5-20-1953

# Studies in the Cinnoline Series

David B. Cox

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COX — STUDIES IN THE CINNOLINE SERIES

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# Studies in the Cinnoline Series

A Dissertation
Presented to
the Faculty of the Department of Chemistry
University of New Mexico

In Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy

by
David B. Cox
May, 1953

This dissertation, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

E H Castetter
DEAN

5/20/53
DATE

STUDIES IN THE CINNOLINE SERIES

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## ACKNOWLEDGEMENT

The author wishes to thank Dr. Raymond N. Castle for his encouragement, advice, and friendship which were of great help in the completion of this investigation.

The author is also indebted to the Upjohn Company for its generous financial support of most of this work.

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# I. INTRODUCTION

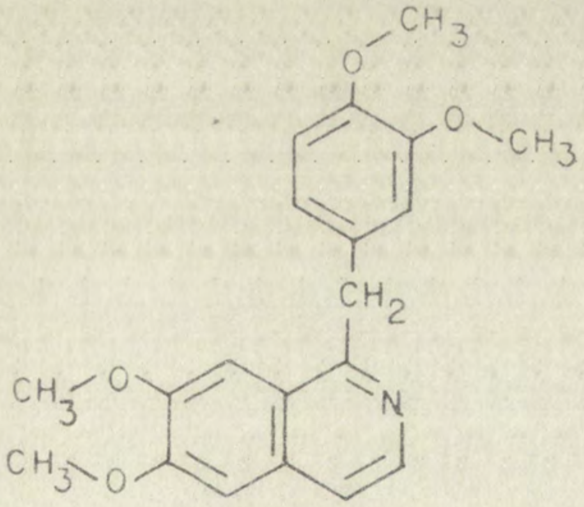
Recent work by Castle and Kruse (16) has partially elucidated the range of reactivity of the chlorine atom in the compounds 4-chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline. Condensations between the chlorinated cinnolines and certain phenylacetonitriles were found to proceed readily; however, condensations with compounds of the malonic ester type were unsuccessful. It was found that hydrolysis of the condensation product obtained from 4-chlorocinnoline and phenylacetonitrile by hot 60% sulfuric acid caused decarboxylation of the intermediate acid, the final product being 4-benzylcinnoline. This compound has a formal resemblance to the basic ring structure of papaverine.

It has long been known that the methyl groups of N-heterocyclic compounds which are located alpha or gamma to the basic nitrogen are reactive toward electrophilic agents. The reactivity of the methyl group of 4-methylcinnolines has been studied by Jacobs, et al. (47), who found that 4-methylcinnoline condensed with benzaldehyde in good yield to give 4-styrylcinnoline, and by Albert and Hampton (1), who similarly condensed 8-hydroxy-4-methylcinnoline with benzaldehyde to obtain the corresponding styryl derivative. Atkinson and Simpson (3) prepared the

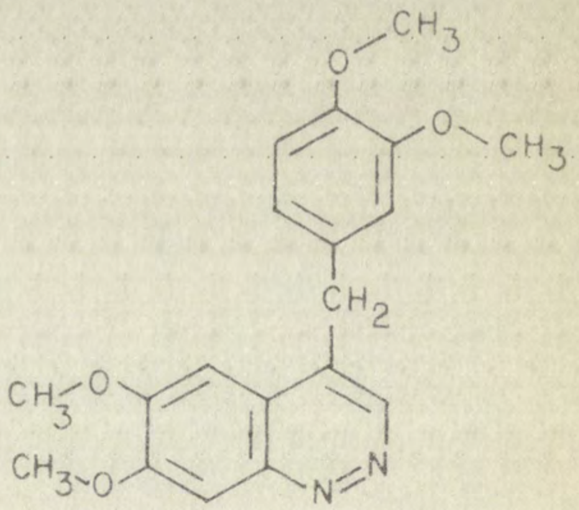
ethiodide of 4-methylcinnoline and condensed it with p-dimethylaminobenzaldehyde to give the corresponding styryl derivative, In this case the activity of the methyl group was enhanced by quaternization of the basic ring nitrogen.

## II. THE PROBLEMS

A. The investigation by Castle and Kruse (16) of the condensation of 4-chlorocinnolines with phenylacetonitriles opened the way to the possibility of an extended series of condensations of that type. A part of the present problem was to study this reaction in order to discover its range and generality. The condensation of 4-chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline with a series of substituted phenylacetonitriles and related acetonitriles was projected. In particular, it was hoped that a cinnoline analogue of papaverine might be obtained by the condensation of 4-chloro-6,7-dimethoxycinnoline with 3,4-dimethoxyphenylacetonitrile, followed by hydrolytic removal of the nitrile group from the product.



PAPAVERINE



CINNOLINE ANALOGUE

It is difficult to obtain the 4-chlorocinnolines

because of poor yields in some of the intermediate steps in their preparation. Thus it was of interest to attempt to improve the yield of existing steps or to find new synthetic routes.

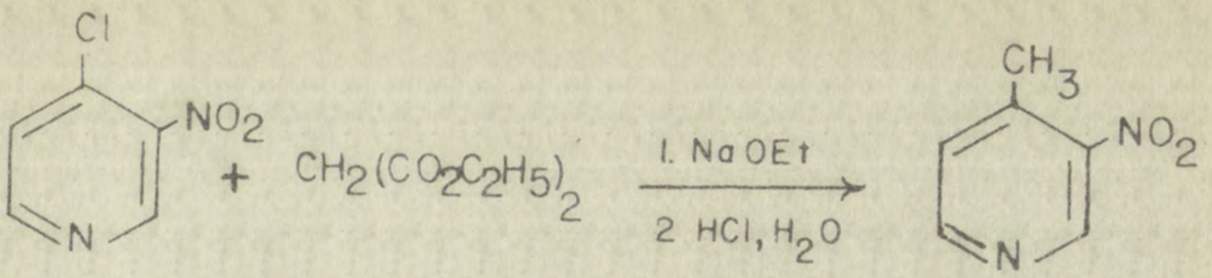
B. Since no investigation of the reactivity of the methyl group of 4-methylcinnoline has been published (with the exceptions noted in the Introduction,) it was of interest to examine the chemistry of the methyl group in a series of reactions known to occur with pyridine and quinoline analogues.

# III. LITERATURE REVIEW

## A. Condensation Reactions of a Few Nuclearly Halogenated Nitrogen Heterocycles.

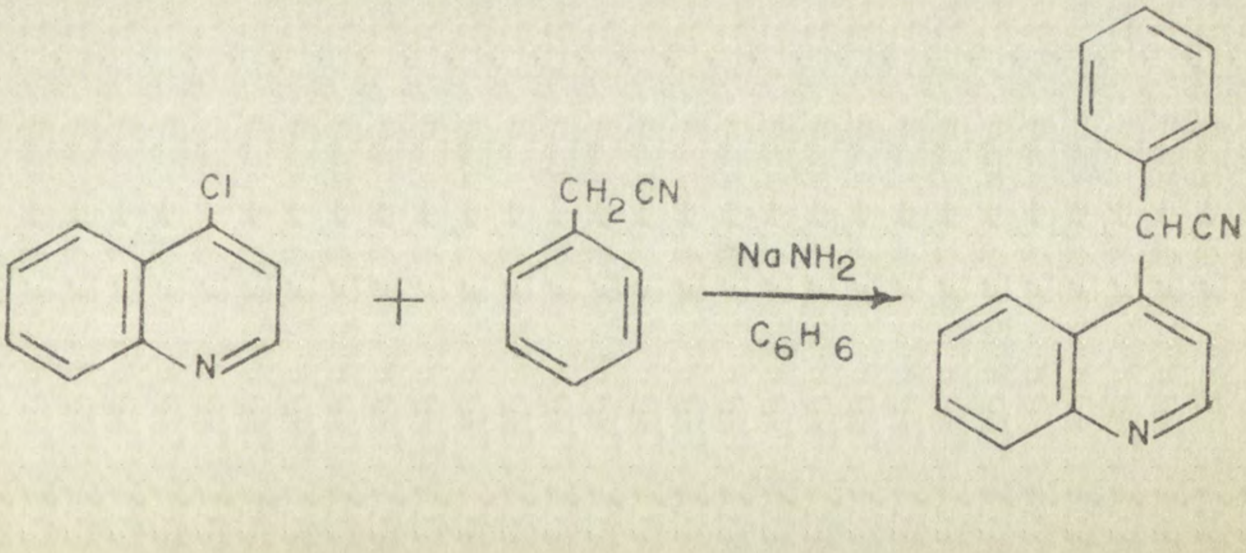
The literature contains very few references to condensation reactions between nuclearly halogenated nitrogen heterocycles and compounds having active methylene moieties. In six membered ring systems of the pyridine type, halogens placed alpha or gamma to the basic nitrogen may be replaced by nucleophilic agents. Recently Mosher (64) has shown that nucleophilic attack may also occur at the beta position by condensing 3-bromopyridine with phenylacetonitrile, using sodium amide as the condensing agent. In general, however, nucleophilic attack is favored at the alpha and gamma positions.

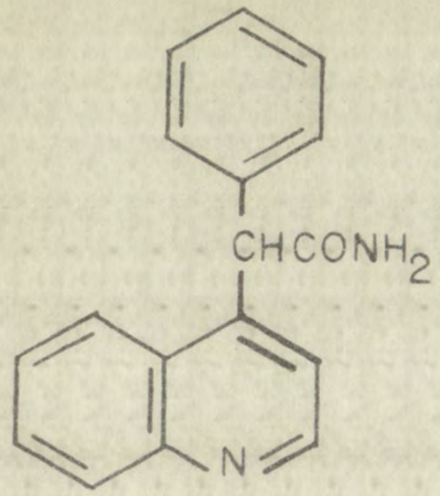
Koenigs and Jaeschke (53) condensed 4-chloro-2,6-dicarbethoxypyridine with sodio derivative of malonic ester, and on subsequent hydrolysis and decarboxylation, obtained 4-methylpyridine-2,6-dicarboxylic acid. Similarly, Koenig and Freter (52) condensed the active 4-chloro-3-nitropyridine with sodio-malonic ester and obtained as an end product 4-methyl-3-nitropyridine.

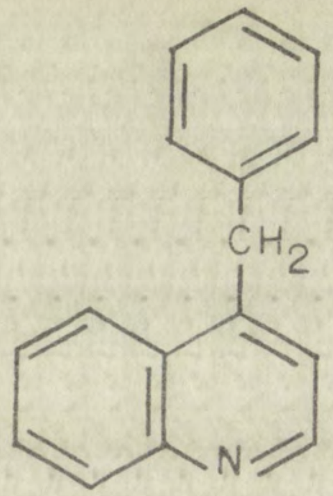


In a series of three patents assigned to CIBA, Hartmann and Panizzon (43, 44, 45) have described the condensation of 2- and 4-chloropyridine with a number of phenylacetonitriles. The reaction was effected by the action of sodium amide in boiling toluene. The cyanide group of the products was variously reduced, esterified, or hydrolyzed.

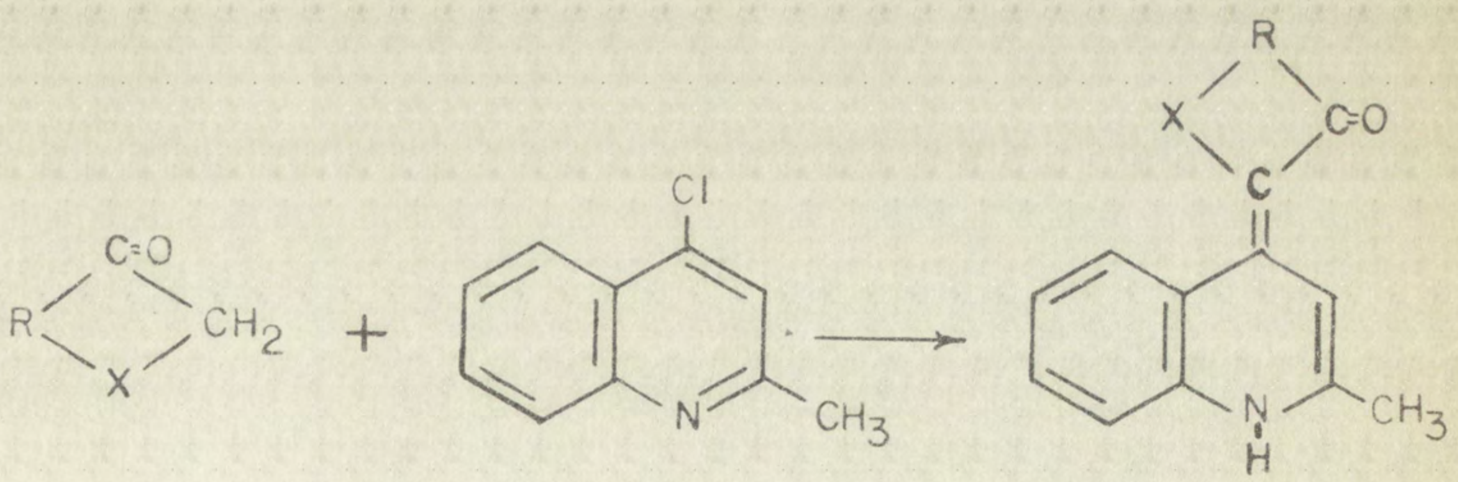
Cutler, Surrey, and Cloke (24) have studied the condensation of the sodio derivative of phenylacetonitrile with 4-chloro-, 4,5-dichloro-, and 4,7-dichloroquinoline under a variety of conditions. The resulting $\alpha$-(4-quinolyl)-phenylacetonitriles were converted to the corresponding $\alpha$-(4-quinolyl)-phenylacetamides and 4-benzylquinolines. Similarly, they prepared $\gamma$-dialkyl-$\alpha$-phenylbutyronitriles and condensed them with the several chloroquinolines.



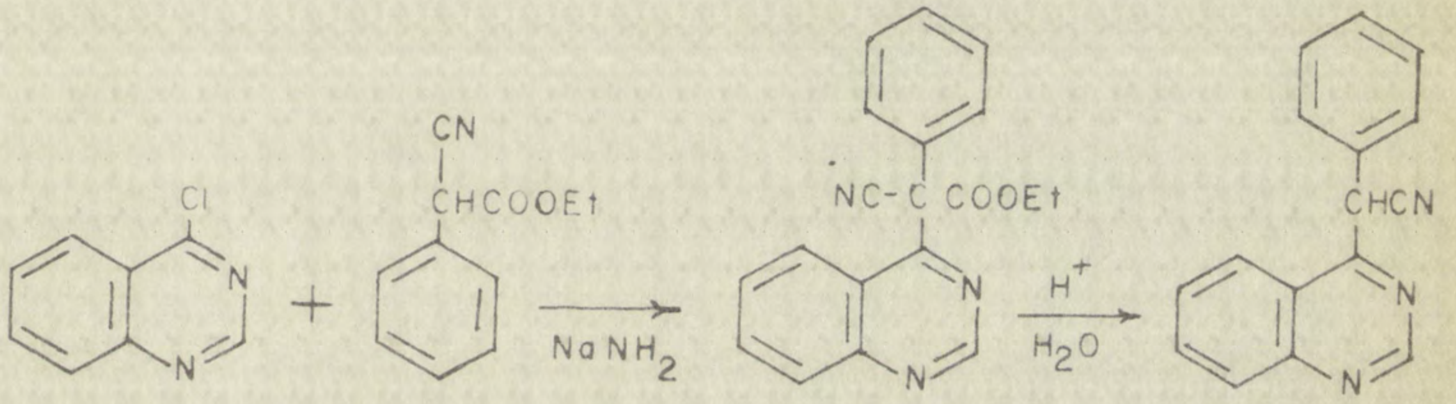




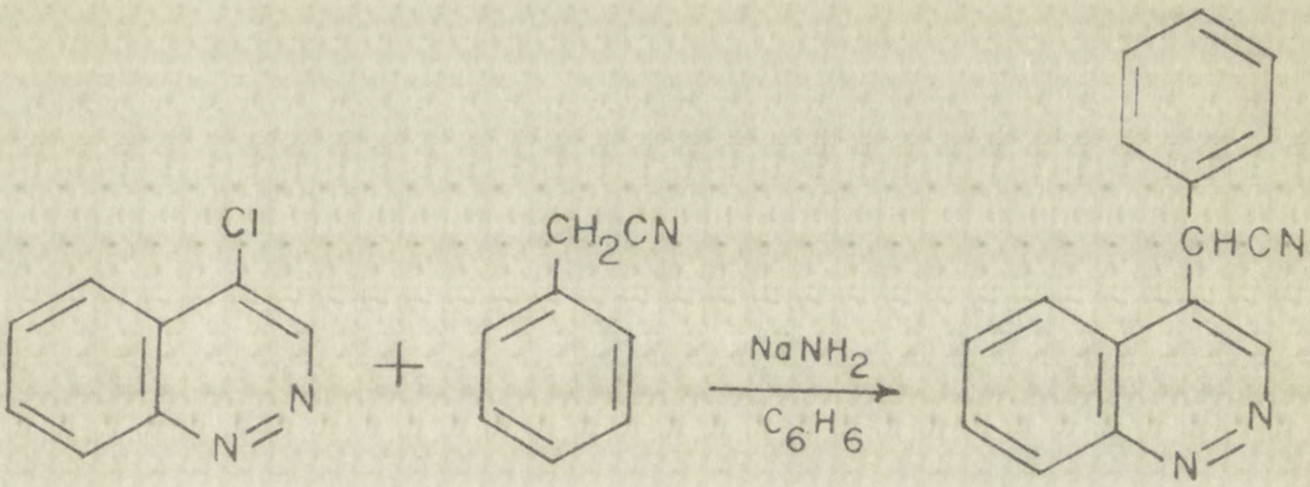
Meyer and Bouchet (61) reported the condensation of 4-chloroquinaldine with several methylenic compounds, the reaction taking place in pyridine with or without acid catalyst. Products were obtained with various pyrazolones, 1,3-diketoisoquinolines, and similar substances. The products were colored, the color being attributed to a quinoid structure in the nitrogen ring of quinoline.



Elderfield and Serlin (37) condensed phenylcyanoacetic ester with 4-chloroquinazoline, using sodium amide as the condensing agent. The ester linkage of the product was hydrolyzed, and the intermediate acid decarboxylated. The α-(4-quinazolinyl)-phenylacetonitrile produced was described as unstable.



Castle and Kruse (16) condensed 4-chlorocinnoline with phenylacetonitrile and its p-methoxy and m-methoxy homologues and 4-chloro-6,7-dimethoxycinnoline was condensed with phenylacetonitrile. Sodium amide was employed as the condensing agent, the reactions taking place in dry benzene. Two of the products were converted to the corresponding amides, and one product was hydrolyzed to 4-benzylcinnoline.



B. Liquid Ammonia as a Solvent for Organic Reactions.

It has long been known that liquid ammonia is comparable to the lower alcohols in its solvent power for organic compounds. Various workers have investigated physical properties of solutions of organic compounds in liquid ammonia, but there is comparatively little literature concerning the use of the medium for reactions primarily of synthetic importance. Much of the literature is concerned with amination of heterocyclic bases, alkylation of acetylenes, and ammonolysis of organic halides. However, there are also a number of instances in which liquid ammonia has been found to be an excellent medium for condensation reactions comparable to the more conventional alkylations in benzene and other common solvents.

Kraus points out (55) that reactions of the type $MA + RX \longrightarrow MX + RA$ may occur in liquid ammonia when the anion $A^-$ is weak, the metal ion $M^+$ is strong, and X is strongly electronegative. Successful reactions of this type have included a variety of organic compounds capable of forming the weak $A^-$. Alkali metals, and occasionally an alkaline earth, are the best sources of the $M^+$ ion, and the electronegative X is usually chloride, although occasionally bromide or iodide will do. Fluorine compounds are too inert to participate.

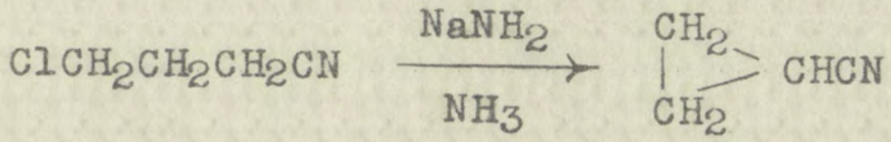
Antik and Spasokukotskii (2) have alkylated the amino nitrogen in a series of aminoquinolines using sodium amide and diethylaminopropyl chloride in liquid ammonia. Alkylation of amines by this method led to di- and trialkyl products.

Wooster and Mitchell (72) found that 1,1,1,2-tetraphenylethane could be prepared from potassium triphenylmethyl and benzyl chloride in good yield in liquid ammonia. The reaction is successful when either potassium metal or potassium amide is used to prepare the organic base. It is apparent that the organic hydrogen donor must be more capable of ionization than ammonia itself.

Bergstrom and co-workers (73, 68) prepared tetraphenylmethane from potassium triphenylmethyl and chlorobenzene in 46% yield using liquid ammonia as the solvent.

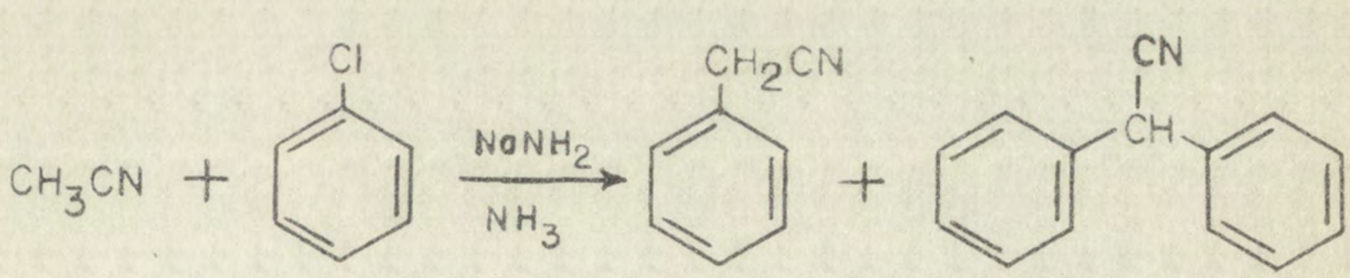
They observed that the amide ion appeared to have a catalytic effect on the reaction.

Cloke, Anderson, Lachmann, and Smith (22) found that a convenient route to cyclopropyl cyanide was obtained through the intramolecular condensation of $\gamma$-chlorobutyronitrile which occurred upon treatment of the nitrile with sodium amide in liquid ammonia.



$$ClCH_2CH_2CH_2CN \xrightarrow[NH_3]{NaNH_2} \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix} > CHCN$$

Bergstrom and Agostinho (10) alkylated acetonitrile in liquid ammonia solution using various alkylating agents and the potassium or sodium salts of acetonitrile. Chlorobenzene and potassium acetonitrile reacted to give phenylacetonitrile and diphenylacetonitrile in approximately equal amounts. Benzoyl acetonitrile was produced by the condensation of ethyl benzoate with sodium acetonitrile.



