

THE REACTIONS OF CERTAIN ACTIVE METHYLENE
COMPOUNDS WITH 2,3-DICHLORO-1,4-NAPHTHOQUINONE

by

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Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

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ACKNOWLEDGMENT

The author is indebted to Dr. Ernest F. Pratt who suggested this investigation and directed it through its entirety. Generous financial support from the Research Corporation and from the National Institutes of Health is sincerely appreciated. The author wishes to express his gratitude to Dr. Robert A. Spurr, Mr. Shih-Chuan Chang, and Mr. Richard A. Jewell for the preparation and aid in the interpretation of the infrared spectra.

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HISTORICAL INTRODUCTION

HISTORICAL INTRODUCTION

The object of this investigation was to study the condensation of 2,3-dichloro-1,4-naphthoquinone with certain active methylene compounds and to determine the structure of the products. The chief active methylene compounds studied were acetoacetic ester, acetylacetone and cyanoacetic ester. This investigation was prompted by the fact that several workers in this laboratory succeeded in isolating, and in some cases identifying, certain related products from the condensation of 1,4-naphthoquinones and active methylene compounds.^{1,2,3}

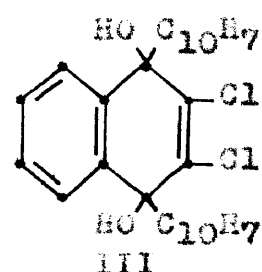
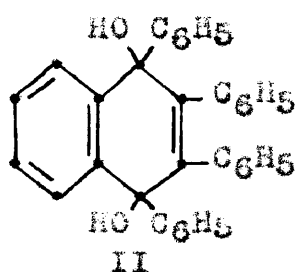
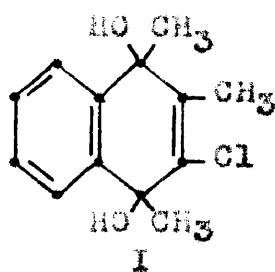
The products of these reactions may have important physiological effects, inasmuch as 2,3-dichloro-1,4-naphthoquinone has fungicidal activity⁴ and also can be regarded as an analog of vitamin K. Buu-Hoi synthesized many arylamine derivatives of 1,4-naphthoquinones some of which were capable of inhibiting the growth of the tubercle bacillus.⁵ More recently a large number of amine derivatives of 2-chloro-1,4-naphthoquinone were prepared because they were found to be active inhibitors of acid production by bacteria in the mouth.⁶

In order better to interpret the results of this investigation, a study was made of the reactions of 2,3-dichloro-1,4-naphthoquinone. As might be expected by analogy with chloranil, 2,3-dichloro-1,4-naphthoquinone is a very

good oxidizing agent. When used as an oxidant it is reduced to the corresponding hydroquinone.⁷ This structural change is accompanied by the disappearance of the yellow color. The quinone may be oxidized, however, in the presence of a strong oxidizing agent to phthalic acid. This reaction was part of Grabe's classic proof of the structure of naphthalene.⁸ In this work it was also shown that when the quinone was treated with phosphorous pentachloride, 1,2,3,4,5-pentachloronaphthalene was formed.

Fries and coworkers succeeded in preparing the 5-nitro- and 5-amino-2,3-dichloro-1,4-naphthoquinones.⁹ When 2,3-dichloro-1,4-naphthoquinone was treated with a mixture of concentrated sulfuric and nitric acids, the product obtained was chiefly the 5-nitro derivative. This was converted to 5-amino-2,3-dichloro-1,4-naphthohydroquinone by reduction with stannous chloride in hydrochloric acid. Oxidation with ferric chloride solution yielded 5-amino-2,3-dichloro-1,4-naphthoquinone.

Grignard reagents react with 2,3-dichloro-1,4-naphthoquinone to yield a variety of products. When methyl, phenyl, and α -naphthyl magnesium halides were reacted with this quinone, there were obtained upon hydrolysis of the reaction mixtures the following products:¹⁰



It was interesting to note that in compound (I), the chlorine atom was not replaceable by aqueous alkali.

The polymerization of 2,3-dichloro-1,4-naphthoquinone was first reported by Scholl and coworkers, and was accomplished by heating the quinone with copper powder above 200°.11,12 This work was discussed in some detail by Boehme.¹

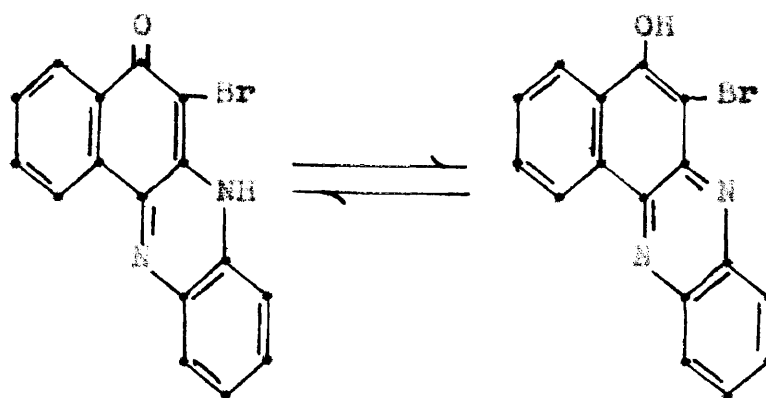
2,3-Dichloro-1,4-naphthoquinone was found to be capable of forming complexes with pyrroles.¹³ With 2,5-dimethylpyrrole the quinone formed brownish black crystals with the empirical formula $3C_6H_9N \cdot 2C_{10}H_4O_2Cl_2$; 2,4-dimethylpyrrole formed a similar product, $C_6H_9N \cdot C_{10}H_4O_2Cl_2$. N-Methyl-2,5-dimethylpyrrole was unusual in that it formed a complex, $C_7H_{11}N \cdot C_{10}H_4O_2Cl_2$, even though the nitrogen was methylated. These compounds were unstable and decomposed on standing in air. Brass and Tengler prepared the more stable complexes, $C_{10}H_4O_2Br_2 \cdot SbCl_5 \cdot CHCl_3$ and $C_{10}H_4O_2Br_2 \cdot SnCl_4$ from 2,3-dibromo-1,4-naphthoquinone.¹⁴

At elevated temperatures in the presence of bromine or hydrogen bromide and a copper salt catalyst compounds containing a loosely bound chlorine atom would have this atom replaced by bromine.¹⁵ In this way 2,3-dichloro-1,4-naphthoquinone was converted to 2-bromo-3-chloro-1,4-naphthoquinone.

Most of the reactions of 2,3-dichloro-1,4-naphthoquinone may be divided into four main categories. The division is based on the type of linkage which results. The four types of linkages are C-N, C-C, C-O, and C-S. More than one type of bond may be found in a single product, e.g. a C-C bond

may form upon replacement of one chlorine atom, and a C-N bond upon replacement of the other chlorine atom.

Most of the early work with 2,3-dichloro-1,4-naphthoquinone dealt with the formation of the C-N linkage. The first reaction reported was that in which the quinone was treated with aniline in an alcoholic solution.¹⁶ The red, crystalline product was shown to be 2-chloro-3-anilino-1,4-naphthoquinone. This reaction was extended to include the substituted anilines; such as *o*- and *p*-nitroaniline, *p*-bromoaniline, and *o*- and *p*-toluidine.¹⁷ The expected products were also obtained with *m*- and *p*-phenylenediamines. However, when *o*-phenylenediamine was reacted with 2,3-dibromo-1,4-naphthoquinone, the following compound, which is capable of tautomerization as shown, was obtained.¹⁸



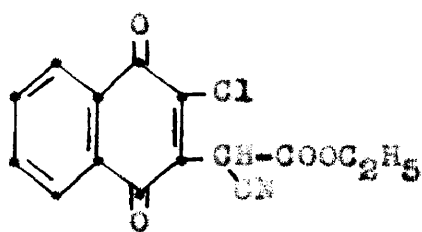
IV

Additional primary and some secondary aromatic amines were used successfully in this reaction.^{5,6}

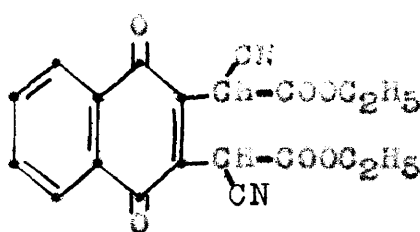
Recently this reaction was extended to the aliphatic series, for octyl- and octadecylamines were found to react in a similar manner.¹⁹ The 2-chloro-3-amino-1,4-naphtho-

quinones, which were formed by this reaction, were not stable to hydrolysis conditions and 2-chloro-3-hydroxy-1,4-naphthoquinone resulted. Fries and Ochwat synthesized 2,3-diaziido-1,4-naphthoquinone by heating a mixture of 2,3-dichloro-1,4-naphthoquinone, alcohol, and concentrated aqueous sodium azide on a steam bath.²⁰ This orange compound was very unstable and a drop of concentrated sulfuric acid caused it to explode.

Considerable work of primary importance on the formation of the C-C bond was reported by Liebermann and Michel.²¹⁻²⁵ They treated 2,3-dihalo-1,4-naphthoquinones with sodium salts of active methylene compounds. A typical example was the reaction of 2,3-dichloro-1,4-naphthoquinone in an alcoholic solution with the sodium salt of ethyl cyanoacetate to give the following products.



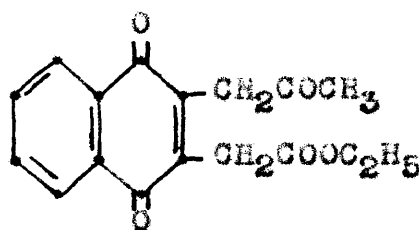
V



VI

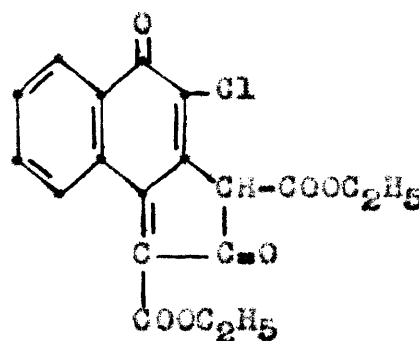
Similar monosubstitution products were obtained with ethyl malonate, ethyl acetoacetate, phenylacetone, methyl benzoylacetate, acetylacetone, benzoylacetone, dihydro-resorcinol and ethyl oxalacetate. A disubstituted product was also isolated with ethyl malonate. With ethyl acetoacetate, however, there was isolated and identified by

elementary analysis and molecular weight determination the following compound.^{24,25}



VII

Michel found that the reaction of 2,3-dichloro-1,4-naphthoquinone with the sodium salt of sym-dicarbethoxyacetone yielded another somewhat different but logical product.²⁵

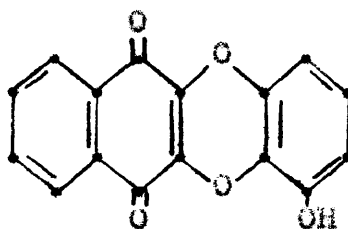


VIII

3-Hydroxythionaphthene and 4,5-benzo-2-coumaranone reacted in boiling alcohol to yield disubstituted quinones.²⁶

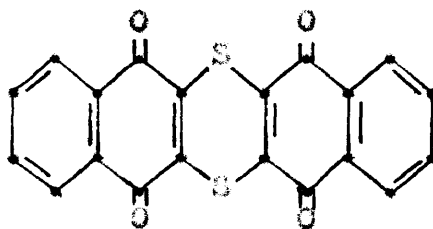
The C-O bond is the third type of linkage formed by the replacement of the chlorine atom; it is, however, of less importance than the first two types. On warming 2,3-dichloro-1,4-naphthoquinone with aqueous sodium acetate the yellow 2-chloro-3-acetoxy-1,4-naphthoquinone was formed, which on treatment with alkali yielded 2-chloro-3-hydroxy-1,4-naphthoquinone.²⁰ In a somewhat similar reaction 2,3-

dibromo-1,4-naphthoquinone was treated in benzene solution with sodium ethoxide to give a mixture of 2-bromo-3-ethoxy- and 2-bromo-3-hydroxy-1,4-naphthoquinones.²² This reaction was extended to form the high melting purple compound (IX) by treatment of 2,3-dichloro-1,4-naphthoquinone with pyrogallol in the presence of dry pyridine.²⁷



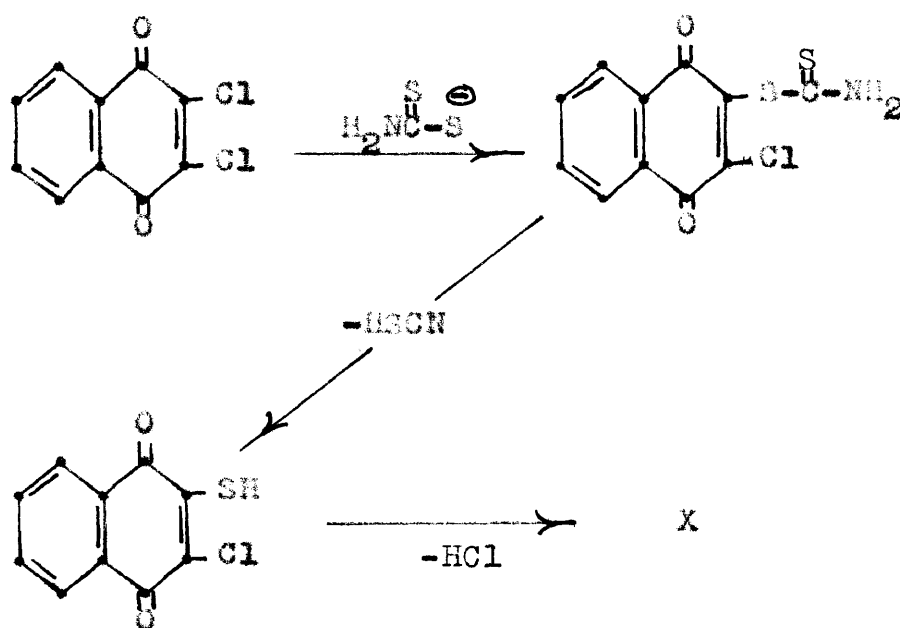
IX

The formation of a C-S linkage which is also of secondary importance was accomplished by treatment of 2,3-dichloro- or 2,3-dibromo-1,4-naphthoquinone with sodium sulfide to give (X).²⁸

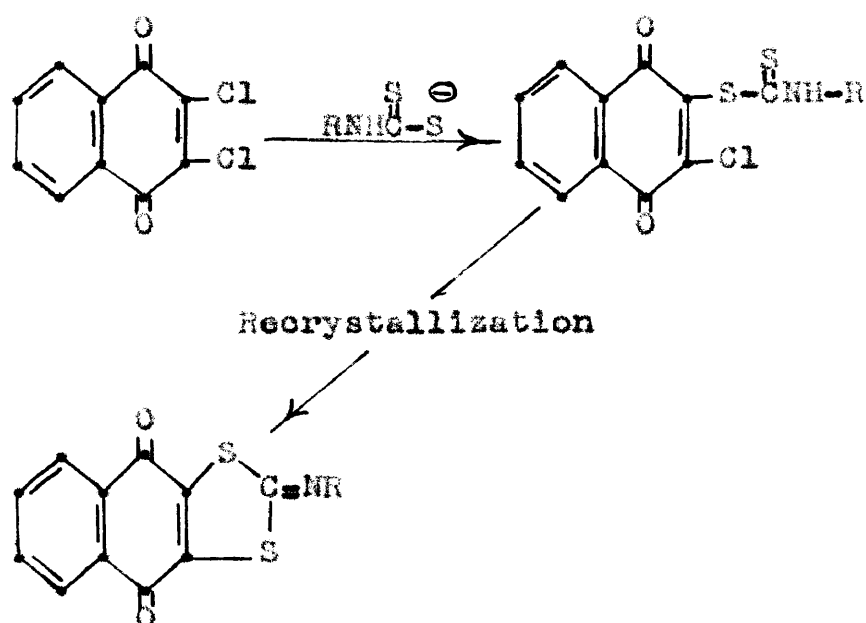


X

In a recent article the synthesis of this compound was reported from 2,3-dichloro-1,4-naphthoquinone and ammonium dithiocarbamate in aqueous solution.²⁹ The mechanism for its formation was postulated to be as follows:



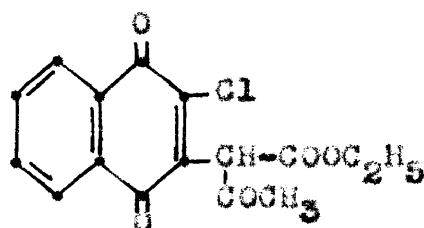
With amine salts of methyl- and ethyldithiocarbamic acid the following series of reactions occurred ($R = \text{CH}_3$ or C_2H_5).



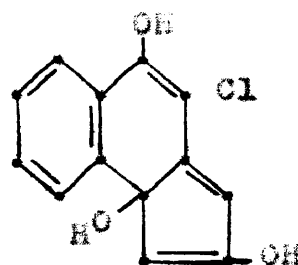
This was the first synthesis of compounds with the naphtho-(2,3)-1,3-dithiole ring system. A product containing the C-S linkage was also obtained by treatment of 2,3-dichloro-1,4-naphthoquinone with orthonitrothiophenol. Two molecules

of hydrogen chloride split out to give the disubstituted product.²⁰ This reaction was recently extended by Fieser and Brown to the aliphatic mercaptans.³⁰

There are a large number of reactions which involve the formation of these linkages in a stepwise manner. This phenomenon may be ascribed to the difference in reactivity of the two chlorine atoms. After the first chlorine is removed, the second is not as reactive. This accounts for the large variety of derivatives of 2-chloro-1,4-naphthoquinones with substituents in the three position. These were used in the preparation of a variety of new ring systems. Treatment of compound (XI) with alkali did not remove the chlorine atom but instead caused cyclization to (XII).³¹



XI

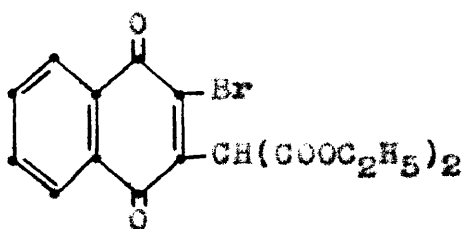


XII

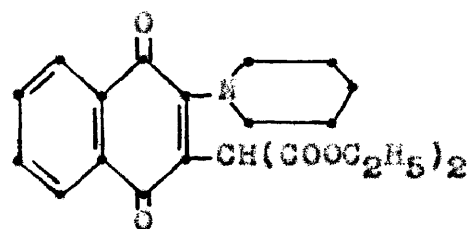
Formula (XII) shows the preferred structure of three possible tautomers as postulated for the corresponding bromo compound by Liebermann.³²

It is important to note that the second chlorine atom is removed readily in some cases. When the 3-amino or 3-anilino group of a substituted 2-chloro-1,4-naphthoquinone was acetylated, the chlorine atom was rendered very reactive.³³

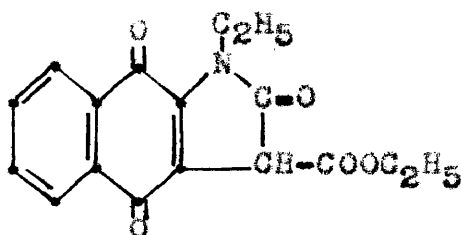
The acetylated product from 2-chloro-3-anilino-1,4-naphthoquinone condensed with the sodium salt of ethyl acetoacetate in 70% to 80% yield. Liebermann removed the halogen easily from compound (XIII) by reacting it with piperidine to yield compound (XIV). When ethylamine reacted, however, the final product was (XV).²⁴



XIII

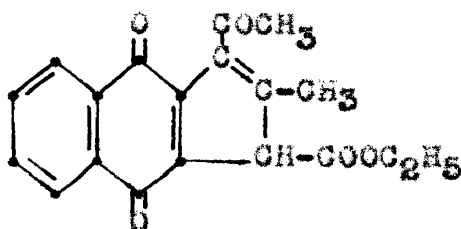


XIV



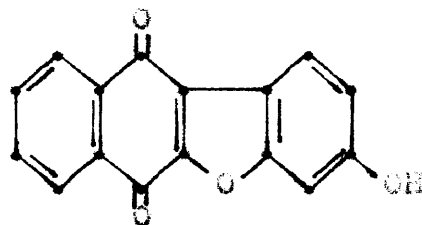
XV

Cyclizations appear to be common in the reactions of 2,3-dichloro-1,4-naphthoquinone. Michel obtained a five membered carbon ring by the reaction of compound (XI) with the sodium salt of acetylacetone.²⁵



