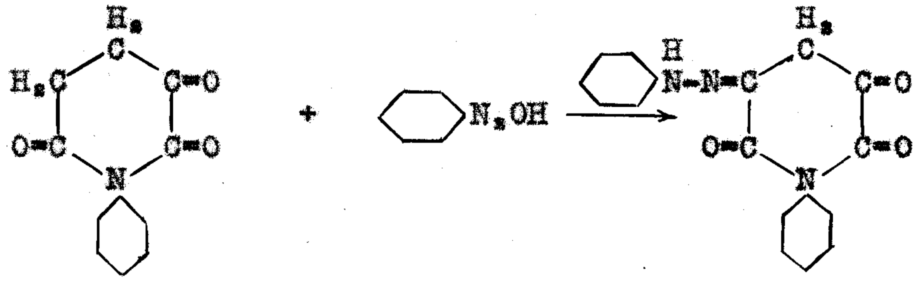
The ring closure of the furfuralaniline color base to a β-hydroxypyridinium salt has already been mentioned. The mechanism of this reaction does not appear applicable to the ring closure of the intermediate of step three of Hill and White's reaction. The reaction of aniline and furfural was carried out in sodium acetate solution in the hope of inducing the pyrrole type of ring closure, but the product was found to be the usual color base.

It was mentioned earlier that by increasing the alkalinity of the solution, the formation of the red compound was favored. If the proposed mechanism of the reaction is valid, this excess of alkali must favor the ring closure to the six membered ring. One possible explanation is that in the more alkaline solution, the aniline salt of the acid is less stable and hence the carboxyl group is freer to enter into the ring closure.

The sixth, and final, step in the reaction appears to be the coupling of the benzenediazonium hydroxide with the products of the ring closures of step five:



(yellow compound)



(red compound)

The displacement of the α-carboxyl group by the entering azo group to form the yellow compound is in agreement with the findings of Fischer and co-workers (65), who found that in the pyrrole series an α-carboxyl group is displaced in preference to coupling in the β-position.

The coupling reaction yielding the red compound is seen to be the usual coupling reaction which takes place with an active methylene group, as in various aliphatic compounds, of which acetoacetic ester is typical (66), cyclohexanones (67), and certain hydroxy aromatic compounds which can take the keto form (68,69,70):

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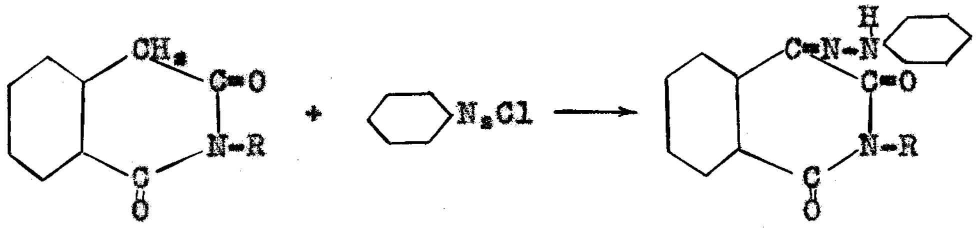
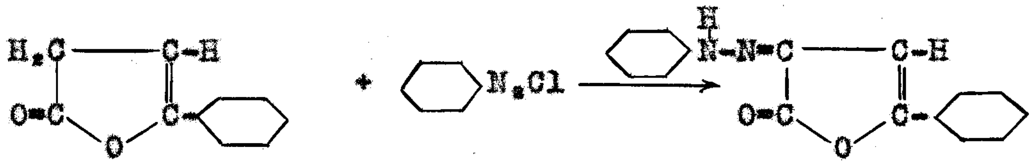
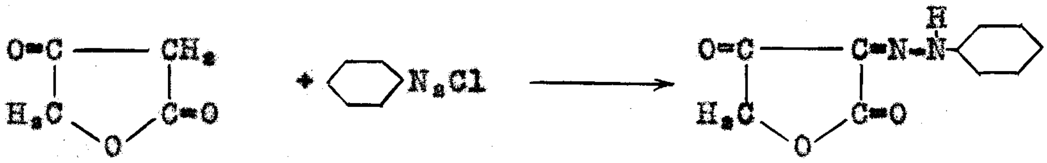
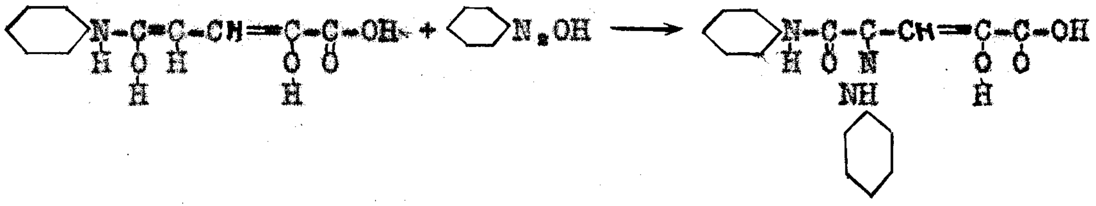
(65) Fischer and Hepp, Ber., 19, 2251 (1886); Fischer and Rothweiler, Ber., 56, 512 (1923).
(66) Meyer and Jacobson, "Lehrbuch der organischen Chemie," Vol. 2, part 1, 1920, p. 330.
(67) Sen and Ghosh, Quart. J. Indian Chem. Soc., 4, 477 (1927).
(68) Pulvermacher, Ber., 20, 2498 (1887); Gabriel, Ber., 20, 1205 (1887).
(69) Dieckmann, Ber., 47, 1439 (1914).
(70) Wolff and Lüttringhaus, Ann., 312, 155 (1900).



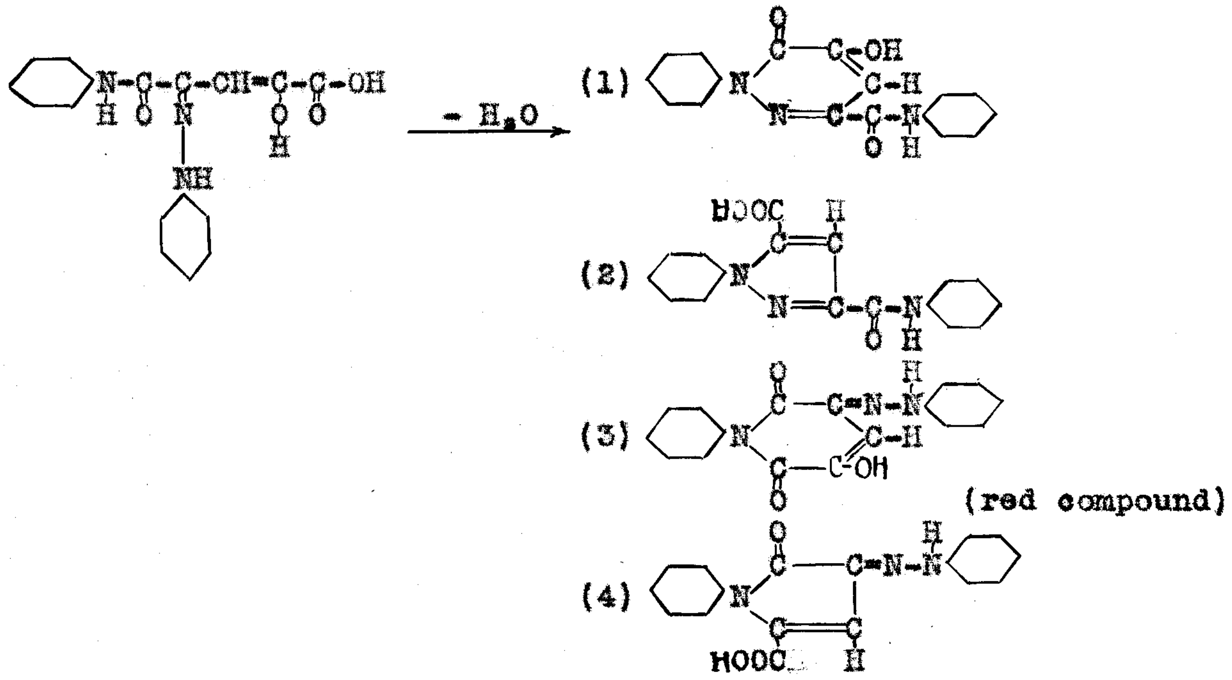




That coupling takes place as a final step seems to be indicated, since coupling of the straight chain intermediate of step three does not lead as clearly to the right product:



This intermediate might possibly lead to the formation of the red compound though there seems to be considerable chance that it would not. Inspection of the formula reveals four possible modes of ring closure:



The yellow compound can not possibly be formed through this intermediate, and since it offers a much less clear cut explanation of the formation of the red compound than the one previously outlined, the coupling of the diazonium compound with a straight chain intermediate is regarded as rather improbable.

In the case of the yellow compound it is particularly clear that coupling must take place either while the furan ring is intact or after the pyrrole ring has been formed; otherwise the azo group would not be found in its proper place, as has just been explained. That the coupling does not occur during the furan stage is indicated by the following experiments. It was found that benzenediazonium chloride coupled easily with 5-nitro-2-furoic acid with the elimination of the carboxyl group. This product, however, could not be made to react with aniline and hence is probably not an intermediate in Hill and White's reaction. Further, the compound is very insoluble in aqueous solutions, and for this reason would precipitate out of the reaction mixture if formed.

In connection with the reaction of nitrofuroic acid with benzenediazonium chloride, it is of interest to note that some furan compounds undergo coupling, though others do not readily react with diazonium compounds. 2-Furoic acid under the conditions used for 5-nitro-2-furoic acid gave a red compound which, however, was never obtained in the pure state. Wright (71) reported that furoic acid did not couple with p-sulphobenzenediazonium hydroxide. Vander Wal (72), following the method of Khotinsky and Soloweitschick (73) for the preparation of α-benzeneazopyrrole, attempted the coupling of furan with benzenediazonium chloride in both neutral and alkaline solution but was unable to isolate a pure product. Furan did not couple with p-sulphobenzenediazonium chloride, but did give a yellow product with p-nitrobenzenediazonium chloride which melted at 153-154°. Analysis of the compound was not conclusive. When the same reaction was run by Paul R. Van Ess (74) in alcoholic potassium acetate solution a very small yield of yellow needles melting at 133-134° was obtained. Ethyl furoate (72) was not successfully coupled with either benzenediazonium chloride in alcoholic sodium acetate solution or with p-nitrobenzenediazonium

