THE CHEMISTRY OF N-ACYLDIHYDROQUINALDONITRILES AND N-ACYLDIHYDROISOQUINALDONITRILES (REISSERT COMPOUNDS)

by

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B. S., Ottawa University, 1951

Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Advisory Committee:

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January, 1955

ACKNOWLEDGEMENT

To Dr. William E. McEwen for his encouragement, his numerous and helpful suggestions, his personal advice and friendship, his efforts in obtaining financial assistance and his unfailing optimism in times of difficulties with this research problem.

The author wishes to thank the Eastman Kodak Company for their unrestricted financial aid in the form of a fellowship. Also, the author is grateful to the State of Kansas for appointments in teaching and research during his graduate study.

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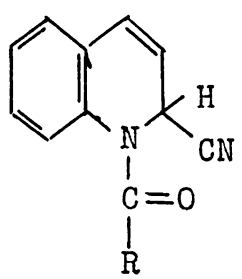
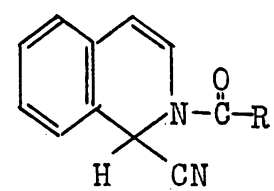
I. Introduction

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II), substances frequently designated as "Reissert Compounds," are readily prepared and serve as valuable intermediates in the synthesis of certain classes of both heterocyclic and non-heterocyclic compounds. This review will be devoted mainly to a discussion of the preparation of Reissert compounds and to a complete survey of their reactions, particularly acid-catalyzed hydrolysis, rearrangement and alkylation reactions. Reaction mechanisms will be discussed whenever there is sufficient information available to justify the proposal of a precise reaction path. The methods of preparation and reactions of other compounds structurally related to I and II will also be covered in abbreviated form.



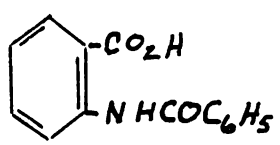
I



II

In 1905, after repeated failures in attempts to introduce the benzoyl group into the benzothiazole ring, Arnold Reissert began a systematic study of the benzoylation of cyclic tertiary amines. Upon treatment of a mixture of quinoline and benzoyl chloride with an

aqueous solution of sodium hydroxide, the reaction conditions being patterned after the Schotten-Baumann procedure, there was obtained a crystalline product, $C_{16}H_{13}NO_2$ (75). The compound was cleaved to quinoline and benzoic acid on treatment with mineral acid or glacial acetic acid. Furthermore, it was converted to N-benzoylanthranilic acid (III) by oxidation with potassium permanganate. On the basis of these facts, and on the basis of analogy with the structures of the pseudo bases formed by the action of alkali metal hydroxides on 1-alkylquinolinium halides, structure IV was originally assigned to the compound, $C_{16}H_{13}NO_2$ (75). Because further investigation showed that the compound gave characteristic aldehyde tests, however, it was subsequently concluded (76) that the structure corresponded to o-benzoylaminocinnamaldehyde (V). Actually, it appears likely that IV and V are tautomeric substances (34). No analogous compound was obtained when isoquinoline was subjected to Schotten-Baumann reaction conditions with benzoyl chloride (76).



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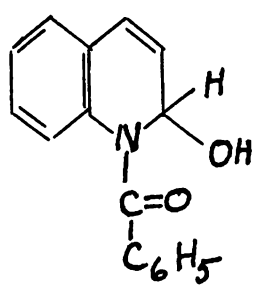
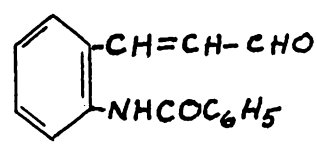


IV



V

Reaction of benzoyl chloride with quinoline in aqueous potassium cyanide solution was tried next, and there was obtained a crystalline compound, $C_{17}H_{12}N_2O$. This compound was found to undergo a remarkable acid-catalyzed cleavage to benzaldehyde, quinaldic acid and, in much smaller amounts, derivatives of the latter. On the basis of these facts it was proposed (75) that the compound possessed the structure of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5).

Other nitrogen heterocyclic compounds, such as isoquinoline (76) and phenanthridine (95) have since been shown to give products analogous to I on reaction with an acid chloride and potassium cyanide or hydrogen cyanide. Furthermore, the preparation of these compounds and their subsequent acid-catalyzed hydrolysis to aldehydes has become a general method for the preparation of aldehydes from acid chlorides.

II. Preparation

Because aldehydes are formed in high yields by acid-catalyzed hydrolysis of Reissert compounds, considerable effort has been expended in the preparation of such compounds from a variety of acid chlorides. Moreover, since a number of functional groups can be introduced into the heterocyclic ring <u>via</u> these compounds, the preparative scope has been extended to include several substituted quinolines and isoquinolines.

A. Preparation in Aqueous Medium

As would be expected, the preparation of Reissert compounds in an aqueous medium has been limited to the use of relatively inactive acid

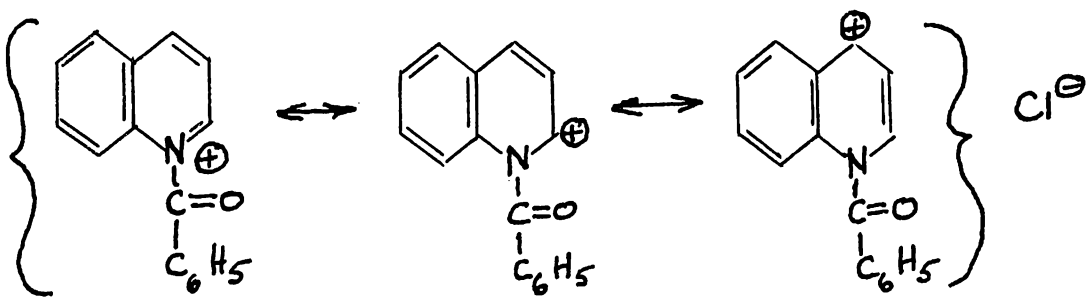
chlorides, specifically the less reactive aroyl chlorides. Aliphatic acid clorides and reactive aroyl chlorides, such as the nitrobenzoyl chlorides, react much too fast with water to permit use of an aqueous medium.

The original preparation of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) was effected in almost quantitative yield by gradual addition, with vigorous shaking, of two moles of benzoyl chloride to a suspension of one mole of quinoline in an aqueous solution of potassium cyanide (75). Under similar conditions, 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) can be obtained from isoquinoline, but in somewhat poorer yield (74, 76, 80). Anisoyl, veratroyl, cinnamoyl, trimethylgalloyl, p-chlorobenzoyl and p-toluyl chlorides also react with quinoline and potassium cyanide under these conditions to give compounds of the general structure I in yields less than 50% of the theoretical (42, 60, 61, 87). Application of efficient mechanical stirring increases ease of operation but does not necessarily increase yields of products (81). An improvement in the yield of 2-benzoyl-1,2-dihydroisoquinaldonitrile has been achieved by a slight modification of reaction conditions (74).

The purity of the reactants has been found to be of importance in determining the yield and purity of the product. It has been emphasized (51) that an optimum yield of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) may be obtained only with pure quinoline. The yield of the product does not seem to be decreased significantly,

however, if technical benzoyl chloride is employed (37). Also, for a reason which is not clear, the use of potassium cyanide appears to give better results than the use of sodium cyanide; in some instances use of the latter salt gives a product that is difficult to purify.

A reasonable mechanism for the formation of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) in aqueous medium involves the formation of benzoylquinolinium chloride (VI) as an intermediate. Addition of the cyanide ion to the 2-position of the ring completes the preparation of I (R = C_6H_5). There is independent evidence that benzoyl chloride adds to quinoline to give VI (24, 99).



VI

B. Preparation in Non-Aqueous Medium

In order to prevent hydrolysis of reactive acid chlorides in attempted preparations of Reissert compounds, the use of several non-aqueous solvents has been explored. No 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) was obtained from benzoyl chloride, quinoline

and potassium cyanide in acetonitrile, benzonitrile, ether, dioxane, chloroform, acetone or excess quinoline (97). Reaction of benzoyl chloride, quinoline and hydrogen cyanide in anhydrous ether (25) gave a small yield of I (R = C_6H_5), but no analogous reaction was observed when benzoyl chloride was replaced with acetyl chloride (97).

By use of liquid sulfur dioxide as the solvent, both 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) and 1-cinnamoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5-CH=CH-) were obtained in 80% and 76% yields, respectively, from quinoline, potassium cyanide and the appropriate acid chloride. However, no 1-acetyl-1,2-dihydroquinaldonitrile (I, R = CH_3) was obtained by the use of acetyl chloride in this solvent (97).

The most general method for the preparation of Reissert compounds which has been developed involves the use of one mole of acid chloride, one mole of anhydrous hydrogen cyanide and two moles of quinoline in anhydrous benzene as solvent (43). This method has been used successfully for the preparation of many compounds of the general structure I from both aliphatic and aromatic acid chlorides. Products and yields are listed in Table 1 (p.).

C. Effect of Structure on Reactivity of Heterocyclic Amine

Although quinoline, isoquinoline and certain substituted derivatives of these bases readily form Reissert compounds, pyridine and acridine fail to yield analogous products (75, 76). The acridine case

will be discussed in a later section, but the reasons for the failure of pyridine to undergo reaction can be considered here.

There is abundant evidence that pyridine reacts readily with acid chlorides to form acylpyridinium chlorides (for leading references, see footnote 2, reference 90). Therefore the failure of pyridine to form compounds analogous to I must be due to the fact that practically all of the resonance energy of the benzoylpyridinium ion would be lost upon addition of the cyanide ion to the α-position of the ring. By way of contrast, less than half the resonance energies of the acylquinolinium and acylisoquinolinium cations are lost upon addition of the cyanide ion to the respective α-positions, and there is more than adequate compensation for the loss in resonance energy by the formation of a new covalent bond. A similar explanation has been proposed for the failure of methylpyridinium hydroxides to form N-methyldihydropyridyl ethers, in contrast to the behavior of the quinoline analogs (3). The argument as presented cannot be the complete picture, however, since some substituted N-acyldihydropyridines have been prepared under conditions analogous to those employed in the preparation of Reissert compounds. Examples will be given in a later section.

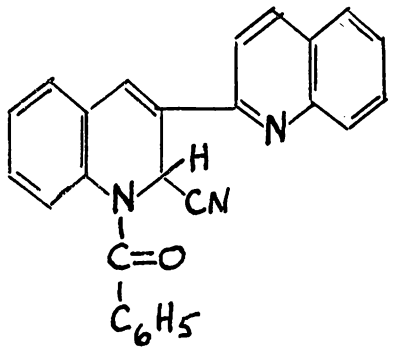
It is also significant that treatment of an acid chloride with hydrogen cyanide in the presence of anhydrous pyridine and an inert solvent affords acylcyanides (15). In the preparation of compounds of structure I from quinoline under similar conditions, acylcyanides are also formed, but only as minor products (43). Thus resonance

energy considerations appear to tip the balance of the two possible reactions in favor of acylcyanide formation, rather than adduct formation, in the pyridine case, but not in the quinoline case.

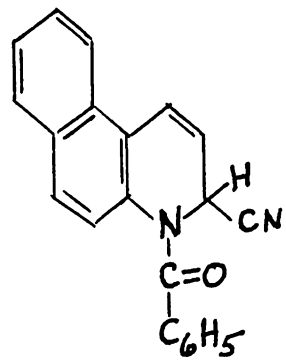
1. Quinolines

The ability of quinoline to react with an acid chloride and a source of cyanide ion to form I is greatly affected by substituents present on the ring. 6-Methoxyquinoline (37), 6-chloroquinoline (35), 6-methylquinoline (35) and 7-methoxyquinoline (86) readily undergo reaction with benzoyl chloride and aqueous potassium cyanide to give the respective substituted derivatives of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5), but when the substituent is the 5-nitro, 5-amino, 5-acetamido, 6-dimethylamino, 7-nitro, 8-hydroxy, 8-methoxy, 8-benzoyloxy, 8-acetoxy or 2-methyl group, the reaction fails (37). Reaction of benzoyl chloride and aqueous potassium cyanide with 2,3'-biquinoline gives 1-benzoyl-3-(2-quinolyl)-1,2-dihydroquinaldonitrile (VII) (48), while reaction with 6,6'-biquinoline gives 1,1'-dibenzoyl-1,1',2,2'-tetrahydro-6,6'-biquinaldonitrile (VIII) (91). 5,6-Benzoquinoline has been reported to give IX in good yield, whereas 7,8-benzoquinoline failed to undergo reaction, but inasmuch as this information was contained only in a footnote of reference 22, reaction conditions were not specified. In those cases where substituted quinolines failed to give derivatives of I, considerable amounts of phenylglyoxylonitrile dimer (X) (59, 93) were frequently formed (37). Clearly, the ease of formation of Reissert compounds is dependent upon steric as well as electronic factors, since the presence of

substituents in the 2- and 8-positions of quinoline inhibit the formation of compounds of the general structure I.



VII



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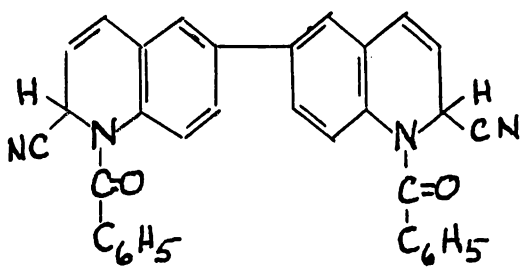

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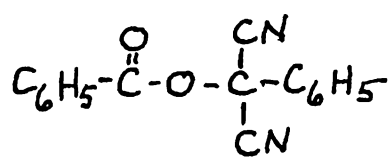


X

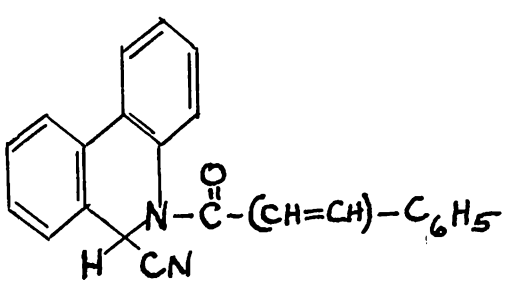
An unusual side reaction has been observed on treatment of 6-methoxyquinoline with benzoyl chloride and aqueous potassium cyanide solution. A significant amount of 6-methoxyquinaldonitrile was obtained in addition to 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (37).