XVI

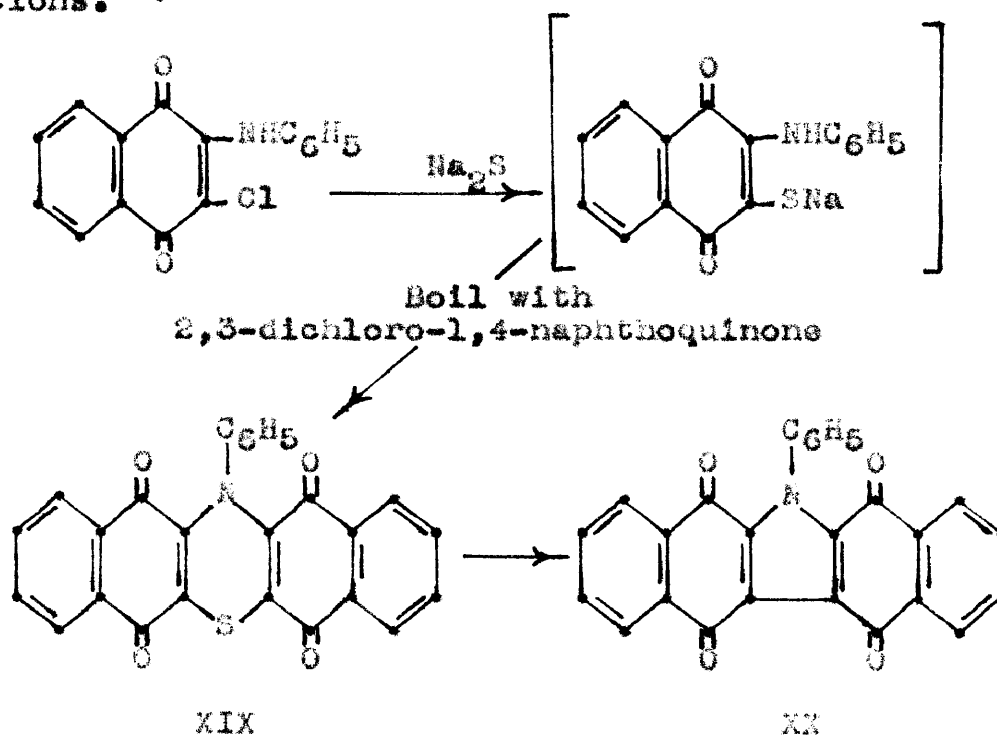
Cyclized products were obtained more directly by reacting resorcinol with 2,3-dichloro-1,4-naphthoquinone in the presence of sodium ethoxide.²³



XVII

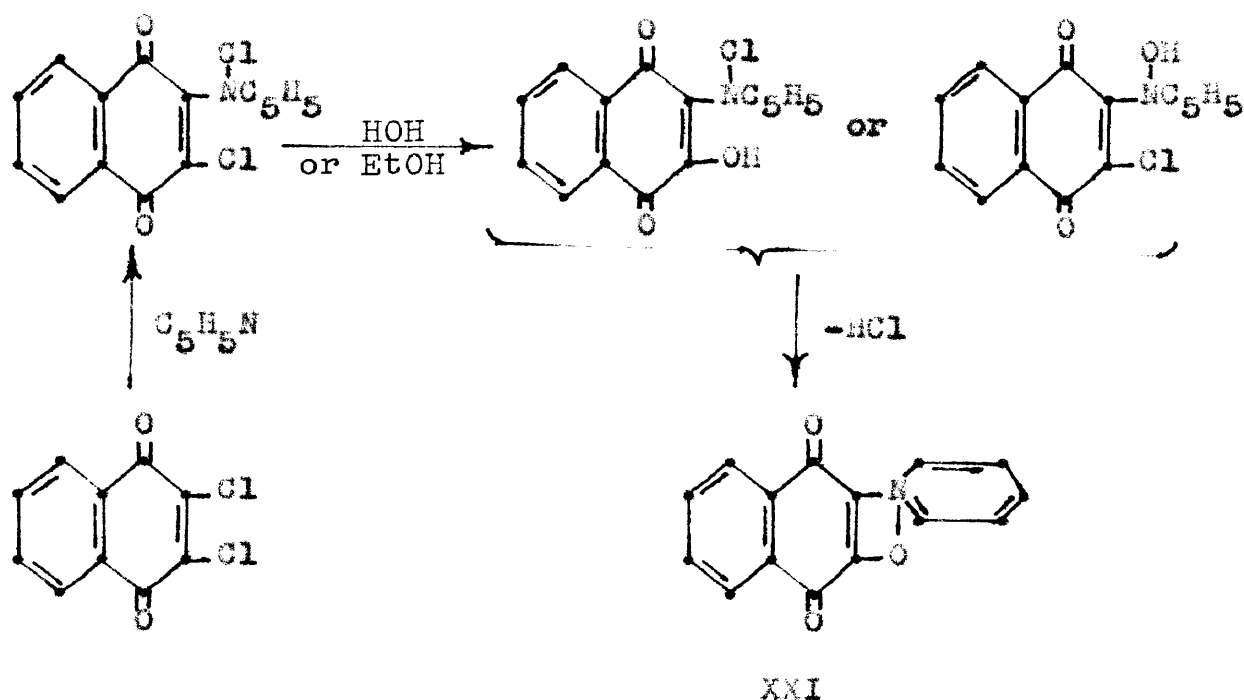
Recently this type of reaction was used in the syntheses of other similar compounds by using pyridine as the condensing agent.³⁴

Cyclizations yielding five membered rings were not the only type reported. Compounds (IX) and (X) furnish examples of the formation of six membered rings. Another six membered ring was formed in the following group of reactions.^{20,35}

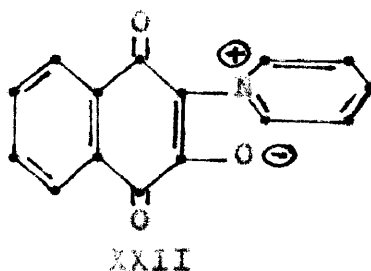


Compound (XIX) appeared to be highly strained because boiling with nitrobenzene, glacial acetic acid, or a little nitric acid converted it to the stable compound (XX).

An unusual reaction of 2,3-dichloro-1,4-naphthoquinone was first reported by Ullmann and Ettisch.³⁶ They observed that on warming this quinone in pyridine solution followed by dilution with alcohol or water, a halogen free, nitrogen containing compound was formed. The reaction was postulated to be as follows:

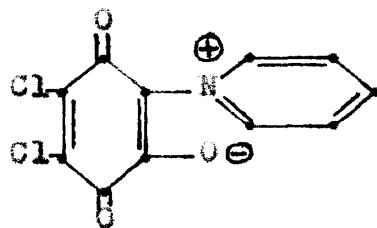


Recently a more logical salt structure was assigned to the yellow, crystalline product.³⁷



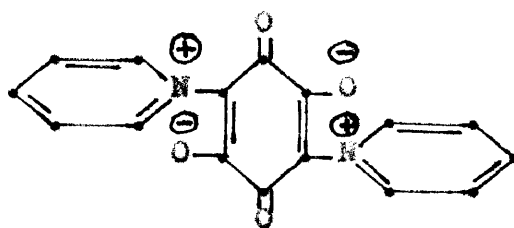
The mono-oxime, mono-phenylhydrazone, and quinoxaline derivatives were prepared; oxidation with potassium permanganate yielded pyridine. No other reactions of this interesting compound were reported. Considerable work of importance has, however, been reported on an analogous product obtained from chloranil, and inasmuch as any reactions of 2,3-dichloro-1,4-naphthoquinone utilizing a tertiary amine as a catalyst may result in this type of product, a summary on the work on chloranil follows.

The greater part of the study of the reactions of chloranil and tertiary amines was reported approximately twenty years before Ullmann and Ettisch made their discovery. Pyridine combined with chloranil in boiling ethyl acetate solution containing a small quantity of acetic acid to form a red compound.³⁸⁻⁴¹ In addition to pyridine, 3-methylpyridine yielded a similar compound; however quinoline and 2-methylpyridine were unreactive. The reactivity of this red compound toward such reagents as aqueous potassium carbonate, aqueous sulphur dioxide, and a hydrochloric acid and potassium chlorate mixture was studied. The conclusion of Imbert was that the formula of this compound was $C_5NH_4 \cdot C_6Cl_2O_2 \cdot OH$. As was the case with the work of Ullmann and Ettisch, a more reasonable structure and a clarification of this work was published by Schonberg and Ismail.³⁷ They ascribed a structure (XXIII) to the compound prepared from chloranil analogous to that of the compound prepared from 2,3-dichloro-1,4-naphthoquinone.



XXIII

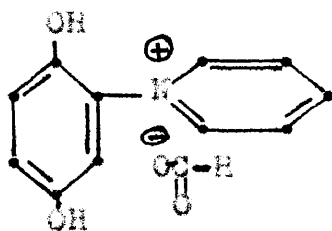
From the observations that oxidation with potassium permanganate or treatment with sodium carbonate yielded pyridine, they concluded that the pyridine residue was not attached to the six membered carbon ring by means of a C-C linkage. When chloranil was acted upon directly with pyridine and water a different product was obtained to which structure (XXIV) was assigned.



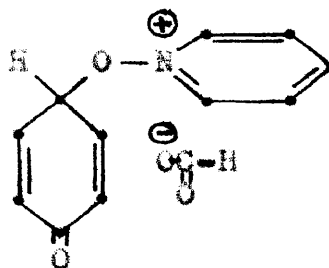
XXIV

Benzoquinone, pyridine, and formic acid reacted in methanol solution to yield a similar type of compound to which structure (XXV) was assigned.⁴² Ismail viewed this structure as incorrect because the compound contained no active hydrogen; for example, the compound was not methylated by diazomethane or dimethyl sulfate, or acetylated by acetic anhydride.⁴³ He preferred structure (XXVI) since it explained why the salt was orange and why pyridine was

obtained by hydrolysis with alkali or by treatment with potassium permanganate.



XXV

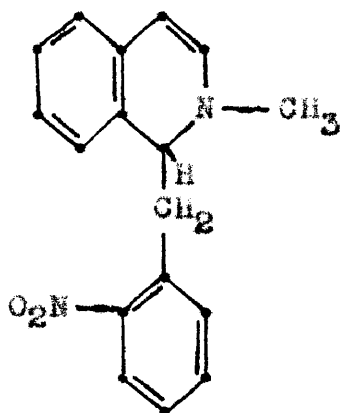


XXVI

Structure (XXVI) would be more conclusively established if similar salts were obtained from tetramethyl-*p*-quinone. Ismail stated that this quinone would be studied, but this work has not been published.

Alkyl and aryl pyridinium compounds have been known for a long time. Several of the more important reactions and applications of these pyridinium salts should be discussed here in order to obtain additional support for the proposed structures of the products obtained in this investigation. Acetyl chloride reacts spontaneously with pyridine to form the *N*-acetylpyridinium chloride. Methyl iodide reacts similarly with pyridine to yield *N*-methylpyridinium iodide, which on treatment with silver oxide in aqueous solution forms the *N*-methylpyridinium hydroxide. This compound is important because of the characteristic reaction which occurs on oxidation with potassium ferricyanide to yield *N*-methyl pyridone.⁴⁴ A different type of reaction was shown to occur with *N*-methylisoquinolinium

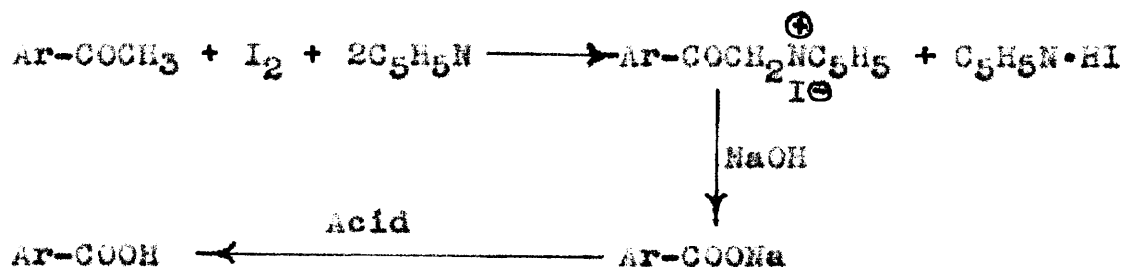
hydroxide. In the presence of a base such as sodium ethoxide, the hydroxide reacted with o-nitrotoluene to form compound (XXVII).⁴⁵



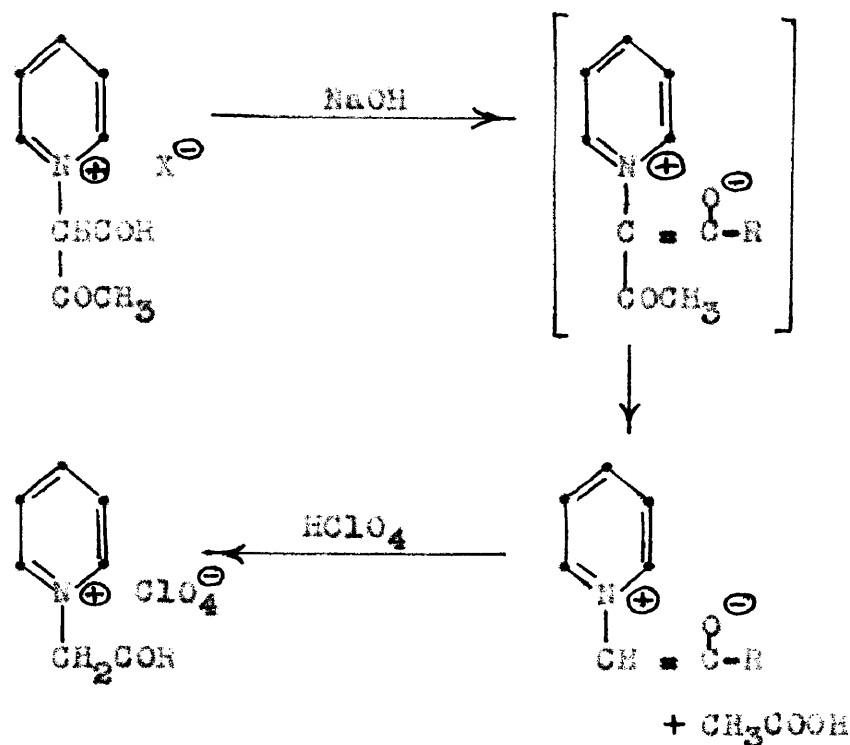
XXVII

1-Nitro-2,3-dimethoxycyanomethylbenzene reacted in a manner similar to that of the nitrotoluene.⁴⁶

Pyridinium salts have been used as a means of opening the pyridine ring. An example of this is the treatment of the N-(2,4-dinitrophenyl)pyridinium chloride with cold alkali and then with acid to form glutaconic aldehyde and 2,4-dinitroaniline.⁴⁴ More recently King found a very practical application for this type of salt. The following reactions furnished an improved route for the conversion of an acetyl group to a carboxyl group.⁴⁷



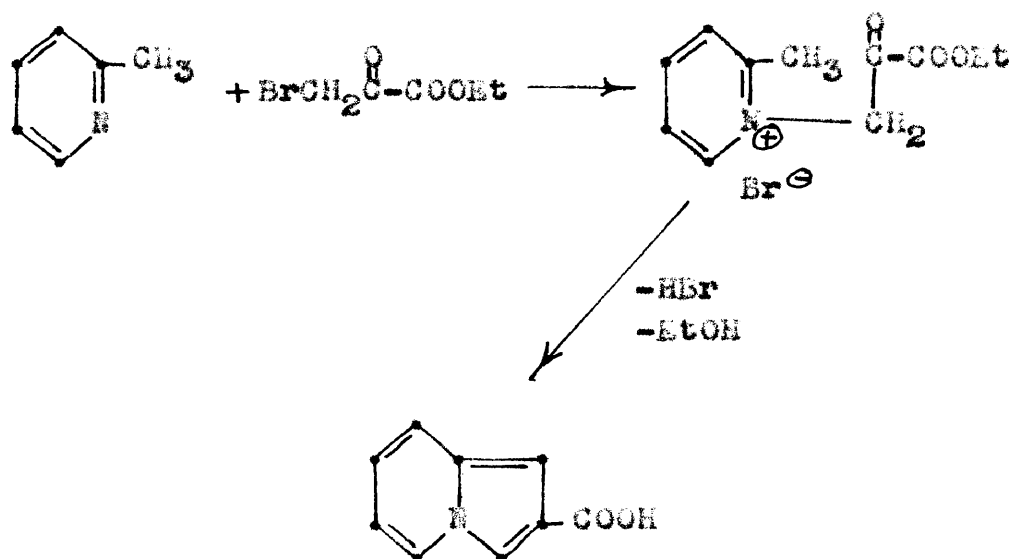
Burrows and Holland in their review article on the preparation of pyrrocoline and its derivatives discussed an important cleavage of a pyridinium salt.⁴⁸ When a pyridinium salt of an alpha halogenated 1,2-diketone was treated with alkali and then acidified, the salt underwent an "acid cleavage" with the loss of an acyl group; the smaller of the two groups present was the group to be lost. The reactions are illustrated below.



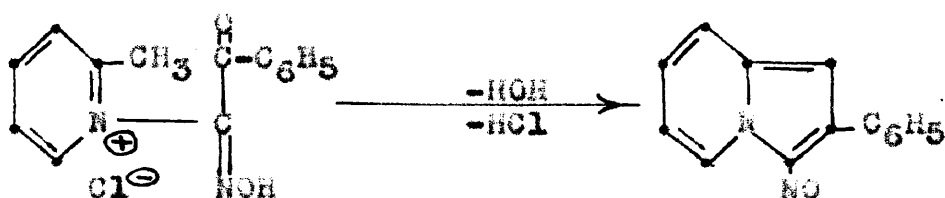
Since pyrrocolines were obtained in this research by related processes several further examples will be considered. Perhaps the simplest example was the reaction of α -picoline with bromoacetone.



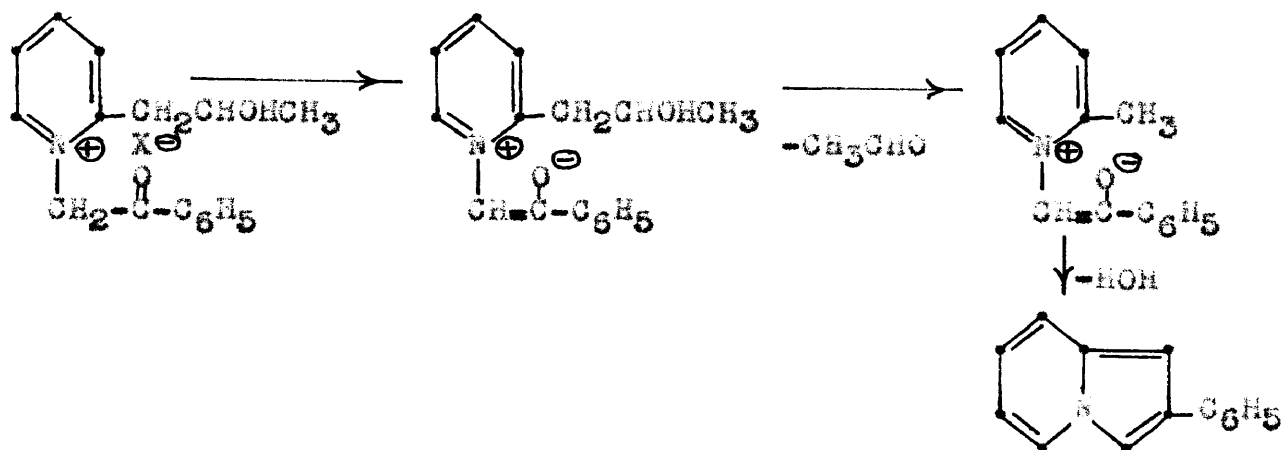
In an interesting modification of this, bromoethyl acetate replaced bromoacetone.