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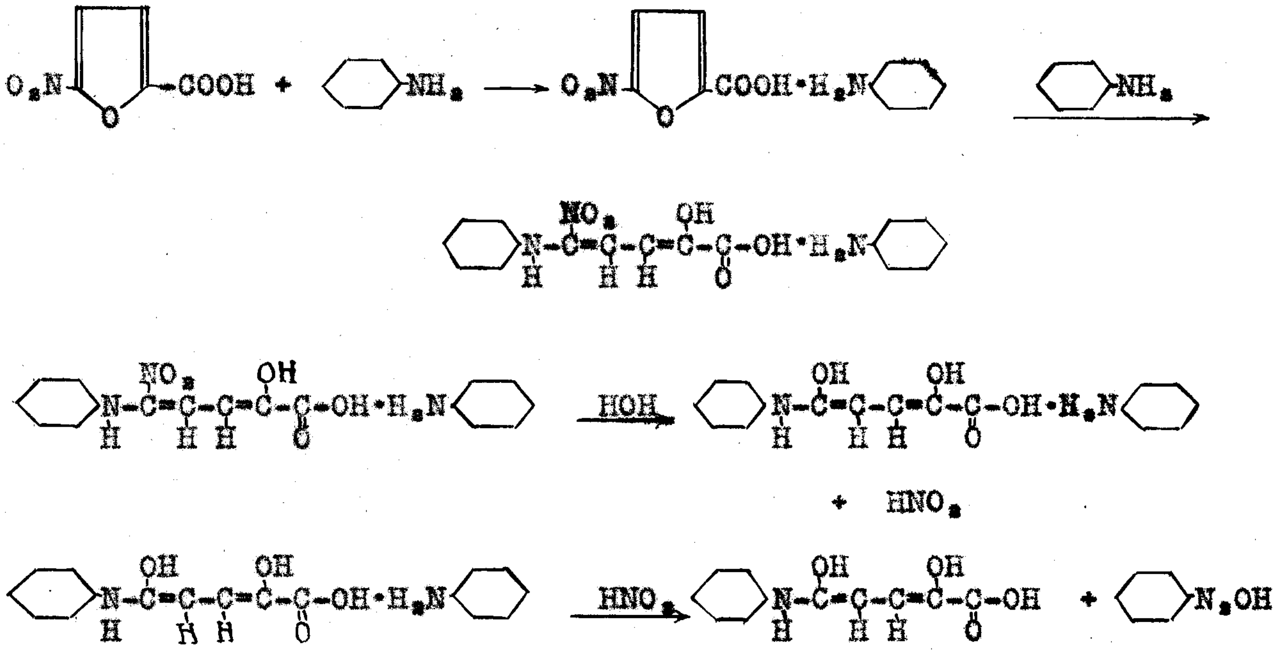
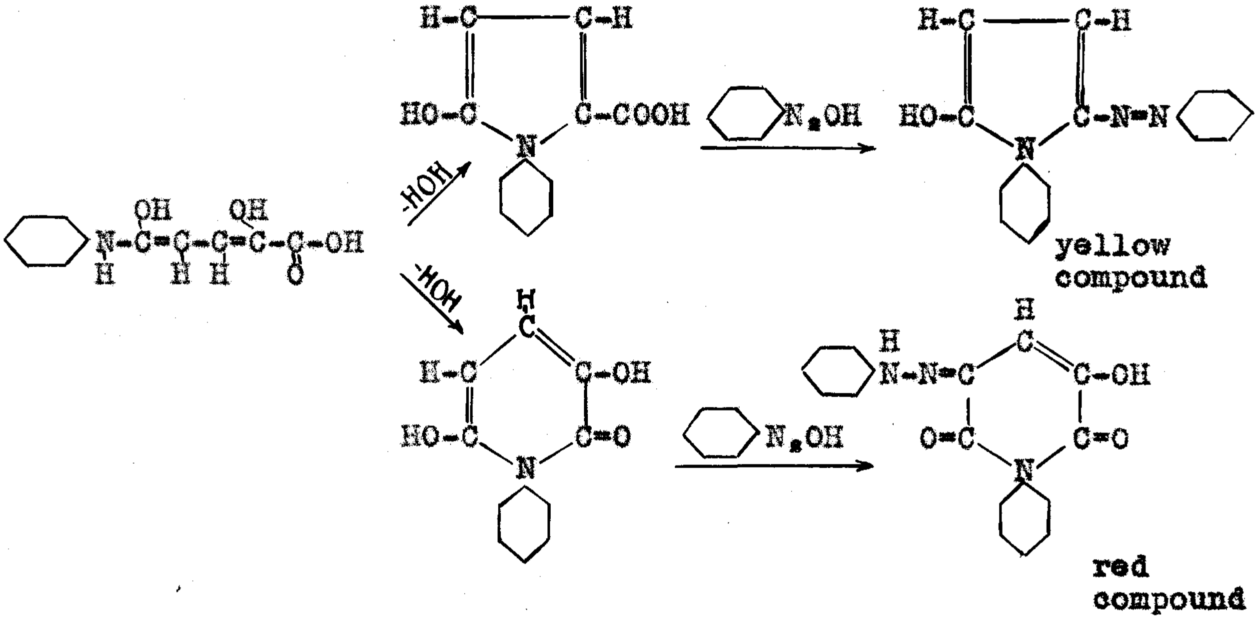
(71) Wright, George, Private Communication.
(72) Vander Wal, R.J., Unpublished work.
(73) Khotinsky and Soloweitschick, Ber., **42**, 2508 (1909).
(74) Van Ess, Paul R., Unpublished work.

chloride in dilute alcohol. Meyer, Irschuck, and Schlösser (75) were successful in reacting furfuryl alcohol with 2,4-dinitrobenzenediazonium sulphate in glacial acetic acid. A yellow brown product melting at 167° with decomposition was produced. Analysis indicated that the furfuryl alcohol had coupled with one molecule of the diazonium compound.

If the validity of all of the preceding postulations be granted, the mechanism of the Hill and White reaction may be summarized as follows:



(75) Meyer, Irschuck, and Schlösser, Ber., 47, 1753 (1914).



yellow compound

red compound

EXPERIMENTAL

Modified procedure for Hill and White's reaction.

The 5-nitro-2-furoic acid, 15.7 g. (0.1 mole), prepared according to the method of Hill and White (1) was suspended in about 35 cc.of water, and almost one equivalent of standard 0.1 N sodium hydroxide run in slowly from a burette. The flask was shaken vigorously during the addition. The resulting solution was then added to 1 liter of 10% sodium acetate solution, to which 25.8 g. (0.2 mole) aniline hydrochloride dissolved in the least amount of water had also been added. The solution turned greenish in a few minutes, then the color darkened and gradually turned red. Finally a red precipitate began to form and bubbles of carbon dioxide were slowly evolved. The reaction was carried out in a large beaker to avoid foaming over. The mixture was allowed to stand 48 hours, at which time the reaction was practically complete. Small amounts of precipitate continued to form in the filtrate for several days, but the quantity thus obtained was insignificant.

The red precipitate was filtered off and washed very thoroughly with water, for the removal of all alkaline material is very necessary. The precipitate was then dried. An average yield was 24 grams. The dried material was finely pulverized and extracted with chloroform until the insoluble portion was no longer tinged with red. The residue was the yellow compound, and was practically pure, melting at 232° with decomposition and evolution of gas. About 8.0 grams was obtained. The yellow compound may be recrystallized from glacial acetic acid from which it is obtained in small four pointed stars which are red by transmitted light, but usually have a bluish luster. When crushed, the crystals yield a bright yellow powder.

By concentrating the chloroform solution to a small volume and adding alcohol, the red compound was obtained in lustrous red crystals. Great care must be exercised that the chloroform be not alkaline (a drop of hydrochloric acid may be added to it) or be evaporated too far, otherwise no red compound will be isolated at all or else it will be contaminated with a tarry material which is extremely hard to remove. If necessary, the red compound may be recrystallized from glacial acetic acid or alcohol. When pure, it melts at 216°, decomposing to form a gas. The yield of red compound is variable; an average is 4 grams.

The procedure as described is recommended when the red compound is particularly desired. Almost twice as large yields of the yellow compound may be obtained by dissolving the nitrofuroic acid in the sodium acetate solution directly without previous neutralization, but the yield of red compound decreases very markedly. In an average run by this simpler procedure, 15 g. of the yellow compound and 1.2 g. of the red compound are obtained in comparison with 8 g. of yellow and 4 g. of red compound by the modified procedure previously described.

Preparation of the acetyl derivative of the yellow compound.

The yellow compound, 0.5 g. (0.019 mole), was gently warmed in 2 to 3 cc. of acetic anhydride to which a drop of concentrated sulphuric acid had been added. Cooling gave 0.3 g. of crude product melting at 177° with decomposition. The product was recrystallized three times from dilute alcohol and once from dilute acetone, and was finally obtained as yellow flattened needles melting at 197°. Analysis indicated a monoacetyl derivative.

Anal. Calcd. for $C_{18}H_{15}O_2N_3$: N, 13.77. Found: N, 13.96 and 13.68.

Acid hydrolysis of the yellow compound.

In order to facilitate the reaction, the yellow compound was first finely pulverized. Of the powdered material, 0.2 g. (0.0076 mole), was refluxed in 20% hydrochloric acid. Solution was practically complete in five hours, at which time the solution was filtered hot, cooled, and a very small amount of brownish material filtered off. The filtrate was made alkaline with sodium hydroxide solution, and distilled until the distillate was clear and had almost no odor of aniline (15 to 20 cc. of distillate). The distillate was made 10% with respect to sodium hydroxide by adding an appropriate quantity of concentrated sodium hydroxide solution, 0.4 g. (0.01 mole) of benzoyl chloride added, and the mixture shaken and stirred at intervals until the odor of benzoyl chloride had disappeared.

The precipitate was filtered off and dried; the melting point was 157-159°, mixed melting point with authentic benzanilide not depressed. The yield was 0.6 g. or 50% of one equivalent. The alkaline solution remaining after distillation was extracted with ether, the ether extract dried over sodium sulphate and evaporated. The small amount of dark brown oil remaining was treated with acetophenone to test for the presence of phenylhydrazine, but no reaction occurred. The alkaline layer after extraction with ether was acidified with hydrochloric acid and evaporated to dryness. No fumaric acid was obtained by vacuum sublimation of this residue.

Synthesis of the yellow compound.

The 1-phenyl-2-benzeneazopyrrole used in this synthesis was prepared according to the method of Plancher and Ghigi (76) from 1-phenylpyrrole. In each run, 2.75 g. (0.011 mole) of 1-phenyl-2-benzeneazopyrrole was added to a freshly prepared chloroform solution of the calculated amount of perbenzoic acid (77). The solution immediately turned green and a little heat was evolved. After standing 24 hours at room temperature, the solution was washed with 10% sodium carbonate, and the chloroform layer evaporated under somewhat diminished pressure (water pump). The viscous brown residue was extracted with 300 cc. of petroleum ether (b.p. 60-68°) in six portions,

(76) Plancher and Ghigi, Gazz. chim. ital., 55, 49 (1925).
(77) The perbenzoic acid was prepared and titrated as described by Brooks and Brooks, J. Am. Chem. Soc., 55, 4309 (1933).

working the tarry material thoroughly with a stirring rod during the extraction. In another run, an alternative procedure was used. The tar was entirely dissolved in benzene and the petroleum ether added to precipitate out a black-brown powder. This powder was redissolved in benzene, and reprecipitated with petroleum ether, then discarded. The petroleum ether solutions were combined and evaporated to 5 cc. and chilled. An oil separated out which crystallized after much stirring. The filtrate was further concentrated, chilled, and the product filtered off, and the process repeated until the precipitate obtained was tarry. The first fractions appeared to be unoxidized material (0.2 to 0.4 g.). The middle fractions melting from 180 to 215° were combined and recrystallized from glacial acetic acid, or alcohol. Partial purification may also be effected by dissolving in alcoholic potassium hydroxide and precipitating with acid. The final product melted at 232° with decomposition to form a gas, and gave no depression with a sample of the yellow compound obtained by the reaction of nitrofuroic acid and aniline in sodium acetate solution. The synthetic material gave all of the color reactions described by Hill and White for the yellow compound. It dissolved in alcoholic potassium hydroxide with a carmine red color, from which it precipitated unchanged by acidification. In concentrated sulphuric acid, it formed an orange-yellow solution which turned blue-green upon the addition of ferric chloride or potassium dichromate. The yield was extremely small; only a few crystals of pure material were obtained. The use of larger runs failed to increase the yield significantly.