2. Isoquinoline

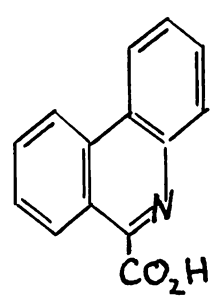
Little is known about the effect of substituents on the reactivity of the isoquinoline ring in the formation of substituted 2-acyl-1,2-dihydroisoquinaldonitriles (II). The formation of Reissert compounds from 6,7-dimethoxyisoquinoline with benzoyl chloride and 2,3-dimethoxybenzoyl chloride has been reported (45). The interest in the preparation of the 6,7-dimethoxy derivatives of II is due mainly to their possible use in the synthesis of certain isoquinoline alkaloids. 3-Methylisoquinoline also undergoes facile reaction with benzoyl chloride and aqueous potassium cyanide solution to give 2-benzoyl-3-methyl-1,2-dihydroisoquinaldonitrile (35).

3. Phenanthridine

A number of 5-acyl-5,6-dihydro-6-phenanthridinecarbonitriles of general structure XI have been prepared by reaction of phenanthridine with hydrogen cyanide and acid chlorides in anhydrous benzene (95). Structures, yields and data on the acid-catalyzed hydrolysis of these compounds to aldehydes and phenanthridine-6-carboxylic acid (XII) are given in Table 1 (p.).



XI



XII

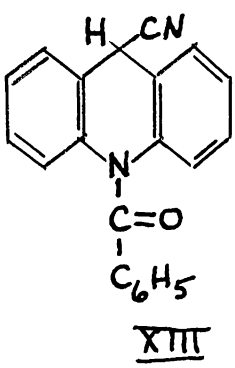
4. Acridine

Inasmuch as hydrogen, hydrogen cyanide, dienophiles and organometallic compounds readily add across the 9,10-positions of acridine (4), it might be anticipated that acridine would form a type of Reissert compound also. However, Reissert reported that acridine fails to yield such a derivative (76).

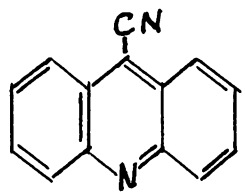
More recently, the preparation of 10-benzoyl-9,10-dihydro-9-acridinecarbonitrile (XIII) has again been attempted (4). After reaction of acridine, benzoyl chloride and aqueous potassium cyanide, 9-acridinecarbonitrile (XIV) was the only heterocyclic product isolated. It was proposed that XIV arose from initially formed XIII by loss of benzaldehyde. Although no benzaldehyde was isolated from the reaction mixture, there was obtained some viscous red oil which gave a qualitative test for mandelonitrile (XV). Therefore it was suggested that the benzaldehyde eliminated from XIII reacts with excess hydrogen cyanide to give XV. The spontaneous cleavage of XIII to benzaldehyde and XIV was attributed to the exceptional mobility of the hydrogen, activated by the cyano group and aromatic rings, in the 9-position of XIII. Since the reaction of acridine, benzoyl chloride and hydrogen cyanide in anhydrous benzene also resulted in formation of 9-acridinecarbonitrile (XIV), it was suggested (4) that the formation of aldehydes from Reissert compounds results from an intramolecular rearrangement rather than a hydrolytic cleavage.

In view of subsequent work (29), the argument that 9-acridinecarbonitrile (XIV) arises from a rearrangement of initially formed

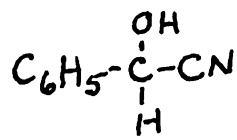
10-benzoyl-9,10-dihydro-9-acridinecarbonitrile (XIII) seems to have little validity. It has been found that benzoyl chloride is not needed in the preparation of XIV, as a reaction of acridine with potassium cyanide in aqueous ethanol gives XIV in 60% yield. There is good reason to believe that XIII is incapable of existence, since attempted benzoylation of 9,10-dihydro-9-acridinecarbonitrile (XVI), a known compound (56), failed to give XIII (19).



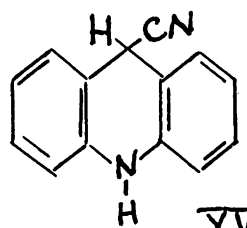
XIII



XIV



XV



XVI

D. Reactivity of Acid Chloride

From the point of view of synthetic organic chemistry, the preparation of aldehydes from acid chlorides is usually effected by the Rosenmund reduction. In those molecules in which another reducible functional group besides the acid chloride group is present, however, the Reissert method for the conversion of the acid chloride to the aldehyde may be superior to the Rosenmund method. As an example, o-nitrobenzoyl chloride cannot be converted to o-nitrobenzaldehyde by

the Rosenmund method, but the Reissert method affords the aldehyde in 60% yield. Therefore it is of importance to consider the effects of variations in the structures of acid chlorides on the preparation of Reissert compounds.

An o-substituted benzoyl chloride, regardless of the electronic character of the substituent, readily forms a 1-acyl-1,2-dihydroquinaldonitrile (I) in good yield. For a reason which is not clear, however, m-nitrobenzoyl chloride and m-chlorobenzoyl chloride give very poor yields of I (43). Also, it has been found that p-nitrobenzoyl, 3,5-dinitrobenzoyl and 2,4-dinitrobenzoyl chlorides fail to give any of I (13).

1-Acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) have been prepared in varying yields from a number of purely aliphatic acid chlorides. α,β-Unsaturated acid chlorides, such as cinnamoyl chloride, have also been used successfully. More spectacularly, a series of acid chlorides of general structure C_6H_5-$(CH{=}CH)_n$-COCl, which are very sensitive to many reagents, have been converted to Reissert compounds of the phenanthridine series (95).

III. Chemical Properties and Reactions

Having a variety of functional groups, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) may undergo many diverse reactions. For example, there are three sites at which nucleophilic agents may make an initial attack on either I or II: (a) the carbonyl carbon atom of the amide group;

(b) the carbon atom of the cyano group; and (c) the acid hydrogen α to the cyano group. Also, reduction may occur in several stages, and by suitable arrangement of conditions a variety of reduction products may be obtained. Finally, there are reactions which appear to involve two or more functional groups at the same time and therefore represent more or less unique chemical properties of Reissert compounds.

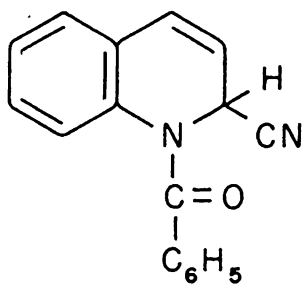
A. Acid-Catalyzed Hydrolysis

The reaction of Reissert compounds that has probably attracted the greatest attention is the acid-catalyzed hydrolysis to aldehydes plus the corresponding heterocyclic carboxylic acids and their derivatives. In general, this reaction proceeds in good yield and under mild conditions.

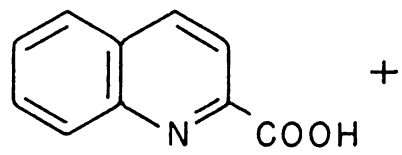
1. Scope

The original acid-catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) resulted in quantitative formation of benzaldehyde. In addition, a good yield of quinaldic acid (XVIII) and smaller amounts of quinaldamide (XIX) and benzoin quinaldate (XX) were obtained (75). Analogous products have been obtained by the acid-catalyzed hydrolysis of other 1-acyl-1,2-dihydroquinaldonitriles (I).

Similarly, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) was found to give, under the same conditions, benzaldehyde, isoquinaldic acid (XXII), isoquinaldamide (XXIII) and smaller amounts of benzoin



XVII



XVIII

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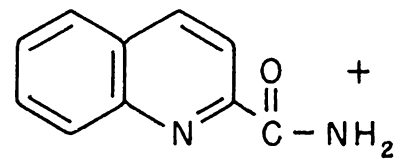

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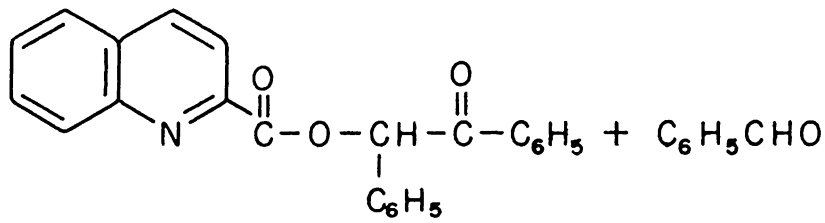
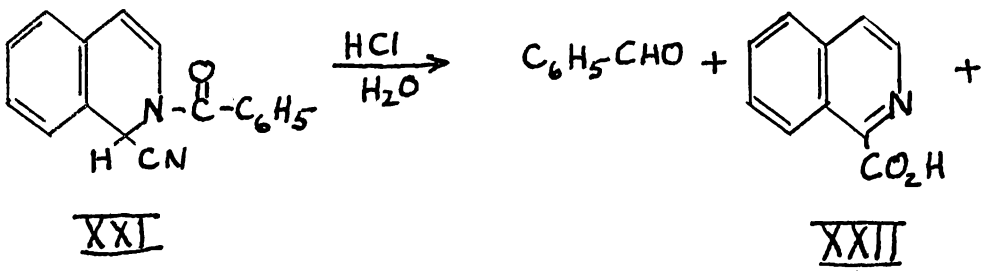
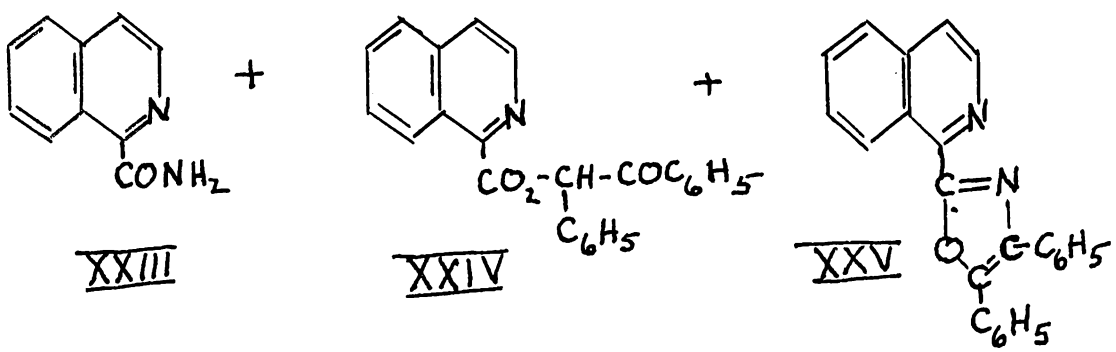


XX

isoquinaldate (XXIV) and a yellow compound originally reported (76) to have the molecular formula $C_{34}H_{23}N_3O$, but which has since been demonstrated (62) to be 2-(1-isoquinolyl)-4,5-diphenyloxazole, $C_{24}H_{16}N_2O$ (XXV).



XXI XXII

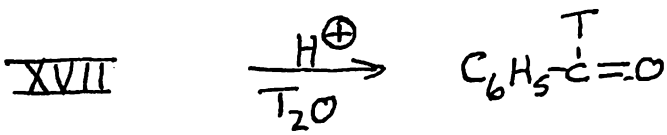


XXIII XXIV XXV

Only phenanthridine-6-carboxylic acid (XII) and the appropriate aldehyde, $C_6H_5-(CH=CH)_n-CHO$, were obtained upon acid-catalyzed hydrolysis of each of the compounds of general structure XI (95).

A somewhat novel use of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) has been in the preparation of tritium-labeled benzaldehyde. Benzaldehyde-$\underline{t}_1$ (XXVI) was obtained in addition to normal benzaldehyde upon hydrolysis of XVII in mineral acid solution containing tritium

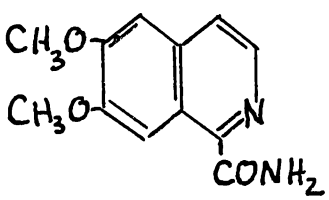
oxide (88). A small isotope effect was observed in the hydrolysis.



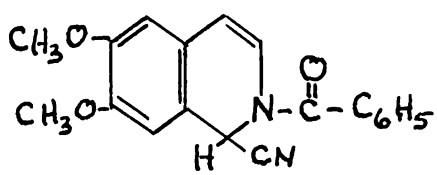
XVII

XXVI

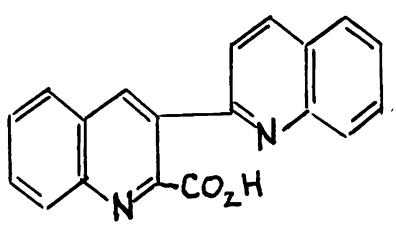
In some cases, the most valuable aspect of the acid-catalyzed hydrolysis of Reissert compounds is in the introduction of the carboxyl group into a heterocyclic nucleus. 2-Benzoyl-1,2-dihydroisoquinaldonitrile (XXI), for example, was found to be a convenient intermediate for the preparation of isoquinaldic acid (XXII) (74, 85). Also, 6,7-dimethoxyisoquinaldamide (XXVII) was synthesized from 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XXVIII) (45), and 3-(2-quinolyl)-quinaldic acid (XXIX) from 1-benzoyl-3-(2-quinolyl)-1,2-dihydroquinaldonitrile (VII) (48).