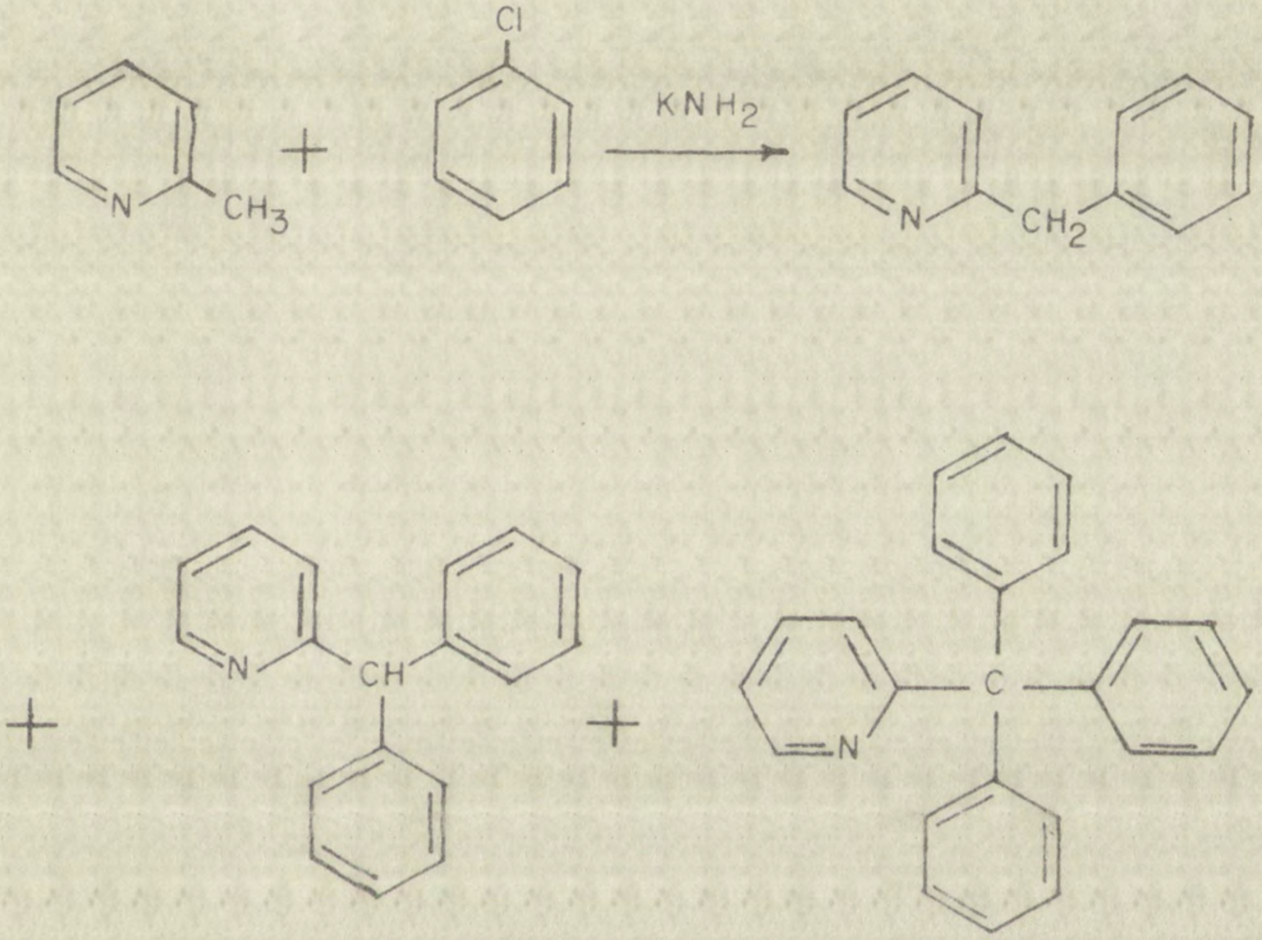
Baldinger and Nieuwland (4) successfully alkylated phenylacetonitrile in liquid ammonia solution with a series of alkyl halides. They concluded from their experiments that the sodium salt of phenylacetonitrile probably exists predominantly in the carbide rather than the nitride form. The alkylated reaction

| $C_6H_5CH{=}C{=}N^-\ \ Na^+$ | $\underset{Na^+}{C_6H_5\bar{C}HCN}$ |
|---|---|
| Nitride form | Carbide form |

product could result from the rearrangement of an imino intermediate, but no such intermediate could be isolated or identified.

Dirstine and Bergstrom (25) employed liquid ammonia in the phenylation of a series of nitrogen heterocyclic compounds having active methyl groups. The potassium salts of 2-picoline, quinaldine, and lepidine were prepared in liquid ammonia, and the addition of chlorobenzene and catalytic amounts of potassium amide caused phenylation to occur. With 2-picoline and quinaldine, the corresponding 2-benzyl, 2-benzhydryl, and 2-triphenylmethyl derivatives of pyridine and quinoline were formed. In the case of lepidine, 4-benzyl and 4-benzhydrylquinoline were formed. The reaction was extended to o-tolunitrile, which was

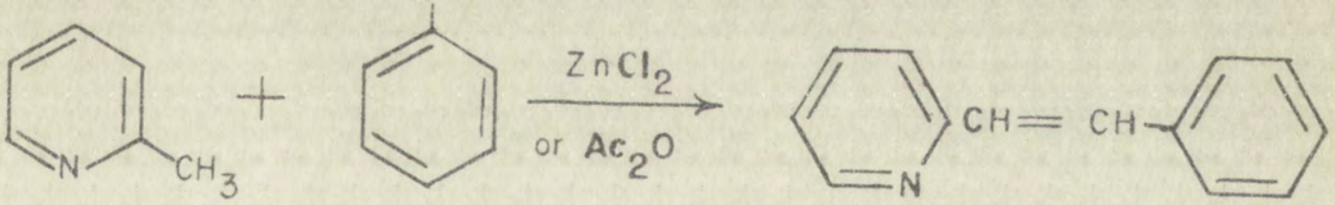
considered a vinylogue of acetonitrile, and the products o-benzyl- and o-benzhydrylbenzonitrile were isolated.



### C. Some Reactions of Active Methyl Groups in Nitrogen Heterocyclic Compounds.

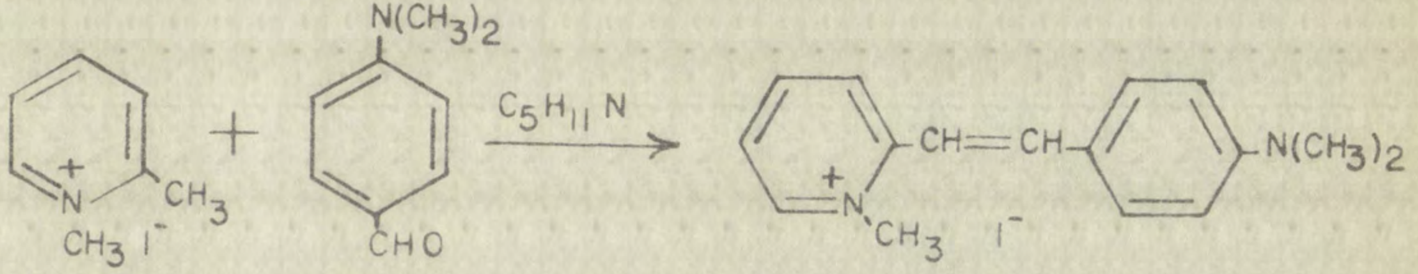
#### 1. Condensations with Carbonyl Compounds.

The reaction of benzaldehyde and 2-picoline has been studied under a variety of conditions. Stilbazole (4-styrylpyridine) is produced when 2-picoline and benzaldehyde are refluxed in acetic anhydride (29) or when the same starting products are heated at 200° in the presence of zinc chloride for twenty-four hours (30). However, if benzaldehyde and 2-picoline are heated in the presence of water and the absence of any acid, the condensation product is the corresponding undehydrated carbinol (67). The condensation of 2- and 4-picolines with substituted benzaldehydes, furfural, piperonal, and other carbonyl compounds has been found to be a general reaction (30).

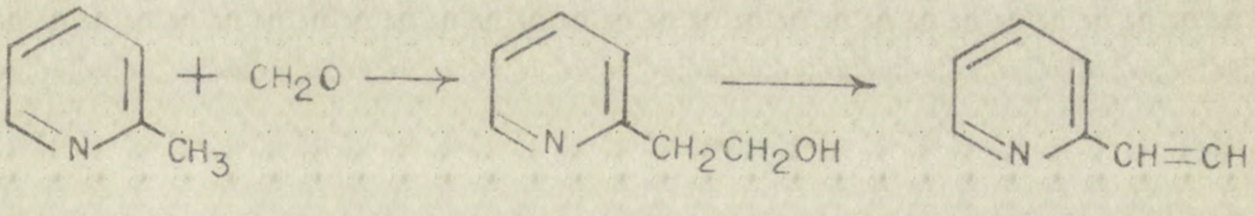


Activation of the picolines by quaternization of the ring nitrogen with alkyl halides enables aldehyde condensations to take place at lower temperatures (27, 66). Alkyl picolinium iodides condense with aldehydes when

refluxed in alcoholic solution in the presence of piperidine. The products are cyanine dyes.



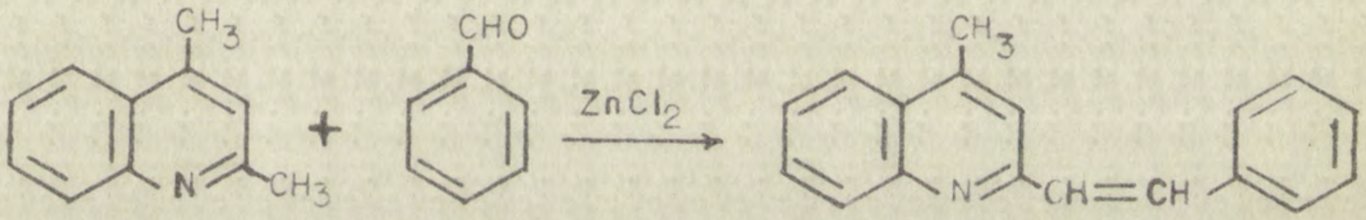
The 2- and 4-picolines undergo aldol type condensations to form various side-chain derivatives. For example, chloral and 4-picoline condense to form trichloromethyl-4-picolylcarbinol (50), which may be treated with alcoholic potassium hydroxide to yield $\beta$-(4-pyridyl)-acrylic acid. Formaldehyde condenses with 2-picoline to give 2-($\beta$-hydroxyethyl)-pyridine, which may easily be dehydrated to 2-vinylpyridine (31).



Mosher (32) states that 2- and 4-picolines will condense with ketones when subjected to more strenuous conditions than those required for aldehyde condensations.

In the quinoline series, it has been found that quinaldine and lepidine condense readily with benzaldehyde and other carbonyl compounds in the presence of suitable

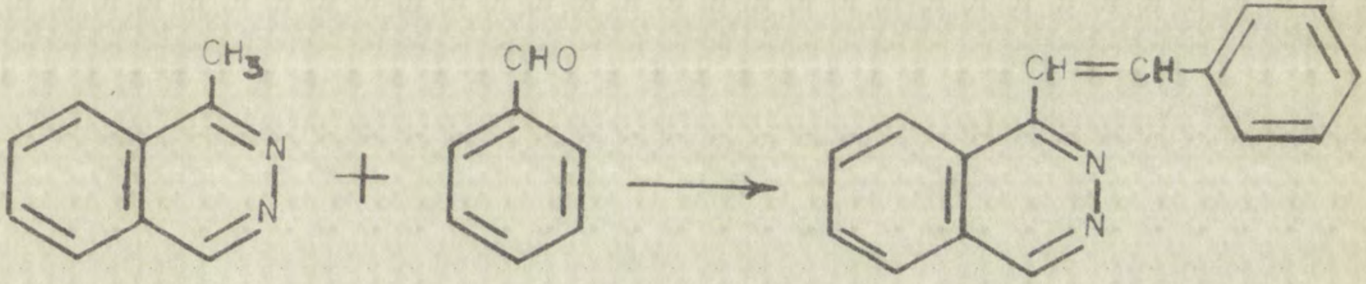
condensing agents such as zinc chloride and acetic anhydride to give styryl-type derivatives (33). If one mole of 2,4-dimethylquinoline is condensed with one mole of benzaldehyde, the product is 2-styryl-4-methylquinoline (49). The reaction illustrates the relative reactivities of the 2- and 4-methyl groups of methylquinolines. A number of other closely related condensations of methylquinolines with aromatic aldehydes are reported in the chapter on quinoline in Elderfield's Heterocyclic Compounds, Vol. IV (34).



The condensation of chloral with quinaldine in the presence of pyridine gives an aldol type product, trichloromethyl-2-quinolylcarbinol (27). Quinaldine and lepidine also condense with formaldehyde to give methylol derivatives (54).

1-Methyl- and 3-methylisoquinoline both condense with benzaldehyde in the presence of zinc chloride to give the corresponding styryl derivatives; however, the 3-methyl group is the less reactive of the two, and the yield is lower with this isomer (35).

Vaughan (70) states that 1-methylphthalazine condenses with benzaldehyde to give 1-styrylphthalazine, but the only condition noted was that the reaction is heated on a steam bath.

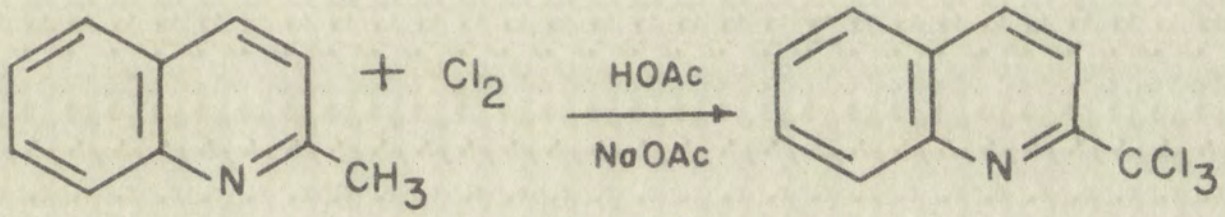


As noted in the Introduction, 4-methylcinnoline has been condensed with benzaldehyde in the presence of zinc chloride (47). The condensation of 8-hydroxy-4-methylcinnoline with benzaldehyde proceeded in best yields when hydrochloric acid rather than zinc chloride was used as the condensing agent (1). The condensation of the ethiodide of 4-methylcinnoline with p-aminodimethylaminobenzaldehyde proceeded readily in the absence of a catalyst (3).

## 2. Halogenations.

Halogenation of the active methyl groups of nitrogen heterocycles may be accomplished by direct action of elemental halogens, but the reaction is not easily controlled, and in general, polyhalogenation

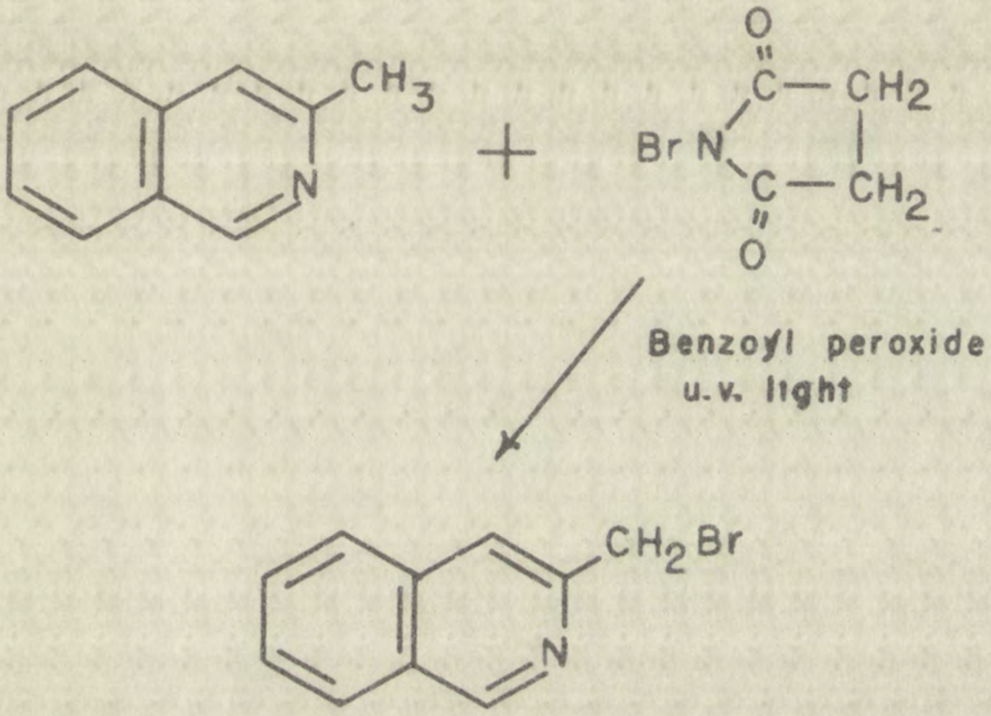
occurs. Brown, Hammick, and Thewlis (12) halogenated a series of methyl pyridines, quinolines, and isoquinolines in acetic acid and sodium acetate solution, and they obtained principally trihalomethyl products. Selective removal of halogen from these products by the action of tin and hydrochloric acid enabled them to obtain some desired monohalomethyl derivatives.



The Wohl-Ziegler reaction is a convenient method of introducing a single bromine atom into a methyl or methylene group activated by an adjacent double bond. Such "allylic" brominations have been discussed in a review by Djerassi (26). Extension of the reaction to heterocyclic systems has been successful in a few cases. Buu-Hoi (13) reported that 2- and 4-picoline and quinaldine were readily brominated by the action of N-bromosuccinimide without the agency of peroxide catalysts or illumination. Lepidine has also been brominated by the Wohl-Ziegler reaction although the resulting 4-bromomethyl derivative was described as unstable (15).

Erlenmeyer and co-workers (38) successfully

halogenated the less reactive 3-methylisoquinoline (compared to 1-methylisoquinoline) with N-bromosuccinimide, benzoyl peroxide, and light.

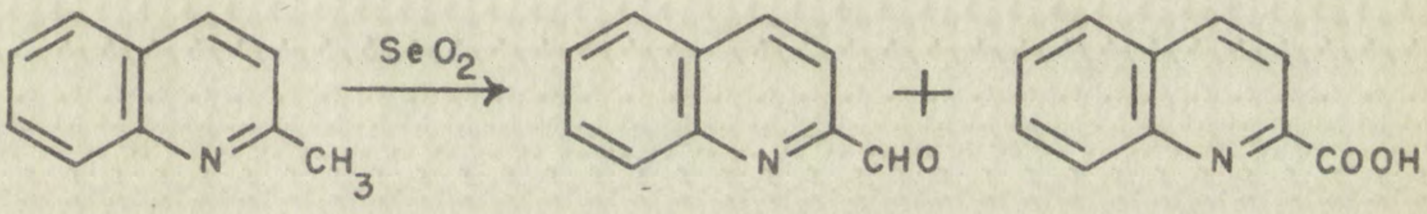


### 3. Oxidations with Selenium Dioxide.

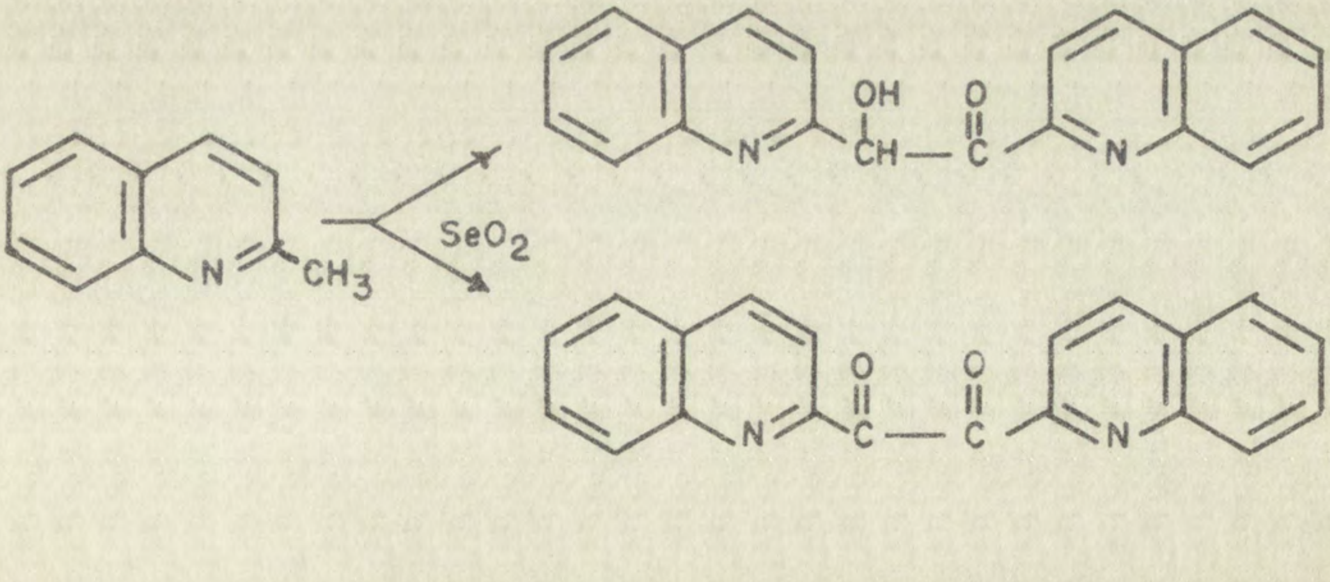
The use of selenium dioxide for the selective oxidation of methyl or methylene groups adjacent to a double bond, carbonyl group, or benzene ring is well known (71). The reaction, which results in the formation of ketone or aldehyde groups in most cases, has been extended to nitrogen heterocycles having a methyl or methylene group adjacent to the carbon-nitrogen bond, as in 2-picoline. Lepidine, 4-picoline, and related compounds having methyl groups in a position gamma to

the basic ring nitrogen may be expected to react similarly by the principle of vinylogy.

Bergstrom (8) and Henze (46) reported the formation of the corresponding acid rather than the expected aldehyde from the action of selenium dioxide on 2-picoline. Henze (46), however, found that oxidation of quinaldine with selenium dioxide caused the formation of both the corresponding acid and aldehyde.

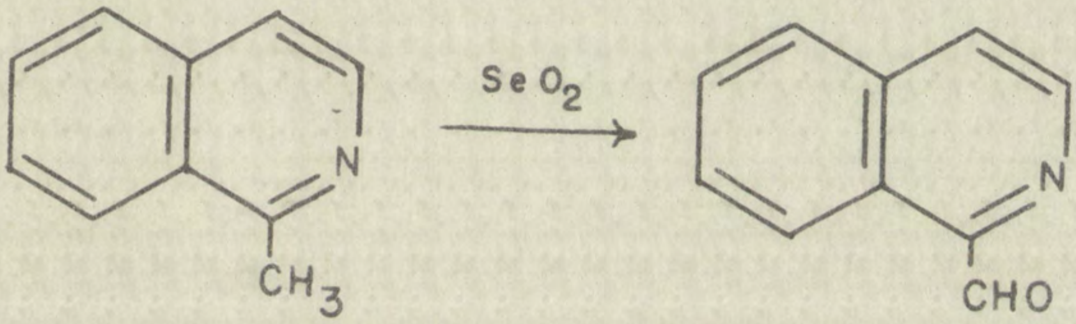


The success of the oxidation depends on the use of freshly prepared or resublimed selenium dioxide. When old selenium dioxide was used, two other products were reported. Kaplan (48) described the formation of quinaldoin from quinaldine, and Linsker and Evans (60) claimed the formation of quinaldil in 91% yield.

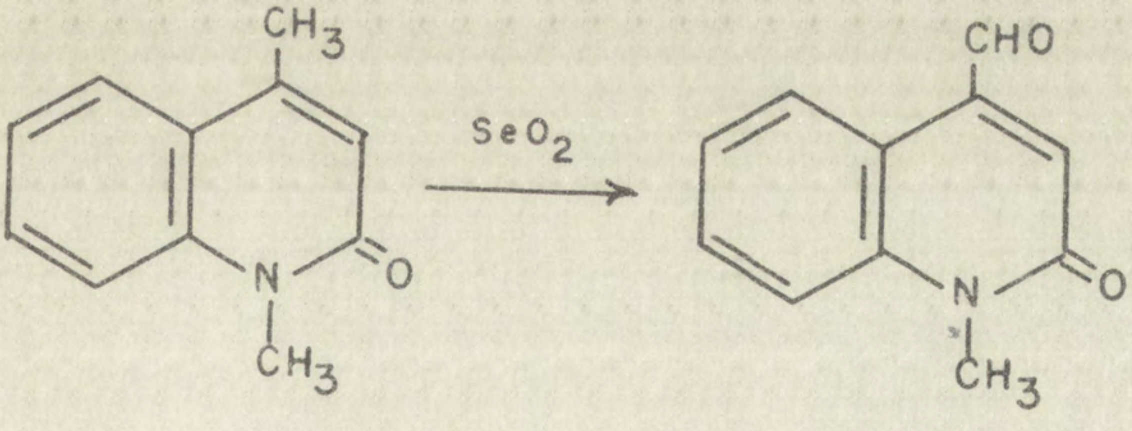


Kwartler and Lindwall (57) found that lepidine and 6-methoxylepidine were readily oxidized to the corresponding aldehydes with the formation of only traces of acid.