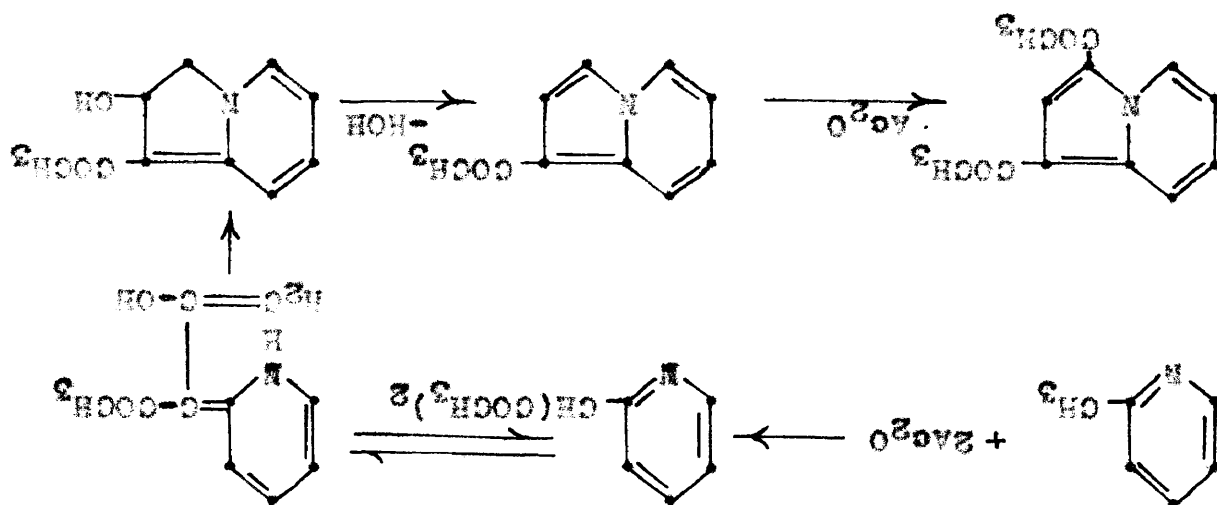
A further alteration of the method gave a phenyl substituted pyrrocoline.



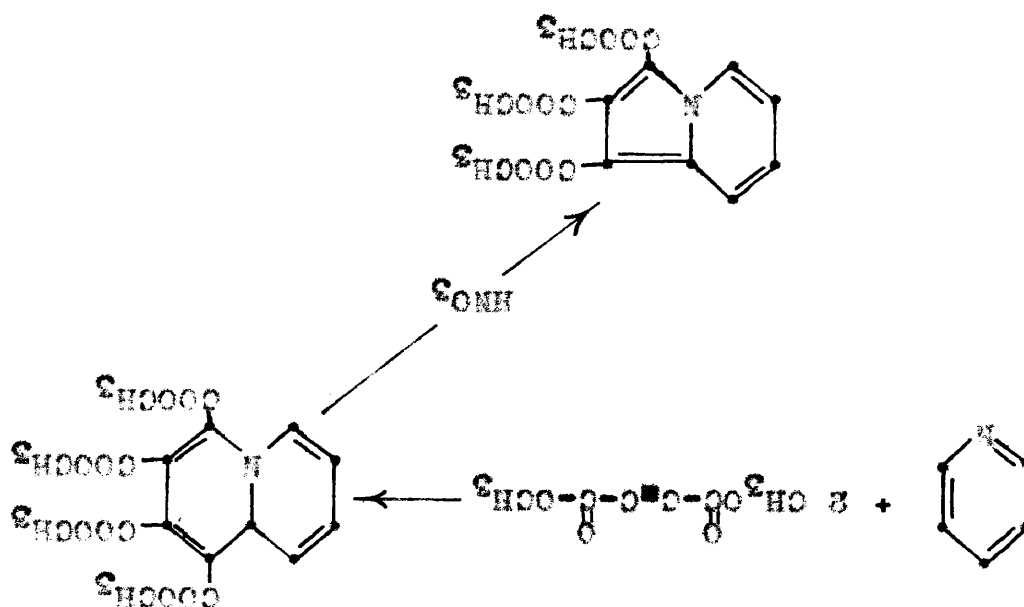
Another interesting related example is as follows:



a fundamentally different route to pyrrocolines involved a diacetyl derivative of α -pycoline.



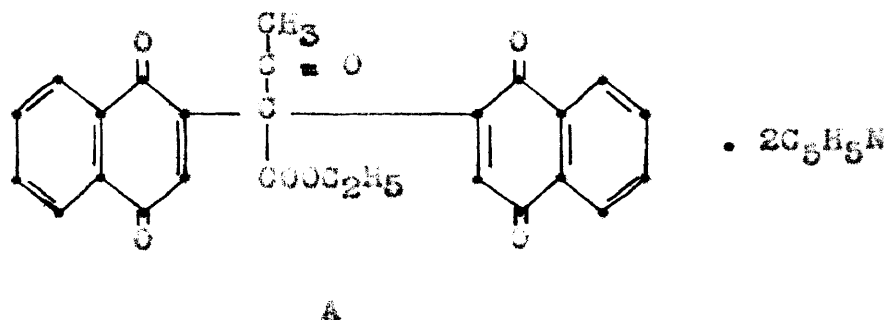
The last example which will be given illustrates the conversion of pyridine itself to a pyrrocoline.



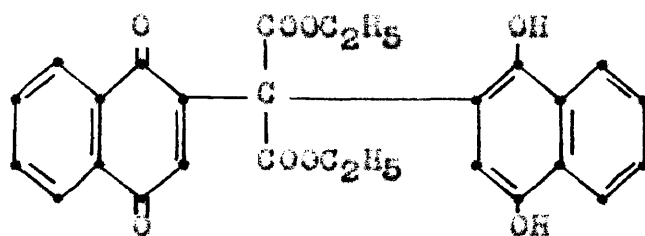
DISCUSSION

Reactions of Acetoacetic Ester and Related Compounds

By the reaction of acetoacetic ester either with 1,4-naphthoquinone or with 2,3-dichloro-1,4-naphthoquinone in the presence of pyridine Erickson² in these laboratories obtained orange needles which melted at 157-158°. A preliminary proposal for the formula of this product was the following:



This structure was based primarily on the results of carbon, hydrogen and nitrogen analyses and on analogy with the product obtained by Boehme¹ in a related reaction using malonic ester. This latter product was proven to have the following structure.



Inasmuch as sufficient time was not available for Erickson to complete the characterization of compound (A), the

investigation was continued by the present writer.

The compound was prepared in 14% yield from 1,4-naphthoquinone and ethyl acetoacetate by allowing a pyridine solution to stand at room temperature for one week. (All yield figures in this and the following sections are based on the final proposed structures.) In the recommended method of Erickson, however, an alcoholic solution of 2,3-dichloro-1,4-naphthoquinone and ethyl acetoacetate, to which a few ml. of pyridine had been added, was refluxed two and one-half hours. This procedure was used by the present investigator to prepare the compound obtained by Erickson, and with a few minor changes a 49% yield was obtained.

When an ethoxyl determination was made, instead of the calculated value of 7.50%, there was obtained a value of 14.12%. The results of the carbon, hydrogen, and nitrogen analyses were not greatly different from those formerly obtained, and no depression was observed when a mixture melting point determination on the two products was made. These observations seemed to indicate that structure (A) was incorrect and that further characterization was necessary.

A molecular weight determination was considered to be of prime importance. In order to do this a number of determinations were made, using the Rast procedure as described by Shriner and Fuson.⁴⁹ An average value of 330 was obtained. In order to check this value, the molecular weight was redetermined by the method based on the lowering of the freezing point of benzene.⁵⁰ An average value of 322 was

obtained by this method. These values obviously do not correspond to the calculated value of 600 for the molecular weight of compound (A). A compound, however, with an empirical formula of $C_{19}H_{13}O_4N$, as determined from the elementary analysis, has a calculated molecular weight of 319. This new formula is supported by a calculation which shows an ethoxyl content of 14.11% for one such group per molecule.

The presence of the naphthoquinone nucleus was indicated by the facile method developed by Storherr.³ Upon heating the compound on a hot plate with concentrated nitric acid until dry, phthalic anhydride sublimed from the reaction mixture.

Since the compound contained nitrogen an explanation must be given as to how the pyridine entered into the reaction. The pyridine is bound in a very stable fashion. This was shown by the fact that treatment with concentrated sulfuric acid or with strong alkali did not remove the nitrogen. This suggests that the pyridine may be bound by a C-C linkage. These conditions are much more stringent than those used on the pyridinium compounds, from which pyridine was easily removed and which were discussed in the above literature survey.

A substitute for pyridine was used in an attempt to synthesize a nitrogen free product. Quinoline was first chosen for this purpose because it was reported to be incapable of forming salts analogous to compounds (XXII) and

(XXIII) (Historical Introduction).^{36,38} In this case, however, orange crystals with a melting point of 238-239° were obtained in 45% yield. A molecular weight determination by the Rast method showed an average value of 376. The results of elementary analyses corresponded to a compound with an empirical formula of $C_{23}H_{15}O_4N$, which has a calculated molecular weight of 369. The difference in elementary analysis between the pyridine product and the quinoline product is C_4H_2 , the same as between pyridine and quinoline. The results of an ethoxyl determination also agreed with the calculated value for one such group per molecule.

An attempt was made to convert the pyridine product to the quinoline product by refluxing the pyridine product in an excess of quinoline for 48 hours; no conversion occurred. This adds support to the previous indications that the amine entered into the reaction and the product was not a salt or an addition complex.

In a second attempt to obtain a nitrogen free product, sym-collidine was used. Red needles with a melting point of 266° were obtained in 37.5% yield. It was difficult to devise a satisfactory empirical formula for this product. The formula $C_{21}H_{17}O_4N$ does, however, agree with the results of elementary analyses, and molecular weight and ethoxyl determinations. This compound will be discussed in greater detail in a later section.

A suitable structure for these products could not be postulated from the empirical formulas and from the other

data obtained. Erickson² found from a literature survey of cleavage reactions that substitution of an unsaturated group, either β or γ to the carbethoxyl group, would favor a cleavage. In the Historical Introduction pyridinium salts obtained from α -halogenated 1,3-diketones were shown to undergo cleavage. Therefore, an attempt was made to determine whether cleavage occurred in this reaction.

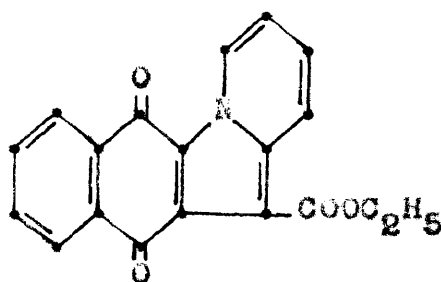
Ethyl malonate was refluxed with 2,3-dichloro-1,4-naphthoquinone in an alcoholic solution containing a few ml. of pyridine. A cleavage which removes the $-\text{COCH}_3$ group in the ethyl acetoacetate reaction would yield the same product as a cleavage which removes the $-\text{COOC}_2\text{H}_5$ group in the malonic ester reaction. The product obtained, however, was the yellow, crystalline salt discussed in the Historical Introduction as compound (XXII). This was confirmed by means of a mixture melting point determination and by conversion to known derivatives. Malonic ester is apparently not as reactive as ethyl acetoacetate so this competitive reaction predominated.

Since quinoline does not form a similar salt with 2,3-dichloro-1,4-naphthoquinone,³⁶ ethyl malonate was again reacted in a similar manner except using quinoline in place of pyridine. This time a reaction did occur and a crystalline product with a $238-239^\circ$ melting point was obtained in 11% yield. Proof of identity of this product and the one obtained above with quinoline and acetoacetic ester was obtained by means of mixture melting point determinations

and by comparison of results of elementary analyses and ethoxyl determinations.

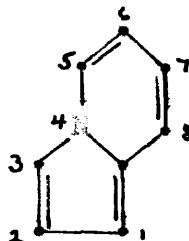
The next compound used to determine whether cleavage occurred was ethyl benzoylacetate. By the same experimental procedure using pyridine this methylene compound was found to yield the same orange needles as obtained from ethyl acetoacetate in 16% yield. These important results proved that cleavage had occurred.

With this additional information a new structure (I) for compound (A) is suggested. The reactions described above are interpreted on the basis of this structure in Chart I.



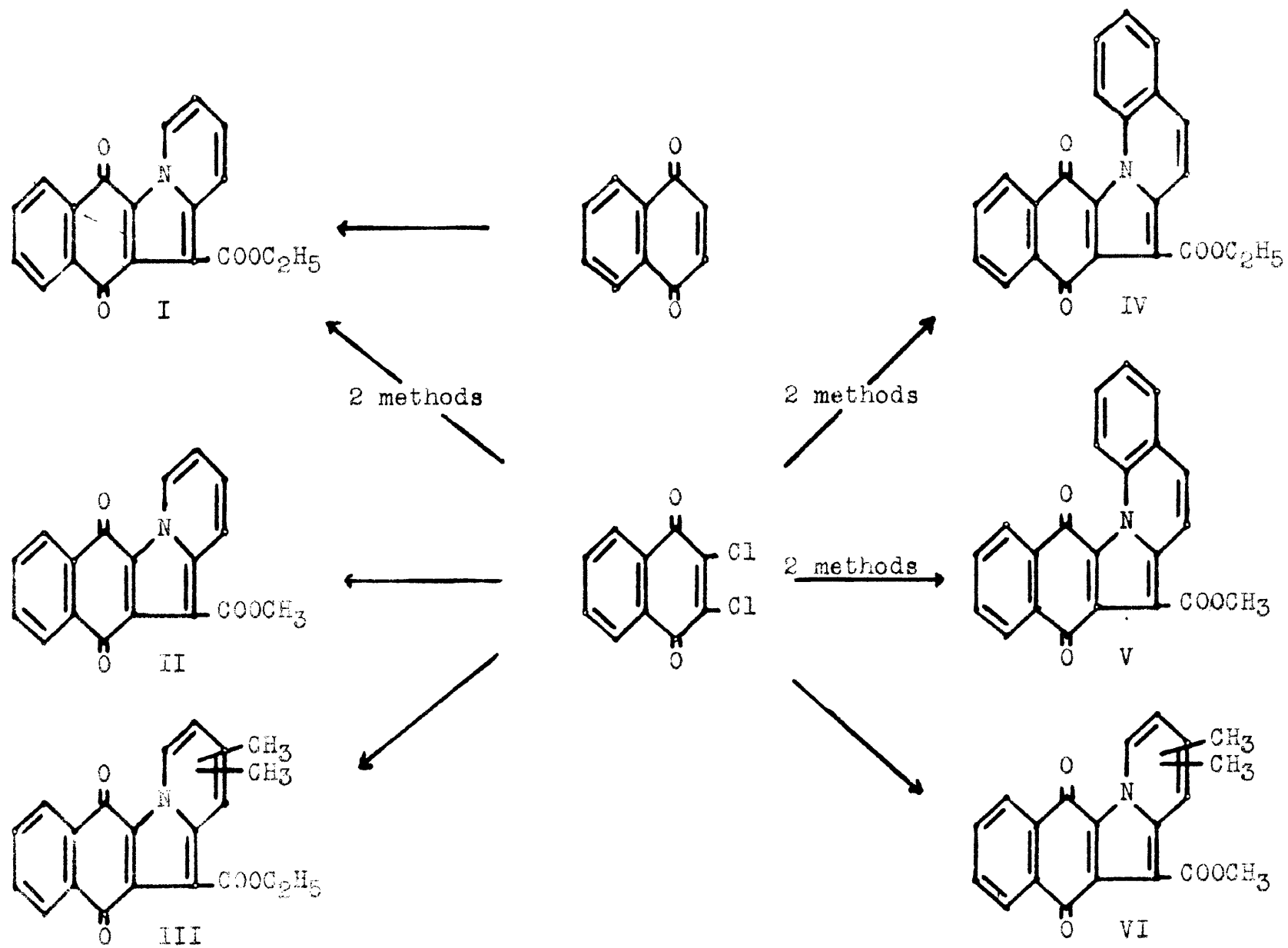
I

Compound (I) may be considered to be a derivative of pyrrocoline,



On this basis it may be named 1-carbethoxy-2,3-phthal-

CHART I



oylpyrrocoline. 1-Carboethoxy-2,3-phthaloyl-5,6-benzopyrrocoline is the name of the analogous compound (IV) (Chart I) obtained from quinoline.

The postulated structure (I) agrees with all the information thus far reported. Before further discussion on the reactivity of these compounds, however, a possible route for their formation will be given. Liebermann has shown that ethyl acetoacetate would condense with 2,3-dichloro-1,4-naphthoquinone to yield readily the monosubstituted product (XI), and with a strong base there was obtained the unusual cleavage product (VII) of a disubstituted quinone (Historical Introduction). With pyridine, a weak base, the monosubstituted product (B) (Chart II) would be expected. This compound should react readily with pyridine for several reasons. It is a vinylog of an α -halogen ketone and also of an acid chloride, both of which are capable of forming pyridinium salts as discussed in the related work in the literature. Compound (B) is also analogous to the acetylated 2-chloro-3-anilino-1,4-naphthoquinone, discussed in the Historical Introduction, which has a very active chlorine. The product of the reaction of (B) with pyridine might logically be compound (C).

The conversion of compound (C) to compound (E) is not improbable. The first step would be the loss of hydrogen chloride to yield compound (D), which is activated toward cleavage by the $-C=O$ or $-NC_5H_5^+$ groups which exert their effect via a vinyl group as well as by the $-COCH_3$ and

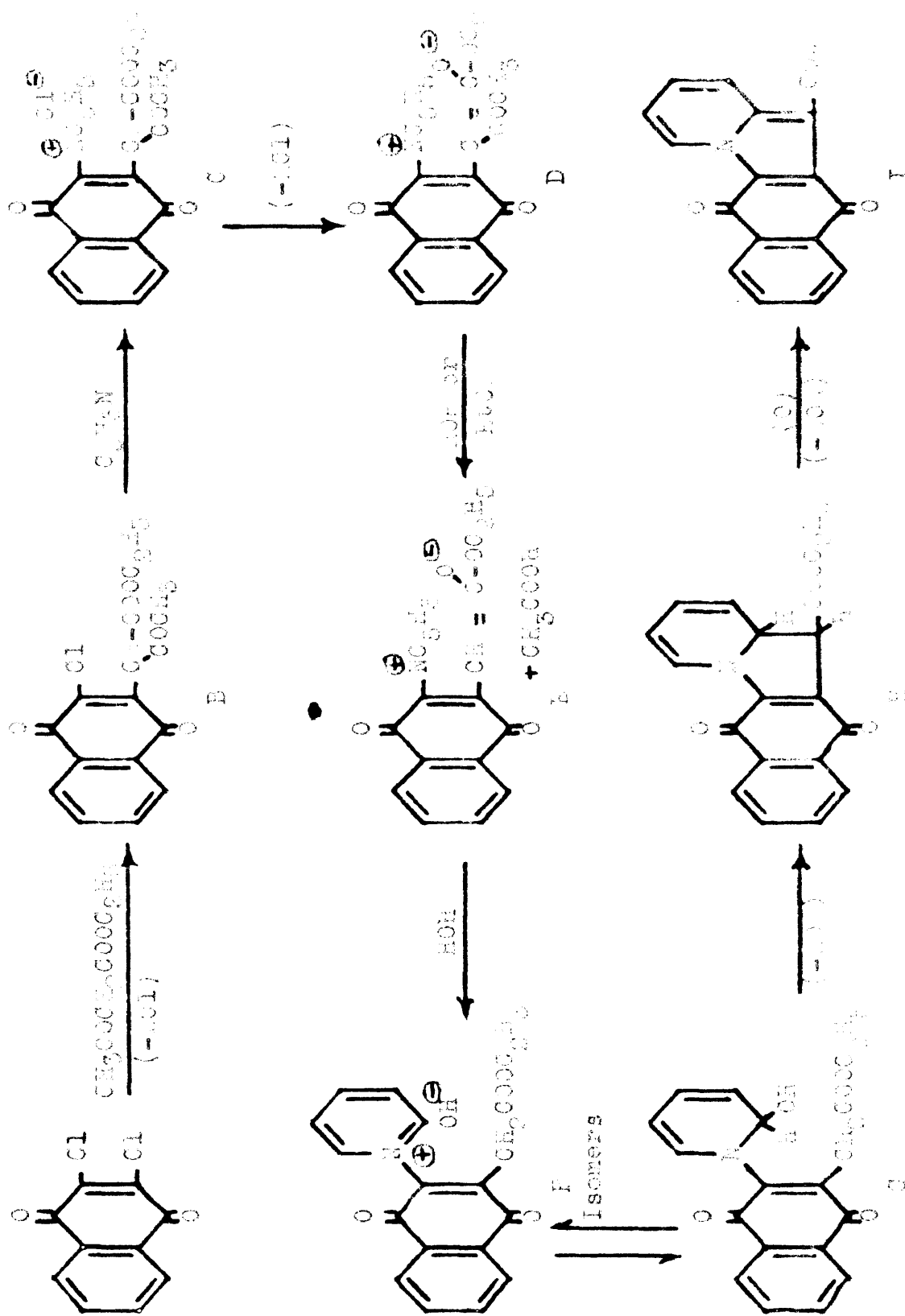
-COOC₂H₅ groups. This betaine type of compound, (D), is a vinylog of the compound discussed in the first section which was capable of "acid cleavage." It is also analogous to the pyridinium salt intermediate in King's conversion of an acetyl group to a carboxyl group, which is considered further below. The β -unsaturation mentioned above also favors a cleavage of this type. The cleavage might be initiated either by water, as illustrated in Chart II, or by ethanol which would form compound (E) and ethyl acetate.