Preparation of the acetyl derivative of the red compound.

Five-tenths gram (0.0016 mole) of the red compound was warmed gently in 2 to 3 cc. of acetic anhydride to which a drop of concentrated sulphuric acid had been added. The product was precipitated by the addition of water. The crude product melted at 166-170°, but after several recrystallizations from dilute acetone, the melting point was 195°. The mixed melting point with the acetyl derivative of the yellow compound was 158-162°. The product crystallizes in red needles. It is a monoacetyl derivative, though it appears likely that some of the diacetyl compound is also present since the values obtained on analysis tend to be low.

Anal. Calcd. for $C_{19}H_{15}O_4N_3$: N, 12.03. Found: N, 11.65 and 11.77.

Reduction of the red compound.

The red compound, 0.5 g. (0.0016 mole), was dissolved in 17 cc. of boiling glacial acetic acid, 1.0 g. (0.0052 mole) of stannous chloride hydrate dissolved in 5 cc. concentrated hydrochloric acid added, and the solution refluxed a few minutes. The deep color of the solution gradually faded to a light red. Cooling deposited a very few white crystals which were not identified. The filtrate was treated in an ice bath with small portions of a 30% sodium hydroxide solution until the precipitate of tin hydroxide had redissolved. The resulting solution was extracted with ether, the ether extract dried over sodium sulphate, and the amine hydrochloride precipitated by passing in dry hydrogen chloride. The hydrochloride was dissolved in dilute sodium hydroxide and 0.4 g. (0.01 mole) of benzoyl chloride added. After the reaction was complete, the precipitate was filtered off, washed and dried. It was identified as benzanilide by a mixed melting point determination with an authentic sample. The benzanilide obtained melted at 159-160°. The yield was 67% of one equivalent.

Alkaline hydrolysis of the red compound.

The red compound may be smoothly hydrolysed by means of dilute alkali. Too concentrated solutions are to be avoided due to the formation of tars. One gram (0.0032 mole) of the red compound was refluxed with exactly two equivalents of 0.1 N. sodium hydroxide for 2.5 hours, or until solution was complete. At the end of this time, 10 cc. of liquid was distilled off and made 10% with respect to sodium hydroxide, and an excess, 1.2 g. (0.0088 mole), of benzoyl chloride added. After standing with frequent shaking until the odor of benzoyl chloride had disappeared, the precipitate was removed, washed, and dried. After one recrystallization from alcohol the melting point was 161°, and was not depressed by mixture with authentic benzanilide. The yield of purified product was 0.4 g. or 77% of one equivalent.

The alkaline solution remaining after the distillation was filtered while hot, then cooled and acidified with hydrochloric acid. A cream colored flocculent precipitate separated out. This precipitate when dried melted at 250° with the evolution of gas. Concentration of the mother liquor gave an additional quantity of the compound. The two fractions were combined and washed with hot benzene, yielding 0.61 g. of insoluble material melting at 264-266°. Further recrystallization from water resulted in a sharp melting point of 266°, which was unchanged by mixing with an authentic sample of 1-phenyl-3,5-dicarboxypyrazole. The yield of partially purified material, m.p. 264-266°, was 81%. The acid was converted to its dimethyl ester by saturating a methyl alcoholic solution of the acid with dry hydrogen chloride at the boiling point of the alcohol. A part of the ester precipitated out upon cooling, and the remainder was precipitated out with water. The ester was recrystallized from methanol. The melting point (126-126.5°) was not depressed when a sample was mixed with an authentic specimen of the ester. The samples of the dicarboxypyrazole and its diester were prepared through 1-phenyl-3-carboxy-5-methylpyrazole as described by Claisen and Roosen (78). The structure of the di-acid was well established by these investigators.

Condensation of 5-nitro-2-furfural with aniline.

The nitrofurfural used in these experiments was synthesized in the manner of Gilman and Wright (79). When this compound

(78) Claisen and Roosen, Ann., 278, 286, 279 (1894).
(79) Gilman and Wright, J. Am. Chem. Soc., 52, 2550 (1930).

was reacted with either one or two equivalents of aniline in alcohol solution at 0° or at room temperature, a bright yellow compound crystallizing in lustrous flakes and melting at 126.5-127° was formed. From the analysis it is evident that only one molecule of the amine reacts with the aldehyde, presumably through the condensation with the carbonyl group.

Anal. Calcd. for $C_{11}H_8O_3N_2$: N, 12.96. Found: N, 13.05 and 12.72.

The same compound was also obtained but in more impure form by reacting the nitrofurfural with aniline hydrochloride in 10% sodium acetate solution, as in the Hill and White reaction.

The compound resisted all attempts to react it with a second equivalent of aniline in the absence of acid. It did not react when warmed on a steam bath with aniline in the absence of other solvents, or when refluxed with an alcoholic solution of aniline. When warmed with aniline hydrobromide in alcohol solution, a red tar was formed. No reaction took place in the cold.

Isolation of Sudan I from the Hill and White reaction in the presence of β-naphthol.

The nitrofuroic acid, 2.5 g. (0.0159 mole), was dissolved in 150 cc. of 10% sodium acetate solution to which 2.29 g. (0.0159 mole) of β-naphthol dissolved in the least amount of 5% sodium hydroxide had also been added. The β-naphthol was partially reprecipitated. Somewhat more than two equivalents of aniline hydrochloride, 4.32 g. (0.0335 mole), was dissolved in water and added to the above mixture. In a short time the precipitate became red, and after standing two days was filtered off. The total weight of dried precipitate was 5.3 g. Extraction with petroleum ether (b.p. 60-68°) removed the unchanged β-naphthol and the Sudan I. The residue was fractionated into 1.1 g. of yellow compound and 0.7 g. of red compound in the usual manner. The petroleum ether solution was washed with dilute sodium hydroxide to remove the excess β-naphthol, dried over sodium sulphate, and evaporated. The product thus obtained was recrystallized from ethanol to a melting point of 126-127°. A mixed melting point determination with authentic Sudan I (1-benzeneazo-2-hydroxynapthalene) proved the identity of the compound. The yield was 0.2 g. or 5%.

2,5-Dimethyl-3-nitrofuran, 1.4 g. (0.01 mole), was dissolved in a few cc. of alcohol and reacted in the presence of β-naphthol with aniline hydrochloride in sodium acetate solution to yield 0.15 g. of Sudan I (6% yield).

Reaction of 5-nitro-2-furoic acid with benzenediazonium chloride.

5-Nitro-2-furoic acid, 3.14 g. (0.02 mole), was dissolved in 200 cc. of 10% sodium acetate solution in a 500 cc. three necked flask equipped with a stirrer, dropping funnel and a thermometer. The diazo solution was prepared by pouring 1.86 g. (0.02 mole) aniline on 15 g. cracked ice, stirring in 5 cc. concentrated hydrochloric acid, and adding in small portions a solution of 1.70 g. (0.02 mole) sodium nitrite in a few cc. water until a permanent test with starch-potassium iodide paper was obtained. Since coupling did not take place at lower temperatures, the nitrofuroic acid solution was not cooled below 20°. The benzenediazonium chloride solution was added dropwise through the previously chilled dropping funnel, and stirring continued until a test for benzenediazonium chloride with β-naphthol was negative, or about 3 to 4 hours. About half of the product was removed by filtration, and the remainder was obtained by extraction of the filtrate with chloroform. The combined crude yield was 2.3 g. (53% of the theoretical) m.p. 115-120°. After several recrystallizations from dilute acetone, the compound crystallized in red-bronze needles melting at 140°.

Anal. Calcd. for $C_{10}H_7O_3N_3$: N, 19.36. Found: N, 19.23 and 19.17.

The compound is soluble in alkaline solutions with bright red color, but is not reprecipitated unchanged by acidification. It gives no color with alcoholic ferric chloride or when ferric chloride is added to a sulphuric acid solution of the compound. From these facts and the analysis, the compound must be formed by the displacement of the carboxyl group to form 2-benzeneazo-5-nitrofuran.

When suspended in a solution of aniline hydrochloride in

10% sodium acetate solution, no reaction took place. A slight reaction occurred with aniline hydrobromide in alcohol solution, but even after standing several days the extent of the reaction was very slight. The compound was also recovered unchanged after warming one hour on a steam bath with aniline hydrochloride in a glacial acetic acid solution of sodium acetate.

SUMMARY

I. A study of the reaction of 5-nitro-2-furoic acid with aniline hydrochloride in sodium acetate solution has been made.

II. Evidence pertaining to the structure of the colored products of the reaction has been obtained.

III. Some of the steps involved in the mechanism of the reaction have been established.

INTRODUCTION

The importance of the study of dibenzofuran in the preparation of synthetic morphine-like compounds has already been completely outlined by Kirkpatrick (80). Since morphine contains an hydroxylated dibenzofuran nucleus, the study of the orientation of the hydroxydibenzofurans is of particular significance. The coupling reactions of the hydroxydibenzofurans with benzenediazonium chloride here reported represent a part of such a study which was undertaken by Paul R. Van Ess (81).

The examination of the orientation of substituents in 4-carbomethoxydibenzofuran also bears an important relationship to the study of morphine-like compounds. The 4- (or 6-) position is one of the most critical positions in the dibenzofuran nucleus, for not only are the hydroxyl groups in morphine in the 4- and 6-positions of the dibenzofuran portion of the nucleus, but also a 4-substituted dibenzofuran (4-acetamino) has the greatest analgesic action of any dibenzofuran derivative yet tested (80). Since 4-carbomethoxydibenzofuran is the most available of the 4-substituted dibenzofurans it is of especial value to know the positions chosen when other substituents are introduced into the molecule. It is also possible that the polysubstituted compounds having the carboxyl (or ester) group in the 4-position might be useful in the preparation of analgesic compounds since such

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(80) Kirkpatrick, W.H., Doctoral Dissertation, Iowa State College, 1935.

(81) Van Ess, Paul R., Doctoral Dissertation, Iowa State College, 1936.

compounds can be converted, through the amides, to substituted 4-aminodibenzofurans.

The first investigation of the substitution reactions of 4-carbomethoxydibenzofuran was that of Hayes (82). A further study of the constitution of the bromination and nitration products of this ester was undertaken by the writer.

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(82) Hayes, D.M., Thesis, Iowa State College, 1934.

DISCUSSION

The 2-, 3-, and 4-hydroxydibenzofurans were coupled with benzenediazonium chloride in order to determine whether such a coupling reaction would involve the same positions as the direct bromination of the hydroxydibenzofurans.

The azo dyes derived from the 2- and 3- hydroxydibenzofurans were found to be insoluble in dilute alkali even when heated, whereas the dye derived from 4-hydroxydibenzofuran was easily soluble in cold alkaline solutions. This difference in behavior immediately suggested that the 2- and 3-hydroxy derivatives are coupled in o-positions, and that the 4-hydroxy derivative is coupled in the p-position. Though in the benzene series the o-hydroxy-azo compounds appear to be generally soluble in alkali, it is to be noted that in the naphthalene series, 1-hydroxy-2-benzeneazonaphthalene (83) and 1-benzeneazo-2-hydroxynaphthalene (84) are insoluble in alkali, and 1-hydroxy-4-benzeneazonaphthalene (84) is readily soluble. The 9-hydroxy-10-p-nitrobenzeneazophenanthrene is difficultly soluble in alkali (85).