Both 1-methyl- and 3-methylisoquinoline may be converted to the corresponding aldehydes by the action of selenium dioxide (5, 69).



Cook and Stamper (23) treated fused 1,4-dimethylcarbostyril with selenium dioxide and obtained a good yield of 1-methylcarbostyril-4-carboxaldehyde.



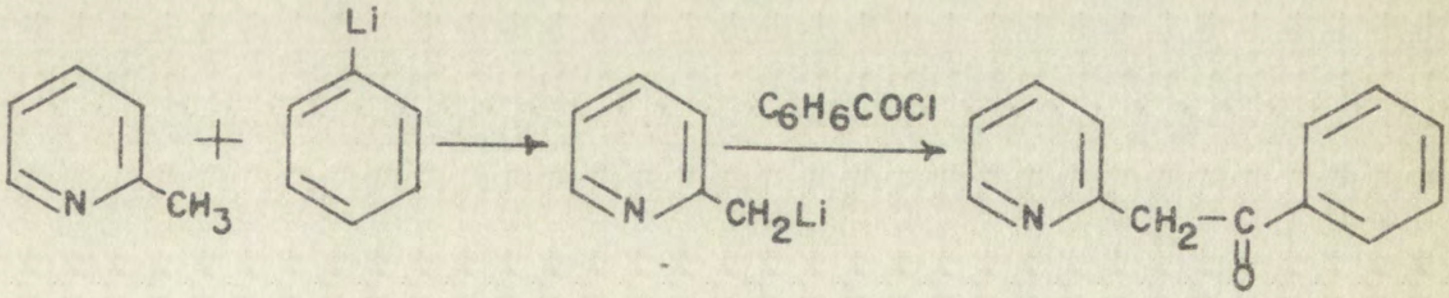
### 4. Alkylations.

It has been found that the hydrogen atoms of active methyl groups of several nitrogen heterocycles are acidic enough to be replaced by alkali metal cations under suitable conditions. The metal salts thus obtained may be alkylated by alkyl halides and other conventional alkylating agents.

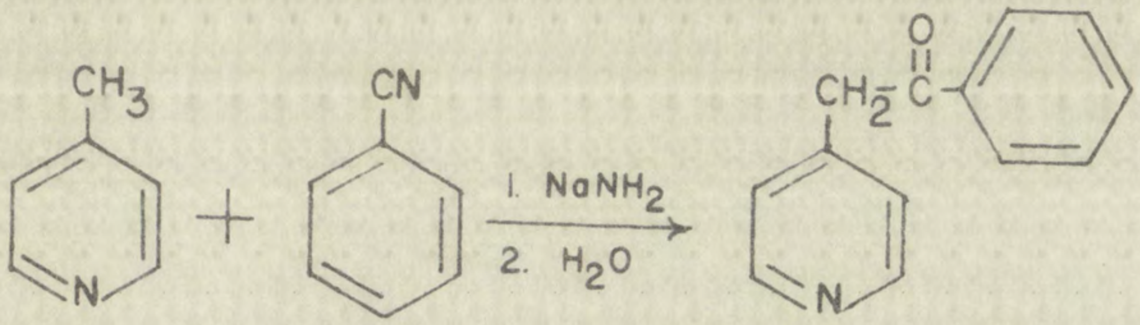
Dirstine and Bergstrom (25), as noted in the preceding section on reactions in liquid ammonia, phenylated the sodium salts of the picolines, quinaldine, and lepidine.

The active 2- and 4-picolines have been alkylated with a variety of agents such a n-butyl bromide, diethylaminoethyl chloride, and similar compounds (17, 18, 20, 51). Sodium amide was used to prepare the metal salts of the picolines.

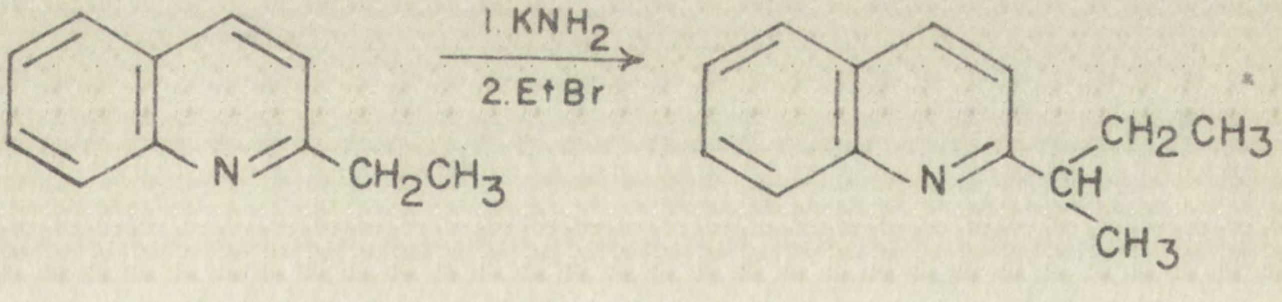
Bergmann and Rosenthal (7) condensed 2-picolyllithium with benzoyl chloride to obtain 2-picolylphenyl ketone.



A more unusual reaction described by Chichibabin (19) was the condensation of benzonitrile with 4-picoline by the agency of sodium amide. Hydrolysis of the intermediate product gave 4-picolylphenyl ketone.



Bergstrom (9) alkylated ethyl and propyl quinolines with alkyl iodides, using potassium amide to prepare the metal salts of the alkylquinolines. He established that it is only the alpha hydrogens which are active.

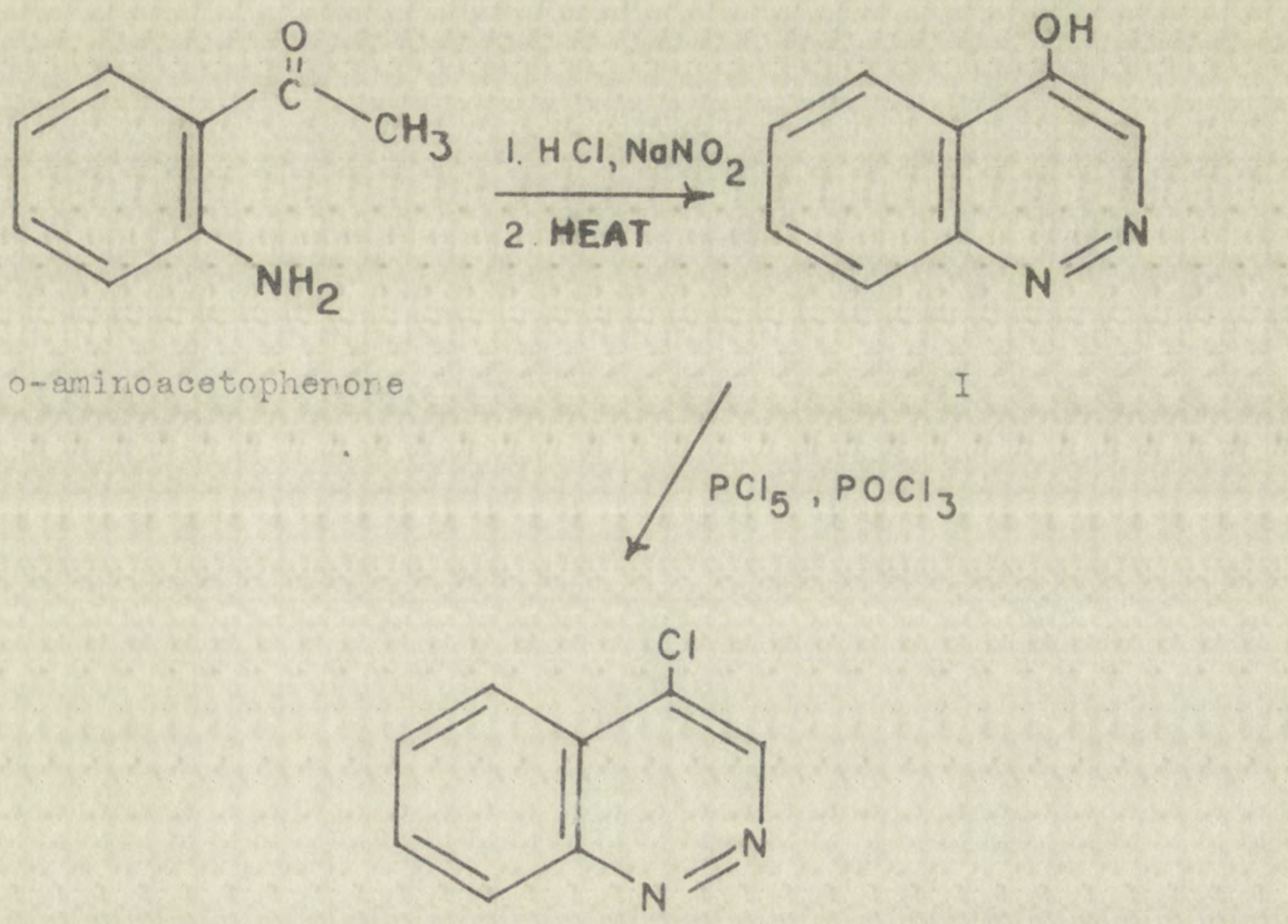


Condensations of quinaldine of the general Claisen type have been successful. A series of such reactions is listed in Elderfield's chapter on quinoline in Heterocyclic Compounds (36).

## IV. A DISCUSSION OF EXPERIMENTAL RESULTS

### A. Improvements in Syntheses of 4-Chlorocinnolines.

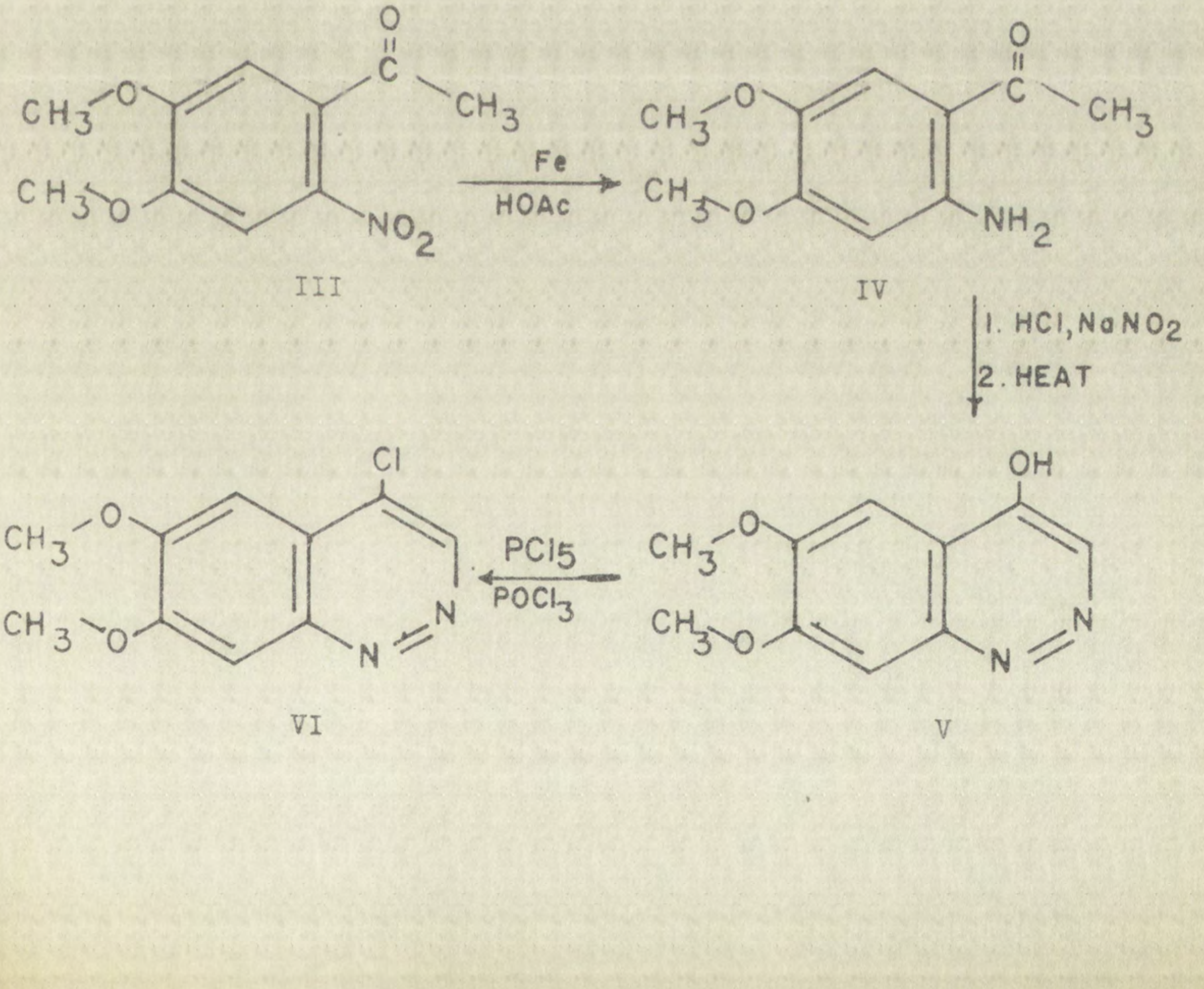
Kruse (58) has described the synthesis of 4-chlorocinnoline (II) starting from acetophenone. The compound had been reported earlier by Leonard and Boyd (59) together with the experimental procedure for its preparation. The final step in the synthetic series is a replacement of the hydroxyl group of 4-hydroxycinnoline (I) with chlorine by the action of phosphorus pentachloride and phosphorus oxychloride. The course of the reaction in the laboratory is variable, the yield of 4-chlorocinnoline being subject to fluctuations the cause of which is not immediately apparent. It has been found that the procedure of Kruse gave better yields when the period of refluxing of the reaction mixture was shortened to approximately fifteen minutes. On several occasions the tea-colored solution of 4-hydroxycinnoline and phosphorus pentachloride in phosphorus oxychloride which formed after ten minutes darkened rapidly when subjected to heating beyond fifteen minutes, and in each case the yield of 4-chlorocinnoline was



o-aminoacetophenone

I

II



III

IV

VI

V

markedly lowered. At best, yields of 4-chlorocinnoline approached 60%.

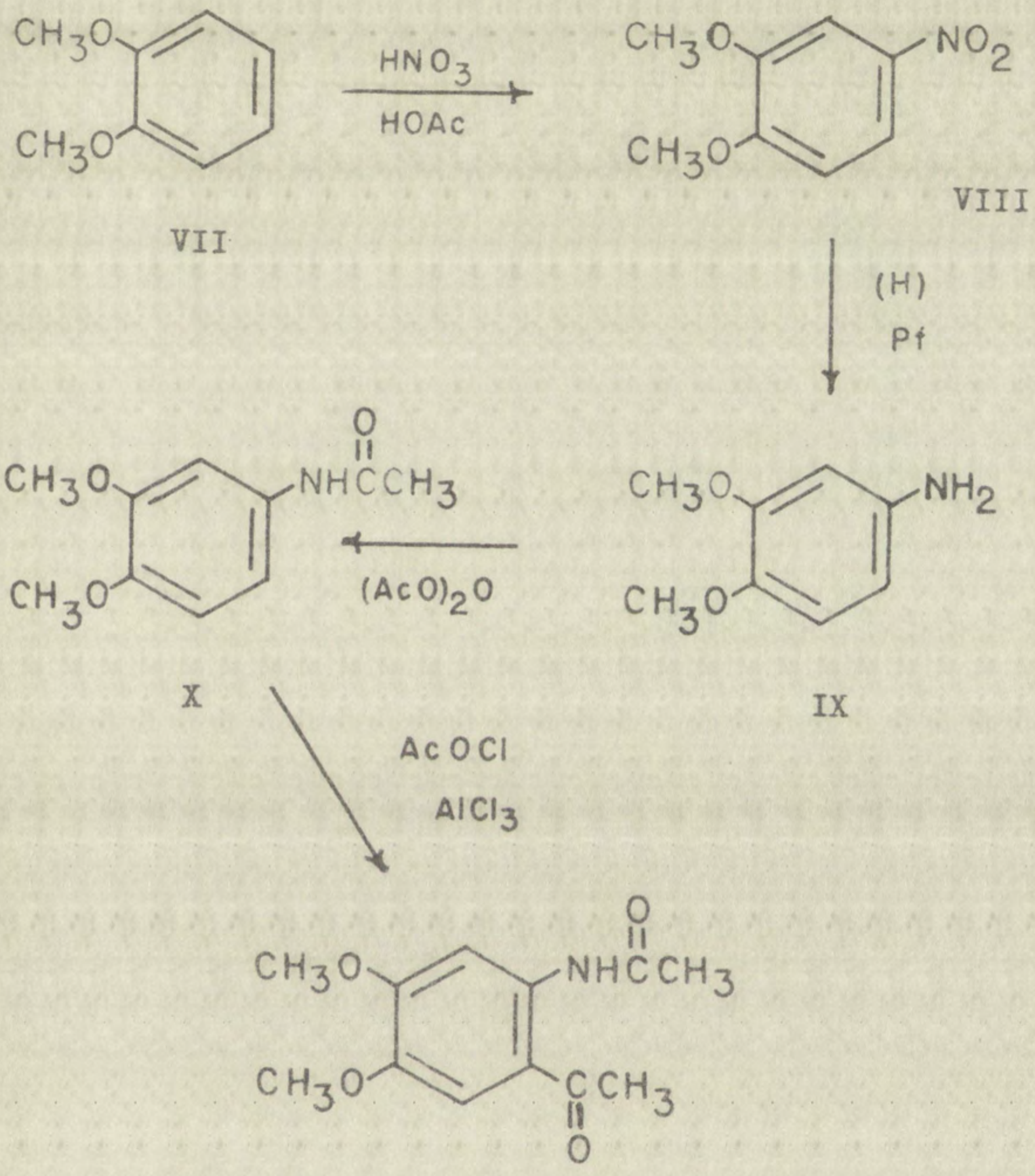
The synthetic steps leading to 4-chloro-6,7-dimethoxycinnoline (VI) as described by Kruse (56) were repeated with one exception. The reported catalytic reduction of 2-nitro-4,5-dimethoxyacetophenone (III) in ethanol using Adam's catalyst could not be repeated. Chemical reduction of the nitro group was successfully accomplished when iron powder was added to a boiling solution of the compound (III) in 80% acetic acid. Recovery of the product in good yield was possible only if as much excess acetic acid as possible was removed by distillation. Yields of 79-84% of 2-amino-4,5-dimethoxyacetophenone (IV) were obtained in several preparations using up to 36 grams of starting product. The melting point of the crude reaction product was much lower than that recorded for the pure amine, and the melting range was usually quite large, but the product contained only a trace of material insoluble in 5% hydrochloric acid, and it was converted to 4-hydroxy-6,7-dimethoxycinnoline hydrochloride (V) in 80% yield.

Preparation of 4-chloro-6,7-dimethoxycinnoline (VI) directly from (V) was found to be practical, thus eliminating the necessity of isolating free 4-hydroxy-6,7-

dimethoxycinnoline before the preparation of (VI). The procedure of Castle and Kruse (16) was otherwise used unchanged.

Before the procedure described above for the reduction of (III) had been worked out, a new route to the amine (IV) was explored. It was hoped that a Friedel-Craft type acetylation of 3,4-dimethoxyacetanilide (X) might produce the acetyl derivative of 2-amino-4,5-dimethoxyacetophenone (XI). The preparation of (X) was accomplished easily and in good yield through a series of steps beginning with the nitration of veratrole (VII). The addition of (VII) to a cold solution of concentrated nitric acid in glacial acetic acid gave an excellent yield of crystalline 4-nitroveratrole (VIII). The procedure used was a modification of that of Clark (21)。 Reduction of (VIII) in ethanol by means of hydrogen and Adam's catalyst gave 4-aminoveratrole (IX). Findlay and Dougherty (42) had previously prepared (IX) by the same procedure, but they vacuum distilled the product. It was found that evaporation and chilling of the reduction solution permitted crystallization of (IX) as white plates having a brown cast。 The procedure described by Fieser (41) for the synthesis of acetanilide was found to be directly applicable to the preparation of 3,4-dimethoxyacetanilide (X)。

The acetylation of (X) was attempted using anhydrous aluminum chloride as the catalyst and both acetic anhydride and acetyl chloride as the acetylating agents. In carbon disulfide as the solvent, no reaction occurred, but when the reaction was attempted in nitrobenzene solution with heating, the starting products apparently decomposed. When the milder anhydrous zinc chloride was used, a crystalline product was produced which appeared to be an acetylated amine. It was insoluble in 5% hydrochloric acid although it was shown to contain nitrogen by the sodium fusion test. When the product was heated with dilute hydrochloric acid for an hour, a new product was obtained which was soluble in 5% hydrochloric acid and which also contained nitrogen. However, the melting point of the supposed amine was nearly one hundred degrees higher than that of the desired (IV). Moreover, the synthesis could not be repeated, so the investigation was discontinued without identification of the new products.

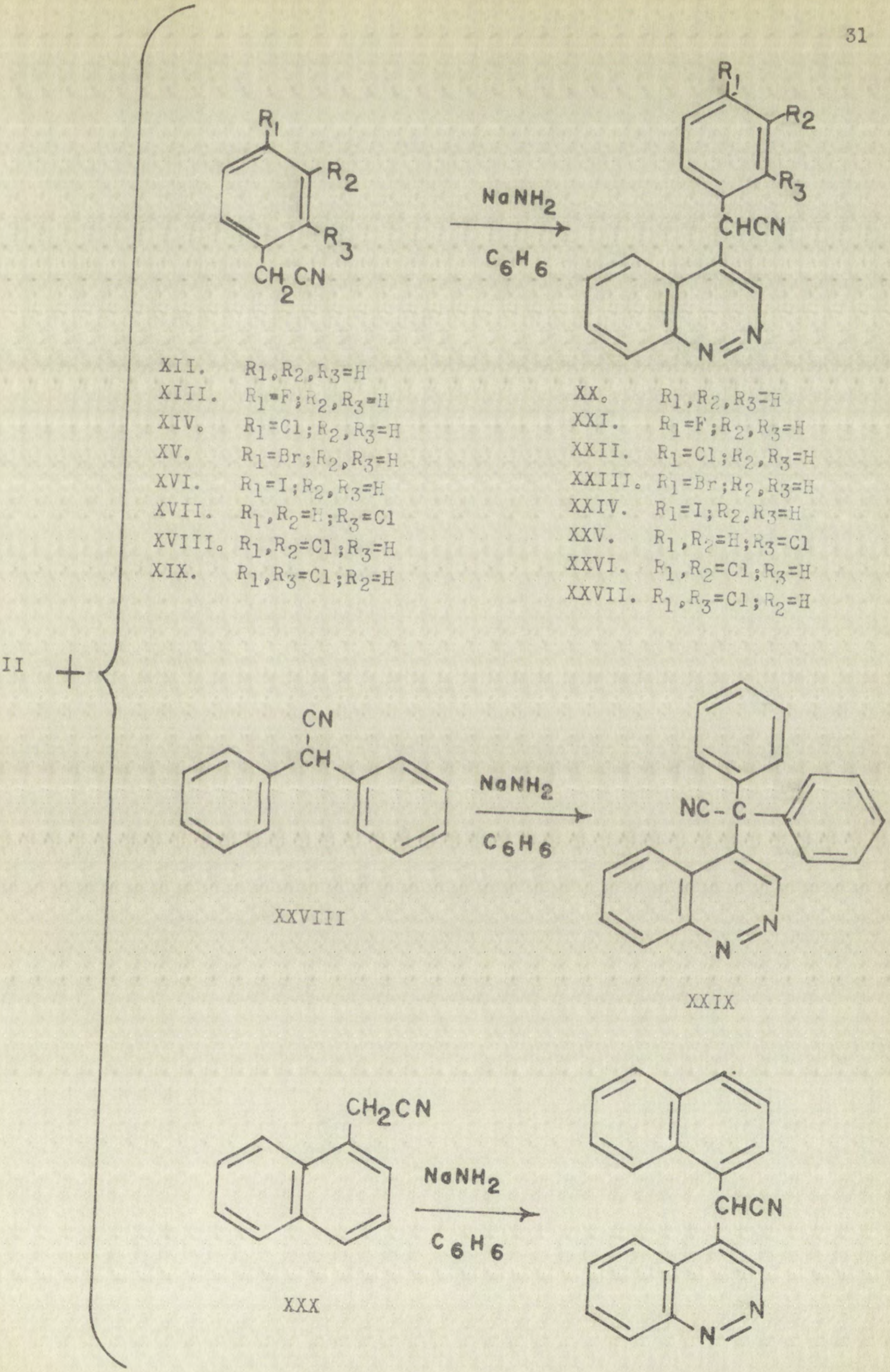


XI

### B. Condensations between 4-Chlorocinnolines and Substituted Acetonitriles.

The similarity of reactivity between 4-chloroquinoline and 4-chlorocinnoline was demonstrated by Castle and Kruse (16) by the condensation of 4-chlorocinnoline with the sodio derivative of phenylacetonitrile. The reaction paralleled that described by Cutler, Surrey, and Cloke (24) for several 4-chloroquinolines. Castle and Kruse extended the investigation to 4-chloro-6,7-dimethoxycinnoline (VI), which was also found to condense with phenylacetonitrile, although in markedly lower yield. The present investigation has shown that the condensation between the two chlorocinnolines (II and VI) and substituted acetonitriles is a general reaction, apparently limited only by the ability of these nitriles to form metal salt derivatives. In most of the condensations, sodium amide was a suitable base, the reaction being carried out in anhydrous benzene. However, in the case of 3,4-dimethoxyphenylacetonitrile and p-aminophenylacetonitrile it was necessary to prepare the potassium derivatives of the nitriles by the action of potassium amide in liquid ammonia solution.