The conversion of compound (E) to the proposed intermediate (H) may occur by three possible routes. Compound (E) could possibly exist as such; however, since most salts of this type readily pick up moisture, compound (F) may be formed.³⁷ Since it is well known that pyridinium hydroxides tautomerize readily, compound (G) might be obtained. The type of hydroxyl group in (G) has been shown to react with active methylene groups in alkaline solution.^{45,46} A similar reaction in this case would yield compound (H).

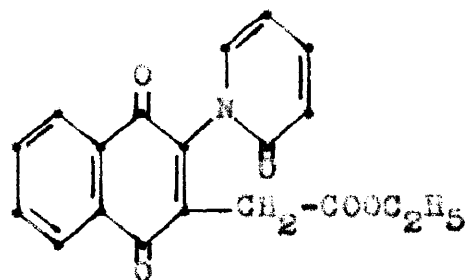
Water is not essential in the conversion of compound (E) to compound (H). This conversion may also be viewed as an addition of hydrogen chloride to compound (E) to form the chlorides analogous to (F) and (G). This product by a similar loss of hydrogen chloride would yield compound (H).

In the previous section of this thesis N-methylpyridinium hydroxide was shown to be capable of yielding N-methylpyridone in the presence of an oxidizing agent. Compound (F) may also be oxidized, by any of the oxidizing

CHART II

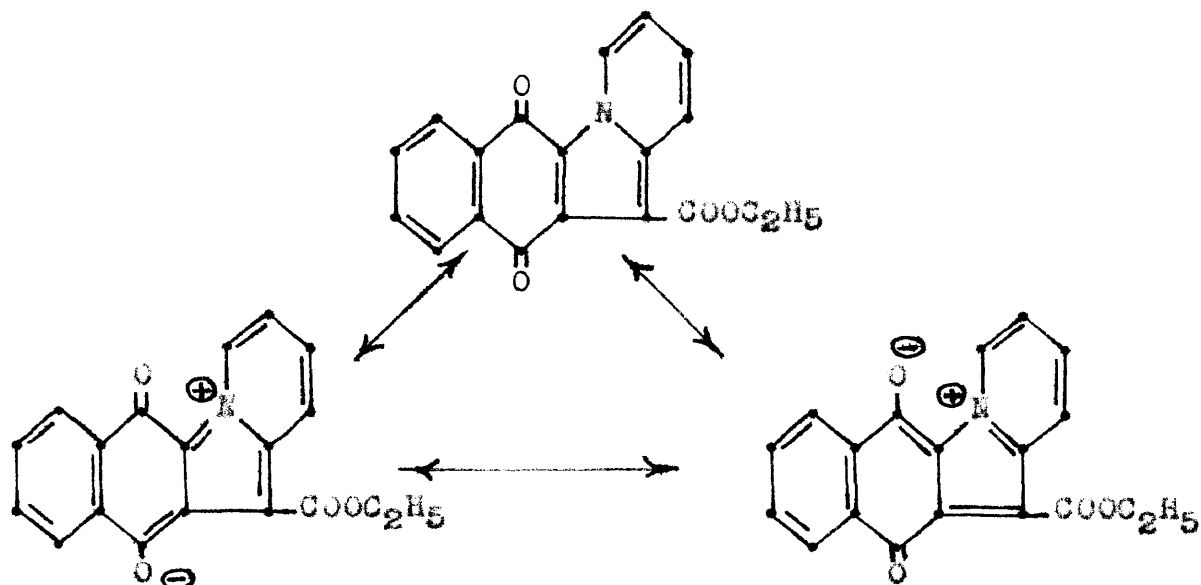


agents present in the reaction mixture, to this ketone.

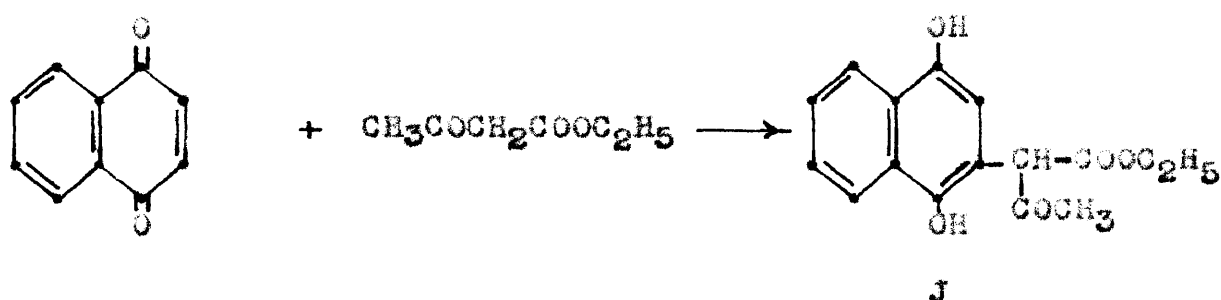


This compound also would yield the product (I) on loss of water.

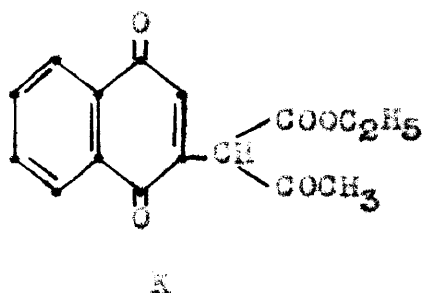
Compound (H) might, however, be unstable in the presence of oxidizing agents. By analogy with the oxidizing ability of chloranil, 2,3-dichloro-1,4-naphthoquinone might be expected to oxidize compound (H) to compound (I). The oxidizing agent, however, may be any of the previously proposed intermediates in this reaction. The final product (I) would appear to be stabilized to a great extent by resonance, as illustrated below, and this would also facilitate its formation.



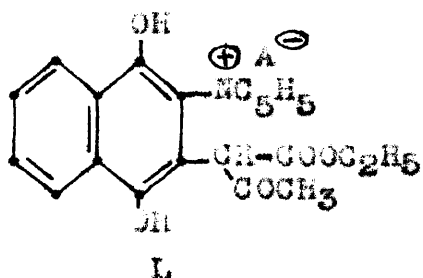
A possible route for the formation of compound (I) from the unsubstituted 1,4-naphthoquinone, which was prepared by Erickson, should be devised. The first step to be expected is 1,4-addition. This was shown to occur in a large number of similar reactions discussed by previous investigators.^{1,2,3}



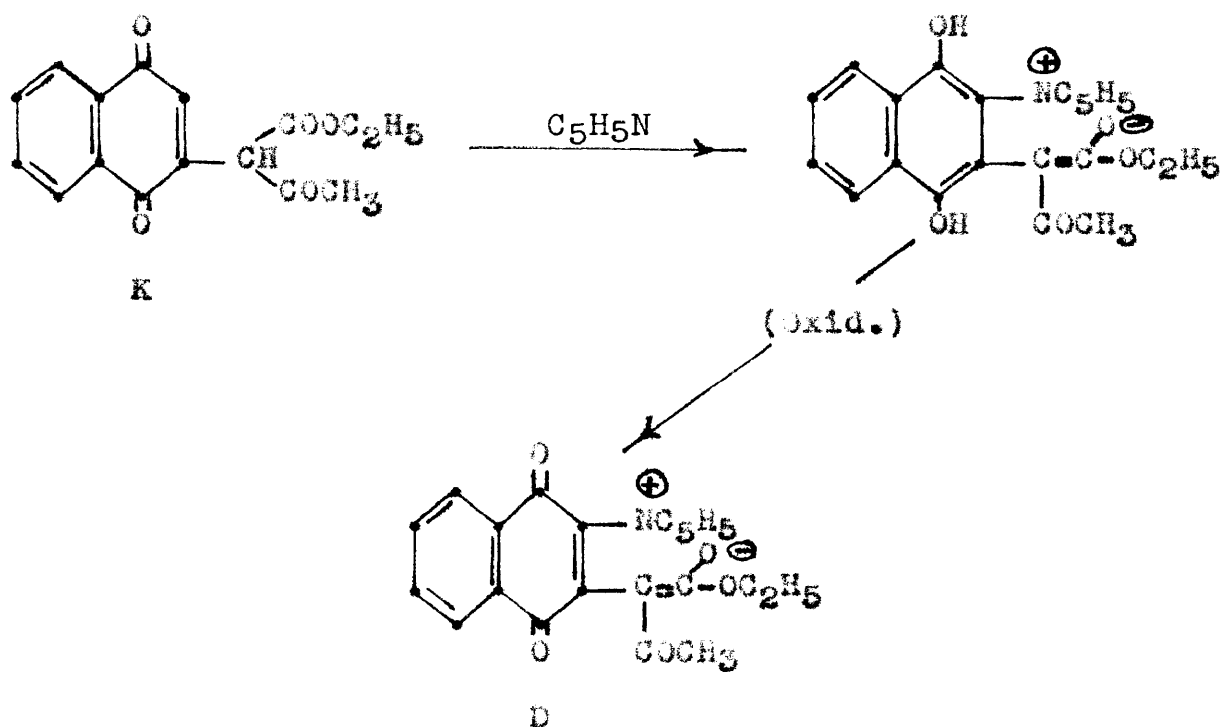
Oxidation of this naphthohydroquinone (J) yields a quinone (K) which might be capable of adding pyridine.



Benzoquinone for example has been shown in the Historical Introduction to be capable of forming pyridinium salts in the presence of pyridine and a carboxylic acid.^{42,43} The pyridinium salt which might be expected by this analogy has the following formula:



In the preparation of compound (I) Erickson added a little hydrochloric acid which could initiate the formation of the salt in which A^{\ominus} is Cl^{\ominus} . After cleavage the acetic acid which is formed, however, could continue this type of salt formation in which case A^{\ominus} would be CH_3COO^{\ominus} . Further oxidation of this salt (L) would yield compound (D) which is an intermediate in the reaction series of Chart II. It is not impossible that (K) itself is sufficiently acidic to promote this reaction with pyridine; this would also yield compound (D) on oxidation.



It may be significant that the yields obtained in this reaction seem to agree with the postulated series of reactions. Since three oxidations are necessary in obtaining the final product from 1,4-naphthoquinone and only one oxidation is necessary when prepared from 2,3-dichloro-1,4-

naphthoquinone, corresponding yields of 12.5% and 50% might be expected.

Using the general procedure of refluxing an alcoholic solution of 2,3-dichloro-1,4-naphthoquinone and methyl acetoacetate with a few ml. of the desired tertiary amine, there were prepared the following: compound (II) in 51% yield, compound (V) in 39% yield and compound (VI) in 26% (Chart I). Also, methyl malonate should yield compound (V) when reacted under similar conditions using quinoline. This reaction was successful and compound (V) was obtained in 20% yield.

In order further to characterize compound (I) certain of its reactions were studied. Upon treatment with sulfuric acid a new high-melting, red compound was obtained, which did not, however, analyze satisfactorily for the corresponding acid. This was probably due to incomplete conversion of the ester to the acid and also to the difficulty of removing all the solvent of crystallization. Erickson² reported the preparation of a similar product by two methods, i.e., treatment of compound (I) with a potassium hydroxide and diethylene glycol mixture followed by acidification, or treatment of an alcoholic solution with sodium ethoxide followed by acidification. With some modifications in the latter procedure a 77% yield of pure acid was obtained. (Compound (X), Chart III). This was converted in a 7% yield to the amide (XI) by treatment with thionyl chloride followed by ammonium hydroxide.

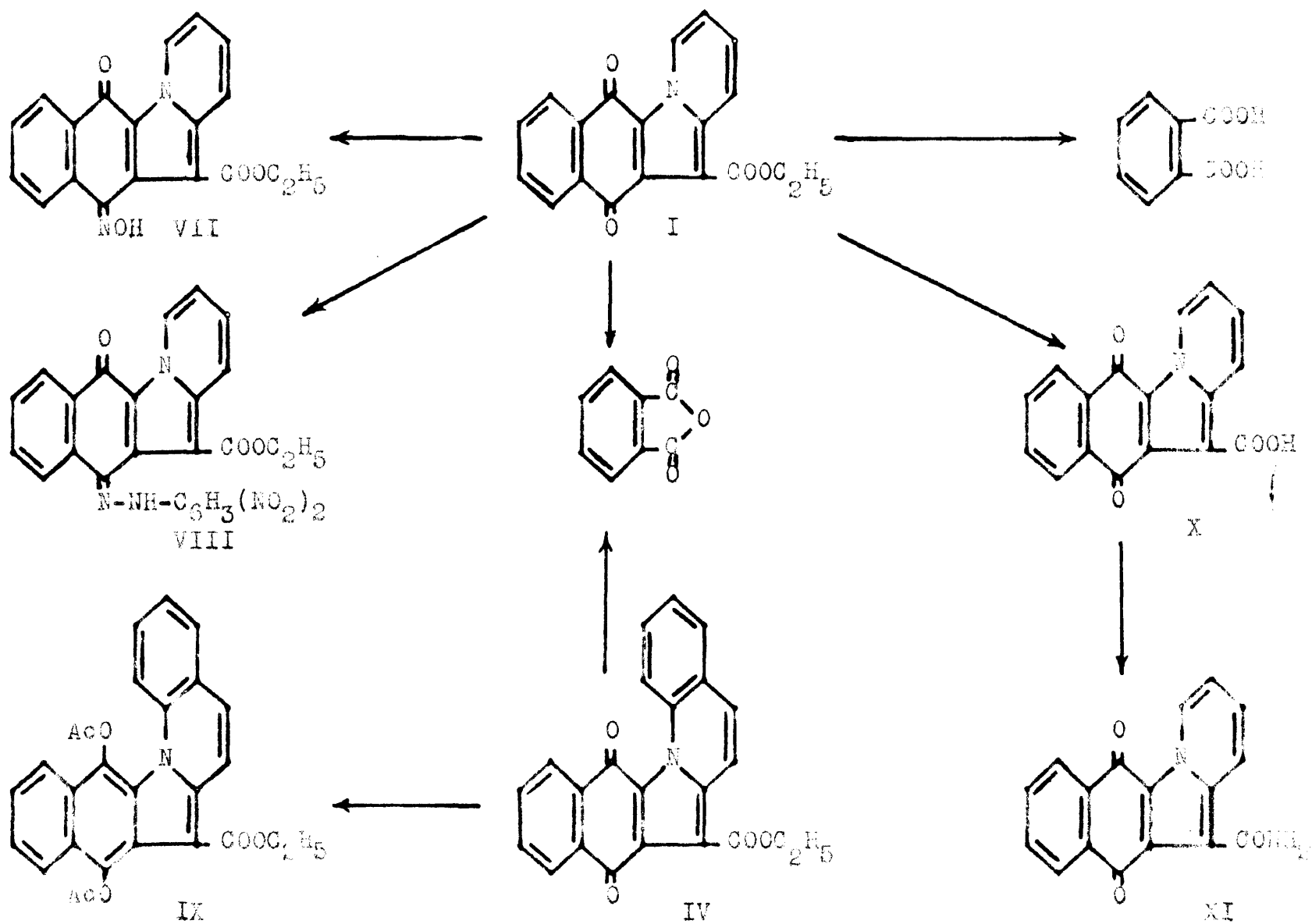
The typical carbonyl reagents were also used in preparing derivatives of compound (I). The crystalline monooxime, compound (VII), and mono-2,4-dinitrophenylhydrazone, compound (VIII), were successfully prepared. These structures were assigned on the basis that steric factors may prevent reaction of the carbonyl nearest the nitrogen.

Reductive acetylation is considered to be an excellent reaction for characterizing quinones. No crystalline product could be isolated upon reductive acetylation of compound (I), but when compound (IV) was used a crystalline diacetate (IX) was readily obtained.

An attempt was made to obtain additional degradation products from compound (I). When warmed with a 30% aqueous hydrogen peroxide solution and glacial acetic acid, oxidation occurred to yield phthalic acid. No other products were isolated, however, from this reaction.

According to the results of elementary analyses, the products obtained when sym-collidine was used with both ethyl acetoacetate and methyl acetoacetate were dimethylpyrrocolines, (III) and (VI) of Chart I. This would seem to imply that a methyl group was lost from the sym-collidine. To check this the collidine, which was used, was fractionated through a three foot column. The boiling point observed was 171.0° and the refractive index at 25° was 1.4990. The literature values for pure sym-collidine are: boiling point 170.4° and refractive index at 25° 1.4964.⁵¹ Apparently the collidine used contained some impurity. Due

CHART III



to the large excess of the base used in this reaction, the product obtained may be merely a derivative of the impurity. 2,4-Dimethylpyridine cannot be the impurity since a pure sample of this amine will not undergo this reaction. The 3,5-dimethylpyridine is another possibility since it has a boiling point of 169-170°. ⁵² None of this material was available for testing, therefore no conclusive evidence can be presented to confirm these results. Further work is indicated in this case.

Reactions of Acetylacetone and Related Compounds

Upon refluxing an alcoholic solution of acetylacetone and 2,3-dichloro-1,4-naphthoquinone to which a few ml. of pyridine was added, there was obtained in 58% yield a red powder which melted at 205-206°. This material was considerably less soluble in organic solvents than the corresponding product from acetoacetic ester discussed above. The product was purified with considerable difficulty by recrystallization from acetic acid and according to the analytical results the empirical formula was $C_{18}H_{11}O_3N$.

This product appeared to be identical with the red powder obtained by Erickson² from the reaction of acetylacetone with 1,4-naphthoquinone. In this latter case, however, a qualitative test for nitrogen was negative. A mixture melting point of the two materials did not show a depression. A quantitative analysis of this sample did show the presence of nitrogen. This particular compound was one of several found during this investigation, which did not give a satisfactory qualitative test for nitrogen.

A molecular weight determination was made on this product in order to obtain additional evidence before postulating a structure. By the Rast procedure an average value of 296 was obtained. The calculated value for $C_{18}H_{11}O_3N$ is 289. It appears to be logical from this evidence and by analogy with the reaction of acetoacetic ester, that a

second derivative of 2,3-phthaloylpyrrocoline has been obtained. Therefore structure (XV), Chart IV, is proposed for this product.

As in the case of the ester, the reaction was tried with other bases. Quinoline gave a 57% yield of orange needles which analyzed satisfactorily for compound (XII). The same apparently impure sym-collidine was used as with the ester; the product obtained in 22% yield was again analogous in that the analytical results corresponded to a dimethylpyrrocoline, compound (XIII).

An attempt was made to synthesize compound (XV) by a different route using benzoylacetone as the methylene compound. In order to avoid purification difficulties since this methylene compound is a solid, only a slight excess of the methylene compound was used. There was obtained a new product in 10% yield instead of the hoped for 1-acetyl product. The results of elementary analyses for this compound indicated that it was 1-benzoyl-2,3-phthaloylpyrrocoline (XIV). As mentioned in the Historical Introduction, in cleavages of this type the smaller of the two groups is usually lost.

Compound (XV) was converted by means of the King modification of the haloform reaction to the 1-carboxy-2,3-phthaloylpyrrocoline (X). This was a very satisfactory and simple laboratory procedure. The pyridinium iodide (XVI) was isolated in 69% yield as orange plates with a melting point of 258-259.5°. A pure sample of the acid (X) was

obtained in a 27% yield from this intermediate. This acid (X) was proven to be identical with the acid obtained from compound (I), Chart I, by the results of analyses, by its melting point, and by the results of a mixture melting point determination.

Reactions of Cyanoacetic Ester and Related Compounds

By the reaction of ethyl cyanoacetate with an alcoholic solution of 2,3-dichloro-1,4-naphthoquinone, to which a few ml. of pyridine was added, there was obtained in 53% yield an orange, crystalline solid with a melting point of 307.4-308.4°. The product was extremely insoluble in most organic solvents with the exception of hot pyridine and nitrobenzene; its appearance and melting point were the same as that of a product obtained previously by Boehme¹ and also by Storch³. To confirm this observation, the results of elementary analyses for this product were compared with the results for the product obtained by Storch from the reaction of a solution of 1,4-naphthoquinone in wet pyridine with ethyl cyanoacetate. This comparison was close and no depression was obtained when a mixture melting point determination on the two materials was made. Storch also obtained a second product when dry pyridine was used in this reaction with 1,4-naphthoquinone. This product will be discussed in more detail in the next section.