XXVII

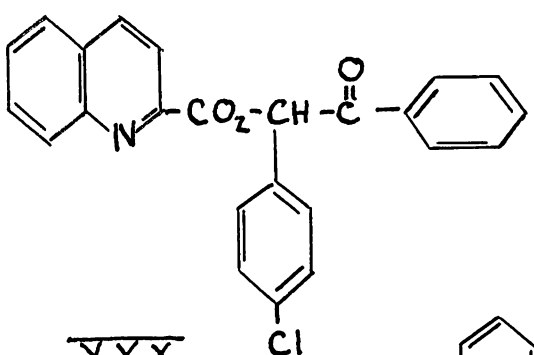


XXVIII

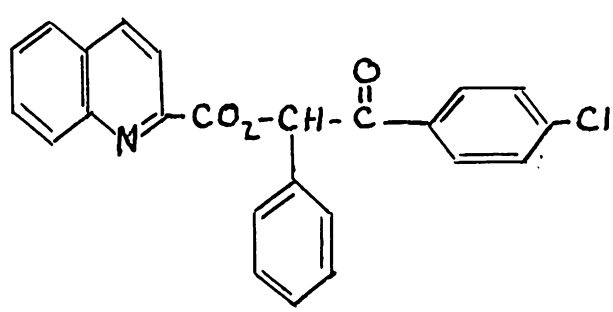


XXIX

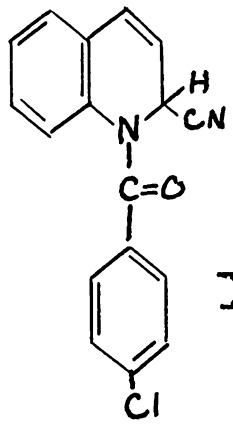
Benzoin quinaldate (XX) and benzoin isoquinaldate (XXIV) are formed in only small amounts upon acid-catalyzed hydrolysis of XVII and XXI, respectively, in the usual manner. It was found, however, that the yields are markedly increased when the hydrolysis is carried out in the presence of an excess of benzaldehyde. Furthermore, substituted benzoin esters can be prepared by addition of a substituted benzaldehyde to the hydrolysis mixture. For example, p'-chlorobenzoin quinaldate (XXX) was obtained in 12% yield upon treatment of a mixture of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) and p-chlorobenzaldehyde with concentrated hydrochloric acid. The isomeric ester, p-chlorobenzoin quinaldate (XXXI), was obtained in 28% yield upon acid-catalyzed hydrolysis of 1-(p-chlorobenzoyl)-1,2-dihydroquinaldonitrile (XXXII) in the presence of an excess of benzaldehyde (61).



XXX

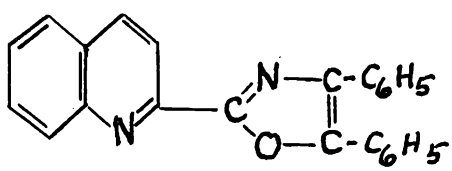


XXXI



XXXII

By passage of anhydrous hydrogen chloride into a suspension of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) in pure benzaldehyde there was obtained a mixture of benzoin quinaldate (XX) and 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIII). Although the yield of XX was undoubtedly greater than that obtained by use of aqueous hydrochloric acid, it was difficult to effect an efficient separation of XX and XXXIII (17).



XXXIII

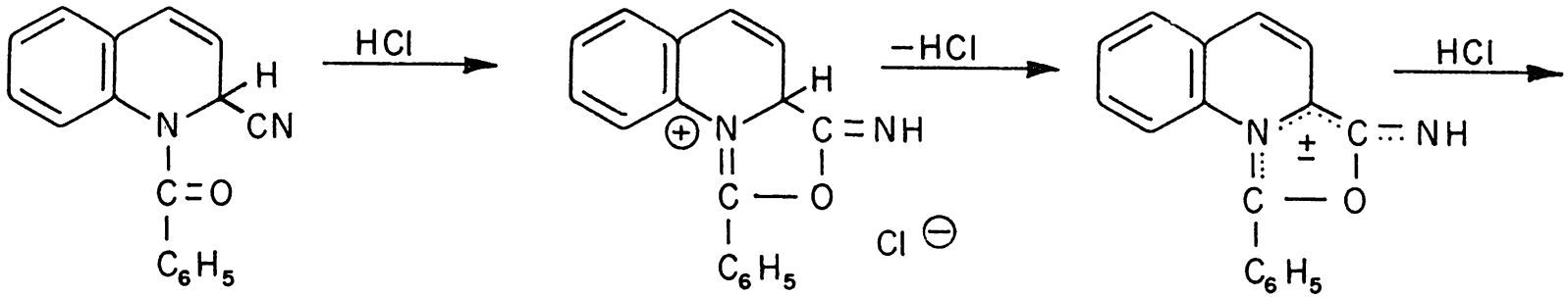
2. Mechanism Studies

Obviously, the mechanism of the acid-catalyzed hydrolysis of a Reissert compound in which an aldehyde is formed is different from the mechanism of ordinary acid-catalyzed hydrolysis of an amide (or nitrile) in which a carboxylic acid is formed. The mechanism of the

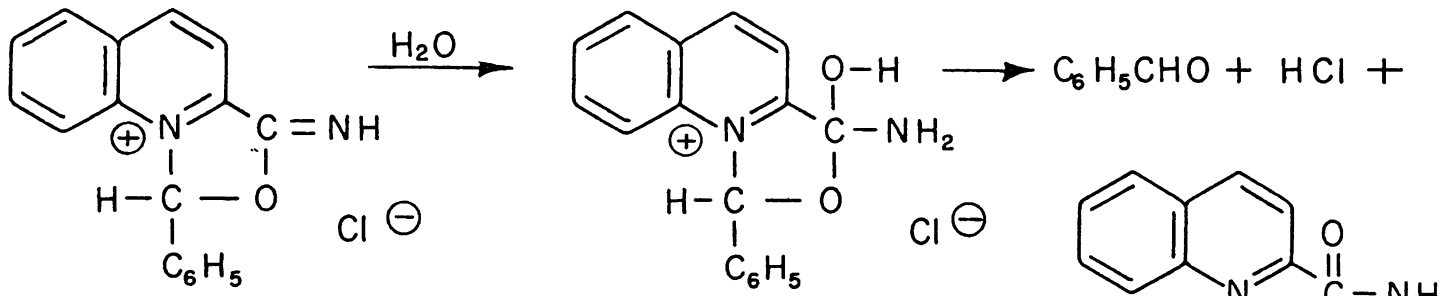
Reissert reaction is clearly more complex than that for a simple hydrolytic process.

A mechanism has recently been proposed (18) which accounts for all of the products obtained by the acid-catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII). It is assumed that the first step in the reaction is formation of the cyclic intermediate XXXIV by action of hydrochloric acid upon XVII. Then isomerization of XXXIV gives XXXVI, probably via the relatively stable meso-ionic intermediate, XXXV. Addition of water to XXXVI gives XXXVII, which then collapses to form benzaldehyde and quinaldamide (XIX). Subsequent hydrolysis of quinaldamide yields quinaldic acid (XVIII). The mechanism also accommodates the formation of benzoin quinaldate (XX), but discussion of this point will be presented later.

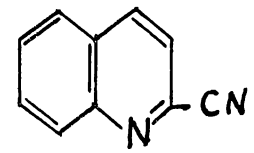
Considerable evidence has been gathered in support of this mechanism. For example, it has been demonstrated (18) that quinaldonitrile (XXXVIII) is not an intermediate in the formation of quinaldic acid (XVIII), quinaldamide (XIX) and benzoin quinaldate (XX) from 1-benzoyl-1,2-dihydroquinaldonitrile (XVII). This fact voids previously proposed mechanism which require the formation of XXXVIII as an intermediate (21, 61). Also, the mechanism cannot involve initial hydrolysis of XVII to 1-benzoyl-1,2-dihydroquinaldamide (XXXIX), since authentic XXXIX fails to give benzaldehyde when treated with mineral acid (18).



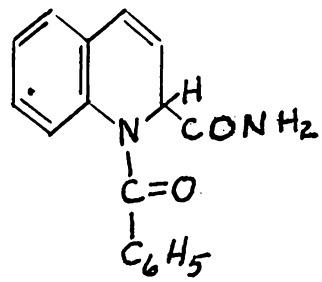
XXII XXXIV XXXV



XXXVI XXXVII XIX



XXXVIII



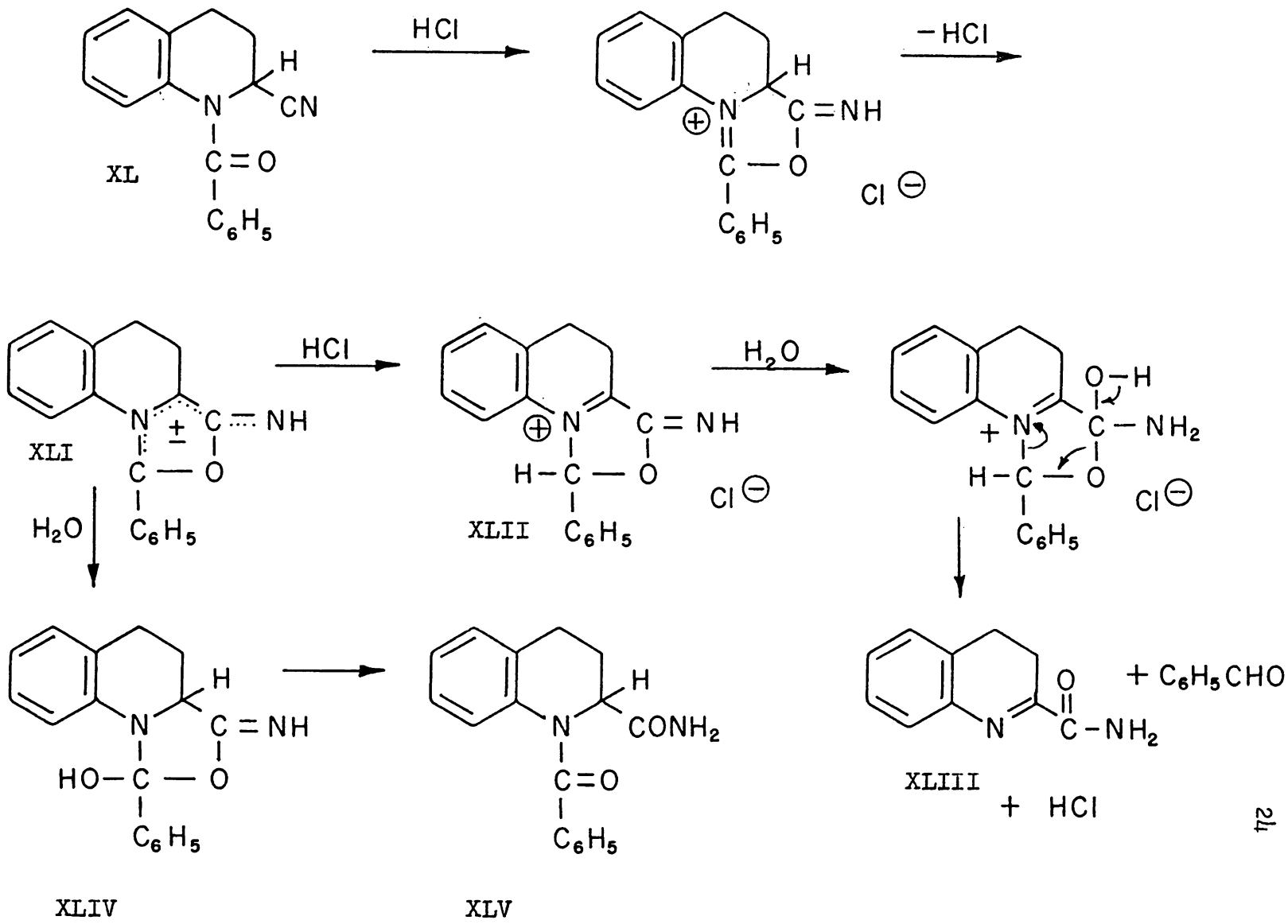
XXXIX

Another fact which supports this mechanism is that the gain in resonance energy derived from conversion of XVII, with its dihydroquinoline structure, to the fully aromatic quinoline derivatives is not an important driving force in the reaction. This conclusion was reached after the behavior of 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XL) upon acid-catalyzed hydrolysis had been observed. Despite the fact that no fully aromatic quinoline derivative may be a primary product of the acid-catalyzed hydrolysis of XL, the rate of formation of benzaldehyde from XL was found to be nearly equal to the rate of formation of benzaldehyde from XVII. The yield of benzaldehyde from XL, however, was only about half that obtained from XVII (18, 63). The reaction which competes with formation of benzaldehyde in the acid-catalyzed hydrolysis of XL is formation of 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XLV) (18). The proposed mechanism is capable of explaining this result. It is assumed, again, that action of hydrochloric acid on XL yields an intermediate meso-ionic compound, XLI. Then two competitive paths are available whereby XLI is transformed into the ultimate products of the reaction:

(a) Addition of a proton to the original carbonyl carbon atom yields XLII, which collapses to benzaldehyde and 3,4-dihydroquinaldamide (XLIII). (b) Addition of a molecule of water to XLI yields XLIV, which collapses to 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XLV) (17). Since little gain in resonance energy is available in either case, the two reactions proceed at comparable rates.

Treatment of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XXVIII) with anhydrous hydrogen chloride in chloroform solution was reported (45) to give an orange solid. Since this solid gave benzaldehyde and 6,7-dimethoxyquinaldamide (XXVII) on treatment with water, it appears likely that it was an intermediate analogous to one of the compounds, XXXIV-XXXVI. Furthermore, treatment of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) with anhydrous hydrogen chloride in benzene, chloroform or ether as solvents gives yellow to red-violet solids which, in turn, afford benzaldehyde on treatment with dilute mineral acid, water alone, or even a weakly basic solution (17, 51, 62). The isolation of these intermediates, having the properties to be anticipated for compounds of the type XXXIV-XXXVI, provides additional support for the proposed mechanism of acid-catalyzed hydrolysis of Reissert compounds.