A series of eleven substituted acetonitriles



XII. $R_1,R_2,R_3$=H
XIII. $R_1$=F;$R_2,R_3$=H
XIV. $R_1$=Cl;$R_2,R_3$=H
XV. $R_1$=Br;$R_2,R_3$=H
XVI. $R_1$=I;$R_2,R_3$=H
XVII. $R_1,R_2$=H;$R_3$=Cl
XVIII. $R_1,R_2$=Cl;$R_3$=H
XIX. $R_1,R_3$=Cl;$R_2$=H

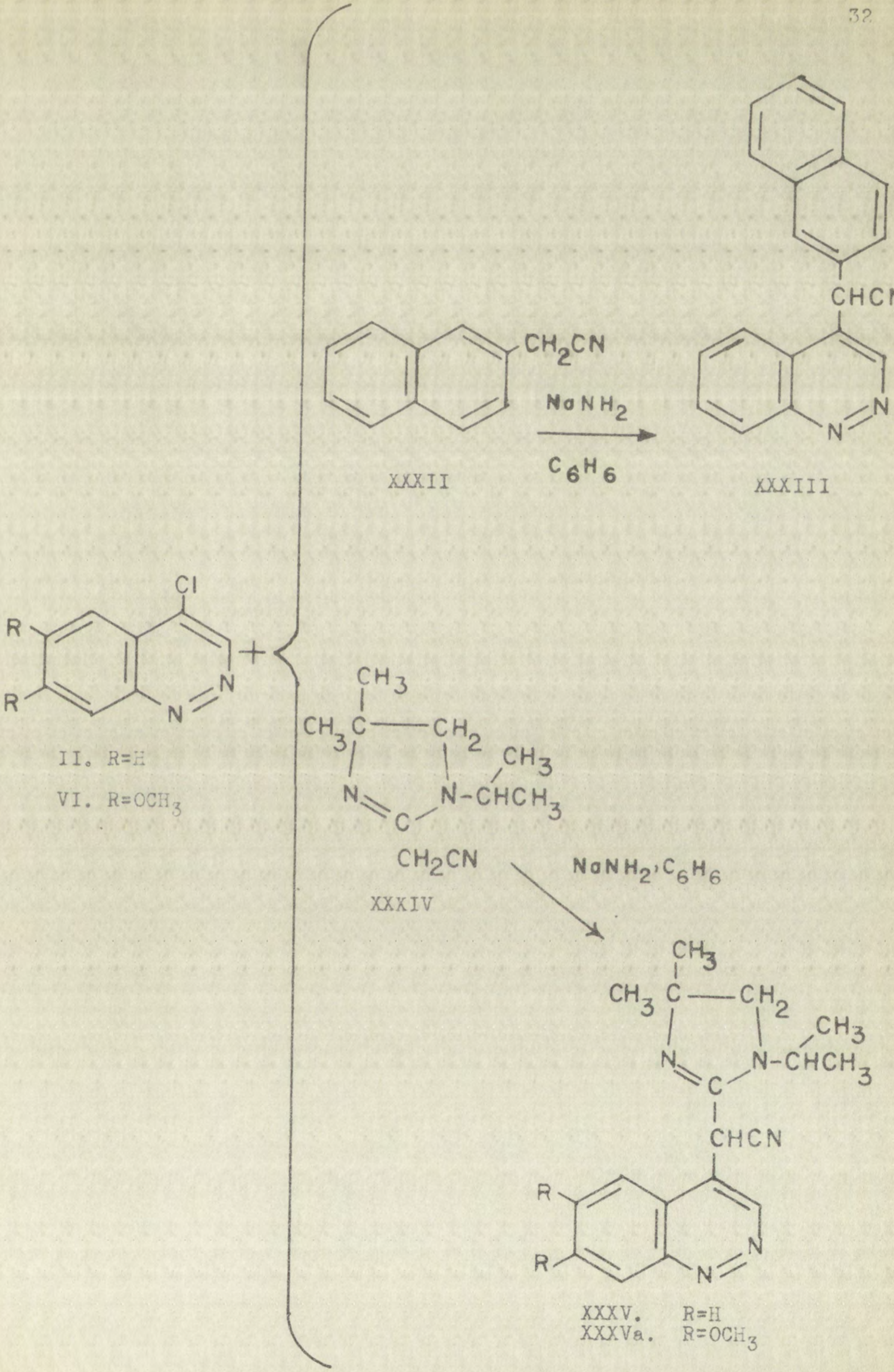
XX. $R_1,R_2,R_3$=H
XXI. $R_1$=F;$R_2,R_3$=H
XXII. $R_1$=Cl;$R_2,R_3$=H
XXIII. $R_1$=Br;$R_2,R_3$=H
XXIV. $R_1$=I;$R_2,R_3$=H
XXV. $R_1,R_2$=H;$R_3$=Cl
XXVI. $R_1,R_2$=Cl;$R_3$=H
XXVII. $R_1,R_3$=Cl;$R_2$=H

XXVIII

XXIX

XXX

XXXI



XXXII

XXXIII

II. R=H
VI. R=OCH$_3$

XXXIV

XXXV. R=H
XXXVa. R=OCH$_3$

was found to condense with (II) when the procedure of Castle and Kruse (16) when sodium amide was employed. Included in the series were the seven halogen-substituted phenylacetonitriles (XIII-XIX), diphenylacetonitrile (XXVIII), α-naphthylacetonitrile (XXX), β-naphthylacetonitrile (XXXII), and 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (XXXIV). Each condensation yielded the corresponding product as illustrated on pages 31 and 32. Yields ranged from 50% to 80% with the exception of diphenylacetonitrile whose condensation product with (II) was obtained in only 20% yield. p-Fluorophenylacetonitrile (XIII) has not previously been reported in the literature. It was prepared in a conventional manner by the reaction between p-fluorobenzyl iodide and potassium cyanide in ethanol solution. Although 3,4-dichlorophenylacetonitrile (XVIII) and 2,4-dichlorophenylacetonitrile (XIX) have been previously reported (58, 14), they were characterized only by a boiling point. The two compounds were prepared for the present investigation by treating the corresponding benzyl chlorides with potassium cyanide in ethanol solution. Both nitriles were obtained as stable white crystalline solids, and their melting points determined. The success of the condensation between (II) and the imidazoline compound (XXXIV) is particularly interesting was found to [illegible] with (III), [illegible]

[illegible]

[illegible] in the [illegible]

[illegible]

(XXXII), [illegible]

[illegible] (XXXII), and [illegible]

[illegible]-indications [illegible]

[illegible] the [illegible]

pages 42 and 52. [illegible]

the exception of [illegible]

[illegible] with (II) was [illegible]

[illegible]

been reported in the [illegible]

a conventional manner. [illegible]

[illegible]

Although [illegible]

[illegible]

reported (57, 11), they were [illegible]

boiling points. The [illegible]

present investigation [illegible]

[illegible]

[illegible] were [illegible]

crystalline solids, and [illegible]

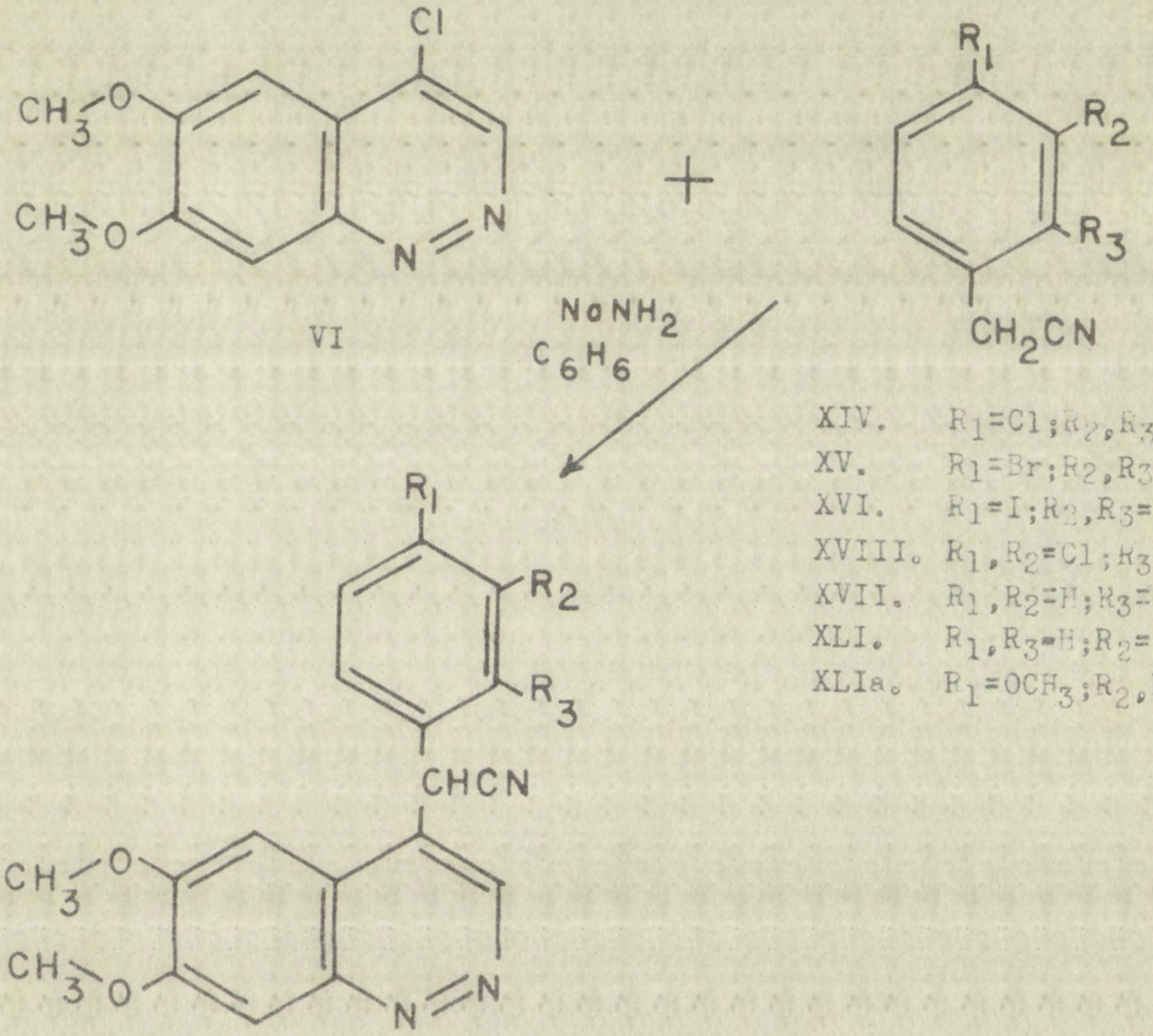
The success of the [illegible]

[illegible]

in view of the failure of (II) to condense with malononitrile (16). However, alkylation of a side-chain in the 2- position of a 2-imidazoline has been accomplished before by Riebsomer and co-workers (65; 39).

A series of ten substituted acetonitriles was employed in attempted condensations with 4-chloro-6,7-dimethoxycinnoline (VI) by the method of Castle and Kruse (16). The eight nitriles which gave identified products included p-chlorophenylacetonitrile (XIV), p-bromophenylacetonitrile (XV), p-iodophenylacetonitrile (XVI), 3,4-dichlorophenylacetonitrile (XVIII), diphenylacetonitrile (XXVIII), α-naphthylacetonitrile (XXX), m-methoxyphenylacetonitrile (XLI), and the cyanomethylimidazoline (XXXIV). In the case of o-chlorophenylacetonitrile (XVII) and p-methoxyphenylacetonitrile (XLIa), condensation apparently occurred, but the products were resistant to purification to a constant melting point, and adequate analyses were not obtained. Yields of the condensation products obtained in this series ranged from 20% to 50%.

Hartmann and Panizzon in U. S. Patent 2,507,631 (43) claimed the successful condensation of 4-chloropyridine with 3,4-dimethoxyphenylacetonitrile (XLII) in the presence of sodium amide in boiling toluene. Kruse (56) failed in an attempt to prepare the sodio

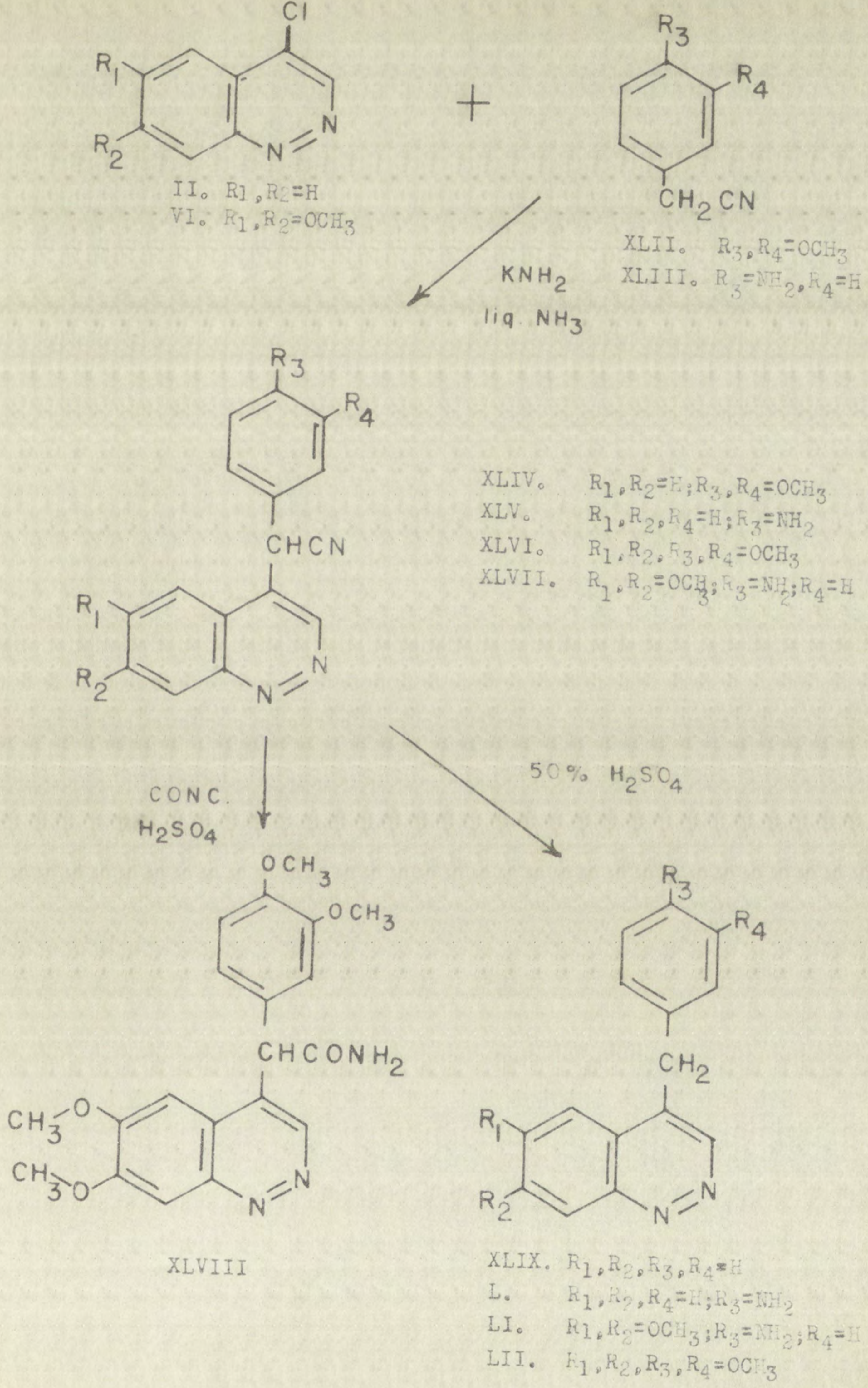


XIV. $R_1$=Cl;$R_2$,$R_3$=H
XV. $R_1$=Br;$R_2$,$R_3$=H
XVI. $R_1$=I;$R_2$,$R_3$=H
XVIII. $R_1$,$R_2$=Cl;$R_3$=H
XVII. $R_1$,$R_2$=H;$R_3$=Cl
XLI. $R_1$,$R_3$=H;$R_2$=$OCH_3$
XLIa. $R_1$=$OCH_3$;$R_2$,$R_3$=H

XXXVI. $R_1$=Cl;$R_2$,$R_3$=H
XXXVII. $R_1$=Br;$R_2$,$R_3$=H
XXXVIII. $R_1$=I;$R_2$,$R_3$=H
XXXIX. $R_1$,$R_2$=Cl;$R_3$=H
XL. $R_1$,$R_2$=H;$R_3$=Cl
XLIb. $R_1$,$R_3$=H;$R_2$=$OCH_3$
XLIc. $R_1$=$OCH_3$;$R_2$,$R_3$=H

derivative of 3,4-dimethoxyphenylacetonitrile by their method. The failure apparently lay in the absence of reaction between the nitrile and sodium amide. In the present investigation, it was found impossible to promote this reaction even when freshly prepared sodium or potassium amide was used. It was known that liquid ammonia suspensions of alkali metal amides had been used for the preparation of metal salts of organic compounds having active methyl or methylene groups, thus this technique was employed for the successful formation of the potassium salt of (XLII). Addition of (II) or (VI) to the salt resulted in good yields of the desired condensation products (XLIV and XLVI). It was noted that the potassium salt of (XLII) did not have the deep red color characteristic of many analogous sodium phenylacetonitrile salts.

It was found that when p-aminophenylacetonitrile (XLIII) was mixed with sodium amide and (VI) in benzene solution and allowed to stand at 35° for several days, no reaction occurred. However, the nitrile formed a deep red potassium salt with potassium amide in liquid ammonia, and the addition of (II) or (VI) to the salt resulted in formation of the condensation product (XLV) and a product assumed to be (XLVII). The former product, α-(4-cinnolyl)-p-aminophenylacetonitrile (XLV) gave the



II. $R_1,R_2=H$

VI. $R_1,R_2=OCH_3$

XLII. $R_3,R_4=OCH_3$

XLIII. $R_3=NH_2,R_4=H$

XLIV. $R_1,R_2=H;R_3,R_4=OCH_3$

XLV. $R_1,R_2,R_4=H;R_3=NH_2$

XLVI. $R_1,R_2,R_3,R_4=OCH_3$

XLVII. $R_1,R_2=OCH_3;R_3=NH_2;R_4=H$

XLVIII

XLIX. $R_1,R_2,R_3,R_4=H$

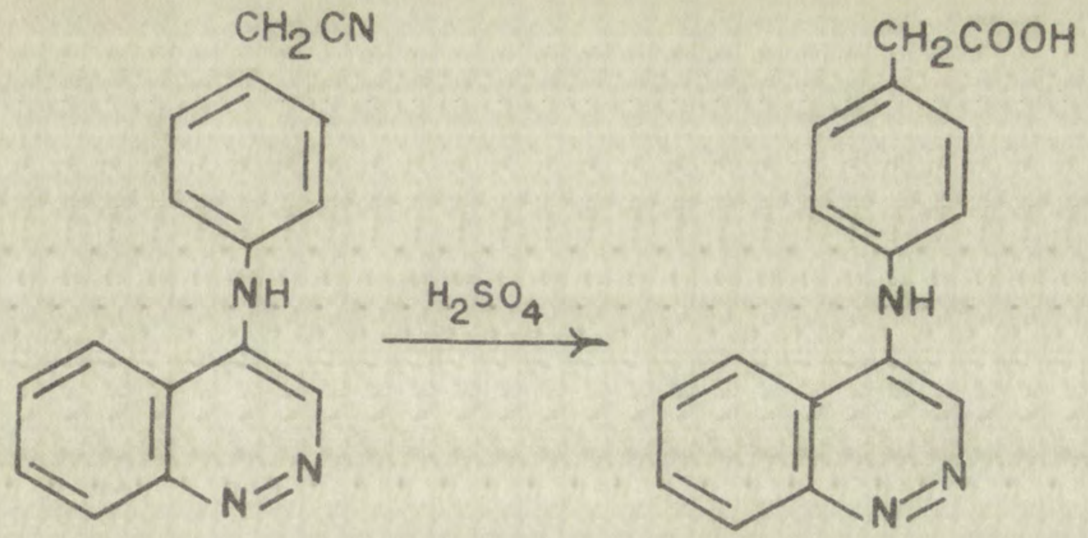
L. $R_1,R_2,R_4=H;R_3=NH_2$

LI. $R_1,R_2=OCH_3;R_3=NH_2;R_4=H$

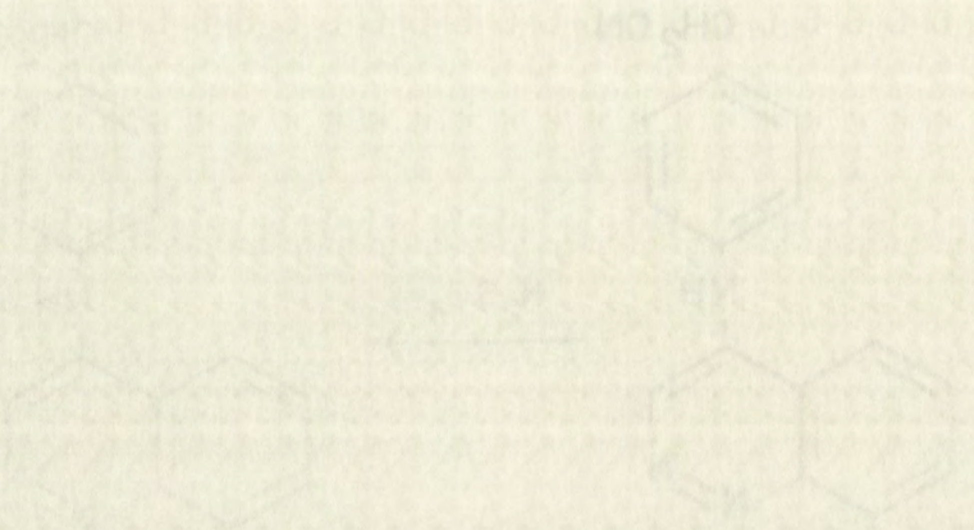
LII. $R_1,R_2,R_3,R_4=OCH_3$

expected analysis, but its homologue (XLVII) could not be completely purified and was not satisfactorily analyzed. The possibility exists that under the conditions of the reaction, condensation may have occurred between the 4- position of the cinnoline ring and the nitrogen atom of the aromatic amino group in (XLIII). Experimental evidence indicates that the condensation actually produced principally the compounds having the desired carbon-to-carbon bond, but no unequivocal proof of structure was obtained. The color of the products (XLV, XLVII) was deep red, comparable to the deep orange and red colors obtained with several assumed homologues.