The previous investigators concluded that it was difficult to devise a suitable structure for this product because of the difficulty in obtaining analytically pure samples and because of the almost complete insolubility of the product in camphor, which prevented a molecular weight determination by the Rast method. Previous attempts to

obtain derivatives by treatment with such reagents as sulfuric acid and nitric acid were also unsuccessful due primarily to solubility difficulties.

The knowledge, gained from the study of the reactions described above with other active methylene compounds, suggested several approaches for the determination of the structure of this product. Oxidation with nitric acid yielded phthalic anhydride by Storherr's method. As mentioned in a previous section, this indicates the presence of the naphthoquinone nucleus in the molecule. The reaction of ethyl cyanoacetate with 2,3-dichloro-1,4-naphthoquinone, using quinoline instead of pyridine, was successful, and yellow needles with the extremely high melting point of 345-346° were obtained in 40% yield.

Methyl cyanoacetate in place of the ethyl cyanoacetate was used with quinoline to determine if cleavage had occurred. The same yellow needles were obtained in 27% yield. Proof of identity of the two products was obtained by means of a mixture melting point determination and by comparison of the results of elementary analyses. Confirmation of the cleavage was obtained when methyl cyanoacetate yielded the same product as ethyl cyanoacetate in the original reaction with 2,3-dichloro-1,4-naphthoquinone in the presence of pyridine.

The similarity of these reactions with cyanoacetic ester to the previous reactions of acetoacetic ester and acetylacetone suggested that the products may be derivatives

of 2,3-phthaloylpyrrocoline. Therefore, the structures (XVII) and (XXI) (Chart V) were assigned to the products which were obtained. The results of elementary analyses of these products were in close agreement with the calculated values for the proposed structures.

Some further attempts were made to obtain additional information about these relatively unreactive products. Reductive acetylation of this pyrrocoline (XXI) gave a satisfactory derivative. A yellow, crystalline diacetate (XVIII) which melted at 269-270° was obtained in 36% yield. This diacetate was considerably more soluble in camphor than the pyrrocoline from which it was derived. A Rast molecular weight determination gave an average value of 365, as compared to a calculated value of 358.

Treatment of the cyanopyrrocoline (XXI) with hot sulfuric acid produced a 36% yield of the corresponding amide (XI). This is another example in which these reaction products were subjected to reagents which should remove any pyridine. As a result of its retention there seems to be little doubt that the pyridine may be linked by a C-C bond as postulated in the pyrrocoline structure.

An infrared absorption spectrum was taken on the 1-cyano-2,3-phthaloylpyrrocoline (XXI). Confirmation of the presence of the =C-CN group may be reached from a study of this spectrum. Griffith and Kitson⁵³ made the observation, in their study of the infrared absorption band due to the nitrile stretching vibration, that some conclusions may be

drawn as to the relation between the nitrile group and other parts of the molecule. They obtained an absorption at $2250 \pm 10 \text{ cm.}^{-1}$ for saturated nitriles or for olefinic nitriles with no conjugation between the nitrile and the olefinic group. In olefinic nitriles, however, where conjugation exists with a double bond or in aromatic compounds with the nitrile group attached to the ring, a shift in the absorption to a wave number of $2225 \pm 8 \text{ cm.}^{-1}$ occurred. The spectrum of compound (XXI) showed an absorption at 2227 cm.^{-1} . This is in excellent agreement with the absorption wavelength which might be expected from the proposed structural formula for this product.

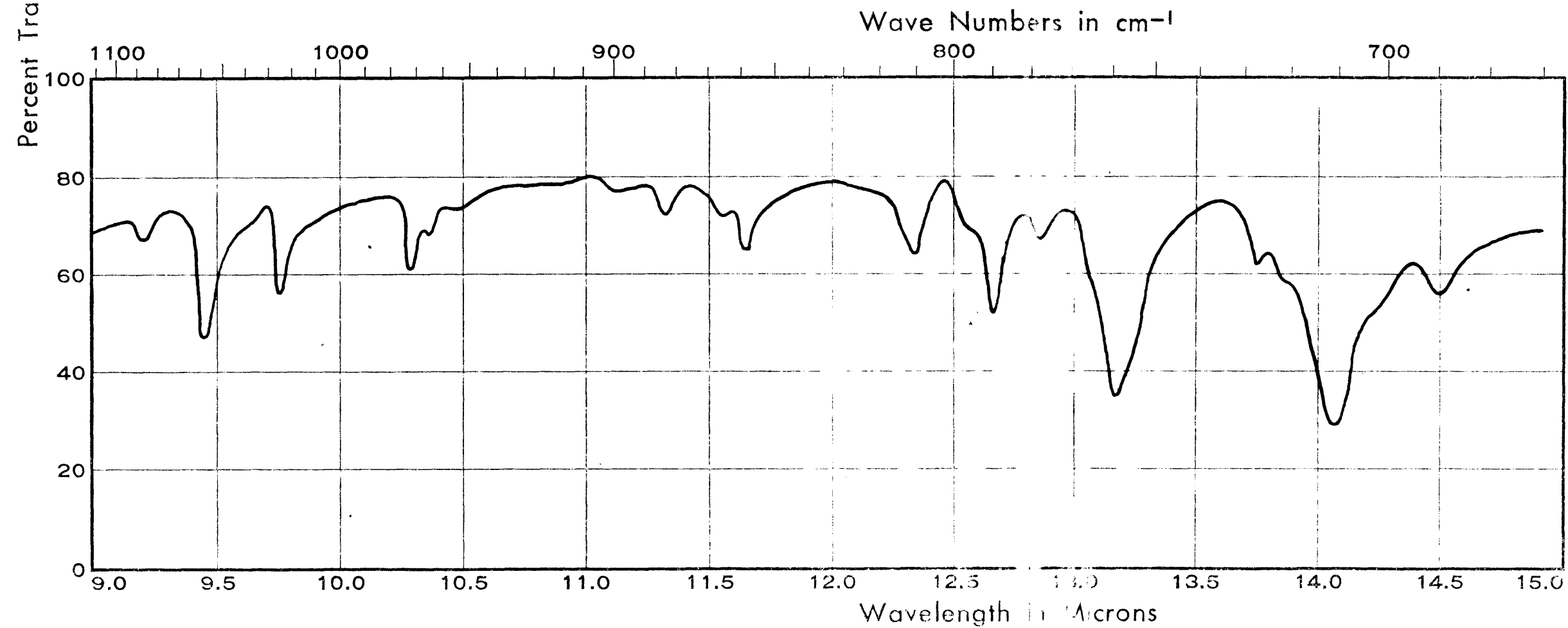
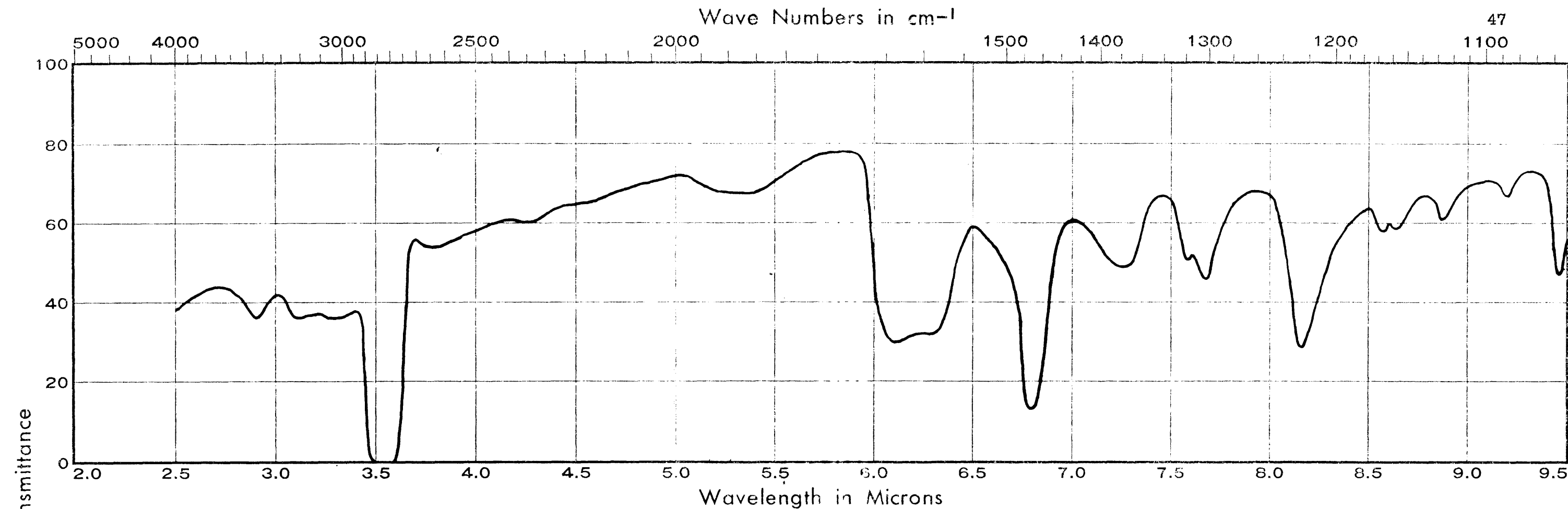
The light orange needles of the amide (XI) obtained from the 1-cyano-2,3-phthaloylpyrrocoline (XXI) melted at $313.5\text{--}314.5^\circ$. When the amide (XI), however, was prepared from 1-carbethoxy-2,3-phthaloylpyrrocoline (I), as described above, it melted at 302° and was more deeply colored. A mixture melting point determination of the amide obtained by the two methods, however, did not show a depression; the mixture melted between the two extremes at $308\text{--}310^\circ$.

The observed differences in appearance and melting points may be due to the occurrence of allotropic forms of a single compound, since the higher melting amide, obtained from the nitrile (XXI), changed in appearance at approximately 250° . Reddish prisms were obtained when this latter amide was heated at approximately 250° for one hour. This product on recrystallization from nitrobenzene yielded maroon needles

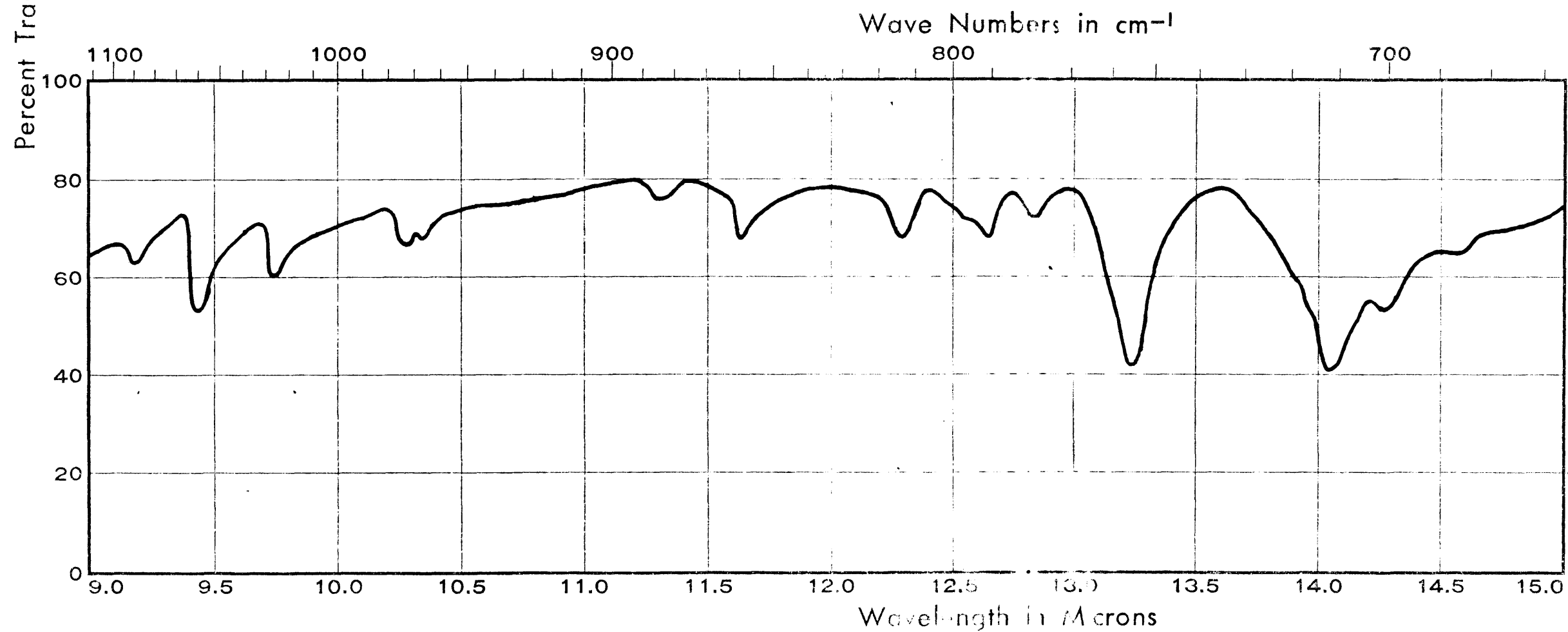
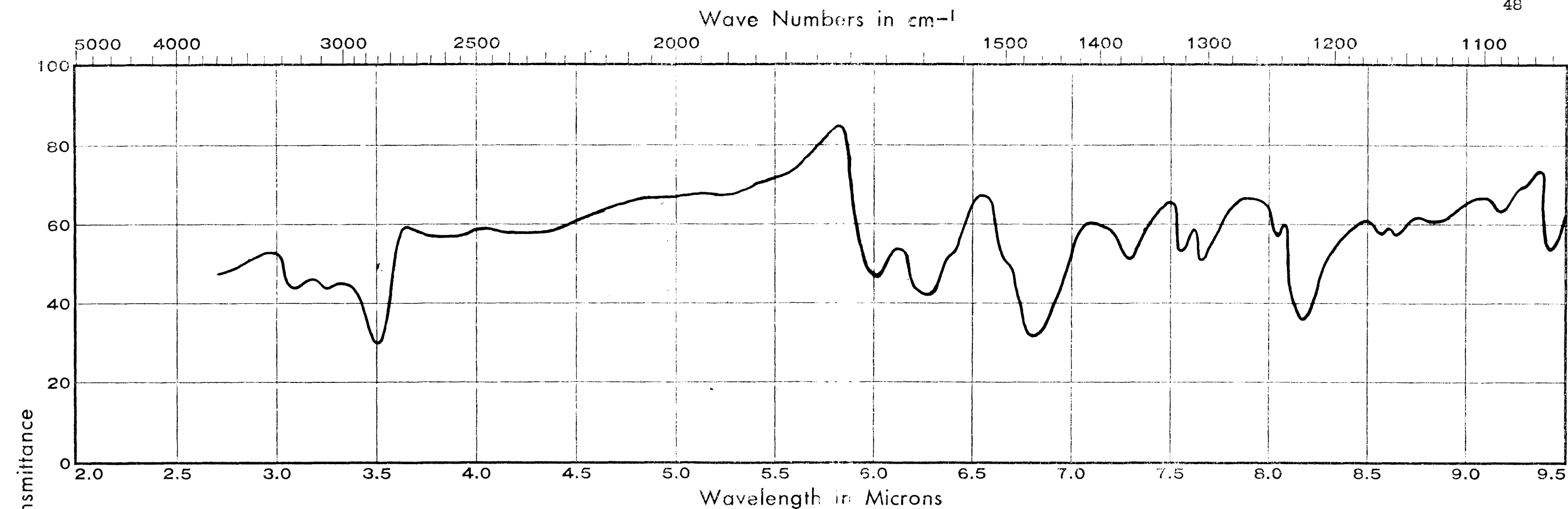
with a melting point of 302-303°. This low melting amide was reconverted to the high melting modification by recrystallization from glacial acetic acid. The low melting amide and the amide from the ester (I) did not give a depression when a mixture melting point determination was carried out.

In order to confirm further the identity of the amide obtained from the two sources, infrared absorption spectra were obtained for these materials. The absorption curves were identical up to approximately 12 microns as may be seen on the following graphs. Above this wavelength the curves are similar in appearance, however, there is a slight shift in the absorption peaks. This shift may be caused by a trace of impurity in the sample of the amide (XI), prepared from the ester (I), which is indicated by the results of elementary analyses. Even though repeated attempts were made to improve the preparation and purification of this amide (XI), the best product obtained analyzed 0.6% low in carbon. Since the spectra are identical in the lower wavelengths, where the characteristic absorptions for functional groups of the type of interest here ordinarily occur, it seems reasonable to conclude that the two products are identical in structure.

The insolubility of the cyanopyrrocoline (XXI) was the chief cause of the failure of all other attempts to prepare derivatives. Reactions occurred upon oxidation with nitric acid or with alkaline potassium permanganate,



COMPOUND
Amide Prepared from 1-Cyano- 2,3-phthaloylpyrrocoline
SOURCE AND PURITY
STATE
TEMPERATURE
CELL LENGTH
LABORATORY

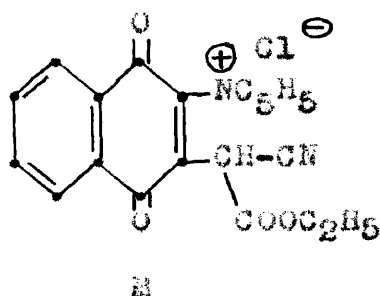


COMPOUND
Amide Prepared from 1-Carboxy- 2,3-phthaloylprocoline. SOURCE AND PURITY
STATE
TEMPERATURE
CELL LENGTH
LABORATORY

or upon the treatment with phosphorous pentachloride; however, no definitely pure crystalline products could be isolated.

An attempt was made to increase the yield of 1-cyano-2,3-phthaloylpyrrocoline obtained from 2,3-dichloro-1,4-naphthoquinone. By the evaporation of the filtrate from the reaction mixture to one-tenth of its original volume, a yellow, crystalline solid, which melted at 277.8-278.8°, precipitated from the solution in 26% yield. Upon the basis of the results of elementary analyses the structure (XX) was assigned to this product. The compound is somewhat unstable, since it showed a slight discoloration on standing in air at room temperature. Upon recrystallization from glacial acetic acid one molecule of the solvent was absorbed per molecule of product. An aqueous solution of this pyridinium salt (XX) gave an immediate precipitate of silver chloride upon the addition of aqueous silver nitrate, and an unidentified red precipitate upon addition of 10% aqueous sodium hydroxide. Due to the type of functional groups present and the water solubility of this compound, it may have some significant physiological effects.

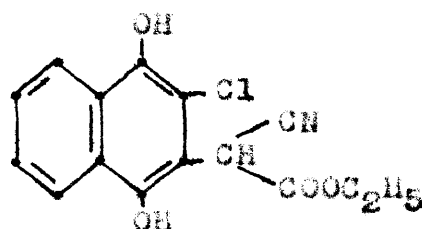
If the reactions to give the cyanopyrrocoline occurred by a route similar to that proposed for ethyl acetoacetate (Chart II) this pyridinium salt (XX) would be a logical by-product. This indicated that the postulated intermediate illustrated below was the oxidizing agent in the reaction.



In order to obtain some additional evidence on the route of the reaction, compound (XIX), Chart V, was prepared by the procedure outlined by Liebermann.²³ All of the work of Liebermann and Michel was concerned with the reactions of 2,3-dihalo-1,4-naphthoquinones with active methylene compounds in the presence of sodium ethoxide.²¹⁻²⁵ Since they never employed tertiary amines, their products had no close relationship to the main products obtained in this investigation. Liebermann's monosubstituted product (XIX), however, may be postulated to be an intermediate in the formation of the cyanopyrrocoline (XXI) by analogy with the reactions of Chart II; also the reduction product of its salt (XX) was isolated as a by-product in the reaction. It was therefore predicted that upon treatment with pyridine compound (XIX) would yield 1-cyano-2,3-phthaloylpyrrocoline (XXI). The prediction proved to be correct and the cyanopyrrocoline (XXI) was obtained in a 74% yield; the pyridinium salt (XX) was isolated also in 24% yield. It is noteworthy that such a high yield of the pyrrocoline was obtained. Apparently some other oxidizing agent must be present. Since the naphthohydroquinone by-product (XX) was observed previously to be unstable in air, some of this

material may be oxidized back to the quinone (K). This would then form more of the pyrrocoline (XXI).

When the reaction of 2,3-dichloro-1,4-naphthoquinone with ethyl cyanoacetate was conducted in the presence of dimethylaniline as the tertiary amine, red needles which melted at 169-170° were obtained in 33% yield. The results of elementary analyses, although not completely satisfactory, seem to indicate that the product might be the following substituted naphthohydroquinone.