The orientation thus indicated for the hydroxydibenzofurans might also have been predicted on the basis that the coupling of phenols with benzenediazonium chloride involves the position para to the hydroxyl group when it is available, otherwise,

(83) McPherson, Ber., 28, 2418 (1895).
(84) Liebermann, Ber., 16, 2860 (1883).
(85) Von Hyde, Ber., 32, 1815 (1899).

the o-positions (86). It is only in the 4-hydroxydibenzofuran that a position para to the hydroxyl group is available, hence the 2- and the 3-hydroxydibenzofurans would be expected to couple in the o-positions.

The dyes obtained from each of the hydroxydibenzofurans were in turn reduced to the corresponding hydroxyaminodibenzofurans which were converted to hydroxy-bromo compounds by the Sandmeyer reaction. In each case, the resulting hydroxybromo derivative was shown to be identical with the product of proven orientation obtained by direct bromination of the corresponding hydroxydibenzofuran (87), proving that the coupling reaction was subject to the same orienting influences as the substitution reaction. The azo dye derived from 3-hydroxydibenzofuran was thus established as 2-benzeneazo-3-hydroxydibenzofuran by its conversion to 2-bromo-3-hydroxydibenzofuran. The 2-hydroxy- and 4-hydroxy azo dyes were similarly proven to be 1-benzeneazo-2-hydroxydibenzofuran and 1-benzeneazo-4-hydroxydibenzofuran by conversion to 1-bromo-2-hydroxy- and 1-bromo-4-hydroxydibenzofuran, respectively. The identity of all of the hydroxy-bromo compounds was proven by mixed melting point determinations with authentic samples provided by Paul R. Van Ess.

An unsuccessful attempt was made to convert 1-amino-2-hydroxydibenzofuran, obtained by the reduction of 1-benzeneazo-2-hydroxydibenzofuran, to 1,2-dibenzofuroquinone. The method

(86) Chattaway and Hill, J. Chem. Soc., 121, 2756 (1922).
(87) The bromination products were prepared by Paul R. Van Ess. See Van Ess, Paul R., Doctoral Dissertation, Iowa State College, 1936.

employed was that used by Groves (88) for the preparation of naphthoquinone from 1-amino-2-hydroxynaphthalene. An amorphous reddish purple material was obtained from which no crystalline products could be separated.

The author was also unsuccessful in nitrosating 2-hydroxydibenzofuran either by the method of Marvel and Porter (89) for the preparation of nitroso-β-naphthol, or the Lagodzinski method (90) for nitroso-2-hydroxyanthracene.

Failure also attended the efforts to couple dibenzofuran itself and certain of its amino derivatives with diazonium compounds. Dibenzofuran did not couple with benzenediazonium chloride in alcohol solution in the presence of potassium acetate, nor with the more active 2,4-dinitrobenzenediazonium chloride (91) in acetic acid. 2,4,6-Trinitrobenzenediazonium chloride (92), like the dinitro derivative has been reported to couple with mesitylene, but the writer experienced considerable difficulty in diazotizing this amine. 2-Amino- or 2-acetaminodibenzofuran also failed to couple with benzenediazonium chloride under conditions which give quantitative yields with β-naphthylamine (93). The principal difficulty in this case seemed to be the greater insolubility of the dibenzofuran amine (or acetamino

(88) Groves, J. Chem. Soc., 45, 298 (1884).
(89) Marvel and Porter, Organic Syntheses, Coll. Vol. I, 403, 1932.
(90) Lagodzinski, Ann., 342, 69 (1905).
(91) Meyer, Ber., 47, 1747 (1914), reported that 2,4-dinitrobenzenediazonium chloride will couple with mesitylene and acenaphthene under these conditions.
(92) Meyer and Tochtermann, Ber., 54, 2283 (1921).
(93) Bamberger and Schieffelin, Ber., 22, 1376 (1889).

analog) in the alcoholic reaction medium even when the reaction was run at a somewhat higher temperature.

At the conclusion of the study of the coupling of dibenzofuran derivatives with benzenediazonium chloride, attention was turned to the completion of the investigation of the orientation of substituents in 4-carbomethoxydibenzofuran. This problem was begun by Hayes (82), who isolated the bromination and nitration products of this ester and partially proved their structure. This investigator showed that bromination in carbon tetrachloride solution gave an ester melting at 166-167°. By hydrolysis this ester was converted to an acid melting at 263-264°, from which the known 2-bromodibenzofuran was obtained by decarboxylation. Nitration of 4-carbomethoxydibenzofuran was reported by Hayes to give two isomers, the principal one melting at 156-158° and the other at 205-205.5°. The 156-158° ester on hydrolysis gave an acid melting at 160-165°, which yielded 3-nitrodibenzofuran on decarboxylation. The 205-205.5° ester yielded an acid melting at 300-305°, which when decarboxylated formed 2-nitrodibenzofuran.

The experiments of Hayes could only be partially duplicated by the writer. The nitro-ester melting at 205-205.5° was not obtained in any one of several runs in which Hayes' directions were followed. Variations of this method also tried to no avail were, the use of fuming nitric acid instead of concentrated nitric acid, the use of lower temperatures, and the use of crude instead of purified ester as starting material (94). The yield of the one ester obtained was 60% of the theoretical based on the weight of the highly purified product. The melting point of the crude material was 115-145°, where Hayes reported 120-170°.

Incidental to the preparation of 4-carboxydibenzofuran used as starting material in these experiments, it was noted that in the carbonation of 4-dibenzofuryl-lithium, varying amounts of a non-acidic product were also formed. On the basis of other reports on the carbonation of organolithium compounds (95), this compound was thought to be di-4-dibenzofuryl ketone. Subsequent analysis of the compound confirmed this expectation. The purified product crystallized in white needles, melting sharply at 172-173°. Attempts to prepare the oxime were not successful.

Owing to the previous work of Hayes, the completion of the proof of structure of the bromo- and nitro-esters derived from 4-carbomethoxydibenzofuran involved only the problem of whether homo- or heterosubstitution had taken place.

The first objective was to definitely prove the orientation of the bromo-ester which he had shown to be

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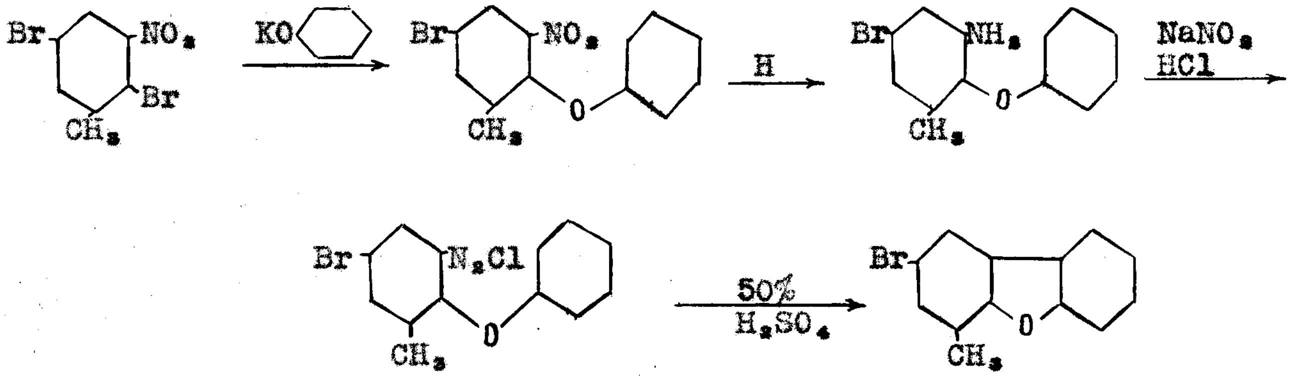
(94) The methods used by Bywater (unpublished work) to increase the formation of isomers in the nitration of dibenzofuran did not come to the attention of the writer until the conclusion of these experiments. Bywater's methods might have been more successful than the ones described.

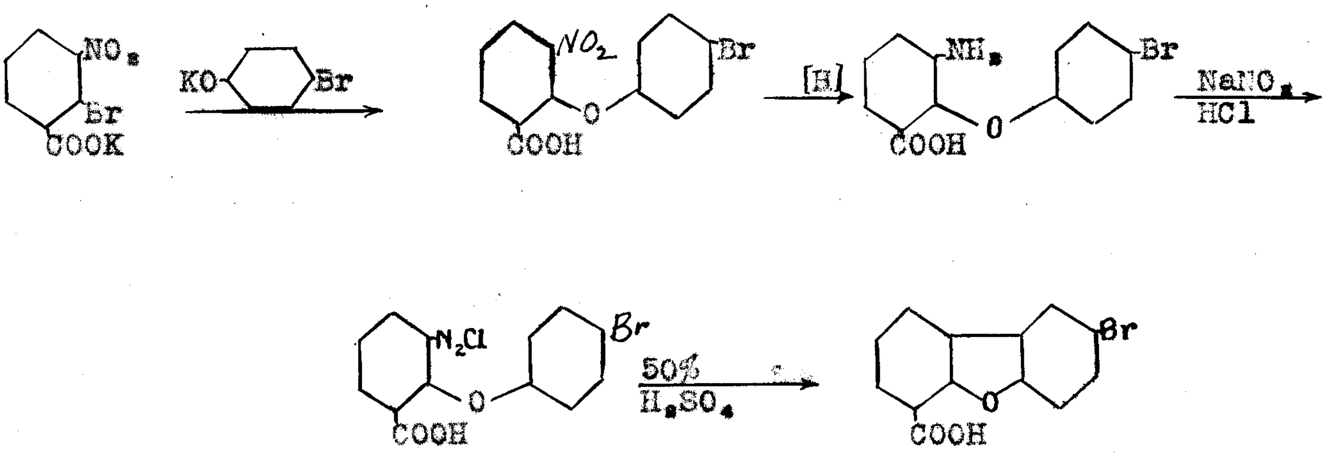
(95) Gilman and Van Ess, Paul R., J. Am. Chem. Soc., 55, 1258 (1933).

2-(or 7-) bromo-6-carbomethoxydibenzofuran. The following ring closure was undertaken in order to prepare 2-bromo-4-methyldibenzofuran, which by oxidation should yield 2-bromo-4-carboxydibenzofuran:



The 2-bromo-4-methyldibenzofuran was obtained but it resisted all efforts to oxidize the methyl side chain to a carboxyl group. It was unaffected by refluxing four days whith alkaline potassium permanganate, a mixture of potassium permanganate and dilute nitric acid at 180° for eight hours, and an alkaline solution of potassium ferrocyanide at reflux temperature for twelve hours. When treated with a glacial acetic acid solution of chromic acid four hours at 50°, the compound was partially destroyed but no acid could be isolated, and a part of the compound was recovered unchanged. In the same solution at the boiling point the compound was completely destroyed. The use of chromic acid in dilute sulphuric acid also destroyed the compound without stopping at the desired dibenzofuran acid.

A second ring closure was then attempted in order to prepare the isomeric 2-bromo-6-carboxydibenzofuran.