Hydrolysis of the products (XLV and XLVII) by the action of hot 50% sulfuric acid gave pale yellow crystalline products whose carbon and hydrogen analysis values agreed with the values calculated for 4-(p-aminobenzyl)-cinnoline (L) and 4-(p-aminobenzyl)-6,7-dimethoxycinnoline (LI), respectively. It was thought that if the original condensation products had had the secondary amine structure, hydrolysis would have produced substituted acetic acids rather than the decarboxylated structures actually obtained.



An attempt to demonstrate the presence of a primary amino group in (L) was made by treating the compound in hydrochloric acid solution with sodium nitrite and hypophosphorus acid. The diazotized amine rapidly coupled with itself to give an intense purple dye. The solution became orange when made alkaline, and it reverted to a purple color upon reacidification. A similar attempted deamination with (XLV) similarly gave a deep blue dye which became red in alkaline solution. The compound (LI) was diazotized and coupled with $\beta$-naphthol. A deep red dye formed which seemed unstable. The product, originally soluble in acetone, slowly changed to a form insoluble in acetone. An attempt was made to analyze the soluble fraction for carbon and hydrogen content, but the analysis did not quite agree with the values calculated for the expected dye structure. Calculated for $C_{27}H_{22}O_3N_4$: C, 71.98, H, 4.92. Found: C, 69.62, 69.75, H, 4.94, 4.68.



An attempt to deaminate [illegible] amine group in III was [illegible] treating the compound in hydrochloric acid solution [illegible] hypophosphorus acid. The diazotized [illegible] coupled at [illegible] The solution became orange [illegible] reverted to a purple salt.

Similar attempts and reactions [illegible] have a deep [illegible] diazonium salt [illegible] solution. The diazonium [illegible] with β-naphthol; [illegible] unstable. The product [illegible] slowly changed to a form [illegible] attempt was made to [illegible] compound and [illegible] found [illegible] quite agree with the [illegible] dye structure. On [illegible] H, [illegible]

Castle and Kruse (16) successfully hydrolyzed $\alpha$-(4-cinnolyl)-phenylacetonitrile (XX) with hot 60% sulfuric acid, obtaining 4-benzylcinnoline (XLIX). Cold concentrated sulfuric acid hydrolyzed the same nitrile to the corresponding amide. The hydrolysis of principal interest to this investigation was that attempted with $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile (XLVI). By analogy to the preparation of 4-benzylcinnoline, it was expected that treatment of the nitrile (XLVI) with hot 50% sulfuric acid would bring about formation of the desired 4-(3,4-dimethoxybenzyl)-6,7-dimethoxycinnoline (LII), the cinnoline analogue of papaverine. However, the hydrolysis attempt produced only a red tar which could not be crystallized. When the heating period was shortened, unreacted nitrile was recovered. The hydrolysis was attempted with 20% hydrochloric acid, and a yellow crystalline product was obtained. In contrast to 4-benzylcinnoline, the material was soluble in 10% sodium hydroxide solution. Treatment of the yellow solid with diazomethane caused formation of an intractable dark-green tar. Analysis of the product gave values for the carbon content which were much lower than that calculated for (LII), and the product was not identified. Another hydrolysis was attempted using potassium hydroxide in

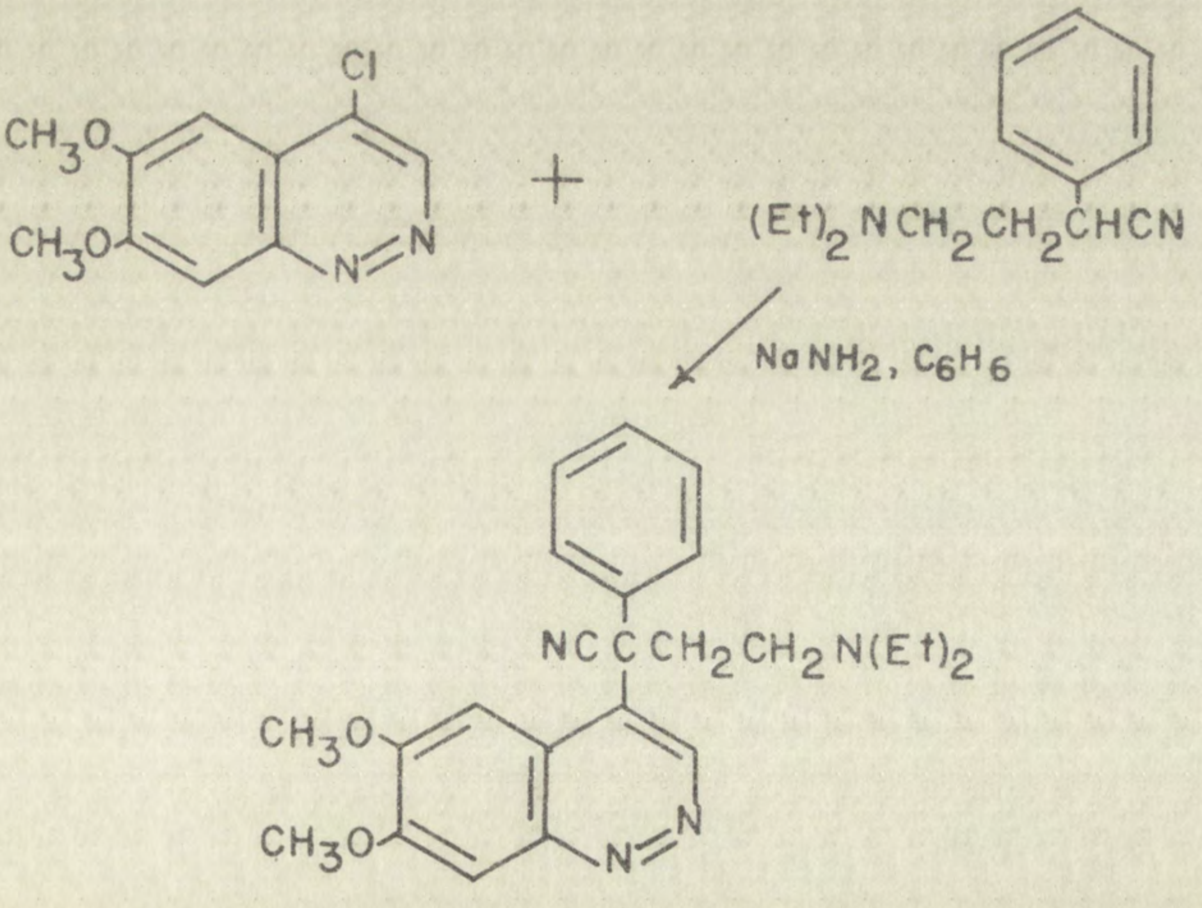
ethanolic solution. The nitrile (XLVI) formed a deep red solution in this medium, but, depending on the period of heating of the solution, either starting material or degraded tars were obtained.

The hydrolysis of (XLVI) to the corresponding amide (XLVIII) was successful when the nitrile was dissolved in concentrated sulfuric acid and allowed to stand at room temperature for six hours. The product was a white solid which crystallized from ethanol as tiny fibrous needles. Three attempts were made to obtain (LII) by further hydrolysis of the amide. Migrdichian (47) recorded a procedure, first described by Bouveault (11) and later modified by Meyer and Holz (62), by which amides were converted to the corresponding carboxylic acids upon treatment of the amide with nitrous acid. Application of the procedure of Meyer and Holz to (XLVIII) caused formation of dark intractable solids. Berger and Olivier (6) found that heating certain amides in 100% phosphoric acid solution produced the corresponding acid, but the technique failed with (XLVIII). Hydrolysis of (XLIII) with hot sulfuric acid caused formation of a red tar much like that obtained in the similar hydrolysis of the original nitrile (XLVI).

The attempted hydrolysis of $\alpha$-(4-cinnolyl)-3,4-dimethoxyphenylacetonitrile (XLIV) by the action of hot

sulfuric acid caused formation of a red tar. On long standing, the tar solidified, but efforts to crystallize the material failed. It was not identified.

Cutler, Surrey, and Cloke (24) prepared a series of α-(4-quinolyl)-γ-dialkylamino-α-phenylbutyronitriles by the condensation of 4-chloroquinolines with the sodio derivatives of the corresponding butyronitriles. The condensation of 4-chloro-6,7-dimethoxycinnoline with γ-diethylamino-α-phenylbutyronitrile was attempted, sodium amide being the condensing agent. A product was obtained whose nature was that of a tar or glass. Extensive efforts to purify the material failed to give a crystalline product. Since no crystalline hydrochloride could be prepared, the investigation was discontinued.



It has been noted that, in contrast to 4-chlorocinnoline (II) which is a skin irritant and is rather unstable, 4-chloro-6,7-dimethoxycinnoline (VI) is apparently completely stable as a dry solid (16). There is also a surprising disparity between the colors and solubilities of the two compounds. While (II), which is a definite yellow in color, is highly soluble in alcohols and benzene at room temperature, (VI) is nearly pure white when crystallized, and it is only moderately soluble in boiling ethanol or benzene. On the basis of relative stability, it might be expected that (VI) would be the less reactive of the two chlorocinnolines. Also, theoretical considerations suggest that (VI) should be less reactive than (II) toward nucleophilic attack at the 4-position. In both the 4-chlorocinnolines, the activity of the chlorine is the result of a decreased electron density at the 4-carbon which is caused by the presence of a basic nitrogen in the 1- position. A contributing resonance structure illustrating the electron shift induced by the nitrogen is shown below. A methoxy group in the 6- position of the cinnoline ring can inhibit the normal electron shift in the hetero ring by contributing electrons along a conjugated path to the 4- position, as shown below. Other resonance structures could be drawn showing more

It has been noted that, hitherto, [illegible]

[illegible] which is a [illegible]

[illegible] 2-dimensional [illegible]

apparently considerably stable as a crystalline [illegible]

There is also a [illegible] discrepancy between the [illegible]

and solubilities of the two compounds. While (13)

[illegible] is a definite yellow in color, [illegible]

[illegible]

nearly pure white when crystallized, and it is only

moderately soluble in boiling ethanol or benzene.

[illegible] of relative stability, it might be expected

[illegible] would be less reactive of the two [illegible]

[illegible] since the [illegible] constituent [illegible]

[illegible] should be less reactive than (13) [illegible]

[illegible] at the 4-position [illegible]

[illegible]

the result of [illegible] electron [illegible]

carbon which is caused by the presence of [illegible]

in the 2-position. A contributing resonance form,

illustrating the electron shift induced by the [illegible]

is shown below. [illegible] in the 4-position of

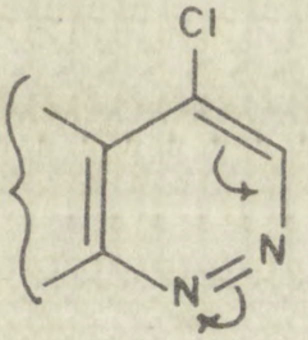
[illegible] the normal electron [illegible]

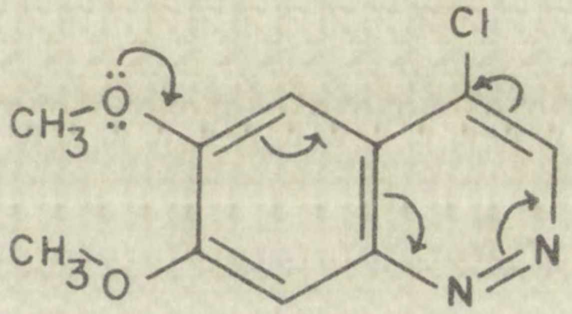
[illegible] contributing electron [illegible]

[illegible] to the 4-position, as shown below.

[illegible]

direct contribution of electrons to the 4- position. The methoxy group of (VI) which is in the 7- position should have no marked influence on the 4- position.





In the instances where the same substituted acetonitriles were condensed with both (II) and (VI), the yield was usually markedly smaller with (VI). On the other hand, the condensations which occurred in liquid ammonia showed no such definite difference, the yields being quite similar for homologous products of (II) and (VI). Comparison of the yields of condensation products of (II) and (VI) (see Table I) may reflect a real difference in reactivity although the comparatively slight solubility of (VI) in benzene as compared to (II) could be expected to limit its rate of reaction. An effort to compensate for this feature was made by allowing longer periods of stirring of the reaction mixture in the condensations involving (VI).

## TABLE I

Comparative Yields in Condensations of (II) and (VI)

| Nitriles | II | VI |
|---|---|---|
| Phenylacetonitrile (XII) | 94(16) | 40(16) |
| p-Chlorophenylacetonitrile (XIV) | 61 | 39 |
| p-Bromophenylacetonitrile (XV) | 71 | 35 |
| p-Iodophenylacetonitrile (XVI) | 53 | 24 |
| 3,4-Dichlorophenylacetonitrile (XVIII) | 77 | 40 |
| α-Naphthylacetonitrile (XXX) | 58 | 53 |
| Diphenylacetonitrile (XXVIII) | 20 | 24 |
| m-Methoxyphenylacetonitrile (XLI) | 55(16) | 64 |
| 3,4-Dimethoxyphenylacetonitrile (XLII)* | 75 | 86 |
| p-Aminophenylacetonitrile (XLIII)* | 71 | 69 |

*Liquid ammonia medium

## C. Reactions of 4-Methylcinnoline.

As noted above (1, 3, 47), three instances of condensation between 4-methylcinnolines and benzaldehydes have been recorded in the literature. In the present investigation, the reaction with 4-methylcinnoline (I) was extended to include two substituted benzaldehydes and two aromatic heterocyclic aldehydes, but many other attempted condensations failed to give crystalline products. The generality of the condensation between 2- and 4-picolines and various aldehydes and ketones noted by Mosher (30) was not paralleled with 4-methylcinnoline.

The only successful reactions between (I) and aldehydes employed anhydrous zinc chloride as the condensing agent. An attempt was made to force one condensation by azeotropic removal of water by boiling xylene, but no reaction occurred. Another condensation attempt was made using pyridine as the solvent and piperidine as the catalyst, but again no product was obtained.

It was found that (I) condensed with p-anisaldehyde (III), veratraldehyde (IV), 2-thiophenealdehyde (VIII), and 2-phenyl—2,1,3-triazole-4-carboxaldehyde (X) in low yield to give the corresponding "styryl"

D. Reactions of [illegible]

As noted above in [illegible]

condensation between [illegible]

have been reported [illegible]

investigation [illegible]

was extended to [illegible]

and two aromatic [illegible]

[illegible]

products. The generality of the [illegible]

[illegible]

noted by [illegible]

chlorides.

The only successful reactions between [illegible]

[illegible]

condensing agent, [illegible]

condensation by [illegible]

xylene, [illegible]

attempt was made [illegible]

[illegible] as the solvent, [illegible]

obtained.

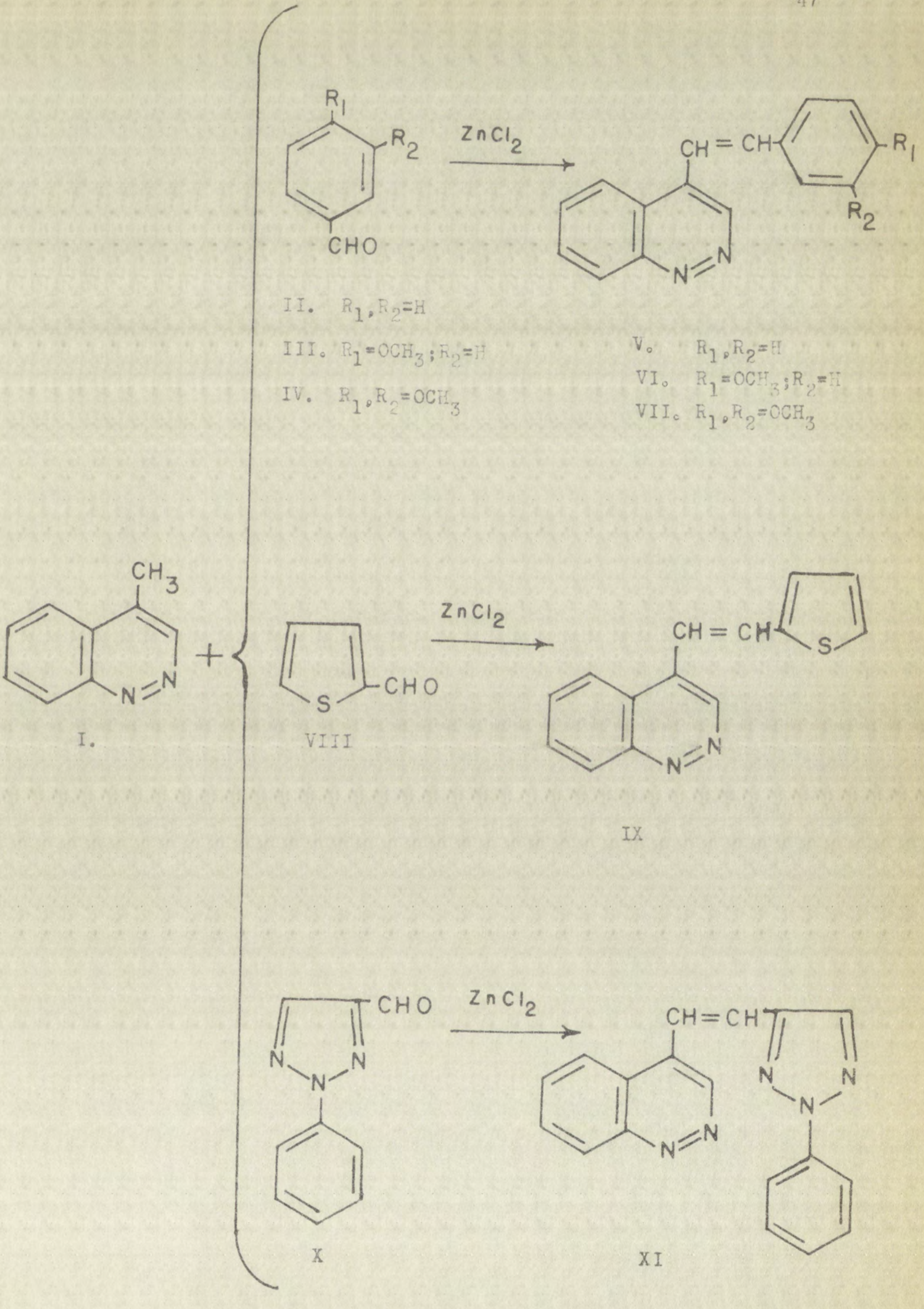
It was found that [illegible]

[illegible] (III) [illegible]

(VIII), and [illegible]

(X) in low yield [illegible]

Reactions from IV C.



derivatives (VI, VII, IX, and XI). The condensation of (I) with benzaldehyde (II) to produce 4-styrylcinnoline (V) was repeated, but on the small scale the yield obtained was smaller than that reported by Jacobs, et al (47).

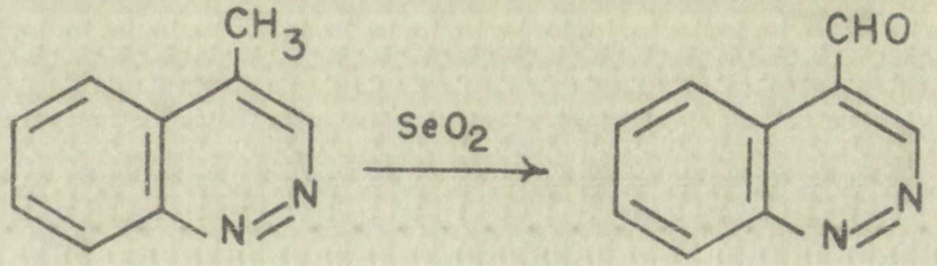
When an attempt was made to condense 9-anthraldehyde with (I) using zinc chloride as the condensing agent, a crystalline product was obtained which differed from either of the starting materials, but it did not contain nitrogen, and its carbon-hydrogen analysis did not match that calculated for any obvious anthracene derivative. With furfural and salicylaldehyde, condensation products apparently were obtained, but they were too unstable to be isolated and identified. Compounds which also failed to give identifiable products with 4-methylcinnoline were p-nitrobenzaldehyde, 2,4-dinitrobenzaldehyde, phenylacetaldehyde, and acetophenone.

Two attempts were made to prepare 4-cinnolinealdehyde by the action of selenium dioxide on (I). The selenium dioxide was freshly prepared or resublimed before each attempt, but in both cases only tars and degraded products were obtained. The ethiodide of (I) reacted very rapidly with selenium dioxide to give a dark tar.

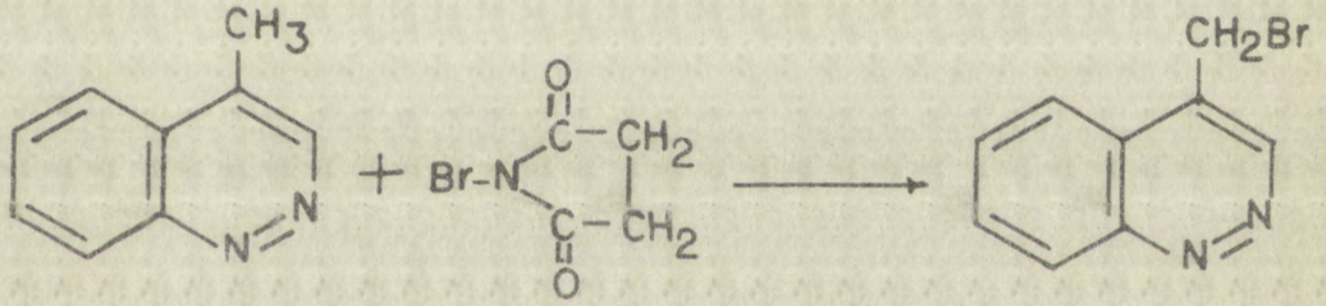
derivative was [illegible] [illegible] [illegible] The yield obtained was [illegible] Jacobs, et al. [illegible]

When an attempt was made to condense [illegible] agent, a crystalline [illegible] from either of the starting materials, and did not contain nitrogen, and its carbon-[illegible] but [illegible] derivative. [illegible] condensation products [illegible] they were too unstable [illegible] compounds [illegible] products were [illegible] 2-pyridinealdehyde [illegible] phenone.

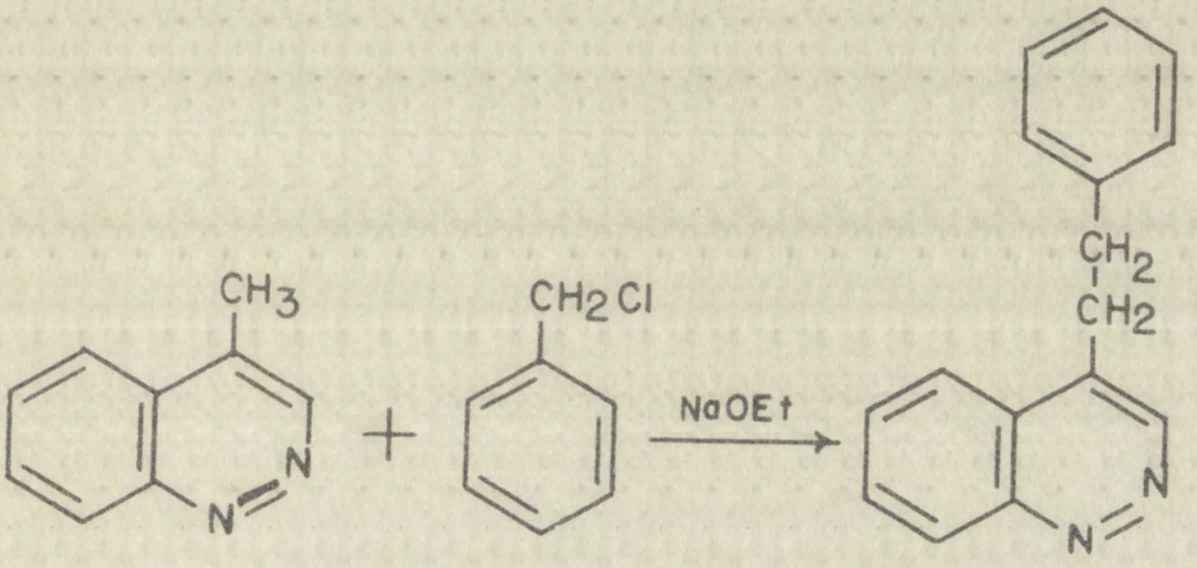
Two attempts were made to [illegible] aldehyde by the action of [illegible] sodium [illegible] before such attempts [illegible] products were [illegible] reacted very readily with [illegible] dark tars.