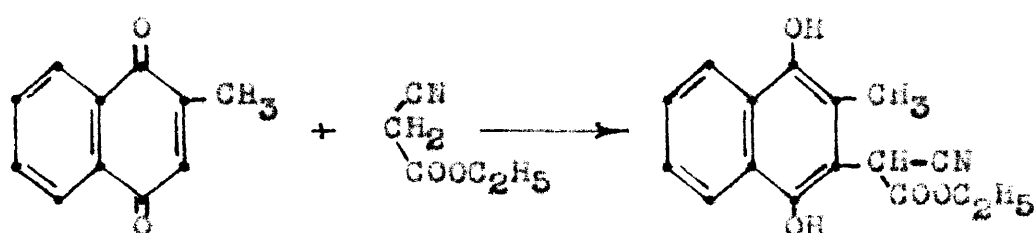
This product does not react with pyridine to give the pyrrocoline as might be expected, since the halogen would not be as activated as in the corresponding naphthoquinone (XIX). Further work, however, is indicated in order to assign a definite structure to this product.

Another interesting and rapid reaction occurred when 2,3-dichloro-1,4-naphthoquinone was reacted with ethyl cyanoacetate in the presence of a few ml. of α -picoline. Beautiful, bluish-black needles which did not melt even at 410° were obtained; the weight of product amounted to 72% of the weight of the quinone reactant. A structure which correlates with results of the elementary analyses has not been devised. A considerable percentage of ethoxyl was

present in the product, which indicated that the reaction followed a different route than the reaction with pyridine or quinoline. Sufficient time was not available to characterize this product completely. It is expected, however, that considerable difficulty would be encountered due to its insolubility and high melting point.

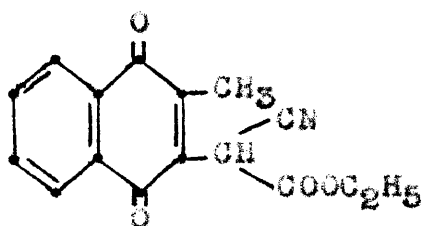
Reactions of Related 1,4-Naphthoquinones and Active Methylene Compounds

In an extension of this investigation various related 1,4-naphthoquinones were reacted with certain active methylene compounds. 2-Methyl-1,4-naphthoquinone, for example, was mixed with ethyl cyanoacetate in a pyridine solution and allowed to stand for one week at room temperature. There was isolated with some difficulty, in 21% yield, a white, crystalline product which melted at 132-133°. The results of elementary analyses indicated that the product may be the result of a 1,4-addition. This also agreed with the fact that the product is colorless, which is common to reduced quinones. The probable reaction is given below:



An extension of this reaction was attempted by using ethyl acetoacetate as the methylene compound. No reaction occurred under the previous conditions or by refluxing an alcoholic solution of the reactants for four hours. When ethyl acetoacetate was refluxed with this quinone in pyridine for four hours, a reaction occurred but no crystalline product could be isolated.

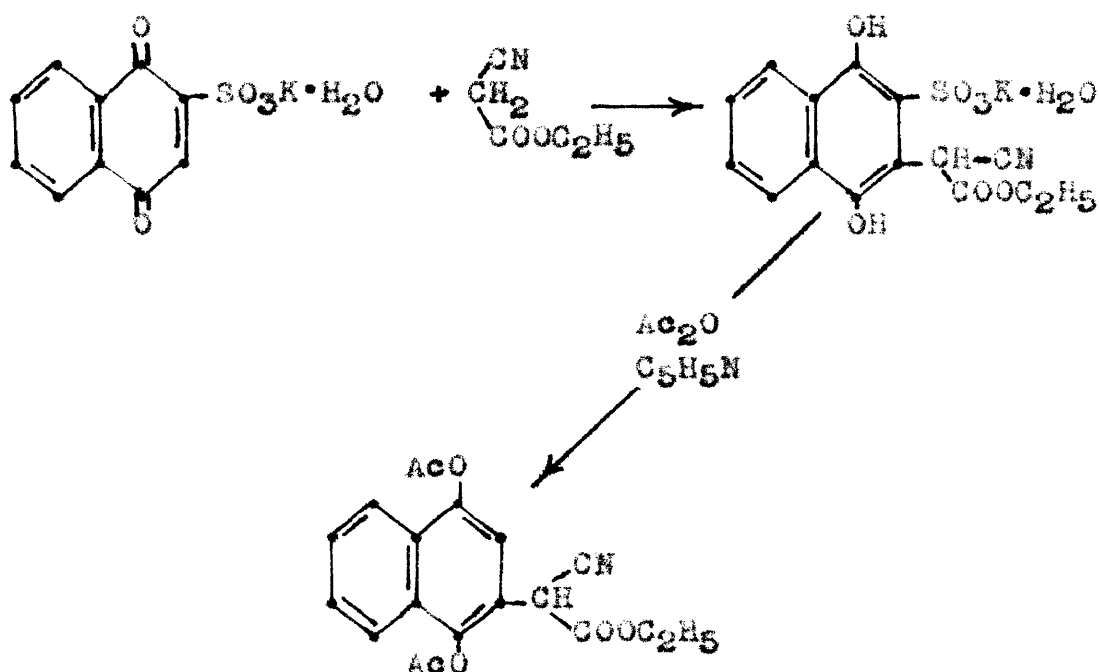
2-Bromo-3-methyl-1,4-naphthoquinone was prepared in an 87% yield from 2-methyl-1,4-naphthoquinone by the method outlined by Fieser and Fieser.⁵⁴ An alcoholic solution of this quinone was reacted with ethyl cyanoacetate in the presence of sodium ethoxide. A yellow, crystalline product with a melting point of 78.5-80.5° was obtained in 28% yield. The results of elementary analyses corresponded approximately to the calculated values for the following quinone.



Attempts to repeat this reaction were unsuccessful; therefore, an analytically pure sample was not obtained, and these results could not be verified. The reaction of ethyl cyanoacetate and of ethyl acetoacetate with this quinone were attempted in the presence of pyridine. In both cases only tarry residues were obtained and no analytically pure crystalline products could be isolated. There appears to be some possibility that the reaction of this quinone with active methylene compounds might be successful. Considerable work would be necessitated, however, in order to determine the proper reaction conditions before satisfactory products might be obtained.

Potassium 1,4-naphthoquinone-2-sulfonate was a third

type of quinone which reacted with active methylene compounds. The reaction, which was found by Storch³ to occur when this quinone was reacted with ethyl cyanoacetate, was confirmed. Also the subsequent reaction which occurred upon acetylation was repeated. These interesting reactions are illustrated below:



It is interesting to observe that this quinone has been reacted to give adequately characterized products with malonic ester,¹ acetoacetic ester,² and cyanoacetic ester,³ and the three products were of fundamentally different types. Malononitrile also reacts easily with this quinone to give the simple 1,4-addition product.³ The only reported reaction of this quinone and a methylene compound, in which the product has not been characterized is the product obtained by Erickson² from the reaction with acetylacetone.

No further work, however, was conducted with this quinone.

It has been shown that 1,4-naphthoquinone reacted with acetoacetic ester (Chart I), acetylacetone (Chart IV), and cyanoacetic ester (Chart V) in the presence of pyridine to yield the corresponding 1-carbethoxy-, 1-acetyl-, and 1-cyano-2,3-phthaloylpyrrocolines. Perhaps the most significant difference observed in the reactivity of 1,4-naphthoquinone with an active methylene compound was found in the reaction with ethyl cyanoacetate. Storherr³ found a different product when dry pyridine was used as the solvent for this reaction, instead of the wet pyridine. The product obtained in the presence of wet pyridine was shown above to be 1-cyano-2,3-phthaloylpyrrocoline. The reaction in the presence of dry pyridine was repeated by the writer and the same orange needles with a melting point of 281-283°, that were reported by Storherr, were obtained. The structure of this product is still in doubt, since the results of elementary analyses do not agree with any formula yet devised. Upon refluxing this low melting product with pyridine for seventy eight hours, a small yield of the 1-cyano-2,3-phthaloylpyrrocoline was obtained. Reductive acetylation of these low melting needles also gave a small yield of the diacetylated pyrrocoline (XIX) (Chart V). The low melting product may contain some impurity or it may contain solvent of crystallization. An entirely satisfactory explanation has not been obtained concerning the exact character of the low melting product. Since, however, it

was impossible to recrystallize until constant analytical results were obtained it is not impossible that it is merely impure cyanopyrrocoline (XXI).

A red, crystalline product with a melting point of 243.5-244.5° was isolated by Stornherr from the reaction of 1,4-naphthoquinone with phenylacetone in the presence of pyridine. This material was found to be one of the compounds which gave a negative qualitative test for nitrogen. The product, however, was found to contain approximately 3.90% of nitrogen. Further work will be conducted in this laboratory to establish the structure of this product.

Some preliminary work was done to determine the possible extent and application of the reaction of 2,3-dichloro-1,4-naphthoquinone with other active methylene compounds. Malononitrile, for example, reacted rapidly with this quinone in a refluxing alcoholic solution to which a few ml. of pyridine was added. No pure product was obtained from this reaction, probably because the conditions were too severe for this very reactive methylene compound. There were some indications of a possible reaction of this quinone with dibenzoylmethane. Some difficulty was encountered in the isolation of a product, however, due to the large excess of the solid methylene compound used in this reaction.

Phenylacetone, ethyl phenylacetate, ethyl *n*-butyl-acetoacetate, acetophenone, and *p,p'*-dinitrodiphenylmethane did not react with this quinone in the presence of pyridine. Instead of the hoped for condensations, the competitive

reaction of the 2,3-dichloro-1,4-naphthoquinone with pyridine occurred to form the pyridinium salt (compound XXII, Historical Introduction).

The reaction of an alcoholic solution of this quinone with additional methylene compounds in the presence of quinoline might be another possible extension of the pyrrocoline syntheses. With the above conditions reactions occurred with phenylacetone and with ethyl phenylacetate to yield crystalline products. Sufficient time was not available to characterize these products and further work will be conducted in this laboratory to determine their structures.

EXPERIMENTAL

Reactions of Acetoacetic Ester and Related Compounds

Syntheses of 1-Carbalkoxy-2,3-phthaloylpyrrocolines.^{a,b}

To a mixture of 0.50 g. of 2,3-dichloro-1,4-naphthoquinone and 5 ml. of redistilled active methylene compound dissolved in 25 ml. of absolute ethanol, there was added 7 ml. of redistilled tertiary amine. The resultant blue solution was refluxed four hours. The final reddish to brown solution was cooled in an ice bath. The crystalline product which precipitated was filtered off, washed with a little ethanol, and then washed thoroughly with ether. The tabulated yields are for products crystallized once from the solvents indicated. In all cases where two or more methods of preparation of the same compound are reported, a determination of the melting point for a mixture of the products from the two routes showed no depression. This procedure was followed in all cases except for experiment (1) which was reported previously by Erickson.²

In order to check the purity of the sym-collidine which was used in experiments (5) and (10), 160 ml. of 2,4,6-collidine (The Matheson Co. Inc. - 5479 Prac.) was distilled slowly through a 3 foot glass helices packed Todd column at atmospheric pressure. The refractive index of a 50 ml.

^aAll melting points are corrected.

^bWe wish to thank Professor Mary Aldridge and Mr. Byron Baer for the analyses.

TABLE I

Physical Constants and Yields

Expt. No.	Quinone	Methylene Compound	Amine	Product ^a	M.p., °C	Solv.	Color & Form	Yield %
1	1,4-Naphtho-	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	$\text{C}_5\text{H}_5\text{N}$	I	157-158	Ethanol	Orange Needles	14
2	2,3-Dichloro-1,4-naphtho-	"	"	I	"	"	"	49
3	"	$\text{C}_6\text{H}_5\text{COCH}_2\text{COOC}_2\text{H}_5$	"	I	"	"	"	16
4	"	$\text{CH}_3\text{COCH}_2\text{COOCH}_3$	"	II	190-191 (dec.)	Glacial acetic a.	Yellow Needles	51
5	"	$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	$\text{C}_8\text{H}_{11}\text{N}^b$	III	266 (dec.)	Ethanol	Red Needles	38
6	"	"	$\text{C}_9\text{H}_7\text{N}$	IV	238-239	Chlorobenzene	Orange Plates	45
7	"	$\text{CH}_2(\text{COOC}_2\text{H}_5)_2$	"	IV	"	Dioxane	Yellow Needles	11
8	"	$\text{CH}_3\text{COCH}_2\text{COOCH}_3$	"	V	244.5-245.5	<i>o</i> -Xylene	Orange Plates	39
9	"	$\text{CH}_2(\text{COOCH}_3)_2$	"	V	"	"	"	20
10	"	$\text{CH}_3\text{COCH}_2\text{COOCH}_3$	$\text{C}_8\text{H}_{11}\text{N}^b$	VI	222-223 (dec.)	Ethanol	Maroon Needles	26

^aRoman numerals refer to Chart 1.

^bCrude collidine was employed and apparently the product was a derivative of a dimethylpyridine impurity. (See Experimental)

TABLE II
Analytical Results

Expt. No.	Formula	Pro- duct ^a	<u>Carbon</u>		<u>Hydrogen</u>		<u>Nitrogen</u>		<u>Alkoxy-</u>	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{19}H_{13}O_4N$	I	71.47	71.98 71.80	4.10	4.42 4.18	4.39	4.61 4.58		
2	$C_{19}H_{13}O_4N$	I	71.47	71.48 71.42	4.10	4.38 4.17	4.39	4.56 4.61	14.11	14.11 14.12
4	$C_{18}H_{11}O_4N$	II	70.82	71.33 70.89	3.63	3.70 3.65	4.59	4.73 4.57	10.17	10.32 10.33
5	$C_{21}H_{17}O_4N$	III	72.16	72.55 72.89	4.93	5.06 5.10	4.03	4.18 4.19	12.97	13.34 13.68
6	$C_{23}H_{15}O_4N$	IV	74.79	74.48 74.34	4.09	4.37 4.31	3.79	3.86 3.93	12.20	12.17 12.13
7	$C_{23}H_{15}O_4N$	IV	74.79	74.52 74.41	4.09	4.38 4.42	3.79	3.89 4.11	12.20	12.16 12.10
8	$C_{22}H_{13}O_4N$	V	74.36	74.43 74.41	3.69	3.81 3.66	3.94	4.00 4.05	8.73	8.88 8.74
10	$C_{20}H_{15}O_4N$	VI	72.06	72.06 71.96	4.54	4.68 4.56	4.20	4.26 4.27	9.31	9.58 9.50

^aRoman numerals refer to Chart I.

fraction which boiled at 171.0° was 1.4990 at 25° (lit. b.p. 170.4° and n_D^{25} 1.4964).⁵¹ When pure redistilled 2,4-lutidine was substituted for the above impure syn-collidine in reaction (5), no crystalline product was obtained.

When 0.20 g. of 1-carbethoxy-2,3-phthalocylpyrrocoline (I) was refluxed with 20 ml. of redistilled quinoline for forty-eight hours, only unchanged starting material (0.18 g.) was isolated from the reaction mixture.

Ethyl malonate was used as the active methylene compound for a reaction carried out by the above general procedure with 2,3-dichloro-1,4-naphthoquinone in the presence of pyridine. There was obtained 0.20 g. (34%) of light yellow needles; m.p. $288-289^{\circ}$. The results of analyses of this product correspond to a monohydrate of the pyridinium salt prepared by Ullmann and Ettisch (Historical Introduction, compound XXII). This monohydrate did not show a depression in melting point when a mixture melting point determination was made with a sample prepared by the method of Ullmann and Ettisch of the anhydrous pyridinium salt (lit. m.p. 292°).

Anal. Calcd. for $C_{15}H_9O_3N \cdot H_2O$: C, 66.91; H, 4.12; N, 5.20.

Found: C, 67.41, 67.37; H, 4.03, 4.05; N, 5.27, 5.23.

The mono-phenylhydrazone was prepared from 0.20 g. of the above salt by warming on a steam bath for one hour with 0.6 ml. of phenylhydrazine in 4 ml. of glacial acetic acid.

There was obtained a quantitative yield (0.27 g.) of light reddish needles; m.p. 252-253° (lit. m.p. 253°).

When 0.20 g. of the salt was heated on a steam bath for two hours with 0.20 g. of *o*-phenylenediamine in 3 ml. of 10% hydrochloric acid, there was obtained 0.24 g. (89%) of the quinoxaline derivative. Recrystallization from ethanol yielded 0.16 g. (59%) of red needles with a melting point of 304-305° (lit. m.p. 305°).

Determination of Molecular Weights. - The first determination was by the standard Rast procedure.⁴⁹ The camphor which was used in all the determinations of molecular weights by this method was purified as follows: Approximately 15 g. was placed in a mortar with a few ml. of ether and ground to a uniform powder. This was spread in a thin layer on filter paper until the ether evaporated. It was kept in a well stoppered bottle. The melting point was found to be 176.5°. The molal depression constant was determined by dissolving 0.042 g. of analytically pure benzoic acid in 0.444 g. of the purified camphor. Five melting point determinations of this mixture packed to a height of 1 mm. in a sealed capillary tube gave depressions in the melting point of 31.9°, 28.7°, 31.5°, 28.0°, and 27.4°. Using the average of these values (29.1°) a molal depression constant of 37.5 was calculated for this camphor.

To check the accuracy of this value 0.053 g. of an analytically pure sample of azobenzene, which like the unknowns is red, was dissolved in 0.511 g. of the camphor.

Five melting point determinations of the solution gave depressions in the melting point of 20.5° , 19.5° , 19.7° , 20.7° , and 21.0° . Using the average of these values (20.3°) and the above molal depression constant a value of 182 was obtained for the molecular weight of azobenzene as compared with an actual value of 182.

The important factor in reproducing these results was in noting the melting point of the solution. This can best be done by having sufficient light to observe the moment that the solution becomes entirely free of solid. The molecular weights of several of the compounds listed in Tables I and II were determined using the purified camphor. The results are listed in Table III.

Table III

Molecular Weight Data by the Rast Method

Compound	(I)	(I)	(III)	(IV)	(IV)
Wt. of Compound	0.043	0.031	0.045	0.046	0.041
Wt. of Camphor	0.420	0.382	0.487	0.362	0.427
Melting point depression	13.1 10.7 11.2 11.5 11.2	8.8 9.8 9.3 9.5	9.7 9.9 10.2 9.6	12.0 11.5 12.1 12.6 12.3	9.5 10.8 9.6 9.7 10.2 10.3 10.1 10.0
Average	<u>11.5$^{\circ}$</u>	<u>9.3$^{\circ}$</u>	<u>9.8$^{\circ}$</u>	<u>12.1$^{\circ}$</u>	<u>10.0$^{\circ}$</u>
Molecular Weight					
Found:	334	326	350	392	360
Calcd.:	319	319	347	369	369

The Beckmann method for determining molecular weights was also used.⁵⁰ In a standard Beckmann apparatus, the freezing point of 15.367 g. of redistilled benzene was determined. The values obtained for six readings with a Beckmann thermometer were 1.443° , 1.447° , 1.444° , 1.445° , 1.450° , and 1.455° . This gives an average value of 1.448° for the freezing point of benzene. To this solvent there was added 0.238 g. of the ester (I). The minimum temperature due to supercooling and the freezing point temperature were observed for the solution. The values obtained for three readings were 1.905° , 1.860° , and 1.885° for the supercooling temperature and 1.705° , 1.704° , and 1.688° for the freezing point temperature of the solution. Using these readings the corresponding pairs of values for the supercooling and freezing point depressions are 0.200° and 0.257° , 0.156° and 0.256° , and 0.197° and 0.240° . With these values and the molal freezing point depression constant for benzene as 5.12, the molecular weight was calculated for the ester (I), and values of 311, 312, and 333 were obtained, the average value being 319.

As a confirmation of the above values, a 0.394 g. sample of (I) in 20.271 g. of benzene produced supercooling temperatures of 1.860° , 1.878° , 1.908° , and 1.890° and freezing point temperatures of 1.748° , 1.743° , 1.750° , and 1.738° . The average freezing point of the pure benzene was found to be 1.437° as calculated from the following readings: 1.435° , 1.437° , 1.436° , and 1.438° . Using these

readings the corresponding pairs of values for the supercooling and freezing point depressions for this solution are 0.112° and 0.311° , 0.135° and 0.306° , 0.158° and 0.313° , and 0.152° and 0.301° . The molecular weight was then calculated, and values of 321, 327, 320, and 332 were obtained. The average value of 325 agrees well with the actual value of 319 for compound (I).