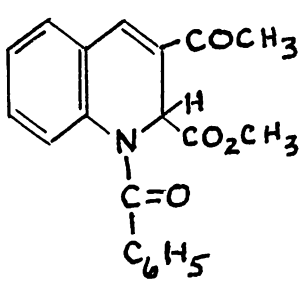
The formation of benzoin quinaldate (XX) as a by-product in the acid-catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) may be rationalized by the assumption that the conjugate acid of benzaldehyde adds to the meso-ionic intermediate, XXXV, to give the complex XLVI. Then, by an intramolecular process, XLVI rearranges


HCl
−HCl
XL
Cl ⊖
HCl
H_2O
XLI
XLII
Cl ⊖
H_2O
Cl ⊖
XLIV
XLV
XLIII
+ C_6H_5CHO
+ HCl

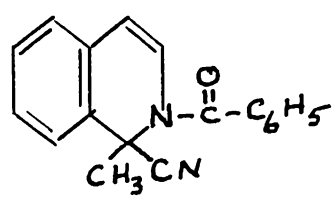
to give XLIX, via XLVII and XLVIII, respectively. Finally, the imino-ether, XLIX, is hydrolyzed to benzoin quinaldate (XX).

It is also possible for the imino-ether hydrochloride, XLIX, to undergo cyclization to the hydroxydihydro-oxazole, L, which can then undergo normal, acid-catalyzed dehydration to form 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIII), a product actually obtained under one set of conditions (17). There is convincing evidence available to substantiate the claim that benzoin quinaldate (XX) and 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIII) arise from an intermediate condensation product of 1-benzoyl-1,2-dihydroquinaldonitrile and benzaldehyde by an intramolecular process (61, 62).

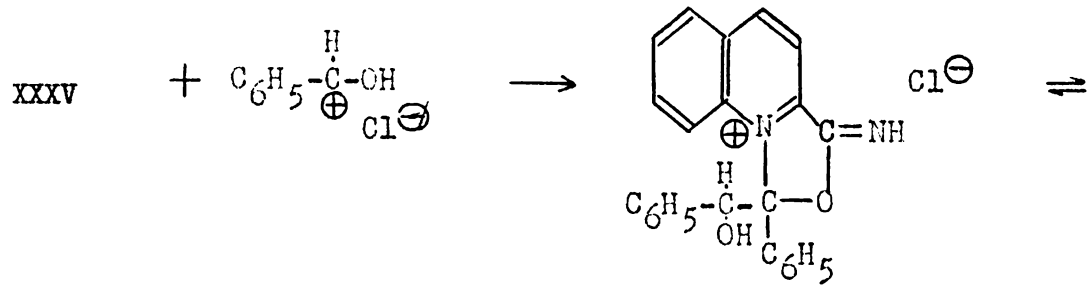
Finally, the necessity for the presence of the cyano group and the hydrogen on the α-carbon for the formation of aldehydes from compounds of the type I and II is emphasized by the observations that methyl 1-benzoyl-3-acetyl-1,2-dihydroquinaldate (LI) and 2-benzoyl-1-methyl-1,2-dihydroisoquinaldonitrile (LII) do not give aldehydes on treatment with mineral acid (9, 98).



LI

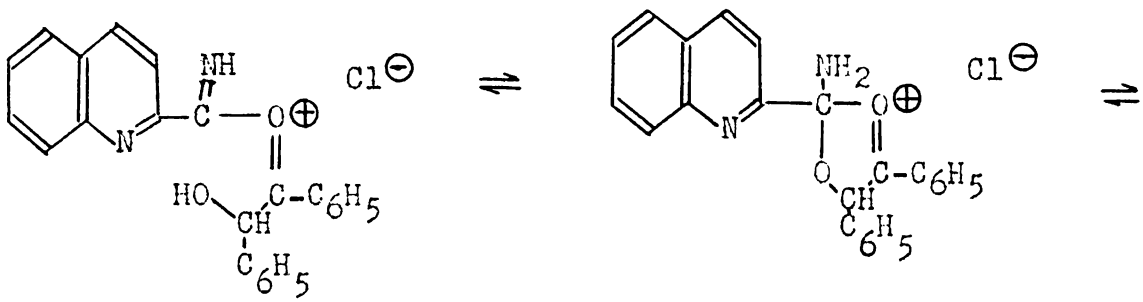


LII



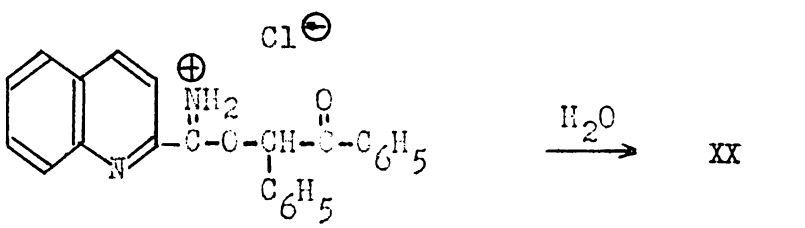
XXXV

XLVI



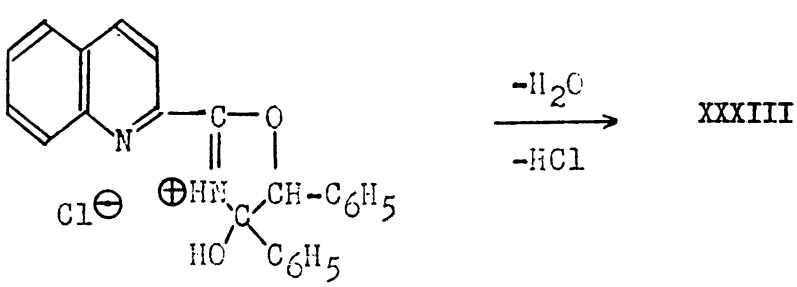
XLVII

XLVIII



XLIX

XX



L

XXXIII

3. General Procedure for the Preparation of Aldehydes

The usual method for the isolation of the aldehyde resulting from acid-catalyzed hydrolysis of a Reissert compound is to distill the aldehyde with steam from the acid solution. For only one series of Reissert compounds has any comparison been made of the effect of the type of mineral acid on the yield of aldehyde. In the series of compounds prepared from phenanthridine and acid chlorides of the general structure $C_6H_5-(CH=CH)_n-COCl$, the aldehydes, once formed, would be expected to be sensitive to an acidic environment. It was found that a superior yield of aldehyde was obtained by use of 40% phosphoric acid than by use of sulfuric acid (95).

A catalog of all known Reissert compounds, including methods of preparation, yields and yields of aldehyde produced on acid-catalyzed hydrolysis, is given in Table 1.

B. Reaction with Phosphorus Pentachloride and Similar Reagents

Since cinchoninonitrile (LIII) had been prepared from 1-methyl-1,4-dihydrocinchoninonitrile (LIV) by oxidation with iodine, followed by vacuum distillation (49, 50, 52), an attempt was made to prepare quinaldonitrile (XXXVIII) from 1-benzoyl-1,2-dihydroquinaldonitrile XVII) by a similar method, but without success (51). By use of phosphorus pentachloride, however, quinaldonitrile (XXXVIII), together with benzoyl chloride, phosphorus trichloride and hydrogen chloride, was obtained from XVII in a very vigorous reaction. A yield of 55-70% of XXXVIII was reported (51) when the reaction was

Table 1

Catalog of Reissert Compounds and Yields of Aldehydes

Obtained Upon Hydrolysis

Base	Acid Chloride	Method of Preparation[1]	% Yield of Reissert Compound[2]	% Yield of Aldehyde[3]	References
Quinoline	Benzoyl	a	94		43, 75,
		b	96	98	81, 97
		c	87		
"	Cinnamoyl	a	34		43, 87,
		b	91	82	97
		c	77		
"	p-Toluyl	a	42	96	42, 60
"	o-Chlorobenzoyl	b	80	94	43
"	m-Chlorobenzoyl	b	28	96	43
"	p-Chlorobenzoyl	a	26	92	43,
		b	77		61

[1] a, in aqueous medium; b, in anhydrous benzene; c, in liquid sulfur dioxide

[2] Dash in column indicates yield has not been reported

[3] Best yields reported given. Underscored yields indicate isolation as a substituted hydrazone or similar derivative. When no yield given, aldehyde is known to be formed, but in unreported yield.

Table 1 (Cont'd.)

Base	Acid Chloride	Method of Preparation[1]	% Yield of Reissert Compound[2]	% Yield of Aldehyde[3]	References
Quinoline	o-Methoxybenzoyl	b	66	97	43
"	Anisoyl	a b	51 88	98	43, 87
"	Veratroyl	a	36	57	87
"	3,4,5-Trimethoxybenzoyl	a b	slight --	--	13, 87
"	2-Nitro-3,4,5-trimethoxybenzoyl	b	80	60	13
"	o-Nitrobenzoyl	b	80	73	13
"	m-Nitrobenzoyl	b	--	--	13
"	Acetyl	b	74	99	43
"	Propionyl	b	10	96	43
"	Butyryl	b	64	97	43
"	Isobutyryl	b	28	98	43
"	Valeryl	b	--	42	43
"	Isovaleryl	b	64	98	43

Table 1 (Cont'd.)

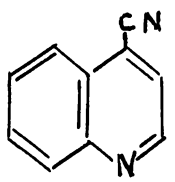
Base	Acid Chloride	Method of Preparation[1]	% Yield of Reissert Compound[2]	% Yield of Aldehyde[3]	References
6-Methoxyquinoline	Benzoyl	a	89	97	37, 63
6-Methylquinoline	Benzoyl	a	60	91	35
6-Chloroquinoline	"	a	48	98	35
7-Methoxyquinoline	"	a	--	--	86
2,3'-Biquinoline	"	a	50	--	48
6,6'-Biquinoline	"	a	--	--	91
5,6-Benzoquinoline	"	--[4]	--	--	22
Isoquinoline	"	a	58	--	74, 76, 80
"	Cinnamoyl	b	91	--	10
"	p-Chlorobenzoyl	a	11	50	42, 60
"	Acetyl	b	85	--	10
3-Methylisoquinoline	Benzoyl	a	66	95	35
6,7-Dimethoxyisoquinoline	"	a	35	--	45

[4]Experimental details lakcing, footnote 19, reference 22.

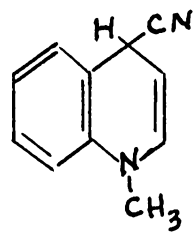
Table 1 (Cont'd.)

Base	Acid Chloride	Method of Preparation[1]	% Yield of Reissert Compound[2]	% Yield of Adlehyde[3]	References
6,7-Dimethoxyios-quinoline	2,3-Dimethoxybenzoyl	a	54	--	45
Phenanthridine	Benzoyl	b	94	97	95
"	Cinnamoyl	b	86	97	95
"	5-Phenyl-2,4-pentadienoyl	b	64	35	95
"	7-Phenyl-2,4,6-heptatrienoyl	b	80	0	95

carried out in chloroform solution. Subsequent workers, however, have been unable to realize this high a yield (14, 44). Thionyl chloride and sulfuryl chloride can be used in place of phosphorus pentachloride (51).

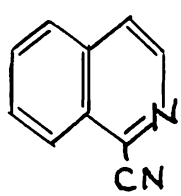


LIII



LIV

No reaction occurs upon treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with phosphorus pentachloride in chloroform solution; upon heating the reagents to a temperature of 125-130° in the absence of a solvent, however, isoquinaldonitrile (LV) was obtained in a reported 82-85% yield (51). Once again, later workers reported a distinctly lower yield, 53%, in this reaction (74). By use of thionyl chloride in place of phosphorus pentachloride, however, a 72% yield of LV can be obtained (47).

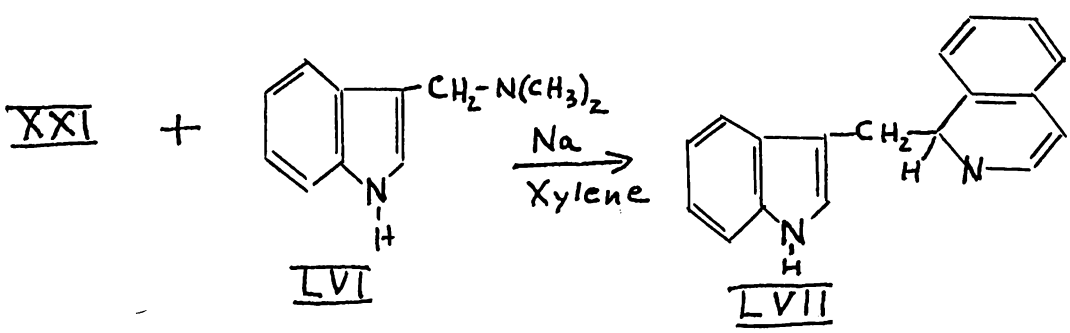


LV

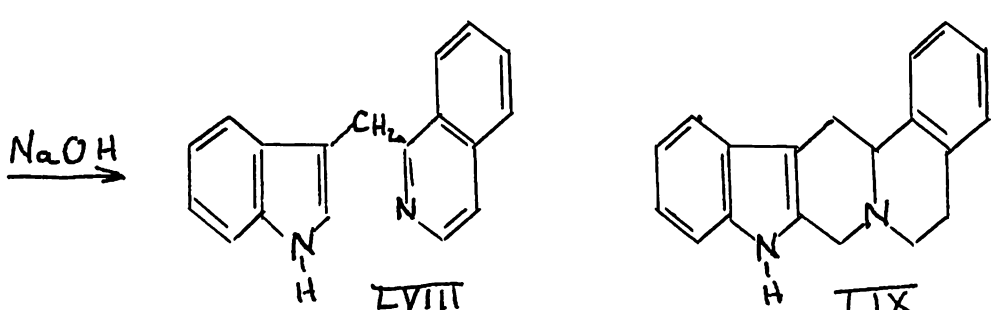
C. Alkylation Reactions

Reactive anions can be formed by treatment of Reissert compounds with a variety of bases, inasmuch as the hydrogen bonded to the carbon α to the cyano group is distinctly acidic. These conjugate bases of the Reissert compounds can be used to good advantage in alkylation reactions.

Treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with gramine (LVI) in hot xylene in the presence of a small amount of sodium has been reported to give 1-skatyl-2-benzoyl-1,2-dihydroisoquinaldonitrile (LVII) in 46% yield (6, 8). Alkaline hydrolysis of LVII gives 1-skatylisoquinoline (LVIII). It was hoped that the latter compound could be converted to a hexahydrobenzoindoloquinolizine, LIX, which constitutes the nucleus of certain calabash curare alkaloids, but this could not be accomplished (8).