Success was realized in this synthesis, and the bromo-acid obtained was found, by the method of mixed melting point, to be identical with the acid obtained by the hydrolysis of Hayes' bromo-ester. As a further check, the acid prepared by ring closure was converted to the methyl ester with diazomethane, which by a mixed melting point, was proven identical with Hayes' ester obtained by brominating 4-carbomethoxydibenzofuran. Hence the structure of Hayes' bromo-ester was unequivocally established as 2-bromo-6-carbomethoxydibenzofuran.

The ring closure reactions are of more than passing interest since they illustrate the wide applicability of this mode of synthesis. They are not only the first successful attempts to prepare 4-substituted dibenzofurans by this method, but also include the first reported instance of the preparation of a carboxydibenzofuran by ring closure. It has been observed by the author that the arrangement of substituents in the diphenyl ether is of particular importance in determining the success of the ring closure. The positions of the groups which are to become the substituents of the dibenzofuran product are, of course, fixed; but the nitro group through which the ring is ultimately closed by reduction and diazotization, theoretically, might occupy a position in either ring ortho to the oxygen bridge. Actually, it appears, that the nitro group must be in the same ring with the group which is to be the 4-substituent of the dibenzofuran product. Thus far, at least, success has attended every synthesis in which these conditions were fulfilled, and every attempt in which these conditions were not met has ended in failure (96,81).

The orientation of Hayes 3- (or 7-) nitro-6-carbomethoxydibenzofuran still remained to be proven. The structure of this ester was established by the introduction of a third substituent. In this manner, it was possible to establish a structural relationship between the nitro-ester and the 2-bromo-6-carbomethoxydibenzofuran established by ring closure.

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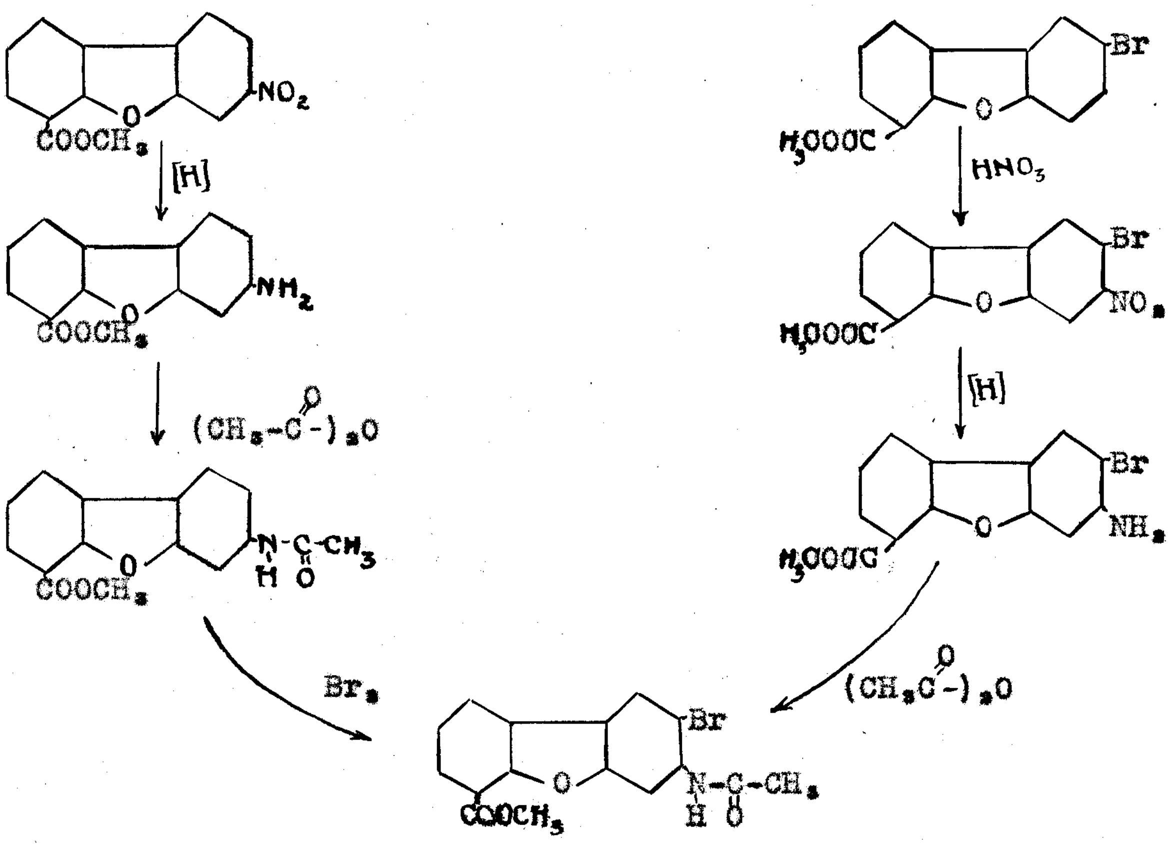
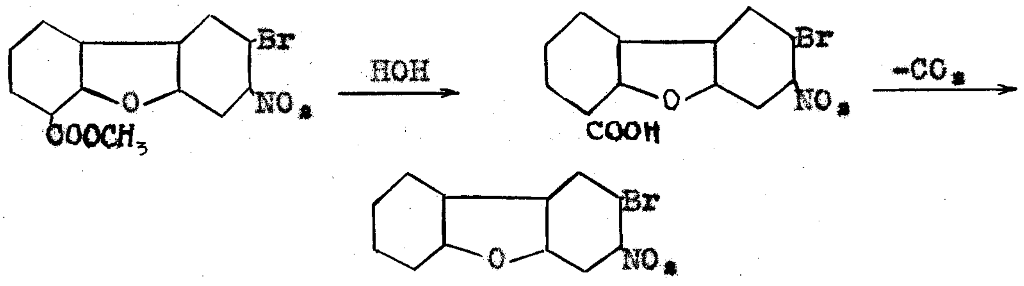
(96) McCombie, Macmillan, and Scarborough, *J. Chem. Soc.*, 529, (1931).



Having prepared the same 2-bromo-3- (or 7-) acetamino-6-carbomethoxydibenzofuran from both the nitro-ester and the proven bromo-ester it was only necessary to prove that the bromo and the acetamino (or amino or nitro) group were *ortho* to each other in order to completely establish the structure of the nitro-ester. Proof of the *ortho* configuration of the bromo-nitro-ester was attempted by the following sequence:



The ester was hydrolysed without difficulty, but decarboxylation by treating the acid in quinoline with copper bronze yielded 3-nitrodibenzofuran. The same result was obtained when copper sulphate hydrate was substituted for the copper bronze (97).

By considering the series of reactions by which 2-bromo-3-(or 7-) nitro-6-carbomethoxydibenzofuran was prepared from the bromo-ester and from the nitro-ester, it is evident that decarboxylation of the bromo-nitro-acid must yield transiently either 2-bromo-3-nitro-dibenzofuran or 2-bromo-7-nitrodibenzofuran, because the bromo-nitro-ester was obtained by nitration of the established 2-bromo-6-carbomethoxydibenzofuran, and the position of the nitro group was known to be either 3- or 7- by the relationship to Hayes' 3-(or 7-) nitro-6-carbomethoxydibenzofuran.

If the acid was certain to form either 2-bromo-3-nitrodibenzofuran or 2-bromo-7-nitrodibenzofuran by decarboxylation, it only remained to prove that only one of these compounds would lose its halogen atom under the conditions of the experiment. Authentic samples of 2-bromo-3-nitrodibenzofuran and 2-bromo-7-nitrodibenzofuran (98) were then subjected to the exact conditions used for the decarboxylation of the bromo-nitro-acid;

(97) Decarboxylation by heating the acid with calcium oxide was not tried since this would almost certainly cause a loss of halogen. For a description of this method, see Smith, E.W., Doctoral Dissertation, Iowa State College, 1936.

(98) The writer is indebted to Dr. Glen Bywater for samples of these two compounds.

2-bromo-7-nitrodibenzofuran was recovered unchanged, whereas 2-bromo-3-nitrodibenzofuran was converted to 3-nitrodibenzofuran. It was thereby established that the bromo-nitro-acid was 2-bromo-3-nitro-6-carboxydibenzofuran. The ease with which the halogen is removed from 2-bromo-3-nitrodibenzofuran is in harmony with the known fact that a _meta_-directing group renders substituents _ortho_ or _para_ to it more labile (99).

When the structure of the bromo-nitro-acid was established as 2-bromo-3-nitro-6-carboxydibenzofuran, it was automatically proven that the 3-(or 7-) nitro-6-carbomethoxydibenzofuran was none other than 3-nitro-6-carbomethoxydibenzofuran by the relationship previously established between these compounds (100).

It is of interest to compare the findings of this study with the results obtained by other investigators with different dibenzofuran esters. The bromination of 2-carboethoxydibenzofuran was shown by Brown (101) to involve the 8-position. Bailie (102) found that the nitration of the 3-carbomethoxydibenzofuran yielded 8- (or 2-) nitro-3-carbomethoxydibenzofuran. Recently, Paul R. Van Ess (81) nitrated the 1-carbomethoxydibenzofuran and obtained 7- (or 3-) nitro-1-carbomethoxydibenzofuran.

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(98) The writer is indebted to Dr. Glen Bywater for samples of these two compounds.
(99) Schöpf, _Ber._, _22_, 900 (1889).
(100) See page 70 of this thesis for these inter-relationships.
(101) Brown, G. E., Unpublished work.
(102) Bailie, J. C., Unpublished work.

The bromination of 2-carboethoxydibenzofuran, like the bromination and nitration of 4-carbomethoxydibenzofuran, has been definitely proven to involve heterosubstitution. The nitration of the 3-carbomethoxydibenzofuran appears quite certainly to involve heterosubstitution, for from the facts already established, had homosubstitution taken place it would require that the entering nitro group take a position ortho to the carboxyl group when the other ring still remained unsubstituted. The 7- (or 3-) nitro-1-carbomethoxydibenzofuran and the 2- (or 8-) nitro-6-carbomethoxydibenzofuran obtained by Hayes are probably heterosubstituted also, though here homosubstitution would not contradict the meta-directing influence of the carbomethoxy group. However, the factors favoring heterosubstitution--the presence of one unsubstituted ring and the presence of a meta-director in the other ring--would appear to be of greater weight. It was observed by the author, that the introduction of a second substituent in a ring already occupied by a "de-activating" group, as in the nitration of 2-bromo-6-carbomethoxydibenzofuran, required considerably harsher conditions than heterosubstitution of a monosubstituted dibenzofuran. Both the 7- (or 3-) nitro-1-carbomethoxydibenzofuran and the 2- (or 8-) nitro-6-carbomethoxydibenzofuran were obtained under mild conditions. Further, as the supporting evidence mounts, one may rely with increasing security on the generalization that in the dibenzofuran series, heterosubstitution will take place when one ring is previously occupied by a meta-director, or to a somewhat lesser extent when a halogen substituent is present.