Reactions of Chart III.— Phthalic anhydride was obtained from 1-carbethoxy-2,3-phthaloylpyrrocoline (I). In a 5 ml. beaker 0.10 g. of compound (I) was dissolved in one ml. of concentrated nitric acid. The beaker was covered with a watch glass and placed on a hot plate in a hood. The solution was evaporated to dryness and the white crystalline residue which sublimed upon the cover was collected. It melted at $129-130^{\circ}$ and a mixture melting point determination with phthalic anhydride showed no depression.

Phthalic acid was also obtained from 1-carbethoxy-2,3-phthaloylpyrrocoline (I). The ester (I) was oxidized by heating 0.20 g. of pure material with a 1:1 solution of 30% hydrogen peroxide and glacial acetic acid. After heating three hours at a temperature of 80° , the solution was evaporated to dryness at 23° (16 mm.). The resultant yellow solid was recrystallized from 2 ml. of methanol and dried on a porous plate. There was obtained 0.04 g. (57%) of yellowish solid; m.p. $168-171^{\circ}$ (dec.). The melting point of phthalic acid as reported in several literature sources varied considerably. Therefore, elementary analyses were made on

this product.

Anal. Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.64.

Found: C, 56.47, 56.97; H, 3.85, 3.79.

Inasmuch as insufficient product was available for further purification, the presence of phthalic acid was confirmed by means of the qualitative test described by Huntress and Bulliken.⁵⁵ A few mg. of the acid was mixed with an equal weight of resorcinol. The mixture was moistened with concentrated sulfuric acid and heated at 150° for three minutes. After cooling and diluting with 2 ml. of cold water, 2 ml. of 10% aqueous sodium hydroxide was added. The solid was dissolved by stirring and the solution was diluted with an equal volume of water and traces of solid were removed by filtration. The positive test for phthalic acid was indicated by the characteristic green fluorescence of fluorescein in the filtrate.

The mono-oxime of 1-carbethoxy-2,3-phthaloylpyrrocoline (VII) was prepared from the ester (I). Compound (I) (0.20 g.) was refluxed with 0.15 g. of hydroxylamine hydrochloride in 30 ml. of 95% ethanol for one and one-half hours. The reaction mixture was allowed to stand overnight at room temperature. The precipitate was filtered off and washed with a little ethanol. The yield of orange needles of the oxime was 0.13 g. (62%); m.p. $205-207^\circ$ (dec.). For analysis the product was treated with norite and recrystallized from glacial acetic acid. After drying the yield of pure yellow needles which melted at $215.5-217.5^\circ$ (dec.) was 0.07 g. (33%).

Anal. Calcd. for $C_{19}H_{14}O_4N_2$: C, 68.26; H, 4.22;
N, 8.38; OC_2H_5 , 13.49.

Found: C, 68.50, 68.24; H, 4.24, 4.08;
N, 8.14, 8.12; OC_2H_5 , 13.61.

Another carbonyl derivative, the mono-2,4-dinitro-phenylhydrazone of 1-carbethoxy-2,3-phthaloylpyrrocoline (VIII), was prepared from the ester (I). A solution of 50 ml. of 95% ethanol and 0.20 g. of compound (I) was heated to boiling with 0.50 g. of 2,4-dinitrophenylhydrazine. After solution was effected, five drops of concentrated hydrochloric acid was added. Heating was continued until a yellow solid separated. The crude product (0.45 g.) was recrystallized from 12 ml. of nitrobenzene. It was washed thoroughly with 95% ethanol and ether. Yellow needles with a melting point of 261° (dec.) were obtained in a quantitative yield (0.31 g.).

Anal. Calcd. for $C_{25}H_{17}O_7N_5$: C, 60.12; H, 3.43;
N, 14.01; OC_2H_5 , 9.02.

Found: C, 60.24, 60.06; H, 3.52, 3.64;
N, 13.70, 13.50; OC_2H_5 , 9.09, 9.20.

The reductive acetylation of 1-carbethoxy-2,3-phthaloylpyrrocoline (I) was attempted. A mixture of 0.38 g. of compound (I), 10 ml. of acetic anhydride, and 10 ml. of dry pyridine was heated to boiling. One gram of zinc dust was added in small portions during a half hour period. After an additional half hour of refluxing, the solution was poured into ice water. The sticky precipitate was extracted with

benzene, and the solution dried over anhydrous magnesium sulfate. The solution was then concentrated to a small volume and again the product separated as a sticky tar. Repeated attempts to crystallize this tar were unsuccessful.

A crystalline diacetate (IX) was obtained by reductive acetylation of 1-carbethoxy-2,3-phthaloyl-5,6-benzopyrrocoline (IV). A mixture of 0.30 g. of the ester (IV) and 20 ml. of a 1:1 solution of pyridine and acetic anhydride was heated to boiling to effect solution. To the refluxing solution there was gradually added 1.0 g. of zinc dust over one-half hour. The solution faded to a light color as this addition progressed. After an additional one-half hour of refluxing, the solution was poured into 200 ml. of cold water. The yellow solid was filtered off, washed with water, and dried. The 0.46 g. of crude product was extracted with 95% ethanol in a Soxhlet apparatus for six hours. The 0.21 g. (55%) of yellow powder which remained in the thimble was recrystallized from a large volume of benzene. The resultant 0.14 g. (33%) of bright yellow prisms melted at 239.5-240.5°. A solution of this product in benzene or ethanol gives a green fluorescence.

Anal. Calcd. for $C_{27}H_{21}O_6$: C, 71.20, H, 4.68;
N, 3.08; OC_2H_5 , 9.89.

Found: C, 71.21, 71.21; H, 4.78, 4.72;
N, 3.19, 3.37; OC_2H_5 , 9.55, 9.78.

The acid, 1-carboxy-2,3-phthaloylpyrrocoline (X), was prepared from 1-carbethoxy-2,3-phthaloylpyrrocoline (I).

Concentrated sulfuric acid (6 ml.) was added to 0.30 g. of compound (I) in a test tube. The dark greenish-blue solution was heated in an oil bath at 125-130° for three hours. The solution was then poured onto cracked ice. The resultant purple precipitate was filtered and washed with a large volume of water. The 0.13 g. (43%) of product was crystallized from 50 ml. of nitrobenzene. There was obtained 0.12 g. (44%) of reddish needles; m.p. 298-300° (dec.).

Anal. Calcd. for $C_{17}H_9O_4N$: C, 70.10; H, 3.12; N, 4.81.

Found: C, 68.17, 68.11; H, 3.12, 3.13;

N, 4.97, 4.82.

It should be noted that the results of the carbon analyses were low. This might be due to impurities or to solvent of crystallization. When calculations were made on the basis of two molecules of acid to one molecule of nitrobenzene, the results were: C, 68.08; H, 3.29; N, 5.95. This product does not, however, show a depression in a mixture melting point determination with the acid obtained by the following more satisfactory method.

Compound (I) (1.0 g.) was dissolved in 200 ml. of hot absolute ethanol and poured into a cold solution prepared from 0.80 g. of freshly cut sodium and 40 ml. of absolute ethanol. The solution was refluxed for ten minutes, whereupon a red, gelatinous mass precipitated. This was filtered off and washed with a little cold absolute ethanol. The filtrate was allowed to stand overnight. The additional salt which precipitated was combined with the previous

product. There was obtained 1.05 g. of red powder upon drying. The product was extracted with glacial acetic acid in a Soxhlet apparatus for fourteen hours, and the red solution allowed to stand several days. There precipitated 0.70 g. (77%) of maroon needles, m.p. 314.4° (dec.) which were insoluble in the common organic solvents. The product was only partially soluble in sodium hydroxide solution but a beautiful red solution was obtained with alkaline aqueous sodium thiosulfate.

Anal. Calcd. for $C_{17}H_9O_4N$: C, 70.10; H, 3.12; N, 4.81.

Found: C, 70.01; H, 3.39; N, 4.86.

For the preparation of the amide of 1-carboxy-2,3-phthaloylpyrrocoline (XI) 0.30 g. of the pure acid (X) was refluxed for four hours with freshly distilled thionyl chloride. The excess thionyl chloride was carefully boiled off and the reddish, solid residue was cooled in an ice bath while 10 ml. of concentrated ammonium hydroxide was added dropwise. The mixture was filtered after standing two days. The solid was pulverized in water with a mortar and pestle. This powder was dried and then crystallized from nitrobenzene to yield 0.02 g. (7%) of maroon needles; m.p. 302° (dec.).

Anal. Calcd. for $C_{17}H_{10}O_3N_2$: C, 70.34; H, 3.47;

N, 9.65

Found: C, 69.86; H, 3.56; N, 9.12.

The above procedure yielded the best product, even though repeated attempts were made to improve the preparation and purification of the amide (XI).

Reactions of Acetylacetone and Related Compounds

Syntheses of 1-Acyl-2,3-phthaloylpyrrocolines.- To a mixture of 0.50 g. of 2,3-dichloro-1,4-naphthoquinone and 4 ml. of redistilled active methylene compound dissolved in 25 ml. of absolute ethanol, there was added 7 ml. of redistilled tertiary amine. The resultant blue solution was refluxed four hours. If no solid precipitated from the red solution, it was cooled in an ice bath. The crystalline precipitate was filtered off, washed with a little ethanol, and then washed thoroughly with ether. The tabulated yields are for products crystallized once from the solvents indicated with the exception of compound (XV), which required treatment with norite and numerous recrystallizations to obtain satisfactory analytical results. The preparation of compound (XV) from the free quinone (Expt. 1) was reported by Erickson,² and a mixture of products from the two methods showed no depression upon determination of the melting point. The above general procedure was used to prepare compounds (XII), (XIII), and (XV). Since benzoylacetone is a solid, only 0.70 g., twice the stoichiometric amount, was used for the preparation of compound (XIV). This modification in procedure was used to avoid purification difficulties.

TABLE IV

Physical Constants and Yields

Expt. No.	Quinone	Methylene Compound	Amine	Pro-duct ^a	M.p., °C	Solv.	Color & Form	Yield %
1	1,4-Naphtho-	$\text{CH}_3\text{COCH}_2\text{COCH}_3$	$\text{C}_6\text{H}_5\text{N}$	XV	205-206	Ethanol & Benzene	Red Powder	41
2	2,3-Dichloro-1,4-naphtho-	"	"	XV	"	Glacial acetic a.	Red Needles	58
3	"	"	$\text{C}_9\text{H}_7\text{N}$	XII	280-280.5	Pyridine	Orange Needles	57
4	"	"	$\text{C}_9\text{H}_{11}\text{N}^b$	XIII	218-219.5 (dec.)	Ethanol	Maroon Needles	22
5	"	$\text{CH}_3\text{COCH}_2\text{COCH}_3$	$\text{C}_5\text{H}_5\text{N}$	XIV	256.5-257.5 (dec.)	Glacial acetic a.	Maroon Needles	10

^aRoman numerals refer to Chart IV.

^bCrude collidine was employed and apparently the product was a derivative of a dimethyl pyridine impurity. (See Experimental.)

TABLE V

Analytical Results

Expt. No.	Formula	Pro- duct ^a	Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{18}H_{11}O_3N$	XV	74.73	73.26 73.40	3.03	4.02 4.03	4.84	5.02 5.04
2	$C_{18}H_{11}O_3N$	XV	74.73	74.23 74.16	3.03	3.06 3.87	4.84	4.90 4.89
3	$C_{22}H_{13}O_3N$	XII	77.87	78.18 77.92	3.06	3.97 3.88	4.13	4.20 4.04
4	$C_{20}H_{15}O_3N$	XIII	75.69	75.57 75.62	4.77	5.01 4.95	4.41	4.48 4.32
5	$C_{23}H_{13}O_3N$	XIV	78.62	78.41 78.18	3.73	3.95 3.91	3.99	4.21 4.14

^aRoman numerals refer to Chart IV.

Determination of the Molecular Weight.- The molal depression of the melting point of the purified camphor, the preparation of which was described above, was determined. Compound (XV) (0.0398 g.) was dissolved in 0.409 g. of the camphor. Five melting point determinations by the capillary tube method of this mixture gave depressions in the melting point of 12.8° , 12.2° , 12.5° , 12.7° , and 12.1° . Using the average value (12.4°) and the molal depression constant of 37.5, the molecular weight of compound (XV) was calculated to be 296, as compared with an actual value of 289. As a confirmation of this result 0.041 g. of compound (XV) was dissolved in 0.433 g. of camphor. This solution gave depressions from five melting point determinations of 11.6° , 11.9° , 12.0° , 12.0° , and 11.9° . The molecular weight obtained from these values is 297.

Preparation of 1-Carboxy-2,3-phthaloylpyrrocoline.-

The 1-acetyl-2,3-phthaloylpyrrocoline (XV) was converted to the 1-carboxy-2,3-phthaloylpyrrocoline (X). Compound (XV) (0.90 g.) was mixed with an equal weight of iodine in 15 ml. of dry pyridine. The mixture was heated in a hot water bath for one hour. After twenty minutes of heating precipitation began. The mixture was allowed to stand overnight at room temperature and the excess pyridine was distilled off under vacuum. The residue was washed from the flask to a filter funnel with a little ethanol. The solid was washed with water, 95% ethanol, and finally with ether. After drying there was obtained 1.04 g. (69%) of orange plates;

m.p. 258-259.5° (dec.) (Compound XVI, Chart IV).

To this intermediate there was added 1.10 g. of solid sodium hydroxide and 30 ml. of water. The resultant mixture was heated in a hot water bath for two hours. The precipitated salt was filtered from the reaction mixture. After heating with glacial acetic acid, there was obtained 0.26 g. of crude product. This was recrystallized from 15 ml. of nitrobenzene, washed with 95% ethanol and ether, and then dried under vacuum for ten hours at 118°. There was obtained 0.18 g. (27%) of beautiful, maroon needles; m.p. 313.4-314.4° (dec.). A mixture melting point determination with the acid (X), prepared previously from the ester (I), showed no depression.

Anal. Calcd. for $C_{17}H_9O_4N$: C, 70.10; H, 3.12;
N, 4.81.

Found: C, 70.13; H, 3.21; N, 4.90.

Reactions of Cyanoacetic ester and Related Compounds

Syntheses of 1-Cyano-2,3-phthaloylpyrrocolines.- A mixture of 0.50 g. of 2,3-dichloro-1,4-naphthoquinone, 4 ml. of redistilled active methylene compound, 7 ml. of redistilled tertiary amine, and 25 ml. of absolute ethanol was refluxed four hours. The original blue solution turned brown in color and a solid precipitated. The product was filtered off, washed thoroughly with 95% ethanol and ether, and dried. The yields reported are for products crystallized once from nitrobenzene. The preparation of compound (XXI) from the free quinone (Expt. 1) was reported by Stornerr³. It was recorded in Table VI for comparison purposes. The low carbon analyses for the product (XVII) obtained in experiments (4) and (5) are to be noted. Treatment of this compound obtained from experiment (5) with norite followed by two additional recrystallizations from nitrobenzene resulted in the more satisfactory analyses reported in Table VII. This compound was difficult to analyze as a result of its high melting point, which would probably account for the low values obtained for the carbon analyses. In all cases where two or more methods of preparation of the same compound are reported, a determination of the melting point for a mixture of the products from the two routes showed no depression.

TABLE VI

Physical Properties and Yields

Expt. No.	Quinone	Methylene Compound	Amine	Pro-ducts	M.p., °C	Solv.	Color & Form	Yield %
1	1,4-Naphtho-	$\text{CNCH}_2\text{COOC}_2\text{H}_5$	$\text{C}_6\text{H}_5\text{N}$	XXI	307.4-308.4	Nitro-benzene	Orange Needles	21
2	2,3-Dichloro-1,4-naphtho-	"	"	XXI	"	"	"	53
3	"	$\text{CNCH}_2\text{COOCH}_3$	"	XXI	"	"	"	50
4	"	$\text{CNCH}_2\text{COOC}_2\text{H}_5$	$\text{C}_6\text{H}_7\text{N}$	XVII	345-346	"	Yellow Needles	40
5	"	$\text{CNCH}_2\text{COOCH}_3$	"	XVII	"	"	"	27

*Roman numerals refer to Chart V.

TABLE VII

Analytical Results

Expt. No.	Formula	Pro- duct ^a	Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{17}H_9O_2N$	XXI	74.99	74.91 75.10	2.96	3.11 3.24	10.29	10.47 10.48
2	$C_{17}H_9O_2N$	XXI	74.99	74.32 74.76	2.96	3.32 3.28	10.29	10.52 10.33
4	$C_{21}H_{10}O_2N$	XVII	78.25	77.36 77.21	3.13	3.32 3.27	8.68	8.79 8.65
5	$C_{21}H_{10}O_2N$	XVII	78.25	77.79 77.92	3.13	3.12 3.14	8.68	8.87 8.76

^aRoman numerals refer to Chart V.

Additional Reactions of Chart V.- Phthalic anhydride
was obtained from 1-cyano-2,3-phthaloylpyrrocoline (XXI) by treatment with concentrated nitric acid as described in the first part of the Experimental section. There was obtained by sublimation from the reaction residue pure phthalic anhydride, which was identified by its melting point of 129-130° and by a mixture melting point determination with authentic phthalic anhydride.

The reductive acetylation of 1-cyano-2,3-phthaloylpyrrocoline (XXI) was attempted. A mixture of 0.50 g. of the nitrile (XXI) and 20 ml. of a 1:1 solution of pyridine and acetic anhydride was heated to boiling to effect solution. One gram of zinc dust was gradually added over one-half hour, and refluxing was continued for an additional one-half hour. The light yellow solution was poured into 200 ml. of ice water, and the flocculent, yellow precipitate was filtered off and dried. The yellow solid was extracted in a Soxhlet apparatus with absolute ethanol until the extract was a pale yellow color. The extraction was continued with 200 ml. of toluene until all of the yellow solid was in solution. The toluene solution was allowed to stand overnight. The precipitate which formed was filtered off, washed with 95% ethanol, and dried. There was obtained 0.24 g. (36%) of yellowish-orange crystals; m.p. 262-267° (dec.). The product was treated with norite and recrystallized from 200 ml. of toluene. The yield was 0.23 g. (35%) of yellow needles; m.p. 268-269° with

sintering at 235°.

Anal. Calcd. for $C_{21}H_{14}O_4N_2$: C, 70.38; H, 3.94;
N, 7.82.

Found: C, 70.20; H, 4.09; N, 7.49.

A molecular weight determination by the Rast method was made on this product (XVIII) because it was more soluble in camphor than the 1-cyano-2,3-phthaloylpyrrocoline. A solution of 0.023 g. of this diacetate (XVIII) in 0.290 g. of the purified camphor, described previously, was prepared. Six melting point determinations of this solution gave depressions of 7.8°, 8.6°, 8.0°, 8.4°, 8.1°, and 8.0°. Using the average of these values (8.15°), a value of 365 was calculated for the molecular weight of this compound as compared with the actual value of 353.

The amide (XI) was also obtained from 1-cyano-2,3-phthaloylpyrrocoline (XXI). A solution of 0.39 g. of compound (XXI) in 7 ml. of concentrated sulfuric acid was heated for three hours at 130°. The resultant violet solution was poured onto cracked ice. The red precipitate was filtered off, washed thoroughly with water and then with a little 95% ethanol. There was obtained 0.45 g. of red powder; m.p. 265-267° (dec.). For analysis the sample was treated with norite and recrystallized twice from 75 ml. of nitrobenzene. The fine, light orange needles (0.15 g.) (36%) melted at 313.5-314.5°. A mixture melting point determination of this product with the amide (XI) obtained previously from 1-carbethoxy-2,3-phthaloylpyrrocoline (I)

gave a melting range of 308-310°.

Anal. Calcd. for $C_{17}H_{10}O_3N_2$: C, 70.34; H, 3.47;
N, 9.65.

Found: C, 70.36, 70.43; H, 3.63, 3.59;
N, 10.24, 10.10.

A 0.30 g. sample of the above amide was heated at approximately 250° for one hour. The product changed in appearance to dark red prisms. Recrystallization of this material from 15 ml. nitrobenzene yielded 0.19 g. of maroon needles; m.p. 302-303°. A mixture melting point determination with the amide obtained previously from 1-carbethoxy-2,3-phthaloylpyrrocoline showed no depression.

Anal. Calcd. for $C_{17}H_{10}O_3N_2$: C, 70.34; H, 3.47;
N, 9.65.

Found: C, 70.24, 70.05; H, 3.60, 3.58;
N, 9.92, 9.39.