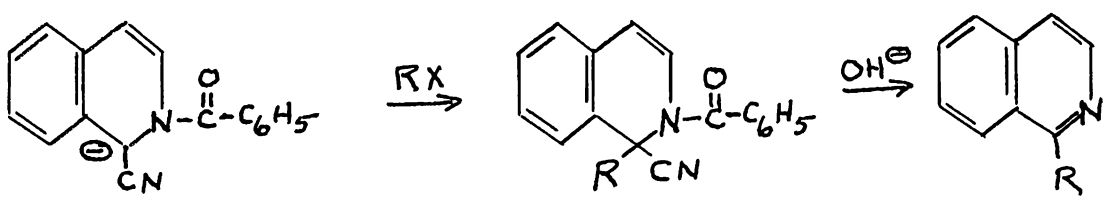


LVI LVII



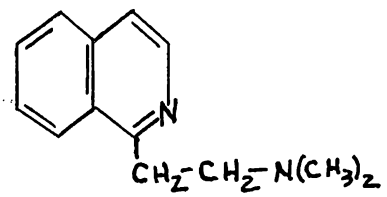
LVIII LIX

The alkylation reaction to produce LVII probably involves an S_N2 type of attack of the anion, LX, formed by action of sodium on XXI, on the side chain carbon atom of gramine (LVI), with displacement of the anion of dimethylamine. The conjugate base, LX, of XXI can also be produced under very mild conditions by means of an exchange reaction involving phenyllithium and XXI. The anion, LX, prepared in this way, has been found to enter into nucleophilic displacement reactions with a variety of alkyl halides to give products of the general structure LXI. The adduct, LXI, may be converted to a 1-alkylisoquinoline, LXII, by heating with an alcoholic solution of an alkali metal hydroxide.

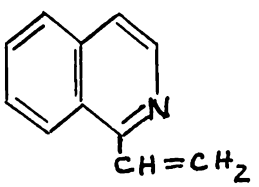


The alkylation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) has been carried out with methyl iodide, benzyl bromide, n-butyl bromide and hydrocinnamyl iodide. The overall yield of the 1-alkylisoquinoline (LXII) in each case was 58% for 1-methylisoquinoline (isoquinaldine), 78% for 1-benzylisoquinoline, 41% for 1-n-butylisoquinoline and 44% for 1-hydrocinnamylisoquinoline (7, 10). Of the methods found in the literature, this has been claimed to be the most

convenient for the synthesis of isoquinaldine (9). A similar series of reactions has been carried out with β-chloroethyldimethylamine as the alkylating reagent, and 1-(β-dimethylaminoethyl)-isoquinoline (LXIII) was obtained in 40% yield. 1-Vinylisoquinoline (LXIV) may be prepared from LXIII by distillation of the latter compound over potassium hydroxide (9).



LXIII



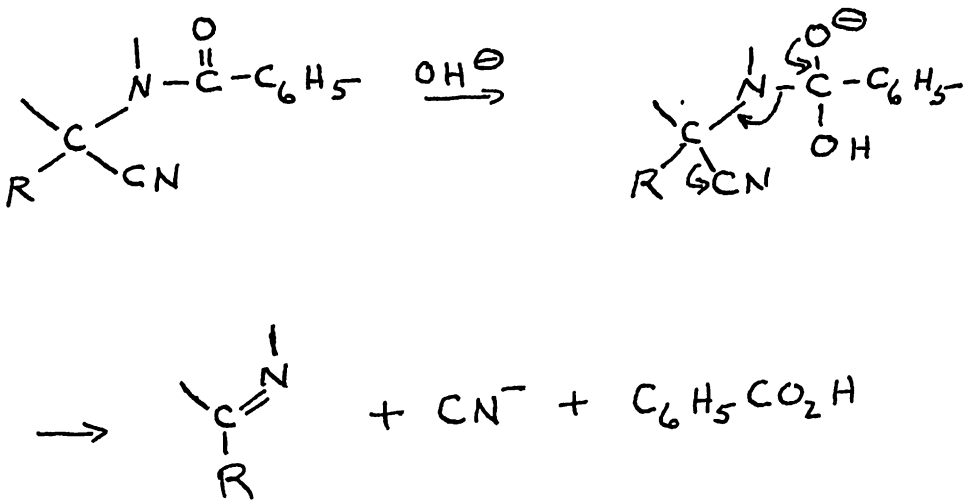
LXIV

Similarly, 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) is easily converted to its conjugate base, LXV, by treatment with phenyllithium. Reaction of LXV with methyl iodide and subsequent hydrolytic cleavage gives lepidine (LXVII) rather than quinaldine (LXVIII) (10). Inasmuch as stabilization of the anion LXV by resonance involves a sharing of the negative charge by the carbon in the 4-position of the ring, this result is not particularly surprising. Evidence will be presented later which supports the contention that the intermediate alkylation product, LXVI, possesses the 1,2-dihydro structure rather than the 1,4-dihydro structure.

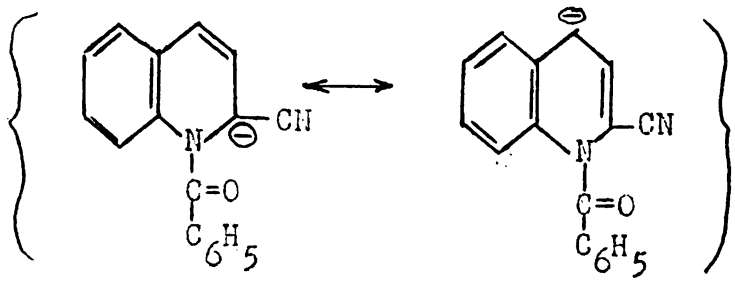
Further reaction of 1-benzoyl-4-methyl-1,2-dihydroquinaldonitrile (LXVI) with phenyllithium, then methyl iodide, gives 1-benzoyl-2,4-dimethyl-1,2-dihydroquinaldonitrile (LXIX), which can be converted

to 2,4-dimethylquinoline (LXX) by alkaline hydrolysis (10). The overall yields of LXVII and LXX are much smaller than the yields of the various 1-alkylisoquinolines (LXII).

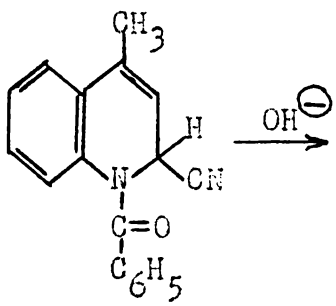
A mechanism has been proposed (10) for the various cleavage reactions brought about by the action of an alcohol solution of alkali metal hydroxide. This involves addition of the hydroxide ion to the carbonyl carbon atom of the amide group, followed by elimination of benzoic acid and the cyanide ion. The driving force in this reaction has been attributed to aromatization of the system (10).



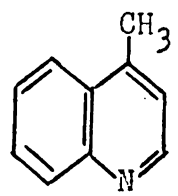
Reaction of the conjugate base, LX, of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with benzoyl chloride gives 1,2-dibenzoyl-1,2-dihydroisoquinaldonitrile (LXXI) in 52% yield. Alkaline cleavage of this product gives only a trace of 1-benzoylisoquinoline, the major heterocyclic product being isoquinoline (10).



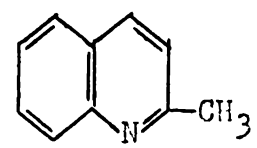
LXV



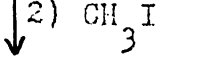
LXVI

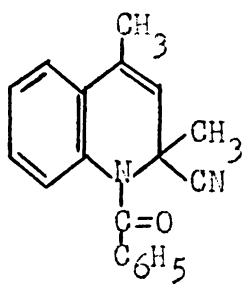


LXVII

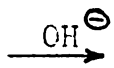


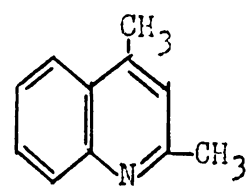
LXVIII



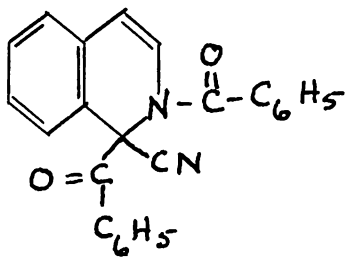


LXIX





LXX



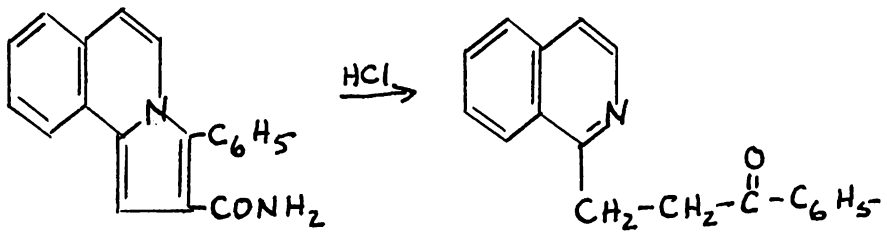
LXXI

D. Michael-Type Addition Reactions

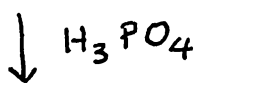
The conjugate bases derived from Reissert compounds have been found to add to acrylonitrile, 2-vinylpyridine and ethyl acrylate in the Michael manner, but the reactions are complicated due to the occurrence of subsequent reactions of the original adducts.

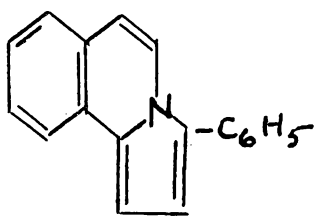
Reaction of the conjugate base, LX, of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with acrylonitrile gives 3-phenyl-2-formamido-6,7-benzopyrrocoline (LXXII) in 76% yield (7). The structure was proven by degradation reactions. Action of concentrated hydrochloric acid on LXXII gave a 95% yield of phenyl β-(1-isoquinolyl)-ethyl ketone (LXXIII), while action of 100% phosphoric acid on LXXII gave 3-phenyl-7,8-benzopyrrocoline (LXXIV). The latter compound was independently synthesized. A similar reaction was found to occur with

2-acetyl-1,2-dihydroisoquinaldonitrile, 3-methyl-2-formamido-7,8-benzopyrrocoline being obtained in 60% yield.



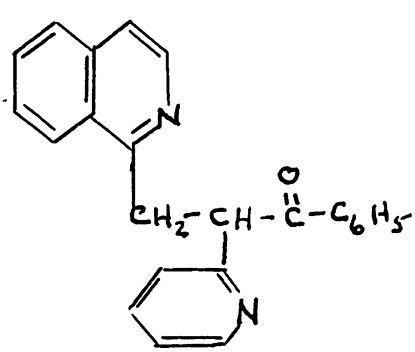
LXXII LXXIII

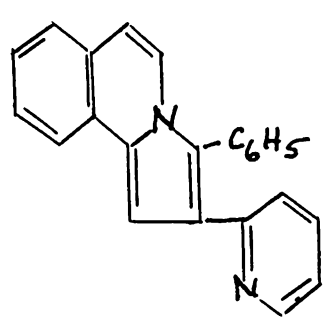




LXXIV

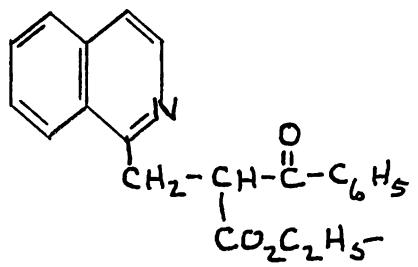
Reaction of LX with 2-vinylpyridine gives the ketone LXXV in 58% yield. 2-(2-Pyridyl)-3-phenyl-7,8-benzopyrrocoline (LXXVI) may be prepared in 50% yield by treatment of LXXV with concentrated sulfuric acid.



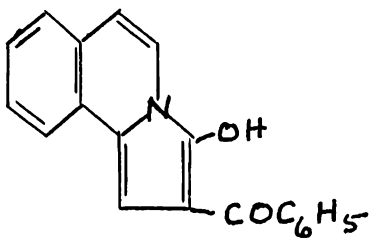


LXXV LXXVI

Condensation of LX with ethyl acrylate affords the ketone LXXVII in 31% yield. The ketone is converted to 2-benzoyl-3-hydroxy-7,8-benzopyrrocoline (LXXVIII) upon sublimation.



LXXVII

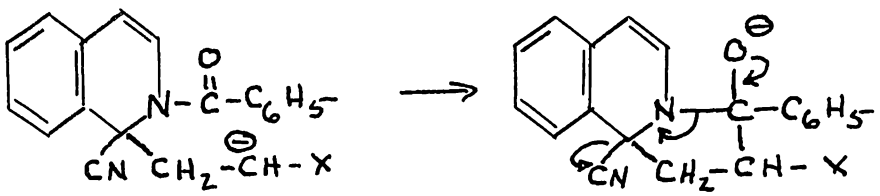


LXXVIII

A Michael-type condensation involving the conjugate base, LXV, of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) and acrylonitrile appears to proceed in a normal manner. After cleavage of the initial addition product by means of hot alcoholic alkali, a substance giving a correct analysis for β-(2-quinolyl)-propionic acid was obtained. In view of the orientation observed upon alkylation of LXV with methyl iodide, however, there is some possibility that β-(4-quinolyl)-propionic acid may have been formed rather than β-(2-quinolyl)-propionic acid (7).

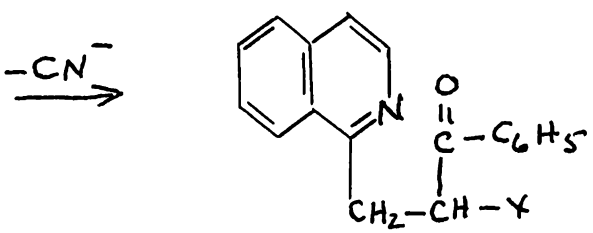
A plausible mechanism has been offered for the formation of the products, LXXII, LXXV and LXXVII, obtained by reaction of the anion LX with acrylonitrile, 2-vinylpyridine and ethyl acrylate, respectively. In a generalized example, LX adds to CH_2=CH-X (where X = CN, $CO_2C_2H_5$ or the 2-pyridyl group) to give LXXIX, which then undergoes cyclization

to LXXX. The latter intermediate may then undergo aromatization either by loss of the cyanide ion and water to give the corresponding substituted benzopyrrocoline, or by loss of cyanide ion and rearrangement to give the ketone, LXXXI (7).