A further point of interest in the orientation of substituents in the dibenzofuran ester series is that it adds more evidence for the general rule that in the heterosubstituted dibenzofurans, the second substituent, be it like or unlike the first, is directed to the position involved in the monosubstitution of the nucleus itself, with the exception of the nitro group which may involve predominantly the 2- rather than the 3- position. In the bromination of the 4- or 2- carbomethoxydibenzofuran, the second substituent has entered its "normal", that is 2- or 8-, positions favored in bromination of dibenzofuran itself. The nitration of the 1-carbomethoxydibenzofuran gives rise to substitution in the normal 7- (or 3-) position, and nitration of the 4-carbomethoxydibenzofuran involves both normal 7- (or 3-) substitution and to a smaller extent the less expected 8- (or 2-) position. Nitration of the 3-carbomethoxydibenzofuran likewise involves substitution in more unusual 2- (or 8-) position. The only other similar instance is the dinitration of dibenzofuran (103) which again involves the introduction of the second nitro group in the 8- position. It is curious that this somewhat anomalous orientation incident to certain heterosubstitutions has never been observed except in

(103) Cullinane, _J_. _Chem_. _Soc_., 2365 (1932).

nitration, and that the nitro group in all of these exceptional cases invariably involves the 2- (or 8-) position. It must be remembered, however, that nitration of dibenzofuran itself gives some 2-nitrodibenzofuran (104). Hence the heterosubstitution by a nitro group in the 2- (or 8-) position is not entirely without basis. It is only the predominance of the 2- (or 3-) position which varies in accordance with the other substituents present.

(104) Gilman, Bywater, and Parker, J. Am. Chem. Soc., 57, 885 (1935).

EXPERIMENTAL

Preparation of 1-benzeneazo-2-hydroxydibenzofuran.

The 2-hydroxydibenzofuran used in this synthesis was prepared as directed by Bywater (105). The general procedure for the coupling reaction was adapted from that used by Werner and Frey (106) in preparing the benzeneazo derivative of 10-hydroxyphenanthrene. The 2-hydroxydibenzofuran, 3.68 g. (0.02 mole), was dissolved in 15 cc. of 15% potassium hydroxide solution, and subsequently diluted with 60 cc. of water, then cooled to 0° in a 200 cc. three-necked flask equipped with a stirrer, dropping funnel, and thermometer. The diazonium solution was prepared by adding 5 cc. of concentrated hydrochloric acid to a mixture of 1.86 g. (0.02 mole) aniline and 15 g. finely cracked ice, then adding dropwise a solution of 1.46 g. (0.021 mole) sodium nitrite in a few cc. of water, until a slight but permanent test for nitrite ion was indicated by a test with starch-potassium iodide paper. The diazonium solution was added dropwise to the cold solution of 2-hydroxydibenzofuran through the chilled dropping funnel. The temperature was maintained at 0° by means of an ice bath. A red precipitate formed at once. To ensure complete reaction the mixture was stirred for 30 minutes after addition was completed. The product was then removed by filtration and washed well with water. Acidification is not necessary since the desired product is insoluble in alkali. The yield was

(105) Bywater, W.G., Doctoral Dissertation, Iowa State College, 1934.

(106) Werner and Frey, Ann., 321, 303 (1902).

almost quantitative. The crude product melted at 161-164°, and two recrystallizations from alcohol gave red needles melting at 165.5-166°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: N, 9.72. Found: N, 9.84 and 9.98.

Preparation of 2-benzeneazo-3-hydroxydibenzofuran.

The 3-hydroxydibenzofuran, prepared according to Bywater's synthesis (105), was coupled with benzenediazonium chloride in exactly the manner described above for 2-hydroxydibenzofuran. It was found to be advantageous, however, to run the reaction at a slightly lower temperature (-5 °). The mixture was filtered at the close of the reaction without previous acidification. The yield from 3.68 g.,(0.02 mole), 3-hydroxydibenzofuran was 4 g. or 73% of the theoretical. The product after twice crystallizing from alcohol, and once from ethyl acetate, and once from a mixture of ethyl acetate and alcohol melted at 177-178°. It crystallized in minute lustrous golden brown plates.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: N, 9.72. Found: N, 9.70 and 9.83.

Preparation of 1-benzeneazo-4-hydroxydibenzofuran.

The 4-hydroxydibenzofuran was prepared by the method described by Bywater (105). It was coupled with benzenediazonium chloride by the procedure described for 2-hydroxydibenzofuran. In this case the resulting azo compound formed a salt which separated in very fine orange crystals. Direct acidification of the reaction mixture gave purplish material which turned green upon drying and was very difficult to purify. In order to obtain a pure sample it was necessary to either filter out the potassium salt from the reaction mixture and then acidify, or to crystallize the purplish material obtained by acidification of the reaction mixture at once from dilute alcohol without allowing it to stand. The purified product separated in yellow-orange needles from dilute alcohol which melted at 174-175°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: N, 9.72. Found: N, 9.77 and 9.99.

Conversion of 1-benzeneazo-2-hydroxydibenzofuran to 1-bromo-2-hydroxydibenzofuran.

The method described by Pschorr (107) for the reduction of 9-hydroxy-10-benzeneazophenanthrene was used as a basis for the reduction of the hydroxyazodibenzofurans. One gram (0.0045 mole) of 1-benzeneazo-2-hydroxydibenzofuran was dissolved in 40 cc. of boiling glacial acetic acid, and a solution of 2.0 g. of stannous chloride hydrate in 15 cc. concentrated hydrochloric acid added gradually. The color of the solution quickly faded to yellow. The solution was then cooled, whereupon fine white needles separated out. These crystals proved to be the hydrochloride of 1-amino-2-hydroxydibenzofuran. A quantitative yield was obtained. The compound had a tendency to oxidize in air, hence it was used at once to prepare the corresponding bromohydroxy compound.

(107) Pschorr, Ber., 35, 2734 (1902).

The diazotization of all of the hydroxyaminodibenzofurans proved rather difficult owing to their marked sensitivity to oxidation. The procedure finally used was based on a patented process for the diazotization of *o*-aminonaphthols (108). The hydrochloride of 1-amino-2-hydroxydibenzofuran was suspended in ether and treated with an equivalent amount of sodium carbonate solution. The ether layer was washed with water, dried over sodium sulphate and the amine hydrobromide precipitated by passing in dry hydrogen bromide (109). Of the hydrobromide, 0.45 g.(0.0025 mole), was suspended in 30 cc. of water at 0°, poured gradually into a similarly cooled solution of 0.12 g. (0.0017 mole) sodium nitrite and 0.08 g. copper sulphate hydrate in 10 cc. of water. A light brown precipitate formed. Fifteen minutes was allowed for the completion of the diazotization, whereupon the mixture was poured into a suspension of 0.81 g. (0.0021 mole) cuprous bromide in 20 cc. of water, and 13 cc. of 40% hydrobromic acid was added gradually. As soon as the evolution of gas ceased, the mixture was boiled a few minutes. Some very dark precipitate was filtered from the hot solution. The filtrate on cooling deposited greyish needles, 0.015 g., melting at 115-116°. When decolorized with charcoal and crystallized from dilute alcohol, the melting point was 121.5-122° and was not depressed by mixture with an authentic sample

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(108) Ger., 172, 446, (J. Chem. Soc., 90, 907 (1906)).

(109) Hydrogen bromide gas was prepared by the method of Ruhoff, Burnett and Reid, Organic Syntheses, Vol. 15, 35, 1935.

of 1-bromo-2-hydroxydibenzofuran (110).

Conversion of 2-benzeneazo-3-hydroxydibenzofuran to 2-bromo-3-hydroxydibenzofuran.

The 2-benzeneazo-3-hydroxydibenzofuran was reduced according to the procedure described for the 1-benzeneazo-2-hydroxydibenzofuran. In the case of the 3-hydroxy derivative, the hydroxyamine formed a complex with the tin salt and hence did not precipitate out directly as the hydrochloride upon cooling the reaction mixture. In order to break up the complex, the solution obtained after reduction was complete, was cooled in an ice bath, and treated with small portions of 30% sodium hydroxide solution until the precipitated tin hydroxide had redissolved, then made barely acid with hydrochloric acid, and finally slightly basic with ammonium hydroxide. The solution was then extracted with ether, the ether layer dried over sodium sulphate, and the amine hydrobromide precipitated with dry hydrogen bromide.

The conversion of the hydrobromide to 2-bromo-3-hydroxydibenzofuran was accomplished by the method employed for the hydrobromide of 1-amino-2-hydroxydibenzofuran. From 0.45 g. (0.0025 mole) of the hydrobromide the yield was 0.04 g. of crude product, which after decolorizing and crystallizing from

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(110) Authentic samples of 1-bromo-2-hydroxydibenzofuran, 2-bromo-3-hydroxydibenzofuran, and 1-bromo-4-hydroxydibenzofuran were obtained through the courtesy of Paul R. Van Ess.

dilute alcohol melted at 111-112°. A mixed melting point determination with authentic 2-bromo-3-hydroxydibenzofuran (110) showed no depression.

Conversion of 1-benzeneazo-4-hydroxydibenzofuran to 1-bromo-4-hydroxydibenzofuran.

The 1-benzeneazo-4-hydroxydibenzofuran was reduced in the same manner as described for 1-benzeneazo-2-hydroxydibenzofuran. The amine hydrochloride did not form a complex with the tin salt, but separated out at once in greenish gray crystals. The hydrochloride was converted to the hydrobromide, diazotized, and the diazonium group replaced by bromine as previously outlined for 1-amino-2-hydroxydibenzofuran. From 0.45 g. (0.0025 mole) of the hydrobromide, a crude yield of 0.015 g. bromo-hydroxydibenzofuran melting at 145-146° was obtained. By decolorizing and crystallizing from dilute alcohol, white needles were produced melting at 150°. Identification of the compound as 1-bromo-4-hydroxydibenzofuran was completed by a mixed melting point determination with an authentic specimen (110).

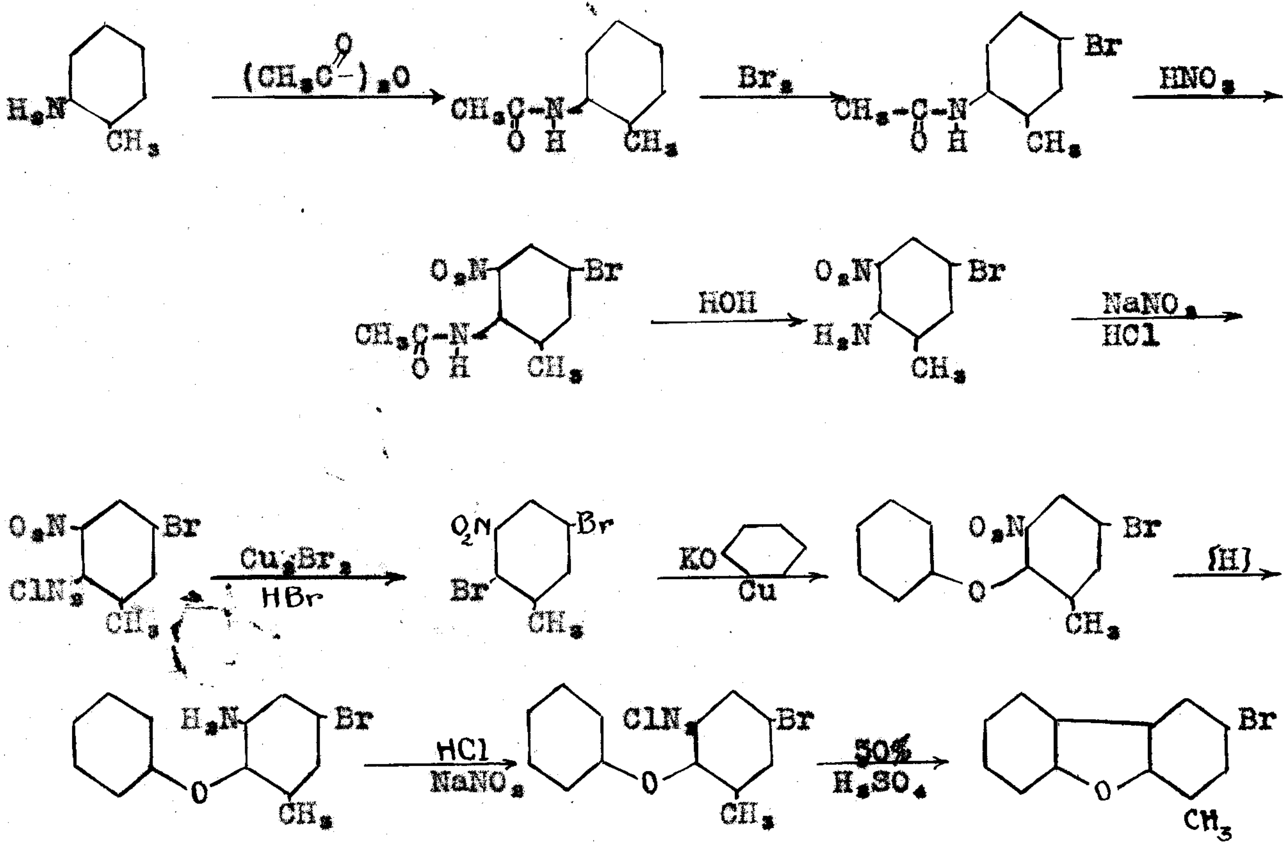
Isolation of di-4-dibenzofuryl ketone.