Wohl-Ziegler bromination of (I) was attempted without success. N-Bromosuccinimide reacted with (I) in carbon tetrachloride solution to produce a deep blue tar which could not be identified. Halogenation of (I) by bromine or iodine in carbon tetrachloride or toluene produced similar colored tars.



An attempt was made to condense (I) with benzyl chloride using sodium methoxide as the condensing agent. A solution of (I) and sodium methoxide in methanol was treated with benzyl chloride, and the addition of a large volume of water caused precipitation of a bright yellow solid which rapidly decomposed to a dark tar.


CH3
N
N
CH2Cl
NaOEt
CH2
CH2
N
N

## V. EXPERIMENTAL RESULTS

Unless otherwise designated, melting points were determined using Anschutz thermometers at total immersion.

Nitrogen analyses were done by the Clark Microanalytical Laboratory, Urbana, Illinois. Carbon-hydrogen analyses, with one exception, were done by the author.

Benzene used as the solvent in condensation reactions employing sodium amide was dried over calcium hydride previous to use.

4-Chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline were prepared according to procedures recorded by Castle and Kruse (16).

### Synthesis of 2-Amino-4,5-dimethoxyacetophenone.

The apparatus employed consisted of a three-neck standard taper round-bottom flask fitted with a reflux condenser and a rubber-sealed stirrer. A solution of 20 g. (0.089 mole) of 2-nitro-4,5-dimethoxyacetophenone in 230 ml. of glacial acetic acid and 100 ml. of water was heated to boiling. Through the reflux condenser 30 g. (0.54 gram atom) of iron powder (Mallinckrodt - Reduced by Hydrogen) was added at a rate sufficient to

maintain a vigorous evolution of hydrogen. The addition required forty minutes. The reaction mixture was stirred and refluxed for an additional four hours. The condenser was arranged for downward distillation, and 200 ml. of distillate was collected. At this time 100 ml. of water was added to the reaction solution, and another 100 ml. of distillate was collected. The reaction solution was poured into approximately 400 g. of ice, and a yellow crystalline solid formed in the resulting liquor. The product was filtered and washed well with water. From this fraction there was obtained 10.2 g. of the desired amine, m.p. 85-94°. The filtrate was extracted three times with 100 ml. portions of ether. The extracts were combined, washed with aqueous sodium bicarbonate and then water, and dried over anhydrous sodium sulfate. Evaporation of the ether to dryness left 4.4 g. of the yellow amine, m.p. 81-103°. The combined weight of product represents an 84% yield. Only a trace of the material was insoluble in 5% hydrochloric acid. A yield of 79% was obtained in two similar experiments.

### Synthesis of 4-Nitroveratrole.

Several procedures are recorded in the literature for the nitration of veratrole. The procedure described here most closely resembles that of Clark (21). A

solution of 13.2 ml. (0.145 mole) of nitric acid (sp. gr. 1.42) in 20 ml. of glacial acetic acid was prepared and stirred in an ice-bath. Twenty grams (0.145 mole) of veratrole was added dropwise over a period of twenty minutes. After the addition was completed bright yellow crystals separated. The product was filtered and washed well with water. There was obtained 23.8 g. (90%) of 4-nitroveratrole, melting point 95-96° (uncorr.).

## Synthesis of 3,4-Dimethoxyaniline.

The procedure of Findlay and Dougherty (42) was followed with the exception that the amine was crystallized from the reduction solution. From 14.0 g. (0.077 mole) of 4-nitroveratrole was obtained 9.0 g. (80%) of white plates of 3,4-dimethoxyaniline. Ethanolic solutions of the amine darken rapidly.

## Synthesis of 3,4-Dimethoxyacetanilide.

The procedure described by Fieser for the preparation of acetanilide (41) was adapted directly to the acetylation of 3,4-dimethoxyaniline. From 15 g. (0.1 mole) of 3,4-dimethoxyaniline was obtained 15.3 g. (79%) of glistening white plates of 3,4-dimethoxyacetanilide, melting point 135° C (uncorr.). Fetscher and Bogert report a melting point of 133° (40).

## Attempted Friedel-Crafts Acetylations of 3,4-Dimethoxyacetanilide.

a. Anhydrous Aluminum Chloride as the Catalyst. To an ice-chilled mixture of 5.0 g. (0.026 mole) of 3,4-dimethoxyacetanilide, 2.4 g. (0.024 mole) of acetic anhydride, and 4 ml. of dry carbon disulfide was slowly added 10.7 g. (0.08 mole) of anhydrous aluminum chloride. No reaction was apparent when the mixture was stirred, so it was heated on a water-bath. At this time 2 ml. of acetyl chloride was added. The mixture was refluxed for forty-five minutes, and then allowed to stand at room temperature for several hours. There was no evidence of any reaction, and on hydrolysis of the mixture there was recovered 3.0 g. of white solid, melting point 134-135° C (uncorr.). The solid was identified as starting material by a mixed melting point determination.

Three attempts were made to acetylate 3,4-dimethoxyacetanilide with acetyl chloride, using anhydrous aluminum chloride as the catalyst, and nitrobenzene as the solvent. Starting material was recovered from two of the attempts. During the third attempt the reaction mixture was heated at 150° C for fifteen minutes. Only intractable tars could be isolated from the reaction mixture.

Attempted Friedel-Crafts Acylations of [illegible] acetanilide.

a. Anhydrous Aluminum Chloride as the Catalyst.

To an ice-chilled mixture of 5.0 g. (0.026 mole) of 2,4-dinitroacetanilide, 2.4 g. (0.024 mole) of acetic anhydride, and 6 ml. of dry carbon disulfide was slowly added 10.7 g. (0.08 mole) of anhydrous aluminum chloride. No reaction was apparent when the mixture was cold, so it was heated on a water-bath. At this time 2 ml. of acetyl chloride was added. The mixture was refluxed for forty-five minutes, and then allowed to stand at room temperature for several hours. There was no evidence of any reaction, and on hydrolysis of the mixture there was recovered 5.0 g. of white solid, melting point [illegible] [illegible]. The [illegible] was identified as starting material by a mixed melting point determination.

Three attempts were made to acetylate 2,4-dinitroacetanilide with acetyl chloride, using anhydrous aluminum chloride as the catalyst, and nitrobenzene as the solvent. Stirring [illegible] was [illegible] each of the attempts. [illegible] the [illegible] mixture was heated at 150° [illegible]. No acetylated [illegible] could be isolated from the reaction mixture.

b. Anhydrous Zinc Chloride as the Catalyst. To a mixture of 3.0 g. (0.015 mole) of 3,4-dimethoxyacetanilide, 2 ml. (0.028 mole) of acetyl chloride, and 10 ml. of nitrobenzene was added 7.0 g. (0.07 mole) of anhydrous zinc chloride. The reaction mixture was heated for one minute. It turned dark green. After five minutes of stirring at room temperature, the reaction mixture was hydrolyzed by the addition of ice. The yellow solid which formed was filtered and dried. There was obtained 1.3 g. of product. Crystallization from ethanol produced small yellow needles, melting point 205° C (uncorr.). The sodium fusion test indicated the presence of nitrogen and the absence of halogen.

A portion of the yellow reaction product was dissolved in 30 ml. of 8.7% hydrochloric acid and refluxed for one hour. Neutralization of the solution with sodium carbonate caused formation of a flocculent yellow precipitate. The filtered and dried solid was crystallized from aqueous ethanol in minute yellow plates, melting point 215-220° C (uncorr.). Since the product was not the desired amine, no attempt was made to identify it and this investigation was discontinued.

Three attempts to repeat the acetylation reaction using anhydrous zinc chloride failed to yield any reaction product.

Synthesis of p-Fluorophenylacetonitrile.

A solution of 24.5 g. (0.108 mole) of p-fluorobenzyl iodide and 9.1 g. (0.135 mole) of 96.3% potassium cyanide in 130 ml. of ethanol and 10 ml. of water was refluxed for ten hours. The solution was evaporated to a small volume, and the potassium iodide which formed was filtered off. An attempt to crystallize the product by addition of water to the boiling filtrate caused separation of an oil. The oil and an ether extract of the mother liquor were combined and dried over anhydrous sodium sulfate. The ether was removed, and the residue distilled under reduced pressure. There was obtained 6.3 g. (43%) of product, b.p. 85-87° C./0.1 mm. Hg.

Analysis. Calculated for $C_8H_6NF$: C, 71.10, H, 4.47. Found: C, 69.44, H, 4.49.

Synthesis of $\alpha$-(4-cinnolyl)-p-fluorophenylacetonitrile.

A solution of 6.2 g. (0.046 mole) of p-fluorophenylacetonitrile in 25 ml. of benzene was added to 1.8 g. (0.046 mole) of sodium amide suspended in 10 ml. of benzene, and the mixture was stirred for twenty-five minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 3.8 g. (0.023 mole) of 4-chlorocinnoline in 30 ml. of benzene

was added over a period of fifteen minutes, and the reaction mixture was stirred for four hours. Approximately 75 ml. of water was added with vigorous stirring to effect hydrolysis. The yellow solid which formed was filtered, washed with water, and dried. After one crystallization from benzene there was obtained 4.0 g. (65%) of the reaction product. After three recrystallizations from benzene, glistening yellow plates were obtained, m.p. 170.0-172.8°.(after drying at 94° and 20 mm. Hg). Depending on concentration, the product crystallizes from benzene in either of two forms, one being yellow plates and the other orange-red needles. The yellow form apparently loses benzene of crystallization when dried at reduced pressure and assumes an orange color.

Analysis. Calculated for $C_{16}H_{10}N_3F$: C, 72.99, H, 3.83. Found: C, 72.45, H, 3.76.

### Synthesis of α-(4-cinnolyl)-p-chlorophenylacetonitrile.

To 2.4 g. (0.06 mole) of sodium amide suspended in 30 ml. of benzene was added 9.2 g. (0.06 mole) of p-chlorophenylacetonitrile, and the mixture was stirred for thirty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 5.0 g. (0.03 mole) of 4-chlorocinnoline in 40 ml. of

benzene was added over a period of ten minutes. The reaction mixture was stirred for three hours and twenty-five minutes. Water was added with vigorous stirring to effect hydrolysis. The orange solid which formed was filtered, washed with water, and dried. After three crystallizations from aqueous ethanol, there was obtained 5.2 g. (61%) of fibrous orange needles, m.p. 177.6-178.4°.

Analysis. Calculated for $C_{16}H_{10}N_3Cl$: C, 68.70, H, 3.60. Found: C, 68.75, H, 3.68.

### Synthesis of $\alpha$-(4-cinnolyl)-p-bromophenylacetonitrile.

A solution of 7.6 g. (0.04 mole) of p-bromophenylacetonitrile in 30 ml. of benzene was added to 1.52 g. (0.04 mole) of sodium amide suspended in 10 ml. of benzene, and the mixture was stirred for thirty-five minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 3.2 g. (0.02 mole) of 4-chlorocinnoline in 20 ml. of benzene was added dropwise, and the reaction mixture was stirred for three hours. Water was added with vigorous stirring to effect hydrolysis. The red solid which formed was filtered, washed with water, and dried. After crystallization from benzene there was obtained 4.5 g. (71%) of the reaction product. After two more crystallizations

from benzene, orange needles were obtained, m.p. 188.2-188.8°.

Analysis. Calculated for $C_{16}H_{10}N_3Br$: C, 59.28, H, 3.11. Found: C, 59.34, H, 3.33.

Synthesis of α-(4-cinnolyl)-p-iodophenylacetonitrile.

A solution of 6.0 g. (0.024 mole) of p-iodophenylacetonitrile in 15 ml. of benzene was added to 0.95 g. (0.024 mole) of sodium amide suspended in 10 ml. of benzene, and the mixture was stirred for twenty-five minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 2.0 g. (0.012 mole) of 4-chlorocinnoline in 15 ml. of benzene was added over a period of fifteen minutes, and the reaction mixture was stirred for three and one-half hours. Seventy milliliters of water was added with vigorous stirring to effect hydrolysis. The orange solid which formed was filtered, washed with water, and dried. After crystallization from benzene there was obtained 2.4 g. (53%) of the reaction product. After two more crystallizations from benzene, glistening orange red needles were obtained, m.p. 185.6-186.4°.

Analysis. Calculated for $C_{16}H_{10}N_3I$: C, 51.35, H, 2.69. Found: C, 51.73, H, 2.67.

### Synthesis of α-(4-cinnolyl)-o-chlorophenylacetonitrile.

A solution of 2.95 g. (0.02 mole) of o-chlorophenylacetonitrile in 17 ml. of benzene was added to 0.76 g. (0.02 mole) of sodium amide suspended in 10 ml. of benzene, and the mixture was stirred for twenty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 1.6 g. (0.01 mole) of 4-chlorocinnoline in 15 ml. of benzene was added over a period of ten minutes, and the reaction mixture was stirred for two and one-half hours. Fifty milliliters of water was added with vigorous stirring to effect hydrolysis. The yellow solid which formed was filtered, washed with water, and dried. After crystallization from aqueous ethanol there was obtained 1.6 g. (60%) of the reaction product. After two more crystallizations from aqueous ethanol, small bright-yellow needles were obtained, m.p. 200.4-201.2°.

Analysis. Calculated for $C_{16}H_{10}N_3Cl$: C, 68.70, H, 3.60. Found: C, 68.51, H, 3.82.

### Synthesis of 2,4-Dichlorophenylacetonitrile.

A solution of 40 g. (0.2 mole) of 2,4-dichlorobenzyl chloride and 13.9 g. (0.2 mole) of 96.3% potassium cyanide in 150 ml. of ethanol and 30 ml. of water was refluxed for six hours. The precipitated potassium

chloride was removed by filtration, and the orange filtrate was treated with Norit. The product tended to separate from aqueous ethanol as an oil, but chilling the mixture in an ice-bath caused crystallization of the product in the supernatant liquor. Successive chillings and reheatings allowed crystallization of nearly all of the product. There was obtained a total of 24.2 g. (64%) of white needles, m.p. 61-62° (uncorrected).

Analysis. Calculated for $C_8H_5NCl_2$: C, 51.64, H, 2.70. Found: C, 51.85, H, 2.69.

### Synthesis of α-(4-cinnolyl)-2,4-dichlorophenylacetonitrile.

To 1.2 g. (0.03 mole) of sodium amide suspended in 10 ml. of benzene was added 5.7 g. (0.03 mole) of 2,4-dichlorophenylacetonitrile in 20 ml. of benzene, and the mixture was stirred for two hours. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 2.5 g. (0.015 mole) of 4-chlorocinnoline in 30 ml. of benzene was added over a period of ten minutes, and the reaction mixture was stirred for three hours. Fifty milliliters of water was added with vigorous stirring to effect hydrolysis. When no solid formed, the green benzene chloride was removed by filtration and the [illegible]

[illegible] was [illegible] with [illegible]

[illegible] from [illegible] ethanol [illegible]

[illegible] in [illegible] crystals [illegible]

The product [illegible]. Upon [illegible]

[illegible] and [illegible] crystallization of

[illegible] of the product. There was [illegible]

of [illegible]

method).

Analysis. Calculated for [illegible]

[illegible] Found: C, [illegible]; H, [illegible].

Synthesis of α-[illegible]

nitrile.

To 2.3 g. (0.03 mole) of [illegible]

in 20 ml. of benzene was added [illegible] mole) of

[illegible]acetonitrile in 20 ml. of benzene,

and the mixture was stirred for [illegible] hours. The

red acid derivative of the [illegible]

evolution of [illegible]. A solution of [illegible]

of [illegible] in 30 ml. of benzene was added

over a period of ten minutes, and the [illegible]

was stirred for three hours. [illegible]

water was added [illegible]

[illegible]. Then the [illegible]

layer was separated and concentrated by evaporation. A dark yellow solid formed as a crust on the bottom of the flask. The benzene was decanted, and the residual solid was crystallized from aqueous ethanol, there being obtained 2.5 g. (52%) of stubby golden needles. The product was recrystallized once more from aqueous ethanol for analysis, m.p. 188.0-188.8°.

Analysis. Calculated for $C_{16}H_9N_3Cl_2$: C, 61.16, H, 2.89. Found: C, 61.21, H, 2.921.

<u>Synthesis of 3,4-Dichlorophenylacetonitrile</u>.

A solution of 40 g. (0.2 mole) of 3,4-dichlorobenzyl chloride and 15.5 g. (0.238 mole) of 96.3% potassium cyanide in 150 ml. of ethanol and 30 ml. of water was refluxed for six hours. The precipitated potassium chloride was removed by filtration, and the filtrate was treated with Norit. Chilling of the ethanol solution in an ice-bath caused crystallization of the reaction product, there being obtained 28.2 g. (74%) of crude white crystals. The product was recrystallized from aqueous ethanol with difficulty since the product tended to separate as an oil. There was obtained 13.3 g. of pure white crystals, m.p. 36-37° (uncorrected).

Analysis. Calculated for $C_8H_5NCl_2$: C, 51.64, H, 2.70. Found: C, 52.19, H, 2.78.

Synthesis of α-(4-cinnolyl)-3,4-dichlorophenylacetonitrile.

To 1.4 g. (0.036 mole) of sodium amide suspended in 10 ml. of benzene was added 7.1 g. (0.036 mole) of 3,4-dichlorophenylacetonitrile and 20 ml. of benzene, and the mixture stirred for thirty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 3.0 g. (0.018 mole) of 4-chlorocinnoline in 20 ml. of benzene was added over a period of fifteen minutes, and the reaction mixture was stirred for two hours and fifteen minutes. Fifty milliliters of water was added with vigorous stirring to effect hydrolysis. The orange solid which formed was filtered, washed with water, and dried. After crystallization from ethanol, there was obtained 4.4 g. (77%) of the reaction product. After recrystallization from ethanol, orange-gold platelets were obtained, m.p. 236.6-237.6°.

Analysis. Calculated for $C_{16}H_9N_3Cl_2$: C, 61.16, H, 2.89. Found: C, 61.41, H, 2.91.

Synthesis of α-(4-cinnolyl)-diphenylacetonitrile.

A solution of 4.7 g. (0.024 mole) of diphenylacetonitrile in 30 ml. of benzene was added to 0.94 g. (0.024 mole) of sodium amide suspended in 10 ml. of

benzene, and the mixture was stirred for fifteen minutes. The dark green sodio derivative of the nitrile formed with the evolution of heat. A solution of 1.6 g. (0.012 mole) of 4-chlorocinnoline in 50 ml. of benzene was added over a period of twenty minutes. Upon the addition of 4-chlorocinnoline, the reaction mixture turned dark red. After stirring for one hour the reaction mixture was allowed to stand at room temperature for an additional twelve hours. Water was added with vigorous stirring to effect hydrolysis. A small amount of yellow solid formed which was left with the aqueous layer on separation. The solid dissolved in the ether which was used to extract the aqueous layer. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. The resulting yellow solid was crystallized twice from aqueous ethanol, and there was obtained 0.62 g. (20%) of the reaction product. Recrystallization from aqueous ethanol produced pale yellow crystals, m.p. 186.2-186.8°.

Analysis. Calculated for $C_{22}H_{15}N_3$: C, 82.22, H, 4.71, N, 13.07. Found: C, 82.37, H, 4.91, N, 12.92.

Synthesis of $\alpha$-(4-cinnolyl)-$\alpha$-(1-naphthyl)-acetonitrile.

To 1.5 g. (0.038 mole) of sodium amide suspended in 20 ml. of benzene was added 6.2 g. (0.037 mole) of

α-naphthylacetonitrile, and the reaction mixture was stirred for twenty-five minutes. The dark green sodio derivative of the nitrile formed with the evolution of heat. A solution of 3.0 g. (0.018 mole) of 4-chlorocinnoline in 30 ml. of benzene was added over a period of ten minutes. Upon the addition of 4-chlorocinnoline, the reaction mixture turned dark red. Stirring was continued for two hours. Water was added with stirring to effect hydrolysis. The orange solid which formed was filtered, washed with water, and dried. After two crystallizations from ethanol there was obtained 2.7 g. (58%) of dark orange crystals, m.p. 224.0-224.8°.

Analysis. Calculated for $C_{20}H_{13}N_3$: C, 81.34, H, 4.44. Found: C, 81.17, H, 4.52.

Synthesis of α-(4-cinnolyl)-α-(2-naphthyl)-acetonitrile.

A solution of 2.5 g. (0.015 mole) of β-naphthylacetonitrile in 20 ml. of benzene was added to 0.36 g. (0.009 mole) of sodium amide suspended in 10 ml. of benzene, and the reaction mixture was stirred for twenty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. A solution of 1.5 g. (0.009 mole) of 4-chlorocinnoline in 10 ml. of benzene was added over a period of ten minutes, and the reaction mixture was stirred for two and one-half hours. Water was added with stirring to effect hydrolysis. The yellow

solid which formed was filtered, washed with water, and dried. After crystallization from aqueous ethanol there was obtained 0.33 g. (12%) of the reaction product. After two recrystallizations from aqueous ethanol, dark golden needles were obtained, m.p. 248.2-249.0°.

Analysis. Calculated for $C_{20}H_{13}N_3$: C, 81.34, H, 4.44. Found: C, 81.40, H, 4.61.

Synthesis of α-(4-cinnolyl)-α- 2-(4,4-dimethyl-1-isopropyl-2-imidazolinyl) -acetonitrile.

To 0.4 g. (0.01 mole) of sodium amide suspended in 10 ml. of benzene was added 1.9 g. (0.01 mole) of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline in 20 ml. of benzene. The mixture was heated to boiling, whereupon the imidazoline dissolved and appeared to react with the sodium amide. After twenty minutes, 0.9 g. (0.005 mole) of 4-chlorocinnoline was added with 10 ml. of benzene. A bright-red precipitate formed which quickly turned bright-yellow on agitation of the mixture. The reaction mixture was stirred for one hour and allowed to stand for one and one-half hours more. Water was added with stirring to effect hydrolysis. The yellow solid which formed was filtered, washed with water, and dried. After crystallization from aqueous ethanol there was obtained 1.4 g. (83%) of the reaction product. After four crystallizations from aqueous

ethanol, brilliant yellow needles were obtained, m.p. 207-208° (uncorrected).

Analysis. Calculated for $C_{18}H_{21}N_5$: C, 70.33, H, 6.89. Found: C, 70.25, H, 7.02.

Synthesis of α-(4-cinnolyl)-3,4-dimethoxyphenylacetonitrile.