LXXIX

LXXX



LXXXI

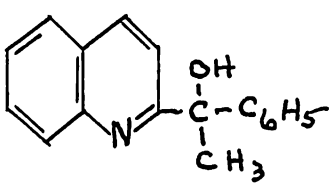
E. Rearrangements

The conjugate bases derived from Reissert compounds have a tendency to undergo rearrangement with elimination of the cyanide ion at somewhat elevated temperatures. Advantage may be taken of this fact to prepare a variety of potentially useful 2-substituted quinolines and 1-substituted isoquinolines. There have also been observations of rearrangements of Reissert compounds occurring during catalytic hydrogenation.

1. Base-Catalyzed Rearrangements

a. Scope

Tertiary alcohols are obtained upon treatment of Reissert compounds with Grignard reagents in dioxane or benzene solution (42, 60, 62). For example, the reaction of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) with methylmagnesium bromide gives a 59% yield of methylphenyl-2-quinolylcarbinol (LXXXII), in addition to a trace of 2-benzoylquinoline (42, 60). Similar reactions have been observed with other Reissert compounds and other Grignard reagents. In general, the maximum temperature at which the reaction is carried out is about 60° for alkylmagnesium halides and about 100° or more for arylmagnesium halides. The results of a number of these reactions are summarized in Table 2.



LXXXII

A similar rearrangement occurs upon treatment of a Reissert compound with sodium hydride in boiling xylene. 1-Benzoylisoquinoline may be obtained in 70% yield, together with sodium cyanide and hydrogen, upon treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with sodium hydride under these conditions (10). 1-Acetylisoquinoline is obtained in 30% yield from 2-acetyl-1,2-dihydroisoquinaldonitrile, 2-benzoylquinoline in 54% yield from 1-benzoyl-1,2-dihydroquinaldo-

Table 2

Reaction of Reissert Compounds with Grignard Reagents

Reissert Compound	Grignard	Product	Yield	Reference
1-Benzoyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-quinolylcarbinol	59%	42, 60, 62
	CH_3MgI		21%	42
	CH_3MgCl		49%	42
	C_2H_5MgBr	Ethylphenyl-2-quinolylcarbinol	20%	42
	C_6H_5MgBr	Diphenyl-2-quinolylcarbinol 2-Benzoylquinoline	8.5% 4%	42, 60
	$MesMgBr$[a]	2-Benzoylquinoline Quinoline	trace 29%	42, 60
1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile	CH_3MgBr	Methylphenyl-2-(6-methoxyquinolyl)-carbinol	56%	42, 60
1-p-chlorobenzoyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Methyl-p-chlorophenyl-2-quinolylcarbinol	26%	42, 60
1-Anisoyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Methyl-p-anisyl-2-quinolylcarbinol	4%	42,
1-p-Toluyl-1,2-dihydroquinaldonitrile	CH_3MgBr		0	42, 60

Table 2 (Cont'd.)

Reissert Compound	Grignard	Product	Yield	Reference
1-Acetyl-1,2-dihydroquinaldonitrile	CH_3MgBr	Quinoline	1%	42
2-Benzoyl-1,2-dihydroisoquinaldonitrile	CH_3MgBr	Methylphenyl-1-isoquinolylcarbinol	32%	42, 60
	C_6H_5MgBr	Diphenyl-1-isoquinolylcarbinol	50%	42, 60
	p-CH_3O-C_6H_4MgBr	Phenyl-p-anisyl-1-isoquinolylcarbinol	34%	77

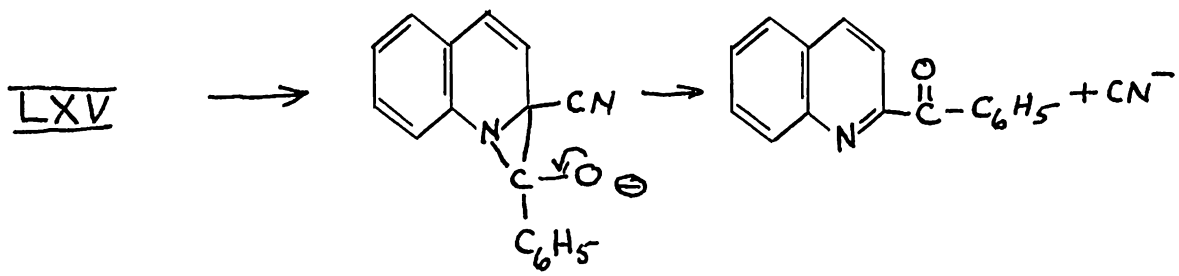
[a] 2,4,6-Trimethylphenylmagnesium bromide

nitrile (XVII), and 2-acetylquinoline in 31% yield from 1-acetyl-1,2-dihydroquinaldonitrile in similar reactions.

b. Mechanism Studies

In the rearrangement brought about by the action of Grignard reagents, it is evident that the Reissert compound is first converted to the α-acyl aromatic derivative, as in the rearrangement brought about by the action of sodium hydride. Since the presence of either an electron-donating substituent (p-methyl or p-methoxyl) or an electron-withdrawing substituent (p-chloro) on the benzoyl part of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) decreases the yield of rearrangement product in the reaction with methylmagnesium bromide, it is difficult to propose any simple, consistent electronic interpretation for the overall reaction. There are three centers in a Reissert compound at which attack by the anion derived from a Grignard reagent may occur, the carbon atom of the cyano group, the carbonyl carbon atom and the acid hydrogen atom. It is probable that changes in the electronic character of the acyl group would cause a change in the relative rates of attack by the Grignard anion at each of the three reactive centers. Since different products would result following attack by the Grignard anion at each of these centers, it is not surprising that no simple correlation can be made relating the electronic effect of a substituent to the yield of rearrangement product. In any event, there can be little doubt that the rearrangement proceeds via the conjugate base of the Reissert compound.

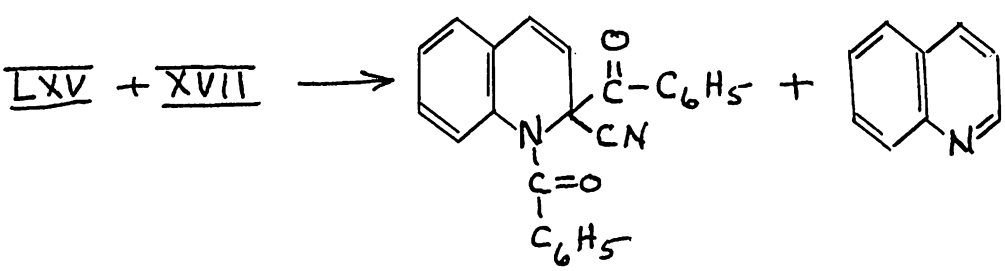
Two possible mechanisms have been considered whereby the conjugate base of a Reissert compound rearranges to the α-acyl derivative, with expulsion of a cyanide ion. For example, it has been proposed (62) that 2-benzoylquinoline arises from the anion LXV, by way of the ethyleneimine intermediate, LXXXIII, by an intramolecular process.



LXV

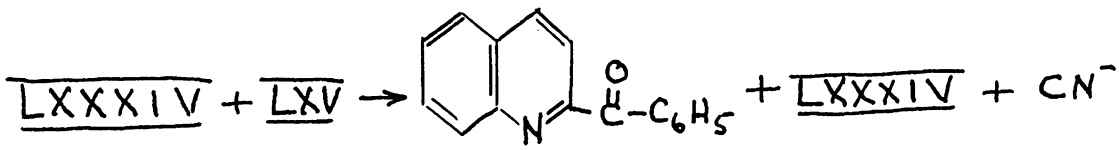
LXXXIII

The other mechanism which has been considered involves a two step intermolecular process, actually an ionic chain reaction, involving formation of 1,2-dibenzoyl-1,2-dihydroquinaldonitrile (LXXXIV) as an intermediate (10).

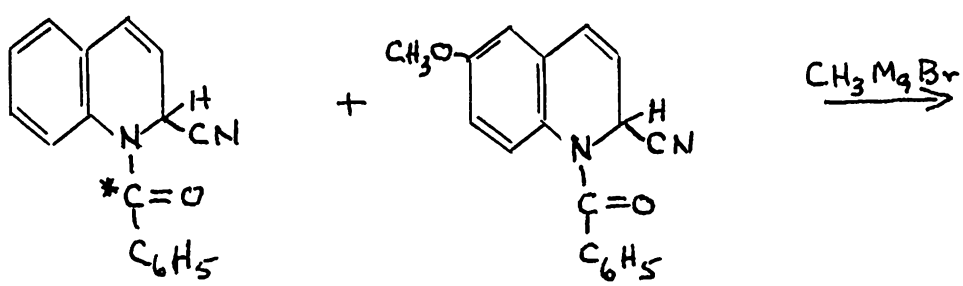


LXV + XVII

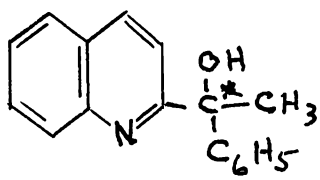
LXXXIV



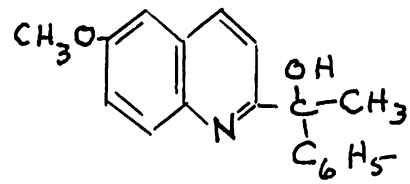
More recently, a convincing proof that the rarrangement is intramolecular has been provided (96). Reaction of methylmagnesium bromide with a mixture of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) and LXXXVI, 1-benzoyl-1,2-dihydroquinaldonitrile labeled with C^{14} at the carbonyl carbon atom, gave LXXXVII, methylphenyl-2-quinolyl-carbinol containing all the isotopic carbon, and unlabeled methylphenyl-2-(6-methoxyquinolyl)-carbinol (LXXXVIII).



LXXXVI LXXXV



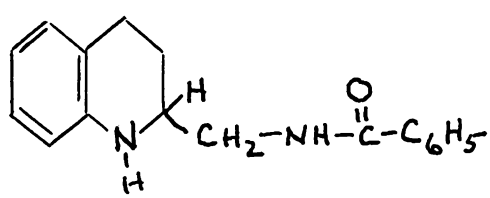
LXXXVII



LXXXVIII

2. Rearrangements Occurring With Reduction

Rearranged products are obtained upon catalytic hydrogenation of Reissert compounds, particularly when the hydrogenation is carried out at a relatively high temperature and pressure (78, 79, 81). Hydrogenation of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) over a nickel catalyst at a temperature of 80-90° and at a hydrogen pressure of 100 atmospheres, for example, gives α-benzamido-1,2,3,4-tetrahydroquinaldine (LXXXIX).



LXXXIX

F. Reductions

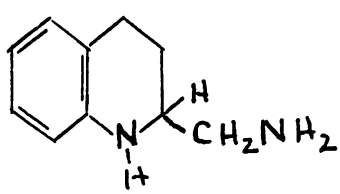
There are several centers susceptible to reduction in Reissert compounds. Under proper conditions it might be possible to selectively

reduce the olefinic double bond or the cyano group, and, by application of more drastic conditions, the amide group and aromatic rings might also be reduced. Actually, well defined reduction products have been obtained only after reduction of the olefinic group alone or both the olefinic and cyano groups.

1. Catalytic Hydrogenation

a. High Pressure Reductions

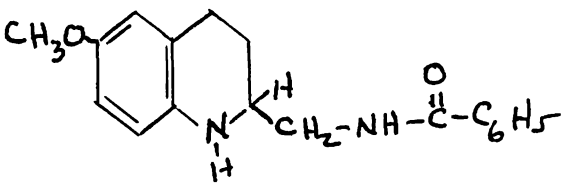
It has already been mentioned that catalytic hydrogenation of XVII gives LXXXIX. The latter compound can be hydrolyzed to α-amino-1,2,3,4-tetrahydroquinaldine (XC) in almost quantitative yield under acidic conditions (81).



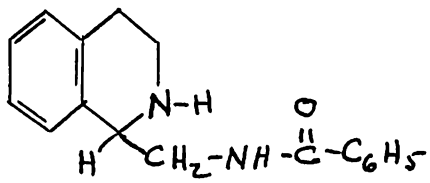
XC

Reduction accompanied by rearrangement also occurs upon catalytic hydrogenation of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI), α-benzamido-6-methoxy-1,2,3,4-tetrahydroquinaldine (XCI) and 1-(benzamidomethyl)-1,2,3,4-tetrahydroisoquinoline (CXII), respectively, being formed (5, 37, 57,

80, 82). Reduction of XXI, however, required a hydrogen pressure of 140 atmospheres and a temperature of 90-100°.



XCI



XCII

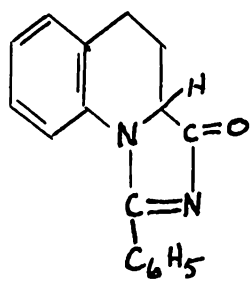
By use of palladium as the catalyst instead of nickel, and inferior yield of LXXXIX was obtained from XVII. There was also obtained in small amount a substance thought to be α,α'-iminobis-(1-benzoyl-1,2,3,4-tetrahydroquinaldine) (81).

b. Low Pressure Reductions

If the hydrogenation of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) is carried out over a platinum catalyst at room temperature and under one atmosphere pressure of hydrogen, it is possible to effect a selective reduction of the olefinic group. By limiting the uptake of hydrogen to one molar equivalent, 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XL) may be obtained in 69% yield (63). 1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) behaves in the same manner, yielding 62% of the 6-methoxy derivative of XL. Although 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) readily absorbs one molar equivalent of hydrogen under these conditions, about half the starting material is recovered unchanged, and the reduction product

(or products) cannot be isolated in crystalline form (33, 63).