The alkali insoluble fraction from the carbonation of 4-dibenzofuryl-lithium (105) was first extracted with boiling petroleum ether (b.p. 60-68°) to remove dibenzofuran. For 5 g. of material, 100 cc. of solvent was used. A second extraction with 300 cc. of boiling ethanol yielded when cool 1.3 g. of fine white needles melting at 171-173°. One recrystallization from the same solvent raised the melting point to 172-173°.

Anal. Calcd. for $C_{22}H_{14}O_2$: C, 82.85; H, 3.90. Found: C, 82.58; H, 3.89.

Preparation of 2-bromo-4-methyldibenzofuran by ring closure.

The method for the synthesis of 2-bromo-4-methyldibenzofuran from a substituted diphenyl ether was based upon the similar syntheses of Mc Combie, Macmillan and Scarborough (96). The reactions which were involved in the preparation of 2-bromo-4-methyldibenzofuran may be summarized as follows:



One hundred thirty-four grams (1.25 moles) of freshly distilled o-toluidine was acetylated by treating the benzene solution of the amine with a slight excess, 143 g. (1.4 moles), of acetic anhydride. After standing 30 minutes an equal volume of petroleum ether (b.p. 60-68°) was added and the product precipitated completely by chilling in the ice box. The compound crystallized in clustered needles which melted at 108°. The acet-*o*-toluidide obtained, 135 g., was brominated in 50 g. lots by the procedure of Bogert and Hand (111), and the product purified by crystallization from a large volume of water. A yield of 167 g. (80% of the theoretical) melting at 153.5-154° was realized. The bromo-acet-toluidide was nitrated by dissolving in fuming nitric acid (d=1.50) allowing 6 cc. of acid to 1 g. of compound (112). The acid was cooled in an ice-salt bath, and the compound added gradually. After standing 30 minutes, the solution was poured on ice, and the product removed by filtration. The acetyl group was removed by boiling 25 g. lots of the nitrated product with 120 cc. ethyl alcohol and 30 cc. concentrated hydrochloric acid for 2 hours; the crude product was recrystallized from petroleum ether (b.p. 60-68°) to give 52 g. of compound melting at 134°. The amino group was then replaced by bromine according to the procedure outlined by Holleman (113). By this means, 23 g. of crude 2,4-dibromo-3-nitrotoluene melting from 59° to 64° was prepared. Two recrystallizations from petroleum

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(111) Bogert and Hand, *J. Am. Chem. Soc.*, *27*, 1479 (1905).
(112) Wroblewski, *Ann.*, *192*, 206 (1878); see also Niementowski, *Ber.*, *25*, 869 (1892).
(113) Holleman, *Rec. trav. chim.*, *27*, 155 (1908).

ether (b.p. 60-68°) raised the m.p. to 68-69°. (Reported m.p. 69-70°).

The 2,4-dibromo-3-nitrotoluene, 14.2 g. (0.048 mole), was heated at a temperature of 170° for 3 hours with 6.86 g. (0.052 mole) potassium phenoxide (114). The cooled reaction mixture was shaken with ether and water. The residue obtained by evaporation of the ether layer was crystallized from petroleum ether (b.p. 60-68°). The purified product, 2-nitro-4-bromo-6-methyldiphenyl ether, melted at 92-94° and was obtained in 81% yield (12 g.). The nitro group was reduced by dissolving the compound, 12 g.(0.039 mole) in 150 cc. dry ether to which 20.85 g.(0.093 mole) stannous chloride hydrate had also been added, and saturating the resulting solution with hydrogen chloride at 0°. The hydrochloride separated out as a light brown solid (10.9 g.). It was diazotized without further purification by dissolving in 200 cc. of 10% hydrochloric acid, cooling to 0°, and adding gradually a saturated solution of sodium nitrite until the solution was permanently positive toward starch-potassium iodide paper. The resulting diazonium solution was added, through a dropping funnel, to 150 cc. boiling 50% sulphuric acid solution in a 500 cc. distilling flask. The side arm of the distilling flask was connected to a condenser making it possible

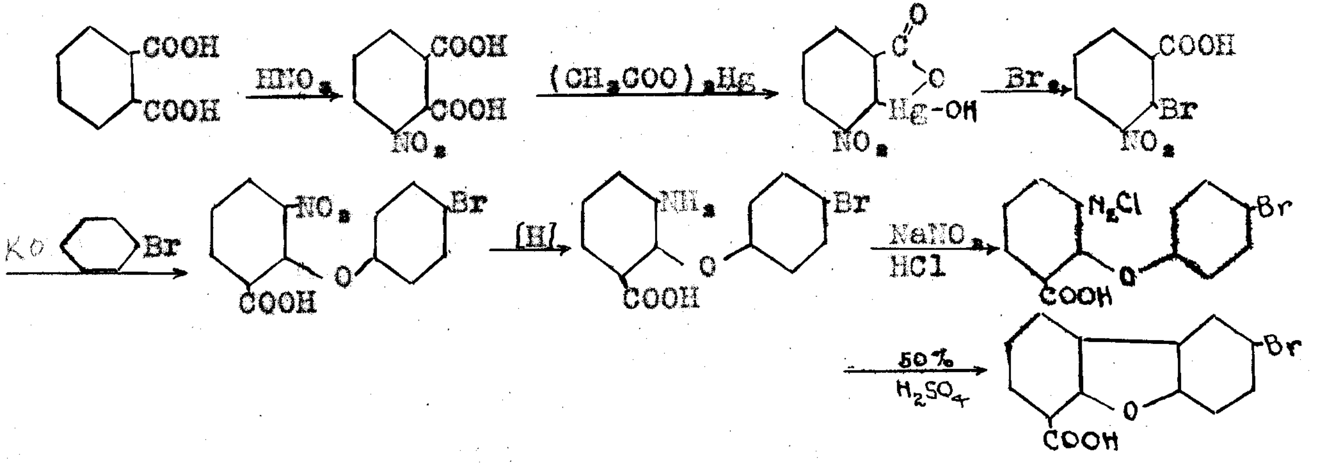
(114) The dry potassium phenoxide was prepared by dissolving phenol in a saturated methyl alcoholic solution of potassium hydroxide, allowing a slight excess of alkali. The resulting solution was diluted largely with anhydrous ether. The precipitated potassium phenoxide was removed by filtration and dried in a vacuum desiccator.

for volatile products to be collected by steam distillation during the addition of the diazonium solution. Only small portions of the diazonium solution were placed in the dropping funnel at a time to minimize decomposition by heat. The rate of addition was so regulated that the volume of liquid in the distilling flask remained constant. When the diazonium solution had all been added, water was dropped in and distillation continued until no more product steam distilled. The distillate was made alkaline with dilute sodium hydroxide to dissolve all phenolic material, and the remaining precipitate removed by filtration. The yield was 4 g. of 2-bromo-4-methyldibenzofuran melting at 90-98°. Recrystallization from alcohol gave white needles which melted at 106-106.5°. Sublimation did not raise the melting point further.

Anal. Calcd. for $C_{13}H_9OBr$: Br, 30.62; Found: Br, 30.43 and 30.23.

Preparation of 2-bromo-6-carbomethoxydibenzofuran by ring closure.

2-Bromo-6-carboxydibenzofuran was prepared by the same general method of ring closure described for the synthesis of 2-bromo-4-methyldibenzofuran:



The preparation of the 3-nitrophthalic acid was accomplished by means of Culhane and Woodward's procedure (115). This compound was mercurated as described by Whitmore, Culhane and Neher, (116), and the mercuri group replaced by bromine (117). The 2-bromo-3-nitrobenzoic acid was converted to its potassium salt by dissolving it in a saturated methyl alcoholic potassium hydroxide solution, allowing a slight excess of the hydroxide. A part of the salt precipitated out directly, and the precipitation was completed by adding dry ether.

The synthesis of the substituted diphenyl ether was effected by dissolving 1.54 g. (0.025 mole) potassium hydroxide in the least amount of hot methanol, cooling, adding 5.19 g. (0.03 mole) p-bromophenol, 7.10 g. (0.025 mole) of the potassium salt of 2-bromo-3-nitrobenzoic acid, 0.5 g. cupper bronze, heating gradually in an oil bath to 170° to drive off the alcohol and water and maintaining the temperature at this point for two hours. The cooled product was shaken with ether and water. The filtered aqueous layer on acidification precipitated a brown oily solid which was dissolved in the least amount of hot benzene and reprecipitated by the addition of petroleum ether (b.p. 60-68°). A yield of 5.0 g. (59% of the theoretical) was realized on the basis of this partially purified product, melting at 165-167°; Further recrystallization by the same procedure raised

(115) Culhane and Woodward, Organic Syntheses, Vol. 7, 70, 1927.
(116) Whitmore, Culhane and Neher, Organic Syntheses, Vol. 7, 1, 1927.
(117) Culhane, Organic Syntheses, Vol. 7, 12, 1927.

the melting point to a constant value of 167.5-168.5°.

Neutral equivalent calcd. for $C_{13}H_8O_5NBr$, 338; Found: 333.

The reduction of the nitro group was brought about by the reaction with tin and hydrochloric acid by the procedure of Schmidt and Kämpf (118). The 2-nitro-6-carboxy-4′-bromodiphenyl ether, 8.4 g. (0.025 mole), was suspended in 60 cc. concentrated hydrochloric acid, warmed on a steam bath, and 12 g. (0.1 atom) granulated tin added in several portions. Heating was continued until all of the metal had dissolved. The greenish yellow amine hydrochloride precipitated during the course of the reaction. At the completion of the reaction, the product was filtered on a mat of glass wool, washed with concentrated hydrochloric acid and finally with water. The dried product, 5.04 g. (67% of the theoretical yield), melted with decomposition at 190-200°. The compound was crushed and suspended in 100 cc. 10% hydrochloric acid, cooled to 0° and the calculated quantity of sodium nitrite, 1.04 g. (0.015 mole), was added gradually. The mixture was allowed to stand at 0° for 3 hours. The diazotization was slow due to the slight solubility of both the amine hydrochloride and the diazonium compound.