A suspension of potassium amide in liquid ammonia was prepared by the addition of 3.1 g. (0.08 gram atom) of potassium to 500 ml. of liquid ammonia to which a small amount of ferric nitrate had been added. To the suspension was added 14.0 g. (0.08 mole) of 3,4-dimethoxyphenylacetonitrile, and the mixture was stirred for thirty minutes. The addition of 6.1 g. (0.037 mole) of 4-chlorocinnoline caused the gray mixture to turn deep red. Stirring was continued for four hours, during which time the ammonia evaporated. Approximately 400 ml. of water and 10 ml. of concentrated hydrochloric acid was added with stirring to effect hydrolysis of the reaction product. The orange solid which formed was filtered, washed with water, and dried. After crystallization from ethanol there was obtained 8.1 g. (75%) of the desired reaction product. After two recrystallizations from ethanol, tiny bright-orange needles were obtained, m.p. 180.6-181.2°.

estimated [illegible]

[illegible] °C [illegible] compound [illegible]

Analysis. Calculated for [illegible]

[illegible] Found: C, [illegible]

Synthesis of [illegible]

nitrile

[illegible] condensation of [illegible]

was prepared [illegible]

of potassium [illegible] 200 g. [illegible]

small amount of [illegible]

suspension was added [illegible]

methoxybenzaldehyde [illegible]

for thirty minutes. The [illegible]

of 4-chloro- [illegible]

was held [illegible]

which time the [illegible]

of water and 10 ml. of [illegible]

was added with [illegible]

first [illegible]

filtered, washed with [illegible]

[illegible] from [illegible]

of the [illegible]

[illegible] from [illegible]

obtained, [illegible]

Analysis. Calculated for $C_{18}H_{15}N_3O_2$: C, 70.81, H, 4.95. Found: C, 70.37, H, 5.11.

From the mother liquor of the first crystallization of the main reaction product there deposited some bright-yellow crystals. After recrystallization from ethanol there was obtained 0.8 g. of yellow crystals, m.p. 178-179° (uncorrected). The mixed melting point of this material with the principal reaction product is 153-165°. The yellow material has not been identified.

Synthesis of α-(4-cinnolyl)-p-aminophenylacetonitrile.

A suspension of potassium amide in liquid ammonia was prepared by the addition of 2.6 g. (0.067 gram atom) of potassium to 400 ml. of liquid ammonia to which a small amount of ferric nitrate had been added. To the suspension was added 9.6 g. (0.073 mole) of p-aminophenylacetonitrile, and the mixture was stirred for fifteen minutes. Addition of the nitrile caused the mixture to become dark red in color. To the mixture was added 5.5 g. (0.033 mole) of 4-chlorocinnoline, and stirring was continued for four and one-half hours while the ammonia evaporated. Water was added to the reaction product to effect hydrolysis, and the brick-red solid which formed was filtered, washed with water, and dried. After crystallization from ethanol there was obtained 6.3 g. (71%) of the reaction product. After recrystallization from ethanol

Analysis. Calculated for [illegible]

N, 6.06; Found: N, 6.15, [illegible]

From the mother liquors of the first crop [illegible] of the main reaction product, there [illegible] small crystals [illegible] there was obtained 0.[illegible] g. [illegible] 179° (uncorrected). The mixed [illegible] material with the [illegible] 150°. The yellow material was not [illegible]

<u>Synthesis of</u> [illegible]

A suspension of [illegible] was prepared in the absence [illegible] of potassium in 200 ml. of [illegible] small amount of ferric nitrate [illegible] suspension was added [illegible] acetonitrile, and the mixture was [illegible] minutes. Addition of the nitrile caused [illegible] become dark red in color. [illegible] (0.0[illegible] mole) of [illegible] continued for four and one-half hours [illegible] evaporated. Water was added [illegible] ether, hydrochloric [illegible] was filtered, washed [illegible]

Elution from alumina [illegible] the reaction product. After [illegible] deep red needles were obtained, m.p. 236.4-237.4°.

Analysis. Calculated for $C_{16}H_{12}N_4$: C, 73.83, H, 4.65. Found: C, 73.51, H, 4.98.

Synthesis of 4-(p-aminobenzyl)-cinnoline.

A solution of 1.0 g. of $\alpha$-(4-cinnolyl)-p-aminophenylacetonitrile in 14 ml. of 50% sulfuric acid was refluxed for four hours. The solution was poured on ice and neutralized with ammonium hydroxide, and the yellow solid which formed was filtered, washed with water, and dried. After crystallization from benzene there was obtained 0.58 g. (64%) of the desired product. After two recrystallizations from benzene, glistening yellow needles were obtained, m.p. 176-177° (uncorrected). The product is insoluble in aqueous sodium hydroxide.

Analysis. Calculated for $C_{15}H_{13}N_3$: C, 76.57, H, 5.57. Found: C, 76.72, H, 5.46.

Attempted Deamination of 4-(p-Aminobenzyl)-cinnoline.

A solution of 0.8 g. (0.0034 mole) of 4-(p-aminobenzyl)-cinnoline in 10 ml. of 18% hydrochloric acid was chilled to -2° in a salt-ice bath. To the solution was added dropwise a solution of 0.235 g. (0.0034 mole) of sodium nitrile in 5 ml. of water. A blue cast immediately appeared in the solution. To the diazotized amine was added 20 ml. of hypophosphorous acid which had [illegible]). The needles were obtained, m.p. [illegible]

Analysis. Calculated for [illegible]

[illegible]. Found: C, [illegible]; H, [illegible]

Synthesis of 4-(p-nitrobenzyl)-[illegible]

A [illegible] g. of [illegible]

[illegible] in 15 ml. of 30% sulfuric acid [illegible]

refluxed for four hours. The solution was [illegible]

[illegible] were present [illegible]

yellow solid which formed was [illegible]

water, and dried. After [illegible]

[illegible] was obtained 0.56 g. [illegible]

After two recrystallizations from [illegible]

yellow needles were obtained, m.p. 152-153° (uncorrected).

[illegible]

Analysis. Calculated for [illegible]

N, 5.85. Found: C, 75.52; H, 5.02.

Attempted Deamination of 4-(p-aminobenzyl)-[illegible]

A solution of [illegible]

benzyl-[illegible] in 10 ml. of 50% [illegible] acid

was cooled to -5° in a salt-ice bath. To this solution

was added dropwise a solution of [illegible]

of sodium nitrite in 5 ml. of water. [illegible]

immediately appeared in the solution [illegible]

solid was [illegible]

been previously chilled to -2°. The solution stood in the ice bath for nine hours, and it became a deep purple in color. After two days of standing at room temperature, the color was so intense that a portion of the solution diluted ten to one with water in a six-inch test tube was opaque to ordinary light. An ether extract of the solution failed to yield a significant amount of solid on evaporation although the extract was yellow in color. When the purple solution was made alkaline with ammonium hydroxide, it became orange, and a solid precipitated. The solid appeared to decompose to a tar, but the tar became purple when acidified. The material was not identified.

A similar deamination attempt with α-(4-cinnolyl)-p-aminophenylacetonitrile gave a product which also appeared to be a dye. The deep blue of the reaction solution became dark red when the solution was made basic. Again, the product was not identified.

### Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-p-chlorophenylacetonitrile.

To 0.94 g. (0.024 mole) of sodium amide suspended in 10 ml. of benzene was added 3.6 g. (0.024 mole) of p-chlorophenylacetonitrile and 20 ml. of benzene, and the mixture was stirred for twenty-five minutes. The

been previous [illegible]
in the [illegible]
people. In [illegible]
temperat[illegible]
of the [illegible]
which [illegible]
stream of [illegible]
amount of [illegible]
was felled [illegible]
alkaline [illegible]
and [illegible]
con[illegible]
material [illegible]

Possible [illegible]
appeared [illegible]
solution became [illegible]
Again, [illegible]

[illegible]

[illegible]

The [illegible]
in 10 [illegible]
Decem[illegible]
the [illegible]

dark red sodio derivative of the nitrile formed with the evolution of heat. To the mixture was added 2.7 g. (0.012 mole) of 4-chloro-6,7-dimethoxycinnoline in 40 ml. of benzene, and stirring was continued for six and one-half hours. Water was added with vigorous stirring to effect hydrolysis. An emulsion of benzene, water, and an orange solid formed which could not be filtered dry with suction. The wet mass was allowed to stand in a Büchner funnel until nearly dry. After crystallization from benzene there was obtained 1.6 g. (39%) of small orange-red crystals. The product was recrystallized from benzene for analysis, m.p. 224.4-225.2° (dec.).

Analysis. Calculated for $C_{18}H_{14}N_3O_2Cl$: C, 63.63, H, 4.15. Found: C, 63.40, H, 4.10.

Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-p-bromophenylacetonitrile.

To 1.32 g. (0.034 mole) of sodium amide suspended in 10 ml. of benzene was added a solution of 6.6 g. (0.034 mole) of p-bromophenylacetonitrile in 30 ml. of benzene, and the mixture was stirred for thirty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. To the mixture was added 3.8 g. (0.017 mole) of 4-chloro-6,7-dimethoxycinnoline and 55 ml. of benzene, and stirring was continued for

seven and one-third hours. Water was added with stirring to effect hydrolysis, and the orange solid which formed was filtered, washed with water, and dried. After crystallization from benzene there was obtained 1.6 g. (35%, based on corrected value for 4-chloro-6,7-dimethoxycinnoline reacting) of the desired reaction product. From the mother liquor of the crystallization was recovered 1.1 g. of 4-chloro-6,7-dimethoxycinnoline, identified by mixed melting point with an authentic sample. After recrystallization from benzene, the reaction product was obtained as a micro-crystalline orange-red powder, m.p. 241.4-241.8° (dec.).

Analysis. Calculated for $C_{18}H_{14}N_3O_2Br$: C, 56.26, H, 3.67. Found: C, 55.98, H, 3.64.

Synthesis of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-p-iodophenylacetonitrile.

To 0.70 g. (0.018 mole) of sodium amide suspended in 10 ml. of benzene was added a solution of 4.4 g. (0.018 mole) of p-iodophenylacetonitrile in 30 ml. of benzene. Salt formation failed to start immediately, so 0.35 g. (0.009 mole) of sodium amide was added and the mixture was heated on a water-bath at 50° for a few moments. The dark red sodium salt of the nitrile was formed during a period of twenty-five minutes while the taken and the [illegible]

stirring to effect [illegible]

which caused [illegible]

ended. After [illegible]

obtained [illegible]

4-chloro-3,5-dinit[illegible]

reaction product [illegible]

[illegible]ication was [illegible]

[illegible], identi[illegible]

authentic sample. [illegible]

the reaction product was [illegible]

[illegible]

Analysis. [illegible]

H, 3.67. Found: C, [illegible]

Synthesis of [illegible]

acetonitrile.

To 0.70 g. ( [illegible]

in 50 ml. of benzene [illegible]

(0.010 mole) of [illegible]

benzene. [illegible]

to 0.55 g. [illegible]

the mixture was [illegible]

moments. The [illegible]

formed during [illegible]

mixture was stirred. Two grams (0.009 mole) of 4-chloro-6,7-dimethoxycinnoline was added with 30 ml. of benzene, and the reaction mixture was stirred for six and one-fourth hours. Water was added with stirring to effect hydrolysis, and the orange solid which formed was filtered, washed with water, and dried. After crystallization from benzene there was obtained 0.9 g. (24%) of the desired reaction product. After crystallization from benzene, tiny orange-red crystals were obtained, m.p. 252.6-253.0° (dec.).

Analysis. Calculated for $C_{18}H_{14}N_3O_2I$: C, 50.13, H, 3.27. Found: C, 50.35, H, 3.36.

Synthesis of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dichlorophenylacetonitrile.

To 1.22 g. (0.031 mole) of sodium amide suspended in 25 ml. of benzene was added 6.1 g. (0.031 mole) of 3,4-dichlorophenylacetonitrile in 15 ml. of benzene, and the mixture was stirred for thirty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. To the mixture was added 3.5 g. (0.016 mole) of 4-chloro-6,7-dimethoxycinnoline in 40 ml. of benzene, and stirring was continued for seven hours. Water was added with stirring to effect hydrolysis, and the orange solid which formed was filtered, washed with mixture was stirred. The [illegible]

6,7-dimethoxyindazole was [illegible]

and the resulting mixture was stirred [illegible]

room temperature. Water was added [illegible]

hydrochloric acid, and the orange [illegible]

filtered, washed with water, and dried.

[illegible] from benzene. There was [illegible]

of the desired reaction [illegible]

from benzene, tiny orange [illegible] were obtained,

M.P. 250.5-252.0° (dec.).

Analysis. [illegible]

N, 9.29. Found: C, 60.[illegible]; H, [illegible]

Synthesis of [illegible]

phenylacetonitrile

To 1.22 g. (0.0[illegible] mole) of [illegible]

in 25 ml. of benzene was added [illegible]

3,4-dichlorophenylacetonitrile [illegible]

and the mixture was stirred [illegible]

[illegible] sodio derivative of the nitrile [illegible]

the evolution of heat. To the mixture was added [illegible]

(0.010 mole) of [illegible]

of benzene, and stirring was continued [illegible]

Water was added with stirring [illegible]

The orange solid which formed was [illegible] water, and dried. After crystallization from ethanol there was obtained 2.3 g. (40%) of the desired reaction product. After recrystallization from ethanol, brilliant orange needles were obtained, m.p. 275.2-276.2° (dec.).

Analysis. Calculated for $C_{18}H_{13}N_3O_2Cl$ : C, 57.77, H, 3.50. Found: C, 57.58, H, 3.48.

### Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-diphenylacetonitrile.

To 0.5 g. (0.0025 mole) of sodium amide suspended in 10 ml. of benzene was added 0.43 g. (0.0022 mole) of diphenylacetonitrile. The mixture was shaken occasionally, and after one hour the dark green sodium salt of the nitrile had formed. To the reaction mixture was added 0.5 g. (0.0022 mole) of 4-chloro-6,7-dimethoxycinnoline. After two hours, the reaction mixture had become red, and after sixteen hours, water was added to effect hydrolysis. The benzene layer was separated, dried over Drierite, and evaporated to small volume. A pale yellow crystalline solid deposited which was filtered and washed with a little ethanol. After crystallization from ethanol there was obtained 0.2 g. (24%) of pale yellow crystals, m.p. 238.6-239.4° (dec.)

Analysis. Calculated for $C_{24}H_{19}N_3O_2$: C, 75.57, H, 5.02. Found: C, 75.45, H, 5.10.

### Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-α-(1-naphthyl)-acetonitrile.

To 0.3 g. (0.008 mole) of sodium amide suspended in 15 ml. of benzene was added 1.0 ml. (0.006 mole) of α-naphthylacetonitrile. The mixture was shaken and warmed, and after one hour, the dark green sodium salt of the nitrile had formed. Upon the addition of 0.6 g. (0.003 mole) of 4-chloro-6,7-dimethoxycinnoline, the reaction mixture became red in color, and it was allowed to stand with occasional shaking at 35° for four hours and at 20° for twelve more hours. Water was added with vigorous shaking to effect hydrolysis. The benzene layer contained a yellow emulsion which was separated and allowed to evaporate to dryness in the air. The resulting solid was crystallized from ethanol, there being obtained 0.5 g. (53%) of the desired reaction product. After recrystallization from ethanol, tiny orange-gold crystals were obtained, m.p. 247.2-248.0° (dec.).

Analysis. Calculated for $C_{22}H_{17}N_3O_2$: C, 74.35, H, 4.82. Found: C, 74.37, H, 4.98.

### Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-m-methoxyphenylacetonitrile.

To a solution of 11.8 g. (0.008 mole) of m-methoxyphenylacetonitrile in 50 ml. of benzene was added 3.3 g.

[illegible]

[illegible] of [illegible] g. ([illegible] mole) of [illegible]

[illegible] in benzene was added [illegible]

of [illegible]

was warmed, [illegible]

with of the [illegible] was formed. [illegible]

[illegible]

The reaction mixture became red in colour [illegible]

allowed to stand with occasional shaking at [illegible]

[illegible] hours and [illegible]

was added, [illegible]

The benzene layer containing a yellow [illegible]

was separated and allowed to evaporate [illegible]

[illegible]

[illegible]

[illegible]

ethanol, long orange-gold crystals [illegible]

m.p. [illegible] (dec.).

Analysis. Calculated for [illegible]

N, [illegible]. Found: [illegible]

[illegible]

[illegible]

To a solution of [illegible] g. [illegible]

[illegible] in [illegible] ml. of benzene [illegible]

(0.085 mole) of sodium amide, and the mixture was stirred for one hour. A dark red reaction product formed with the evolution of heat. To the mixture was added 9.0 g. (0.04 mole) of 4-chloro-6,7-dimethoxycinnoline and a mixture of 35 ml. of benzene and 35 ml. of toluene, and stirring was continued for three and three-fourths hours. Fifty milliliters of water and 3 ml. of concentrated hydrochloric acid was added with vigorous stirring to effect hydrolysis, and the orange solid which formed was filtered, washed with water, and dried. After crystallization from ethanol there was obtained 8.6 g. (64%) of red-gold needles. A portion of the product was recrystallized from ethanol for analysis, m.p. 222.2-223.2° (dec.).

Analysis. Calculated for $C_{19}H_{17}N_3O_3$: C, 68.05, H, 5.11. Found: C, 67.99, H, 5.12.

Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-α- 2-(4,4-dimethyl-1-isopropyl-2-imidazolinyl) -acetonitrile.

To 0.78 g. (0.02 mole) of sodium amide suspended in 25 ml. of benzene was added 3.6 g. (0.02 mole) of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline in 15 ml. of benzene, and the mixture was heated nearly to reflux with stirring. After twenty-five minutes a clear solution of the sodio derivative of the imidazoline had formed, and 2.24 g. (0.01 mole) of 4-chloro-6,7-

dimethoxycinnoline was added, followed by 20 ml. of benzene. The stirred mixture assumed a deep yellow color and became homogeneous within five minutes. After four hours of stirring at room temperature, the reaction mixture was hydrolyzed with 100 ml. of water, and approximately 0.5 g. of bright yellow solid was collected by filtration. The benzene layer was separated and evaporated to approximately 20 ml. More bright yellow crystals formed, the combined weight of product being 4.6 g. After three crystallizations from aqueous lower alcohols, the melting point of the reaction product had a wide range beginning at 175°. A benzene solution of the product was passed into a column of activated alumina, and the yellow band of adsorbed product which formed remained homogeneous when development was attempted. The yellow band was eluted from the alumina with ethanol, and the product crystallized when the eluate was diluted at the boiling point with water. At this point the product melted at 235° after extensive preliminary darkening. A recrystallization from aqueous ethanol failed to improve the melting point, but two further recrystallizations from aqueous ethanol after treatment with Norit raised the melting point to a reproducible 242-243° (dec.)(uncorrected). No yield was calculated.

Analysis. Calculated for $C_{20}H_{25}N_5O_2$: C, 65.37, H, 6.86, Found: C, 65.09, H, 6.75.

### Attempted Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-p-methoxyphenylacetonitrile.

A solution of 4.8 g. (0.033 mole) of p-methoxyphenylacetonitrile in 40 ml. of benzene was added to 1.27 g. (0.033 mole) of sodium amide, and the mixture was stirred in an ice bath for forty-five minutes while the dark red sodio derivative of the nitrile formed. To the mixture was added 3.66 g. (0.016 mole) of 4-chloro-6,7-dimethoxycinnoline and 30 ml. of benzene, and there was a slight warming of the reaction mixture. After four hours, water was added with stirring to effect hydrolysis, and the orange solid which formed was filtered and dried. Crystallization of the product from ethanol gave orange needles mixed with a few needles of unreacted 4-chloro-6,7-dimethoxycinnoline. Neither crystallization nor chromatographic purification yielded a homogeneous sample of the product. The expected analysis could not be obtained.

### Attempted Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-o-chlorophenylacetonitrile.

A solution of 3.4 g. (0.022 mole) of o-chlorophenylacetonitrile in 20 ml. of benzene was added to

Analysis. [illegible]

H, 6.8%. Found: C, [illegible]

Attempted synthesis [illegible]

p-chlorophenylacetol [illegible]

A solution of [illegible]

phenylacetaldehyde [illegible]

11.8 g. (0.05 mole) [illegible]

was stirred in an ice water [illegible]

the dark and solid [illegible]

The mixture was [illegible]

[illegible]

and there was a [illegible]

after four hours, [illegible]

hydrolysis, [illegible]

filtered and dried [illegible]

from ethanol gave [illegible]

of unreacted 4-chloro[illegible]

crystallization from [illegible]

a homogeneous sample of [illegible]

analysis could not be obtained.

Attempted synthesis [illegible]

o-chlorophenylacetol [illegible]

A solution of [illegible]

phenylacetic [illegible]

0.87 g. (0.022 mole) of sodium amide suspended in 10 ml. of benzene, and the mixture was stirred for thirty minutes. The dark red sodio derivative of the nitrile formed with the evolution of heat. To the mixture was added 2.5 g. (0.011 mole) of 4-chloro-6,7-dimethoxycinnoline and 40 ml. of benzene, and stirring was continued for twenty-two and one-half hours. Water was added with stirring to effect hydrolysis, and a bright yellow emulsion formed. The emulsion was collected in a Büchner funnel and allowed to dry. The product was highly soluble in both ethanol and benzene, and a mixture of benzene and petroleum ether proved most satisfactory for crystallization. Four recrystallizations from benzene-petroleum ether failed to bring the yellow product to an adequate state of purity as evidenced by the variability and range of the melting point. The melting point having the highest upper limit was 155-164°. The product was not further identified.

## Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-p-aminophenylacetonitrile.

A suspension of potassium amide in liquid ammonia was prepared by the addition of 1.4 g. (0.036 gram atom) of potassium to 400 ml. of liquid ammonia to which a small amount of ferric nitrate had been added. To the suspension was added 4.5 g. (0.034 mole) of p-aminophenyl-

acetonitrile, and the mixture was stirred for fifteen minutes. After the addition of 3.8 g. (0.017 mole) of 4-chloro-6,7-dimethoxycinnoline, stirring was continued for three and one-half hours while the ammonia evaporated. Water was added with stirring to the reaction product, and the brick-red solid which formed was filtered, washed with water, and dried. Crystallization from aqueous ethanol gave deep red needles which could not be further purified to a constant melting point. The best melting point obtained was 206-207° (uncorrected). An attempt to purify the product by chromatography on activated alumina caused apparent degradation of the organic material.

Analysis. Calculated for $C_{18}H_{16}N_4O_2$: C, 67.48, H, 5.04. Found: C, 65.59, 65.38, H, 5.69, 5.47.

A portion of the product was converted to a tan hydrochloride by the passage of dry hydrogen chloride through an ether suspension. The hydrochloride was partially hydrolyzed during attempted crystallizations, and when it was neutralized with sodium hydroxide, an altered product was recovered. The new material was crystallized from ethanol with difficulty as golden-brown plates and melted 235-237°. The material was not identified.

## Synthesis of 4-(p-aminobenzyl)-6,7-dimethoxycinnoline.

A solution of 0.9 g. of α-(6,7-dimethoxy-4-cinnolyl)-p-aminophenylacetonitrile in 30 ml. of 50% sulfuric acid was heated just below the boiling point for six hours. The solution was then poured on ice and neutralized with concentrated ammonium hydroxide. The flocculent, light-orange solid which formed was filtered with suction, washed with water, and dried. After crystallization from benzene and recrystallization from ethanol, there was obtained 0.5 g. (69%) of the desired product. After recrystallization from benzene, pale yellow crystals were obtained, m.p. 175.8-177°.

Analysis. Calculated for $C_{17}H_{17}N_3O_2$: C, 69.13, H, 5.80. Found: C, 68.27, H, 5.87.

## Attempt to Prepare an Azo Dye from 4-(p-aminobenzyl)-6,7-dimethoxycinnoline.

A solution of 1.2 g. (0.004 mole) of 4-(p-aminobenzyl)-6,7-dimethoxycinnoline in 23 ml. of concentrated hydrochloric acid and 25 ml. of water was cooled to -10° C in a salt-ice bath. An aqueous solution of 0.28 g. (0.004 mole) of sodium nitrite was added dropwise with stirring. A solution of 0.6 g. (0.004 mole) of β-naphthol in 15 ml. of 10% sodium hydroxide was then added dropwise. Each drop caused a floc of pale red solid to separate.

Stirring was continued for twenty minutes, after which time the mixture was allowed to come to room temperature. Neutralization of the mixture with 20% sodium hydroxide solution caused precipitation of a dark red solid. Approximately half of the solid was soluble in acetone. Successive crystallizations of this fraction from aqueous acetone raised the melting point to 239-242° (uncorr.), but each crystallization was attended by a marked loss of product. It appeared that the acetone-soluble material was unstable, slowly reverting to the nature of the original acetone-insoluble fraction. The latter material chars and decomposes above 250°. It burns completely with no ash.