Although addition of one molar equivalent of hydrogen to 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) in ethanol suspension over platinum at three atmospheres pressure of hydrogen gave 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XL) in 19% yield, the major product, obtained in 38% yield, was 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XCIII), an isomer of XL. In addition, α-benzamido-1,2,3,4-tetrahydroquinaldine (LXXXIX) was obtained in 7% yield (33).



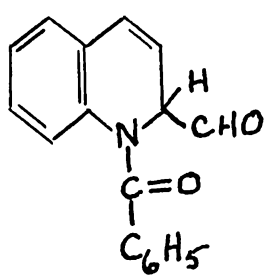
XCIII

The proof of structure of XCIII was based mainly on the demonstration that the compound can also be prepared by dehydration of 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XLV) with phosphorus pentoxide and by the fact that XCIII may be reconverted to XLV upon treatment with hydrogen peroxide and sodium bicarbonate solution. Furthermore, XCIII may also be prepared by treatment of tetrahydroquinaldamide with benzoyl chloride in pyridine solution or by reaction of 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XL) with potassium permanganate in

acetone solution. Benzoic acid is obtained upon either acid- or base-catalyzed hydrolysis of XCIII, and ethyl tetrahydroquinaldate by ethanolysis of XCIII, catalyzed by sulfuric acid (17).

2. Chemical Reductions

Many nitriles have been converted to aldehydes by treatment with stannous chloride and hydrogen chloride (Stephens reduction). It was thought that 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) might be converted either to 1-benzoyl-1,2-dihydroquinaldaldehyde (XCIV) or to a mixture of benzaldehyde and quinaldaldehyde by application of the Stephens method. Actually, neither XCIV nor quinaldaldehyde were obtained upon treatment of XVII with stannous chloride and hydrogen chloride, but benzaldehyde was formed (53, 62).



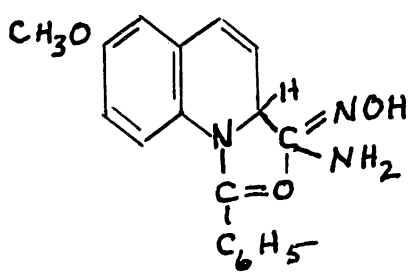
XCIV

An attempted reduction of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) with sodium and ethanol brought about a reductive cleavage of the molecule, but the products were not isolated and characterized (81).

G. Reactions at the Cyano Group

An amide may be prepared from a nitrile by treatment of the nitrile with hydrogen peroxide in an alkaline medium. 1-Benzoyl-1,2-dihydroquinaldonitrile (XVII) behaves normally in this reaction. Treatment of SVII with 30% hydrogen peroxide in acetone solution in the presence of sodium bicarbonate gives a 65% yield of 1-benzoyl-1,2-dihydroquinaldamide (XXXIX). The structure of XXXIX was proven by its reconversion to XVII on treatment with phosphorus pentoxide and by its catalytic hydrogenation to 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XLV) (18), a compound which has been synthesized by an independent method (17).

Another reaction usually undergone by nitriles is their conversion to amidoximes by reaction with hydroxylamine. In the case of the only Reissert compound investigated, 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) gave the amidoxime XCV in a facile reaction (37).

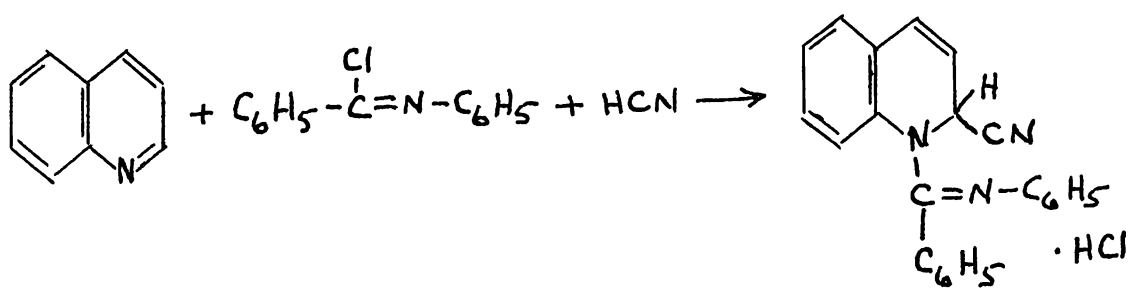


XCV

IV. Related Compounds and Reactions

A. 1-(α-Phenyliminobenzyl)-1,2-dihydroquinaldonitrile

As part of an investigation of the effect of various amines on the preparation of N-phenylbenzimidyl cyanide, it was found that a reaction of N-phenylbenzimidyl chloride with anhydrous hydrogen cyanide in the presence of quinoline led to formation of an addition compound. This product was thought to be 1-(α-phenyliminobenzyl)-1,2-dihydroquinaldonitrile hydrochloride (XCVI) (68).

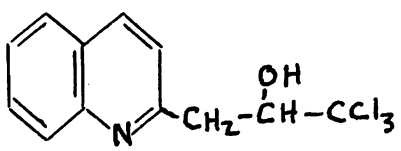


XCVI

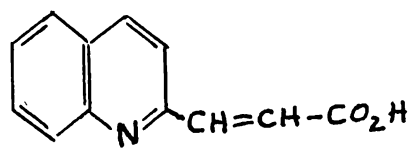
This compound (XCVI) is a nitrogen analog of a Reissert compound, and the analogy is strengthened by the fact that the odor of benzaldehyde develops upon heating XCVI with dilute hydrochloric acid. Pyridine, but not acridine, was reported to form an addition product similar to XCVI, but its properties were not thoroughly investigated.

B. Methyl 3-Acetyl-1,2-dihydroquinaldate

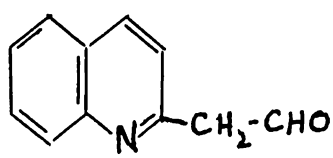
It was reported in 1886 that alkaline hydrolysis of α-(trichloromethyl)-2-quinolineethanol (XCVII), better known as chloral quinaldine (1, 30), gives two amphoteric compounds, β-(2-quinolyl)-acrylic acid (XCVIII) and a compound of empirical formula $C_{12}H_{11}NO_3$ (30, 31). Upon decarboxylation, the latter compound was found to give a carbonyl compound; this, when treated with o-aminobenzaldehyde, gave 2,3-biquinoline. The decarboxylated material was therefore assumed to be 2-quinolylacetaldehyde (XCIX) (32).



XCVII



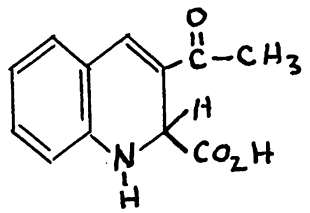
XCVIII



XCIX

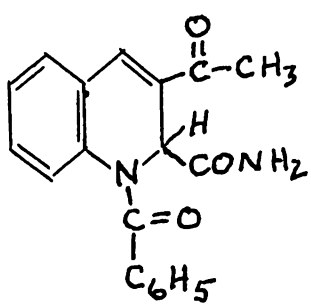
Later it was shown that the carbonyl compound obtained upon decarboxylation of the product of empirical formula $C_{12}H_{11}NO_3$ could be oxidized to quinoline-3-carboxylic acid (11). Quite recently, a complete proof of structure of the compound, $C_{12}H_{11}NO_3$, has revealed that it is 3-acetyl-1,2-dihydroquinaldic acid (C), and that the compound obtained upon oxidative decarboxylation is actually 3-acetyl-

quinoline (98). The mechanism whereby XCVII is converted to C has been discussed at some length (12, 23, 98), but it is beyond the scope of this review to give the details.



C

Esterification of 3-acetyl-1,2-dihydroquinaldic acid (C) with methanol, followed by benzoylation, gives methyl 1-benzoyl-1,2-dihydroquinaldate (LI), quite similar in structure to Reissert compounds. However, action of mineral acid on this compound yields 1-benzoyl-3-acetyl-1,2-dihydroquinaldic acid, and no benzaldehyde is formed (98). Similarly, 1-benzoyl-3-acetyl-1,2-dihydroquinaldamide (CI), prepared by ammonolysis of methyl 3-acetyl-1,2-dihydroquinaldate, with subsequent benzoylation, gives no benzaldehyde on treatment with mineral acid (17).



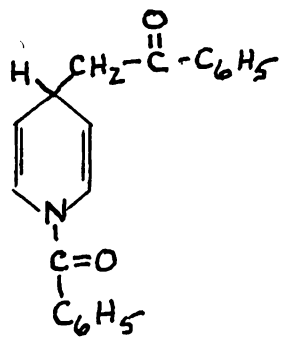
CI

C. Other N-Acyldihydro Aromatic Nitrogen Heterocyclic Derivatives

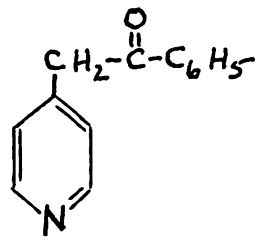
In many cases, compounds analogous to Reissert compounds are formed when the cyanide ion is replaced by other nucleophilic agents in the reaction with quinoline and an acid chloride. Furthermore, reactions of this type have been observed with pyridine also. No attempt will be made to describe all such reactions in this review, but some of the more important and representative ones will be considered.

1. Pyridine Derivatives

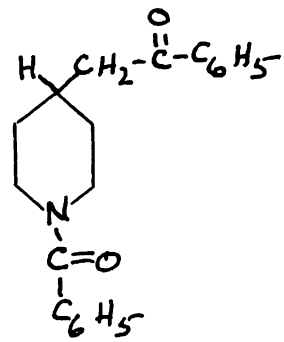
1-Benzoyl-4-phenacyl-1,4-dihydropyridine (CII), or the isomeric compound having the 1,2-dihydro structure, is formed by reaction of acetophenone, pyridine and benzoyl chloride for a prolonged period of time at room temperature (16, 28). Air oxidation of CII gives 4-phenacylpyridine (CIII), and addition of one molar equivalent of hydrogen to CII over a platinum catalyst gives 1-benzoyl-4-phenacyl piperidine (CIV). Products similar to CII are obtained by the use of propiophenone and cyclohexanone instead of acetophenone in the reaction with benzoyl chloride and pyridine (28). Treatment of these compounds with mineral acid gives no benzaldehyde; instead, benzoic acid, pyridine and the original ketone are formed.



CII

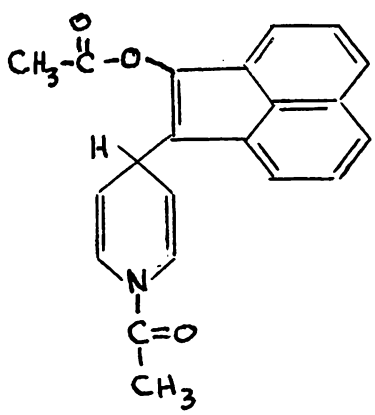


CIII

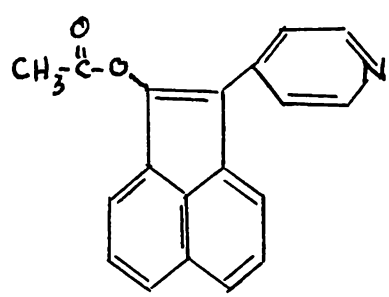


CIV

A similar type of condensation reaction occurs upon treatment of acenaphthenone with acetic anhydride and pyridine (38, 39, 40). The structure of the resulting condensation product has been elucidated by a combination of degradation (39, 40) and oxidation (28) studies and shown to be 1-acetoxy-2-(1-acetyl-1,4-dihydro-4-pyridyl)-acenaphthylene (CV) (28). It is of interest that CV gives 1-acetoxy-2-(4-pyridyl)-acenaphthylene (CVI) and acetaldehyde on being heated (39).

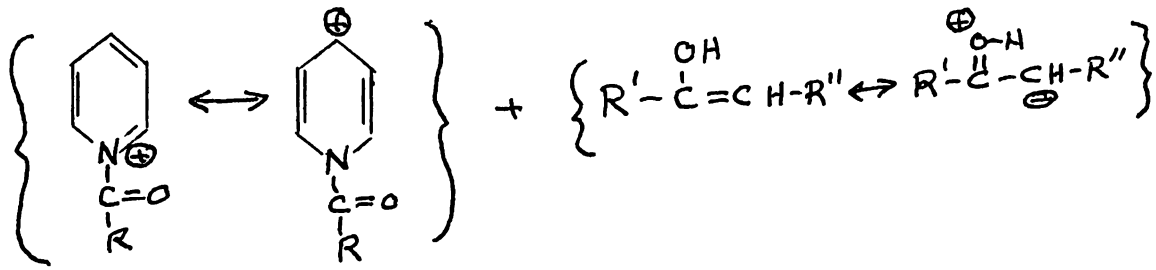


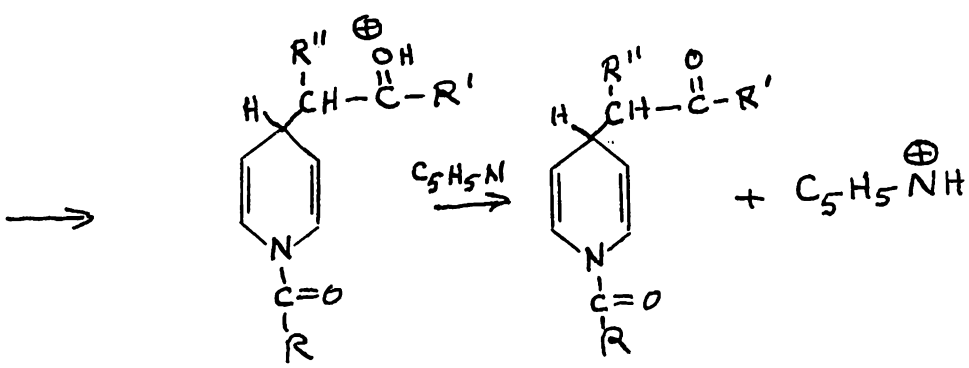
CV



CVI

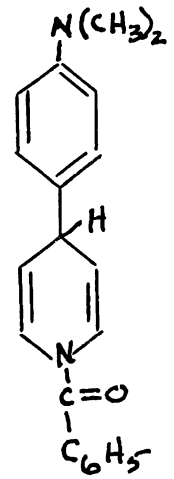
A mechanism has been proposed for the condensation reactions which give rise to these dihydropyridine derivatives (28). In the general case, the product is formed by reaction of the initially formed acylpyridinium salt, electron deficient at the 2- and 4-positions, with the nucleophilic (electron-donating) enolic tautomer of the ketone.