The suspension of the diazonium compound was added to 100 cc. boiling 50% sulphuric acid as described in the synthesis of 2-bromo-4-methyldibenzofuran. The mixture was boiled for

(118) Schmidt and Kämpf, Ber., 36, 3738 (1903).

3 hours at constant volume after the addition of diazonium compound had been completed. The contents of the distilling flask were diluted with half the volume of water, cooled, and filtered. The black precipitate was treated with a small volume of 10% sodium hydroxide. The major portion dissolved, but a quantity of light colored material was insoluble. The insoluble portion was filtered off, digested with dilute hydrochloric acid for a few minutes, and again filtered. The acid thus obtained, 0.5 g., melted at 260-262°, and the melting point was not depressed by mixture with the acid obtained by hydrolysis of Hayes' 2- (or 8-) bromo-6-carbomethoxydibenzofuran.

As a further check, the acid obtained by ring closure was converted to its methyl ester. The acid was suspended in 10 cc. ether and treated at 0° with an excess of diazomethane (119) in ether solution. After standing 30 minutes at 0°, the solution was filtered and the excess diazomethane and ether allowed to evaporate. A crystalline residue melting at 160-162° remained. One recrystallization from glacial acetic acid, and one decolorization in methanol solution with boneblack raised the melting point to 165-166°. No depression was observed in a mixed melting point determination with Hayes' 2- (or 8-) bromo-6-carbomethoxydibenzofuran.

Conversion of 3-nitro-6-carbomethoxydibenzofuran to 3-acetamino-6-carbomethoxydibenzofuran.

(119) For the preparation of diazomethane, see Arndt, Organic Syntheses, Vol. 15, 3, 1935.

3-Nitro-6-carbomethoxydibenzofuran, 6.78 g. (0.025 mole) was dissolved in 250 cc. boiling glacial acetic acid. A solution of 17.5 g. (0.078 mole) stannous chloride hydrate in 115 cc. concentrated hydrochloric acid was added slowly and the solution heated at reflux temperature about 2 minutes. Cooling deposited 7.0 g. (quantitative yield) of the amine hydrochloride which browned but did not melt at 240°. It was soluble in cold water, and was converted to the free amine by treating the water solution with ammonium hydroxide. The amine was converted to the acetamino derivative by dissolving it in the least amount of hot benzene, adding a slight excess of acetic anhydride, and allowing the mixture to stand overnight. Petroleum ether (b.p. 60-68°) was added to precipitate the product when necessary. The acetamino-ester was best crystallized from a mixture of methyl alcohol and glacial acetic acid. The pure ester crystallized in yellowish needles melting at 245-246°.

Anal. Calcd. for $C_{16}H_{13}O_4N$: N, 4.95. Found: N, 5.17 and 5.34.

Preparation of 2-bromo-3-acetamino-6-carbomethoxydibenzofuran

A. From 3-acetamino-6-carbomethoxydibenzofuran.

Five-tenths gram (0.0018 mole) of 3-acetamino-6-carbomethoxydibenzofuran was dissolved in 75 cc. hot glacial acetic acid, cooled to room temperature and 1.8 cc. of 1 M bromine solution in glacial acetic acid (0.0018 mole of bromine) added dropwise. On standing overnight, 0.4 g. fine white needles separated out. The melting point was 242-243°; the yield, 81% of the theoretical. Recrystallization from glacial acetic acid gave a melting point of 247-247.5°. Though the product melted only 2° higher than the original acetamino-ester, the two compounds are distinct, as shown by analysis and a mixed melting point.

<u>Anal</u>. Calcd. for $C_{16}H_{12}O_4NBr$: N, 3.87. Found: N, 3.77 and 3.77.

B. From 2-bromo-3-nitro-6-carbomethoxydibenzofuran.

The 2-bromo-3-nitro-6-carbomethoxydibenzofuran, 0.45 g. (0.0013 mole), was dissolved in 15 cc. boiling glacial acetic acid and reduced by adding slowly 0.7 g. (0.0031 mole) stannous chloride hydrate in 5 cc. concentrated hydrochloric acid and refluxing five minutes. Cooling of the resulting solution deposited crystals which proved to be the complex composed of the tin salt and the amine hydrochloride. The crystals were suspended in ether, and treated in an ice bath with cold 30% sodium hydroxide until both layers were clear. The ether layer was washed with water, dried over sodium sulphate and saturated with dry hydrogen chloride to precipitate the amine hydrochloride. An additional amount was obtained by diluting the original acetic acid mother liquor and working up with sodium hydroxide and ether in the manner described. The hydrochloride was suspended in water and treated with ammonium hydroxide to liberate the free amine. The amine obtained, 0.2 g. (50% of the theoretical yield), was converted to the acetamino derivative by adding a slight excess of acetic anhydride to the hot benzene solution and allowing it to cool. The 0.1 g. bromo-acetamino-ester thus prepared melted at 241-242°. Recrystallization from a mixture of methyl alcohol and glacial acetic acid raised the melting point to 245°. The melting point was not depressed, when the compound was mixed with the product prepared by the bromination of 3-acetamino-6-carbomethoxydibenzofuran.

Nitration of 2-bromo-6-carbomethoxydibenzofuran.

A. Dinitration.

When 1.25 g. (0.0041 mole) 2-bromo-6-carbomethoxydibenzofuran was added slowly to 4 cc. fuming nitric acid (d=1.50) at room temperature the ester dissolved, but after standing 30 minutes the whole mass solidified. The product was broken up and stirred into cracked ice. When the ice had melted, the nitrated ester was filtered off. The crude product, 1.95 g., melted at 235-245°. Recrystallization from glacial acetic acid, in which the ester was but sparingly soluble, gave 1.0 g. pale yellow crystal aggregates melting at 258-260°. A second recrystallization from benzene and petroleum ether (b.p. 60-68°) raised the melting point to 259.5-260.5°. The yield of product melting at 258-260° was 62% of the theoretical.

Anal. Calcd. for $C_{14}H_7O_7N_2Br$: N, 7.09. Found: N, 7.17 and 7.45.

B. Mononitration.

The 2-bromo-6-carbomethoxydibenzofuran was rather resistant to nitric acid. It was not nitrated by treating for 30 minutes with fuming nitric acid in glacial acetic acid at 75°. Nitration with mixtures of concentrated nitric acid and fuming nitric acid gave poor results due to the formation of a mixture of mono- and dinitration products. The best yields of the mononitration product were obtained by treating the ester with concentrated nitric acid at steam bath temperatures. The 2-bromo-6-carbomethoxydibenzofuran, 2.5 g. (0.0082 mole), was added to 7 cc. concentrated nitric acid (d=1.42) and the mixture heated with stirring for one hour. During this time the ester partly passed into solution, and at the close of the reaction two layers were present. The product was poured on ice and the precipitate removed by filtration and dried. The dry material after powdering was extracted with hot methanol which removed all un-nitrated 2-bromo-6-carbomethoxydibenzofuran. The residue was then recrystallized from glacial acetic acid to produce 0.8 g. (28% of the theoretical yield) of material melting at 203-205°. Further recrystallization from the same solvent brought the melting point to 205-206°. The 2-bromo-3-nitro-6-carbomethoxydibenzofuran crystallized in small, pale yellow needles. The inconvenience of the low yield is in part compensated by the easy recovery of the unattacked bromo-ester which may be resubjected to the nitration treatment. Attempts to increase the yield of the mononitro-ester resulted in the formation of the dinitro derivative making purification most difficult.

Anal. Calcd. for $C_{14}H_8O_5NBr$: N, 4.00. Found: N, 3.93 and 3.90.

Hydrolysis of 2-bromo-3-nitro-6-carbomethoxydibenzofuran.

2-Bromo-3-nitro-6-carbomethoxydibenzofuran, 0.72 g. (0.002 mole), was refluxed 3 hours with a mixture of 30 cc. glacial acetic acid and 30 cc. concentrated hydrochloric acid, as described by Hayes (82). At the close of the reaction, the mixture was cooled and diluted with water to complete the precipitation. The precipitate was extracted with 100 cc. boiling glacial acetic acid. On cooling this extract, 0.48 g. of yellow needles was obtained. This yield represented 70% of the theoretical. The melting point was 331-334°. Owing to the great insolubility of both the acid and its salts, it was not possible to secure the neutral equivalent.

Decarboxylation of 2-bromo-3-nitro-6-carboxydibenzofuran.

A sample of 2-bromo-3-nitro-6-carboxydibenzofuran, 0.24 g. (0.00071 mole), was heated with 1 g. copper bronze and 5 cc. freshly distilled quinoline in a small pyrex test tube (120). The test tube was immersed in a metal bath, and the mouth of the tube connected to a short piece of glass tubing bent in an inverted U shape. The other end of the tubing led the evolved gas into a solution of barium hydroxide. When the metal bath reached a temperature of 180°, vigorous bubbling began and a heavy precipitate formed in the barium hydroxide solution. Heating was continued at 200-210° for 30 minutes. At the end

(120) Shepard, Winslow, and Johnson, J. Am. Chem. Soc., 52, 2083 (1930).

of this time, the contents of the test tube were poured into 10% sulphuric acid solution and the whole subjected to steam distillation. The steam distillate yielded 0.04 g. of material melting at 174-179°. Recrystallization from alcohol raised the melting point to 178-179° which was not depressed by mixture with authentic 3-nitrodibenzofuran. Decarboxylation in the presence of copper sulphate hydrate instead of copper bronze, required a higher temperature, but also gave 3-nitrodibenzofuran.

An authentic sample of 2-bromo-3-nitrodibenzofuran (121), 0.1 g., was heated at 200-210° for 30 minutes with 0.5 g. copper bronze and 2.5 cc. freshly distilled quinoline. The product, worked up in the same manner as the above decarboxylation, gave 0.04 g. material melting at 172-177°. Recrystallization from alcohol raised the melting point to 178-180°, which was not depressed when a sample was mixed with an authentic specimen of 3-nitrodibenzofuran.

An authentic sample, 0.1 g., of 2-bromo-7-nitrodibenzofuran (121) was treated in a manner identical with that just described for 2-bromo-3-nitrodibenzofuran. In this case, steam distillation yielded no product. The contents of the flask after the attempted steam distillation were cooled and filtered. The solid residue was extracted with glacial acetic acid, from which 0.06 g. grayish white needles precipitated. The melting point was 250-251°, and was not altered by mixing with a sample of

(121) Samples of 2-bromo-3-nitrodibenzofuran and 2-bromo-7-nitrodibenzofuran were supplied by Dr. Glen Bywater.

the original 2-bromo-7-nitrodibenzofuran.

SUMMARY

I. The 2-, 3-, and 4-hydroxydibenzofurans have been coupled with benzenediazonium chloride.

II. The structures of the azo derivatives thus obtained have been determined.

III. The proof of structure of the principal nitration and bromination products from 4-carbomethoxydibenzofuran has been completed.