Recrystallization of this low melting amide (302-303°) from a small quantity of glacial acetic acid, yielded light orange needles; m.p. 313.5-314.5°. A mixture melting point determination of this material and the original high melting amide showed no depression.

Permanganate oxidation of 1-cyano-2,3-phthaloylpyrrocoline (XXI) was attempted. A solution of 2.0 g. of potassium permanganate in 40 ml. of water was added to 0.37 g. of the nitrile (XXI). One ml. of 10% sodium hydroxide was added, and the mixture was heated for three hours. After the mixture was cooled, it was acidified carefully with

sulfuric acid. The mixture was heated for an additional one-half hour, cooled, and then the excess manganese dioxide was destroyed by the addition of sodium bisulfite solution. The pinkish-white precipitate was filtered off and then washed and dried. The 0.15 g. of product was extracted with absolute ethanol in a Soxhlet apparatus. Upon cooling the solution 0.04 g. of pinkish solid was obtained; m.p. 288.6-290.6°. No structure corresponding to the analytical results was devised.

Anal. Found: C, 64.25; H, 3.07; N, 8.65.

The 1-cyano-2,3-phthaloylpyrrocoline (XXI) (0.30 g.) was heated in a test tube with 2.0 g. of phosphorous pentachloride until melted. Cracked ice was added until all the excess phosphorous pentachloride was decomposed. The mixture was filtered, and the precipitate was extracted in a Soxhlet apparatus with 95% ethanol for thirteen hours. The residue consisted of 0.23 g. of black, carbon-like solid which could not be recrystallized.

A 0.50 g. sample of 1-cyano-2,3-phthaloylpyrrocoline (XXI) was heated to boiling for two minutes with 3 ml. of concentrated nitric acid. It was then diluted with water and allowed to cool. The resultant 0.24 g. of orange solid decomposed at about 150-180°. Recrystallization from nitrobenzene yielded 0.02 g. of orange solid; m.p. 272-308° (dec.). None of the high-melting (above 360°) product obtained by Stornerr³ with this reaction was obtained.

Isolation of the Reaction By-Product.- In experiment (2) of Table VI the filtrate from the reaction mixture was evaporated slowly until all the alcohol was removed. The precipitate which formed was filtered off and washed thoroughly with ether. There was obtained after drying 0.22 g. (26%) of yellow, crystalline solid; m.p. 277.8-278.8° (dec.). This material showed some discoloration on standing in air at room temperature.

Anal. Calcd. for $C_{20}H_{17}O_4N_2Cl$: C, 62.42; H, 4.45; N, 7.28; Cl, 9.21.

Found: C, 62.69, 62.49; H, 4.47, 4.55; N, 7.33, 7.45; Cl, 9.50, 9.23.

When the above product was recrystallized from glacial acetic acid, one molecule of solvent was absorbed per molecule of product; the m.p. again was 277.8-278.8° (dec.).

Anal. Calcd. for $C_{20}H_{17}O_4N_2Cl \cdot C_2H_4O_2$: C, 59.39; H, 4.77; N, 6.30; Cl, 7.97.

Found: C, 59.53; H, 4.66; N, 6.43; Cl, 7.84, 8.08.

An aqueous solution of this product upon addition of aqueous silver nitrate gave an immediate precipitate of silver chloride. When 10% aqueous sodium hydroxide was added to an aqueous solution of this product, the solution turned red in color and a small amount of red precipitate formed. An insufficient quantity was available for determination of its identity.

A mixture of 0.30 g. of compound (XIX), Chart V, which

was prepared by Liebermann's method,²³ 7 ml. of dry pyridine and 25 ml. of absolute ethanol was heated under reflux for four hours. The solution changed from a blue to a yellowish-brown color, and an orange, crystalline solid separated. The product was filtered off, washed with 95% ethanol, and then with ether. There was obtained 0.20 g. (74%) of 1-cyano-2,3-phthaloylpyrrocoline (XXI); m.p. 307.4-308.4°. The filtrate was evaporated nearly to dryness, and the yellow precipitate filtered off and washed thoroughly with ether. The yellow, crystalline by-product (XX) was obtained in a 24% yield (0.09 g.); m.p. 277.8-278.8° (dec.). The identity of both of these products was shown by their melting points, and by the results of mixture melting point determinations with samples of compounds (XX) and (XXI) prepared previously.

Reactions in the Presence of Other Tertiary Amines.-

Dimethylaniline was used as the tertiary amine in the general reaction procedure described previously for the syntheses of pyrrocolines. The characteristic color change was observed; however, no product precipitated from the solution even upon cooling with an ice bath. Most of the ethanol was then evaporated from the solution and the residue was diluted with ether. The ether layer was washed with dilute hydrochloric acid and water. The red oil which was obtained upon evaporation of the ether layer was crystallized by adding a little aqueous ethanol and cooling in an ice bath. There was obtained 0.65 g. of a sticky,

maroon solid. Treatment with norite and recrystallization from a 1:1 ethanol-water mixture yielded 0.22 g. of red crystals; m.p. 167-169° (dec.). Another recrystallization from the same solvent yielded beautiful, violet crystals which turned a maroon color on drying at 110°. There was obtained 0.15 g. (33%) of product which melted at 169-170° (dec.).

Anal. Calcd. for $C_{15}H_{12}NO_4Cl$: C, 58.93; H, 3.96; N, 4.58; Cl, 11.60.

Found: C, 59.05, 59.08; H, 3.46, 3.37; N, 4.56, 4.46; Cl, 12.81, 13.08.

This product (0.10 g.) was refluxed with 7 ml. of dry pyridine in 25 ml. of ethanol for four hours. No crystalline product could be isolated from the reaction.

When α -picoline was used in this reaction as the tertiary amine, only one hour of refluxing was necessary to obtain a considerable amount of precipitate. The product was filtered off, washed thoroughly with 95% ethanol and ether, and then dried. There was obtained 0.36 g. of product which amounted to 72% of the weight of the quinone reactant. The product consisted of beautiful, bluish-black needles which did not melt when heated in a copper block to 410°. No structure corresponding to the analytical results was devised.

Anal. Found: C, 67.15, 67.15; H, 4.21, 4.15; N, 7.78, 7.82; OC_2H_5 , 14.12, 14.00.

Reactions of Related 1,4-Naphthoquinones and
Active Methylene Compounds

Reactions of 2-Methyl-1,4-naphthoquinone.- A solution of 1.0 g. of the quinone, 4 ml. of ethyl cyanoacetate, and 10 ml. of dry pyridine was allowed to stand at room temperature for one week. The resultant reddish-brown solution was evaporated nearly to dryness at atmospheric pressure. Since a precipitate did not form after standing two days at room temperature, the solution was diluted with ether. The ether layer was washed thoroughly with water and evaporated nearly to dryness. A few ml. of 95% ethanol was added to this solution which was then cooled in a dry ice-acetone bath. The precipitate which formed was filtered off and dried. There was obtained 0.34 g. (21%) of colorless crystals; m.p. 129-131°. For analysis a few mg. was recrystallized from an ethanol-water mixture until a constant melting point of 132-133° was obtained.

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30;
N, 4.91.

Found: C, 67.34, 67.41; H, 5.21, 5.14;
N, 5.18, 4.92.

The above procedure was repeated using ethyl acetoacetate in place of the ethyl cyanoacetate. In this case, however, only unreacted quinone was isolated from the reaction mixture. The temperature of this reaction was

increased by refluxing a solution of these reactants in 25 ml. of absolute ethanol for four hours. Again only unreacted quinone was obtained. A reaction was obtained, however, when the solution of only the quinone, acetoacetic ester, and pyridine was refluxed five hours. A black, sticky oil was obtained when this solution was carefully evaporated nearly to dryness. Repeated Attempts to isolate a crystalline product from this oil were unsuccessful.

Reactions of 2-Bromo-3-methyl-1,4-napthoquinone.-

This quinone was prepared according to the procedure outlined by Fieser and Fieser.⁵⁴ Since details were not given the complete procedure follows: Two grams of 2-methyl-1,4-napthoquinone was dissolved in 10 ml. of glacial acetic acid. Liquid bromine was added dropwise until a deep red color was obtained which did not fade on standing. The solution was cooled and the precipitate filtered off. This intermediate was dissolved in 10 ml. of glacial acetic acid and an excess of anhydrous sodium acetate was added. After heating under reflux for five minutes, the solution was cooled and the crude, yellow product (2.93 g.) was filtered off. Recrystallization from a small amount of 95% ethanol yielded 2.48 g. (87%) of yellow crystals; m.p. 152-154° (lit. m.p. 155°).

A solution of 0.25 g. of this quinone, 4 ml. of ethyl cyanoacetate, and 10 ml. of absolute ethanol was added to a solution prepared from 0.30 g. of freshly cut sodium in 10 ml. of absolute ethanol. The resultant blue solution

was cooled to 15° and let stand for one-half hour. It was then diluted with an equal volume of water and acidified with 50% acetic acid. No precipitate was formed after standing two days in the refrigerator. The solution was extracted with ether, and the ether layer was evaporated nearly to dryness. The residue was diluted with a little water and cooled for four days in the refrigerator. There was obtained 0.29 g. of a sticky, brown solid. After two recrystallizations from an ethanol-water mixture and treatment with norite, there was obtained 0.08 g. (28%) of yellow crystals; m.p. 78.5-80.5°.

Anal. Calcd. for $C_{16}H_{13}O_4N$: C, 67.84; H, 4.63;
N, 4.94.

Found: C, 66.83, 66.66; H, 4.71, 4.84;
N, 5.10, 5.06.

Attempts to repeat this reaction were unsuccessful; therefore, an analytically pure sample was not obtained, and these results could not be checked.

A solution of 0.50 g. of 2-bromo-3-methyl-1,4-naphthoquinone, 4 ml. of ethyl cyanoacetate, and 25 ml. of absolute ethanol was mixed with 7 ml. of dry pyridine. After standing at room temperature for four days, the solution turned from a blue to a reddish-brown color. All attempts to isolate a crystalline product from the reaction mixture gave only a tarry residue. The above reaction was repeated with ethyl acetoacetate in place of the ethyl cyanoacetate; again only a tarry residue which could not be crystallized was obtained.

Reactions of Potassium 1,4-Naphthoquinone-2-sulfonate

Monohydrate.- According to the directions of Stornherr³, 1.2 g. of the quinone was dissolved in 30 ml. of water. This solution was added to a solution of 6 ml. of 95% ethanol, 2.2 ml. of 10% aqueous potassium hydroxide, and 1.6 ml. of ethyl cyanoacetate. There was obtained 1.16 g. (70%) of bluish needles. After two recrystallizations there was obtained 0.40 g. (24%) of light blue needles; m.p. 201.5-202.5° (dec.). A solution of this cyanoacetic ester addition product in 6 ml. of a 2:1 solution of pyridine and acetic anhydride was stirred in a water bath at 100° for fifteen minutes. The dark blue solution turned to a yellowish color during the stirring. No precipitate formed in this case although one was obtained at this point by Stornherr. However, when the solution was poured into cold water and allowed to stand one hour, a crystalline precipitate was formed. This product was filtered off and recrystallized from aqueous ethanol. There was obtained 0.17 g. (49%) of tan needles; m.p. 188.5-189.5°. A mixture melting point determination on this material and the product obtained by Stornherr showed no depression.

Reactions of 1,4-Naphthoquinone.- A mixture of 15.8 g. of 1,4-naphthoquinone and 50 ml. of dry pyridine (dried over barium oxide) was warmed until solution occurred. To this solution there was added 60 ml. of redistilled ethyl cyanoacetate. After standing two weeks at room temperature, 5.30 g. of orange, crystalline product precipitated. For

analysis 0.50 g. of this crude product was recrystallized twice from 50 ml. of nitrobenzene. There was obtained 0.46 g. of orange needles; m.p. 281-283°. A mixture melting point determination with the product obtained by Storch⁵ by this same procedure showed no depression. No structure corresponding to the analytical results was devised. The product may be a mixture since the analytical results show such a variation. For this product the results of elementary analyses are the following: C, 74.09, 73.80; H, 3.38, 3.52; N, 9.13, 9.16. The results of analyses as reported by Storch for this product were the following: C, 75.33, 74.83; H, 3.41, 3.29; N, 8.84, 8.82. This product of Storch's upon recrystallization from nitrobenzene was found to have the following new values: C, 74.32; H, 3.48; N, 7.43. A portion (0.40 g.) of the crude product obtained by the above procedure was recrystallized twice from chlorobenzene instead of nitrobenzene. A yield of 0.18 g. of orange needles were obtained which melted above 315°. Found: C, 75.57, 75.24; H, 3.99, 3.72; N, 6.63, 6.26.

When 0.15 g. of the orange needles (m.p. 281-283°) was refluxed seventy-eight hours with 20 ml. of dry pyridine, there was obtained 0.03 g. of orange needles with a melting point of 307.4-308.4°. A mixture melting point determination with 1-cyano-2,3-phthaloylpyrrocoline (XXI) showed no depression.

Reductive acetylation, as described previously for 1-cyano-2,3-phthaloylpyrrocoline, was attempted with 0.35 g.

of the above orange needles (m.p. 231-233°). The diacetate (XVIII), Chart V, was obtained in a yield of 0.02 g.; m.p. 233-239° with sintering at 236°. Proof of the identity of this diacetate was obtained when a mixture melting point determination with the diacetate prepared previously showed no depression of the melting point.

The red, crystalline product, m.p. 243.5-244.5°, which was isolated by Störherr³ from the reaction of 1,4-naphthoquinone with phenylacetone in the presence of pyridine, was analyzed for nitrogen. Found: 4.01, 3.80. No new structure corresponding to the analytical results was devised.

Reactions of 2,3-Dichloro-1,4-naphthoquinone and Other Active Methylene Compounds.- The general procedure as outlined in the previous sections for the syntheses of 2,3-phthaloylpyrrocolines was used for these reactions; i.e., 0.50 g. of 2,3-dichloro-1,4-naphthoquinone, 4 ml. of active methylene compound, 25 ml. of absolute ethanol, and 7 ml. of tertiary amine were refluxed four hours.

With malononitrile in the presence of pyridine, a rapid reaction occurred as indicated by the change in color of the solution from blue to brown. Only a sticky, black oil was isolated from the reaction mixture upon careful evaporation. All attempts to obtain a crystalline product from this residue were unsuccessful.

When 4.0 g. of dibenzoylmethane was reacted in the presence of pyridine under the above conditions, the

characteristic color change from blue to reddish-brown was obtained. No crystalline precipitate separated from the reaction solution on cooling. Careful evaporation of the solution yielded only unreacted dibenzoylmethane. The large excess of the solid dibenzoylmethane which was used probably prevented the isolation of any reaction product.

In the presence of pyridine the following active methylene compounds were reacted under the above conditions: phenylacetone, ethyl phenylacetate, ethyl *n*-butylacetate, acetophenone, and *p,p'*-dinitrophenylmethane. In all these experiments the isolated product was the pyridinium salt (XXII) described in the Historical Introduction. This was the same result which occurred in the reaction with ethyl malonate and described in the first part of the Experimental section. In all cases the product was identified by its melting point and by the results of a mixture melting point determination with the pure material.

quinoline was used as the tertiary amine in the general reaction procedure with phenylacetone as the active methylene compound. The color change from deep blue to yellowish-brown was observed. Orange crystals precipitated from the solution on standing overnight. There was obtained 0.16 g. of crude product; m.p. 308.4-309.4° (dec.). Recrystallization from nitrobenzene yielded 0.05 g. of orange needles; m.p. 310.4-311.4°. No structure corresponding to the analytical results was devised.

Anal. Found: C, 83.06, 83.22; H, 4.16, 4.18;
N, 4.20, 4.21.

Quinoline was also used in this procedure with ethyl phenylacetate as the active methylene compound. The characteristic color change was observed. On cooling the reaction solution in the refrigerator overnight, a precipitate was formed. The product was filtered off, washed with a little ethanol, and then thoroughly washed with ether. The resultant orange solid (0.18 g.) melted at 299.6-304° (dec.). Recrystallization from nitrobenzene yielded 0.09 g. of yellow needles; m.p. 311.4-312.4° (dec.). A mixture melting point determination with the product obtained in the above reaction with phenylacetone showed a depression in the melting point to 285.5-287.7° (dec.). No structure corresponding to the analytical results was devised.

Anal. Found: C, 75.50, 75.39, 75.39; H, 3.87, 3.71, 3.78.

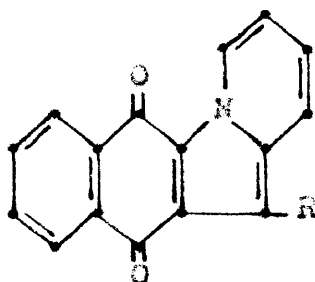
Treatment of this product with norite and further recrystallization from nitrobenzene did not alter markedly the analytical results.

Anal. Found: C, 75.58, 75.67; H, 3.73, 3.69.

SUMMARY

SUMMARY

It has been found that 2,3-dichloro-1,4-naphthoquinone reacts with acetoacetic ester, acetylacetone, and cyanoacetic ester in the presence of pyridine to form substituted 2,3-phthaloylpyrrocolines in approximately 50% yields.



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The products obtained are those in which R is $-\text{COOC}_2\text{H}_5$, $-\text{COCH}_3$, and $-\text{CN}$. These products were proven to be identical to the uncharacterized materials which were obtained by previous investigators in these laboratories from the reaction of the same methylene compounds with 1,4-naphthoquinone. It was interesting to find that ethyl benzoylacetate gave the same carbethoxy derivative and that methyl cyanoacetate gave the same cyano derivative.

The pyrrocoline structure was assigned to these products on the basis of the results of elementary analyses, the results of alkoxyl and molecular weight determinations, and by analogy with related reactions in the literature.

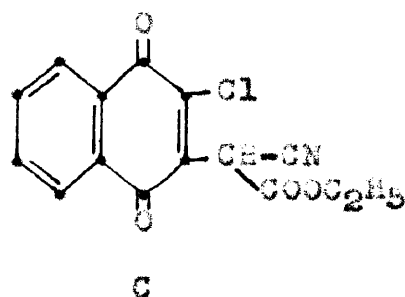
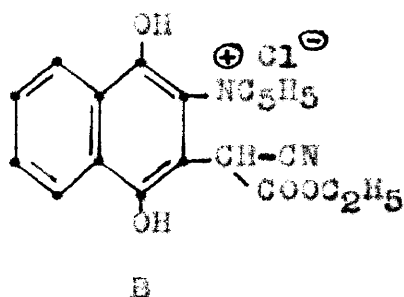
The postulated structure was also supported by additional chemical evidence; for example, oxidation yielded phthalic anhydride. By means of carbonyl reagents, crystalline mono-oxime and mono-2,4-dinitrophenylhydrazone derivatives were prepared for the 1-carbethoxy-2,3-phthaloylpyrrocoline. Reductive acetylation was used to prepare the diacetate of the reduced 1-cyano-2,3-phthaloylpyrrocoline.

The various substituted pyrrocolines were interrelated through 1-carboxy-2,3-phthaloylpyrrocoline and its corresponding amide. The conversion of the 1-carbethoxy-2,3-phthaloylpyrrocoline to the acid was accomplished in 77% yield by treatment with sodium ethoxide followed by acidification. The 1-acetyl-2,3-phthaloylpyrrocoline was converted to this same acid in 19% yield by a modification of the haloform reaction. This 1-carboxy-2,3-phthaloylpyrrocoline was converted to the amide in 7% yield upon treatment with thionyl chloride followed by ammonium hydroxide. This same amide was obtained in 36% yield by hydrolysis of the 1-cyano-2,3-phthaloylpyrrocoline.

The original reaction was extended to the syntheses of 2,3-phthaloyl-5,6-benzopyrrocolines by substituting quinoline for the pyridine. The 1-carbalkoxy-2,3-phthaloyl-5,6-benzopyrrocolines were synthesized from either acetoacetic ester or malonic ester. Reductive acetylation was used to prepare a crystalline diacetate of the reduced 1-carbethoxy-2,3-phthaloyl-5,6-benzopyrrocoline.

A seven step reaction sequence for the conversion of

2,3-dichloro-1,4-naphthoquinone to the 1-carbethoxy-2,3-phthaloylpyrrocoline has been postulated. Satisfactory analogies for each of the steps have been found in the literature. Some additional information as to the route of the reaction was obtained by the isolation of a by-product (B) in the formation of the 1-cyano-2,3-phthaloylpyrrocoline, and by the synthesis of an intermediate (C) which was reacted with pyridine to yield 1-cyano-2,3-phthaloylpyrrocoline and compound (B).



A total of twelve primary reaction products and eight closely related compounds all of which were previously uncharacterized are described.

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