The acetone-soluble fraction forms intense red solutions in acetone, ethanol, dioxane, or toluene. Prolonged heating of the material in dioxane solution caused fading of the solution color to pale yellow.

Analysis. Calculated for $C_{27}H_{22}N_4O_3$: C, 71.98, H, 4.92. Found: C, 69.62, 69.75, H, 4.94, 4.68.

Attempted Hydrolysis of $\alpha$-(4-cinnolyl)-3,4-dimethoxyphenylacetonitrile.

A solution of 1.0 g. of $\alpha$-(4-cinnolyl)-3,4-dimethoxyphenylacetonitrile in 25 ml. of 50% sulfuric acid was refluxed for eight hours and allowed to stand at room temperature for an additional three hours. The

Stirring was continued for [illegible]

time the mixture was [illegible]

Neutralization of the mixture with [illegible]

solution caused precipitation [illegible]

approximately half of the [illegible]

Successive crystallization [illegible]

constant value of the melting point [illegible]

but much practically [illegible]

of product. It appeared that the [illegible]

was unstable, slowly [illegible]

Additional [illegible]

[illegible]

The [illegible]

[illegible]

Prolonged [illegible]

caused fading of the [illegible]

Analysis. Calculated for [illegible]

H, 4.62. Found: C, 69.85, H, [illegible]

Attempted Hydrolysis of [illegible]

phenylacetonitrile.

A solution of [illegible]

[illegible]

acid was refluxed for [illegible]

at room temperature [illegible]

solution was poured on ice and neutralized with ammonium hydroxide. The product collected as a tar which was found to separate from aqueous ethanol as an oil. The oil solidified and darkened on standing. It was not identified.

Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile.

A suspension of potassium amide in liquid ammonia was prepared by the addition of 1.0 g. (0.026 gram atom) of potassium to 500 ml. of liquid ammonia to which a little ferric nitrate had been added. To the suspension was added 4.55 g. (0.026 mole) of 3,4-dimethoxyphenylacetonitrile and the mixture was stirred for fifteen minutes. The addition of 3.0 g. (0.013 mole) of 4-chloro-6,7-dimethoxycinnoline caused the reaction mixture to become a deep red. Stirring was continued for three and one-half hours while the ammonia evaporated. The addition of 250 ml. of water hydrolyzed the reaction product, and the orange solid which formed was filtered, washed with water, and dried. After crystallization from ethanol there was obtained 4.2 g. (86%) of the desired product. After recrystallization from ethanol, fine orange needles were obtained, m.p. 250.0-250.8°.

Analysis. Calculated for $C_{20}H_{19}N_3O_4$: C, 65.65, H, 5.24, N, 11.50. Found: C, 65.65, H, 5.33, N, 11.33.

solution was p[illegible]

hydroxide. The [illegible]

found to decompose [illegible]

all melting [illegible]

the [illegible]

[illegible]

[illegible]

A suspension [illegible]

was prepared by [illegible]

of potassium [illegible]

allowed to [illegible]

was added [illegible]

acetonitrile and [illegible]

mixture. The [illegible]

dissolved [illegible]

became a deep [illegible]

and one-half hours [illegible]

addition of [illegible]

product, and the [illegible]

washed with water. [illegible]

from ethanol, there [illegible]

desired product. [illegible]

This orange [illegible]

Analysis [illegible]

N, [illegible]

### Synthesis of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetamide.

A solution of 5.0 g. of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile in 50 ml. of concentrated sulfuric acid was allowed to stand at room temperature for six hours. The solution was poured on ice and neutralized with ammonium hydroxide. A white solid formed which was filtered and washed with water. The product was difficultly soluble in ethanol, but a portion of it was crystallized and obtained as fibrous needles, m.p. 250-252° (uncorr.). Combined fractions weighed 2.4 g. (46%).

Analysis. Calculated for $C_{20}H_{21}N_3O_5$: C, 62.65, H, 5.52. Found: C, 62.38, H, 5.32.

### Attempted Hydrolyses of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile.

a. Sulfuric Acid as the Hydrolytic Agent. A solution of 2.0 g. of the nitrile in 20 ml. of 65% sulfuric acid was refluxed for one and one-quarter hours. The solution was then poured on ice and neutralized with ammonium hydroxide. The flocculent precipitate which formed rapidly, darkened and became a tar. Repetition of the procedure with 48% sulfuric acid and a reflux period of one hour again resulted in formation

of tar. A third attempt with 50% sulfuric acid and only thirty-two minutes of refluxing resulted in recovery of starting product, identified by mixed melting point with an authentic sample.

b. Hydrochloric Acid as the Hydrolytic Agent. A solution of the nitrile in 75 ml. of 20% hydrochloric acid was refluxed for five and one-half hours. The yellow solid which deposited when the reaction mixture stood overnight was filtered, washed with water, and dried. After three crystallizations from ethanol-ether, there were obtained tiny yellow crystals, m.p. 105-106.5° (uncorr.). The product was soluble in 10% sodium hydroxide but insoluble in sodium bicarbonate solution. Carbon-hydrogen analysis gave values in wide disagreement with the value calculated for the desired product. The material was not further identified.

c. Potassium Hydroxide as the Hydrolytic Agent. A mixture of 1.3 g. of the nitrile, 33 ml. of ethanol, and 5.0 g. of potassium hydroxide was refluxed for one and one-fourth hours. The nitrile formed a deep red solution. The reaction mixture was poured on ice and neutralized with hydrochloric acid, and the orange solid which formed was separated by suspension in ether. The ether was evaporated, and the orange solid was crystallized from ethanol. Its identity as unreacted starting material

was established by mixed melting point with an authentic sample. When the procedure was repeated with an extended reflux period of forty-six hours, only a red gum was recovered which could not be identified.

Attempted Hydrolyses of $\alpha$-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetamide.

a. Sulfuric Acid as the Hydrolytic Agent. A solution of 0.5 g. of the amide in 2.25 ml. of 80% sulfuric acid was heated near 100° for one hour. The solution was poured on ice and neutralized with ammonium hydroxide. The red tar which formed could not be crystallized from ethanol, and it was not identified.

b. Bouveault's Method (63). A solution of 0.27 g. of the amide in 3.0 ml. of concentrated hydrochloric acid was chilled in an ice-bath, and to the resultant slurry was added a solution of 0.20 g. of sodium nitrite in 1.0 ml. of water by means of a long capillary pipet. Vigorous foaming occurred, and on warming of the mixture in a water-bath, the solid dissolved. A delivery tube was attached to the reaction vessel, and the effluent gas was led into lime water with resultant clouding, and later clearing, of the lime-water. The solution was heated to 70° for fifteen minutes, after which it was cooled by means of an ice-bath. Upon neutralization of the solution with was established by mixed melting point with an authentic sample. When the above was repeated with 1 g. of [illegible] period of [illegible], only a [illegible] was residue which could not be identified.

Attempted Synthesis of [illegible] from [illegible]-dimethyl[illegible]

a. Sulfuric Acid in the [illegible] solution of [illegible] g. of the amine in [illegible] of sulfuric acid was heated near 100° for one hour. The solution was poured on ice and neutralized with [illegible] hydroxide. The red, very soluble [illegible] could not be crystallized from ethanol, and it was not identified.

b. Bamberger's Method ([illegible]). A solution of [illegible] chloric acid was diluted in an ice bath, and to the resultant slurry was added a solution of 0.30 g. of sodium nitrite in [illegible] ml. of water by means of a long capillary pipet. Vigorous foaming occurred, and on warming of the mixture in a water bath, the solid dissolved. A delivery tube was attached to the reaction vessel, and the effluent gas was led into lime water. With periodic shaking, and [illegible] cleaning of the lime water, the solution was heated to 90° for thirteen minutes, after which it was cooled by means of an ice bath. Upon [illegible] of the solution with ammonium hydroxide, a dark solid formed which was removed by filtration, but it rapidly blackened and decomposed. No identifiable material was recovered from the filtrate.

The procedure was repeated without preliminary cooling of the hydrochloric acid solution, but again no identifiable product could be isolated.

c. The Method of Berger and Olivier (63). A solution of 0.5 g. of the amide in 100% phosphoric acid was heated on an oil bath at 140-150° for forty minutes. The solution was then poured on ice and neutralized with ammonium hydroxide, and the gray solid which precipitated was collected and crystallized from aqueous dioxane. The purified product failed to lower the melting point of a sample of starting material.

When the procedure was repeated with the exception that the phosphoric acid solution was heated for two hours, some decomposition of the starting material occurred.

### Condensation of γ-Diethylamino-α-phenylbutyronitrile with 4-Chloro-6,7-dimethoxycinnoline.

The γ-diethylamino-α-phenylbutyronitrile used in the condensation was prepared by the alkylation of phenylacetonitrile with diethylaminoethyl chloride

according to the procedure of Cutler, Surrey, and Cloke (24).

Fresh sodium amide was prepared by the reaction of 2.0 g. (0.087 gram atom) of sodium metal with liquid ammonia in the presence of ferric nitrate. The excess ammonia was allowed to evaporate, and 25 ml. of benzene was added to protect the sodium amide from the atmosphere. A solution of 9.5 g. (0.044 mole) of $\gamma$-diethylamino-$\alpha$-phenylbutyronitrile in 20 ml. of benzene was added with stirring. The dark red sodio derivative of the nitrile formed with the evolution of heat. After ten minutes, 10.0 g. (0.044 mole) of 4-chloro-6,7-dimethoxycinnoline was added with 50 ml. of benzene, and stirring was continued for two hours. The addition of water with stirring caused the dark red mixture to become orange. The crystalline solid which collected at the benzene-water interface was removed by filtration and dried. There was obtained 2.5 g. of unreacted 4-chloro-6,7-dimethoxycinnoline, identified by mixed melting point with authentic material. The benzene layer of the filtrate was separated, dried over Drierite, and evaporated under reduced pressure. A viscous red oil remained which failed to crystallize from petroleum ether. The oil remaining after petroleum ether treatment was taken up in isopropyl alcohol from which

solution a little crystalline solid deposited. This solid was also identified as 4-chloro-6,7-dimethoxycinnoline. To the remaining isopropyl alcohol solution was added a solution of hydrogen chloride in isopropyl alcohol. The addition of ether caused precipitation of a gummy yellow hydrochloride which was soluble in water or methanol. The hydrochloride failed to crystallize from alcohol-ether mixtures. A water solution of the hydrochloride was neutralized with aqueous sodium hydroxide, and the resultant mixture was extracted with ether. The washed and dried ether extract was evaporated, leaving a red oil. A benzene solution of the oil was passed through a column of activated alumina, and several poorly defined bands separated upon elution with a benzene-ether mixture. The main band extruded and eluted with ethanol in a Soxhlet apparatus. Evaporation of the solvent under reduced pressure left a red tar which was again taken up in benzene and passed through a column of activated alumina. Only one band formed on the column, and it was eluted by ethanol. Evaporation of the ethanol left a red oil which solidified to a glass on long standing. The glass redeposited as an oil from a crystallization attempt. The material was not identified.

Synthesis of 4-Methylcinnoline.

The procedure of Jacobs, Winstein, Henderson, and Spaeth (47) was followed. From 250 g. of methyl anthranilate there was obtained 45 g. of 4-methylcinnoline, melting point 76-77° C (uncorrected).

Synthesis of 4-Styrylcinnoline.

The procedure of Jacobs, et al. (47), for the preparation of 4-styrylcinnoline was followed, however on a smaller scale. There was obtained from 2.0 g. (0.014 mole) of 4-methylcinnoline, 0.9 g. (0.007 mole) of anhydrous zinc chloride, and 15 ml. of benzaldehyde 2.0 g. (62%) of green-gold platelets which melted at 121.8-122.6° C after crystallization from aqueous methanol.

Analysis. Calculated for $C_{16}H_{12}N_2$: C, 82.61, H, 5.21, N, 12.06. Found: C, 83.45, H, 5.55, N, 12.11.

Synthesis of 1-(4-cinnolyl)-2-(4-methoxyphenyl)-ethene.

To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline in 40 ml. of p-anisaldehyde was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was heated at 150° C for four and one-half hours. The reaction mixture was cooled, treated with 10 ml. of benzene and 10 ml. of 2N hydrochloric acid, and heated on a water bath for one hour. The dark red hydrochloride

was filtered, washed with water, and dried. The free base was regenerated by shaking the hydrochloride with a dilute aqueous sodium hydroxide solution. The solid base was filtered and recrystallized three times from aqueous methanol. There was obtained 1.5 g. (42%) of golden plates, melting point 112.2-112.6° C. The compound was crystallized once more for analysis.

Analysis. Calculated for $C_{17}H_{14}N_2O$: C, 77.84, H, 5.38, N, 10.68. Found: C, 77.30, H, 5.44, N, 10.80.

Synthesis of 1-(4-cinnolyl)-2-(2-thenyl)-ethene.

To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline in 10 ml. of 2-thiophenealdehyde was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was heated at 150° C for one and three-fourths hours. The reaction mixture was cooled, treated with 10 ml. of benzene and 10 ml. of 2N hydrochloric acid, and heated on a water bath for one hour. The red hydrochloride did not solidify, however, until after standing two days at room temperature. The filtered and washed hydrochloride was dried before regeneration of the free base. On shaking the hydrochloride with dilute aqueous sodium hydroxide solution a solid was obtained which was not completely soluble in methanol. The insoluble fraction was not identified. The methanol solution, was filtered, and [illegible]

base was regenerated [illegible]

base was filtered and [illegible]

aqueous solution. [illegible]

golden plates, melting point [illegible]

compound was crystallized [illegible]

Analysis. [illegible]

H, 5.50; N, 10.[illegible]. Found: C, [illegible]; H, [illegible]; N, [illegible]

Treatment of [illegible]

10.4 [illegible]

[illegible] in 10 ml. [illegible]

8.2 g. (0.027 mole) of [illegible]

mixture was heated [illegible]

hours. The reaction mixture was [illegible]

10 ml. of benzene and [illegible]

and heated on a water bath for one hour. [illegible]

chloride [illegible]

two days at room temperature [illegible]

hydrochloride was [illegible]

base. On heating the [illegible]

sodium hydroxide solution [illegible]

not completely soluble in [illegible]

Treating [illegible]

after partial evaporation, deposited large orange rods. The filtrate of this fraction was concentrated further and diluted with water yielding an amorphous powder which could not be identified. The orange rods were recrystallized from aqueous methanol as bright yellow needles. There was obtained 0.41 g. (12%). Another crystallization from aqueous methanol gave fine needles, melting point 113.0-113.6° C.

Analysis. Calculated for $C_{14}H_{10}N_2S$: C, 70.55, H, 4.23, N, 11.75. Found: C, 70.44, H, 4.40, N, 11.52.

### *Synthesis of 1-(4-cinnolyl)-2- 4-(2-phenyl)-2,1,3-triazolyl -ethene.*

To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline and 4.8 g. (0.028 mole) of 2-phenyl-2,1,3-triazole-4-carboxaldehyde in 50 ml. of dry xylene was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was refluxed for one and one-fourth hours. Some dark tar formed in the bottom of the flask and the supernatant liquid became cloudy. On cooling, the supernatant liquid cleared, and it was decanted and evaporated in a stream of air. The resulting yellow solid appeared to consist of two components when it was crystallized from methanol. The less soluble fraction crystallized as yellow rods, and the residue, which appeared to be

unreacted aldehyde, could be recovered only after evaporation of the filtrate to dryness. After two crystallizations from methanol, 0.32 g. (8%) of product was obtained as bright yellow needles, melting point 205.2-205.6° C.

Analysis. Calculated for $C_{18}H_{13}N_5$: C, 72.22, H, 4.38, N, 23.40. Found: C, 72.77, H, 4.59, N, 23.60.

Synthesis of 1-(4-cinnolyl)-2-(3,4-dimethoxyphenyl)-ethene.

To a solution of 2.0 g. (0.014 mole) of 4-methyl cinnoline and 2.3 g. (0.014 mole) of veratraldehyde in 40 ml. of dry xylene was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was refluxed for four and one-half hours. During the period of heating a solid red lump formed in the bottom of the reaction flask. The supernatant xylene solution was decanted and evaporated. The red lump yielded some 4-methylcinnoline after purification. The oily residue from the evaporation of the xylene solution failed to solidify on standing, so it was distilled at about 17-18 mm. The distillate remained red and viscous at first, but it solidified after standing six months. After one year, the solid was extracted with petroleum ether. The extract yielded some impure 4-methylcinnoline. The

solid residue from the petroleum ether extraction was crystallized once from ethanol and twice more from aqueous ethanol. There was obtained 0.4 g. (10%) of pale yellow needles, melting point 193-194° C (uncorrected). The compound is soluble in 5% hydrochloric acid and insoluble in 10% sodium hydroxide.

Analysis. Calculated for $C_{18}H_{16}N_2O_2$: C, 73.95, H, 5.52. Found: C, 74.15, H, 5.75.

### Attempted Condensations with 4-Methylcinnoline and Carbonyl Compounds.

a. Attempts with Anhydrous Zinc Chloride as Catalyst. To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline and 2.86 g. (0.014 mole) of 9-anthraldehyde in 50 ml. of dry xylene was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was refluxed for fifty hours. A yellow solid was obtained by evaporation of the supernatant xylene. This was crystallized from methanol. After a crop of yellow needles identified as 9-anthraldehyde (by mixed melting point) was removed, some yellow rhombs were obtained. After two crystallizations from methanol, there was obtained 1.6 g. of product, melting point 143.4-143.8° C. The material was found not to contain nitrogen. It was insoluble in 10% sodium hydroxide, and the analysis is

not consistent with any compound derived from 9-anthraldehyde.

Analysis. Found: C, 81.48, 81.09, H, 6.71, 6.61,

Several other aldehydes failed to give identifiable condensation products with 4-methylcinnoline. Procedures used involved either an excess of the aldehyde or dry xylene as the solvent. Apparently both furfural and salicylaldehyde condensed with 4-methylcinnoline, but neither product could be satisfactorily isolated or purified. 2,4-Dinitrobenzaldehyde was recovered unchanged. With p-nitrobenzaldehyde a friable black resin was formed. Both phenylacetaldehyde and acetophenone also apparently failed to react.

b. Attempts to Force Condensation by Azeotropic Removal of Water. A solution of 2.0 g. (0.014 mole) of 4-methylcinnoline and 5 ml. (0.045 mole) of p-anisaldehyde in 50 ml. of dry xylene was refluxed for eighteen hours in a flask fitted with a Dean and Stark azeotropic water-removal head. Water did not separate by azeotropic distillation with xylene, and the known condensation product could not be isolated from the reaction mixture. 2,4-Dinitrobenzaldehyde behaved similarly.

Attempt Using Pyridine as a Solvent and Piperidine as a Catalyst. To a solution of 2.0 g. (0.014 mole) of

4-methylcinnoline and 2 ml. (0.021 mole) of benzaldehyde in 35 ml. of dry pyridine was added three drops of piperidine. The reaction flask was heated on a water bath for nineteen hours at 90-94° C. The pyridine was evaporated, but no 4-styrylcinnoline or other condensation product was identified.

Attempted Synthesis of 4-Cinnolylcarboxaldehyde by the Action of Selenium Dioxide on 4-Methylcinnoline.

a. Ethanol and 1,4-Dioxane as Solvent. To 3.0 g. (0.021 mole) of 4-methylcinnoline dissolved in 50 ml. of 1,4-dioxane and 30 ml. of ethanol was added with stirring 2.3 g. (0.021 mole) of sublimed selenium dioxide. The reaction mixture was cooled in an ice-bath. After the reaction mixture had been stirred for three and one-half hours, the selenium dioxide disappeared and the mixture turned dark green. Stirring was continued for several hours, and the reaction mixture was allowed to stand overnight at room temperature. Only green or black tar could be obtained in attempts to isolate a compound.

b. Methanol and Water as Solvent. The addition of 2.3 g. (0.021 mole) of selenium dioxide to 3.0 g. (0.021 mole) of 4-methylcinnoline dissolved in 150 ml. of methanol and 10 ml. of water caused a brief rise in temperature which subsided. The reaction mixture rapidly turned red. Only intractable solids were recovered.

c. Water as Solvent for the Ethiodide of 4-Methylcinnoline. About 100 mg. of 4-methylcinnoline ethiodide was prepared by a previously known method (3). A water solution of the compound was chilled in an ice-bath, and approximately 100 mg. of selenium dioxide was added. The mixture rapidly turned red-gray. Only gray selenium and dark tar remained.

### Attempted Synthesis of 4-Bromomethylcinnoline.

To a solution of 1.0 g. (0.007 mole) of 4-methylcinnoline in 60 ml. of carbon tetrachloride was added 1.23 g. (0.007 mole) of N-bromosuccinimide. The mixture was refluxed for fifty minutes. Shortly after refluxing began, the yellow solution turned green and a dark solid appeared. The only solids recovered from the reaction were green to blue-black. Attempts to purify these failed. Repetition of the reaction with a shorter reaction time failed to give any cleaner products.

The admixture of dry 4-methylcinnoline and N-bromosuccinimide followed by fusion of the mixture resulted in a vigorous reaction producing a brittle black resin.

### Reaction of 4-Methylcinnoline with Iodine and Bromine.

The addition of iodine or bromine to solutions of 4-methylcinnoline in carbon tetrachloride or toluene caused the formation of dark tars of a similar appearance

to those produced in the addition of N-bromosuccinimide to 4-methylcinnoline.

### Attempted Condensation of 4-Methylcinnoline with Benzyl Chloride.

A solution of sodium methoxide in methanol was prepared by the addition of 0.6 g. (0.026 gram atom) of sodium metal to 30 ml. of Mallinckrodt Methyl Alcohol (Absolute). When the solution had been cooled in an ice-bath, a solution of 3.7 g. (0.026 mole) of 4-methylcinnoline in 80 ml. of methanol was added slowly. To the clear red solution which resulted was added dropwise 3 ml. (0.026 mole) of benzyl chloride. The solution was heated cautiously to 52° C, at which temperature it began to darken. On hydrolysis of the solution a finely divided yellow solid precipitated. The solid coagulated and decomposed into a dark oil on standing. The results were similar when the experiment was repeated without heating the reaction mixture.

## VI. SUMMARY

Some improvements have been made in the synthetic steps leading to 4-chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline; in particular, the reduction of 2-nitro-4,5-dimethoxyacetophenone to the corresponding amine has been accomplished in good yield for the first time.

The condensation reaction between substituted acetonitriles and both 4-chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline in the presence of sodium amide has been shown to be general, being limited only by the ability of the nitrile to form a sodium salt. A procedure involving potassium amide and liquid ammonia as the solvent was used successfully to prepare potassium salts of 3,4-dimethoxyphenylacetonitrile and p-aminophenylacetonitrile, neither of which formed a sodium salt in the presence of sodium amide in benzene.

$\alpha$-(6,7-Dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile was hydrolyzed to the corresponding amide, but various attempts to hydrolyze the same nitrile or the amide to the corresponding benzyl cinnoline (the cinnoline analogue of papaverine) failed.

Experimental evidence seemed to support the theoretical expectation that 4-chlorocinnoline should be

more active toward nucleophilic attack than 4-chloro-6,7-dimethoxycinnoline.

Four aromatic aldehydes were condensed with 4-methylcinnoline in the presence of zinc chloride to give stable products. Attempts to condense six other aldehydes and acetophenone with 4-methylcinnoline failed to give identifiable products. Condensations between 4-methylcinnoline and benzaldehyde or p-anisaldehyde failed when piperidine was used as the catalyst or when azeotropic removal of water was attempted in the absence of any catalyst.

Wohl-Ziegler bromination of 4-methylcinnoline failed to give an identifiable product, as did also selenium dioxide oxidation and alkylation with benzyl chloride. The course of these reactions is not known although in no case was 4-methylcinnoline recovered.

more active toward [illegible]

[illegible]

Four substances [illegible]

Phenylmercaptide in the presence [illegible]

nickel sulphide, [illegible]

and some decrease of [illegible]

[illegible]

[illegible]

Piperidine was used as the [illegible]

removal of water was necessary [illegible]

catalyst.

[illegible]

failed to give an [illegible]

Selenium dioxide [illegible]

[illegible]

although [illegible]

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