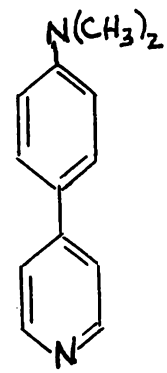


A dialkylaniline may serve as the nucleophilic agent in the condensation reaction with an acylpyridinium salt. For example, a reaction of dimethylaniline, benzoyl chloride and pyridine in the presence of a copper-bronze catalyst was found to give a 67% yield of 4-(p-dimethylaminophenyl)-pyridine (CVIII). This product was assumed

to have arisen from initially formed 1-benzoyl-4-(p-dimethylamino-phenyl)-1,4-dihydropyridine (CVII), because benzaldehyde was also isolated from the reaction mixture (55). On reinvestigation of the condensation reaction under the mildest possible conditions in an attempt to isolate CVII, it was found (63) that the reaction would go at room temperature and without use of a copper-bronze catalyst, but once again the only products which could be isolated were CVIII and benzaldehyde.



CVII



CVIII

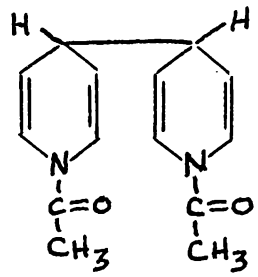
Other dialkylanilines were found to give products analogous to CVIII on reaction with benzoyl chloride and pyridine, but the yields gradually dropped as the size of the alkyl groups was increased. From a reaction mixture of m-dimethylaminotoluene, benzoyl chloride and pyridine there was obtained a compound, which, on the basis of

the analytical data, may have been a dihydropyridine derivative analogous in structure to CVII. This compound was not further investigated (55).

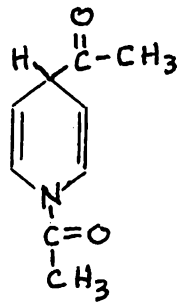
4-Phenylpyridine has been obtained in 16% yield after reaction of phenylmagnesium bromide with a mixture of benzoyl chloride and pyridine (58). In addition, a product thought to be the probable intermediate in the formation of 4-phenylpyridine, viz. 1-benzoyl-4-phenyl-1,4-dihydropyridine, was isolated in 4% yield. Similarly, sec-butylmagnesium bromide condensed with benzoylpyridinimium chloride to give a small yield of 2-(4-pyridyl)-butane, but no product corresponding in properties to the probable dihydropyridine intermeidate could be isolated.

In a somewhat different type of condensation reaction, a reductive acylation, 1,1'-diacethyl-1,4,1',4'-tetrahydro-4,4'-bipyridine (CIX) was isolated after reaction of pyridine with zinc dust and acetic anhydride (26, 27). Further investigation revealed that 4-ethylpyridine and 1,4-diacetyl-1,4-dihydropyridine (CX) are also formed in this reaction in small yields (94). Thermal decomposition of CIX was found to give mainly pyridine and CX, but small amounts of 4-ethylpyridine and 4,4'-bipyridine were also obtained. Reduction of 1,4-diacetyl-1,4-dihydropyridine (CX) with zinc and acetic anhydride was found to give a small amount of 4-ethylpyridine, but in this reaction the major product was a zinc complex which could be decomposed to give 2,3-di-(4-pyridyl)-butane (CXI). However, action of zinc dust and acetic acid on CX was found to give mainly 4-ethylpyridine,

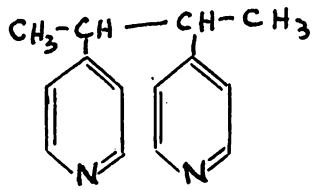
with a trace of acetaldehyde also being obtained (94).



CIX



CX

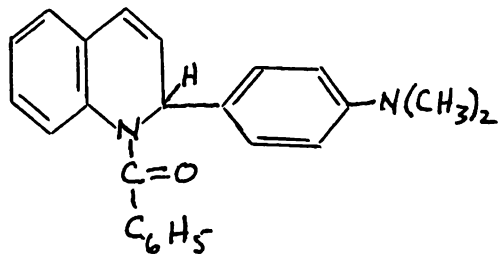


CXI

The yield of 4-ethylpyridine can be raised to 60-70% by reaction of pyridine, acetic anhydride, acetic acid and zinc dust under the proper conditions (2, 36). Furthermore, the method has been extended to permit preparation of a variety of 4-alkylpyridines, by use of other acid anhydrides in place of acetic anhydride (2, 92). However, no analogous reaction occurs with certain homologs and other derivatives of pyridine (84).

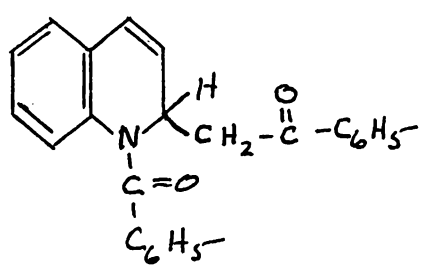
2. Quinoline Derivaties

1-Benzoyl-2-(p-dimethylaminophenyl)-1,2-dihydroquinoline (CXII) has been obtained in 43% yield by reaction of dimethylaniline, benzoyl chloride and quinoline (63). No copper-bronze catalyst was used in this reaction, although previous workers (55) had claimed that its presence was necessary for the condensation reaction to occur. No benzaldehyde could be obtained from CXII under a variety of conditions (63).



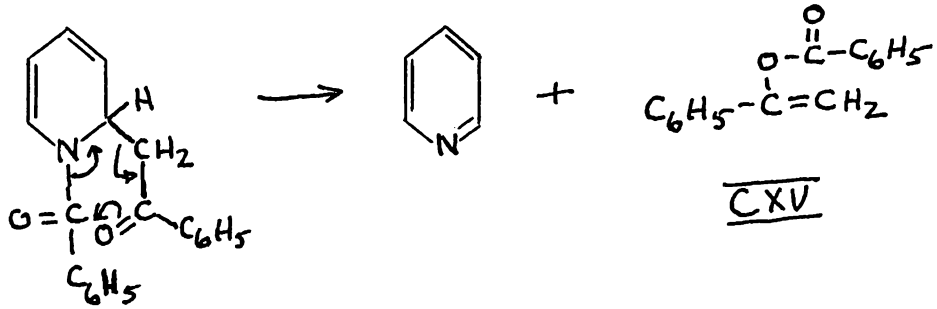
CXII

Condensation of acetophenone with benzoylquinolinium chloride (VI) has been reported to give 1-benzoyl-2-phenacyl-1,2-dihydroquinoline (CXIII), or an isomer differing only in the position of the non-aromatic double bond, in 10% yield (99). Products probably similar in structure to CXII and CXIII have also been obtained on reaction of ethyl cyanoacetate (64, 89) and ethyl benzoylacetate (99) with VI, but the structures of the products have not been proved in a rigorous manner.



CXIII

In all of the stable products formed upon condensation of a nucleophilic agent with an acylpyridinium salt, the nucleophilic agent has been found bonded to the 4-position of the pyridine ring. In contrast, the condensation of nucleophilic agents with acylquinolinium salts appears to give rise only to 2-substituted quinolines. Despite the evidence based upon isolation of heterocyclic products, however, there is reason to believe that at least some nucleophilic agents condense with acylpyridinium salts at both the 2- and 4-positions. For example, reaction of acetophenone, benzoyl chloride and pyridine gives O-benzoylacetophenone (CXV) in addition to 1-benzoyl-4-phenacyl-1,4-dihydropyridine (CII), and the suggestion has been made that CXV arises from initially formed 1-benzoyl-2-phenacyl-1,2-dihydropyridine (CXIV), a non-isolable intermediate (28). Mechanism studies carried out on related systems have provided support for this point of view (41, 99).



CXIV

CXV

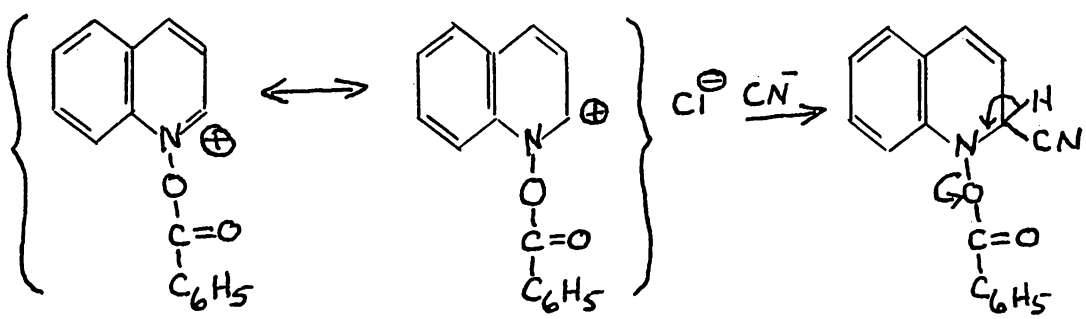
D. "Reissert Reaction" With Quinoline-1-oxide

The reaction of quinoline-1-oxide, benzoyl chloride and an aqueous solution of potassium cyanide to form quinaldonitrile (XXXVIII) in nearly quantitative yield has been termed a "Reissert reaction," although the presumed intermediate condensation product, 1-benzoyloxy-1,2-dihydroquinaldonitrile (CXVII) has not been isolated (46). The reaction has become a general one for the preparation of a variety of quinaldonitriles. A number of 4-alkoxyquinaldonitriles have been prepared from the corresponding 4-alkoxyquinoline-1-oxides in yields of 80-90% (69, 70, 71, 72). In addition, 4-chloroquinaldonitrile (72), 4-benzamidoquinaldonitrile (72), 6-methoxyquinaldonitrile (65) and 6-methylquinaldonitrile (65) have been prepared from the appropriately substituted quinoline-1-oxides. 4-Nitroquinoline-1-oxide gives 4-chloroquinaldonitrile in this reaction, however, a chloride ion evidently displacing the nitro group as a nitrite ion during the course of the reaction (72).

In the only reported reaction in the isoquinoline series, 7-aminoisoquinaldonitrile was prepared from 7-nitroisoquinoline-1-oxide, but details were not given (73). 5,6-Benzoquinoline-1-oxide and 7,8-benzoquinoline-1-oxide give the expected nitriles in good yields upon treatment with benzoyl chloride and aqueous potassium cyanide (22).

Quinoline-1-oxide does not undergo reaction with potassium cyanide to produce quinaldonitrile (XXXVIII) in the absence of an

acid chloride (46), although certain other nucleophilic agents, such as Grignard anions, do attack the ring (20). Therefore the function of the benzoyl chloride in the reaction with the cyanide ion must be to form an intermediate addition product, benzoyloxyquinolinium chloride (CXVI). The bonding of the electron-withdrawing acyl group to the oxygen atom of the quinoline-1-oxide increases the electrophilic reactivity of the quinoline ring and permits the cyanide ion to add to the 2-position of the ring, giving the non-isolable intermediate CXVII. The collapse of CXVII to quinaldonitrile (XXXVIII) follows. The driving force in the latter reaction is apparently aromatization of the system, but there can be little doubt that the stability of the released benzoate ion also aids in the successful completion of the reaction (58).



CXVI CXVII

XXXVIII

E. N-Alkyldihydroquinaldonitriles

Although a variety of nucleophilic agents condense with alkylquinolinium salts, only the reaction with the cyanide ion will be

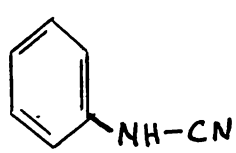
considered here. In the original reaction of this type, a 60% yield of 1-methyl-1,4-dihydrocinchoninonitrile (LIV) was obtained upon reaction of methylquinolinium iodide with an aqueous solution of potassium cyanide (50). In later work, LIV was oxidized by iodine in either alcohol or alcohol-pyridine as solvent to give nearly a quantitative yield of cinchoninonitrile methiodide. Distillation of the latter compound gave methyl iodide and a 90% yield of cinchoninonitrile (LIII) (49, 52). An overall yield of LIII of 56-65% has been obtained by this method (44).

There has b een some controversy over the 1,4-dihydro structure proposed for LIV. The argument has been raised (see private communication from C. K. Ingold given in footnote 19, reference 22) that the most thermodynamically stable product, as far as the degree of conjugation is concerned, would be 1-methyl-1,2-dihydrocinchoninonitrile.

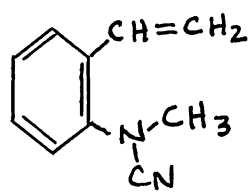
F. 1,2-Dicyanodihydroquinolines

When quinoline is treated with cyanogen bromide and hydrogen cyanide, a quinoline dicyanide is formed (66). This compound is converted to an isomer of higher melting point by treatment with ammonia in alcohol solution. Isoquinoline also reacts with cyanogen bromide and hydrogen cyanide to form an isoquinoline dicyanide, but this condensation product was not isomerized by treatment with ammonia. In later investigations, the isomeric quinoline dicyanides were both shown to have the 1,2-dicyano structure, and they were assigned the structures of <u>cis</u>- and <u>trans</u>-1,2-dicyano-1,2-dihydro-

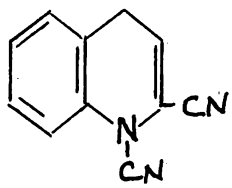
quinoline (67). Since configurationally stable trivalent nitrogen compounds are unknown unless the nitrogen is part of a rigid system, the structures of the quinoline dicyanide isomers have recently been reinvestigated (83). A comparison of the molecular refractions of the two compounds indicated that they were not cis,trans isomers. A study of the ultraviolet absorption spectra furnished evidence that the compounds are structurally different, and, since there seemed to be no question as to the location of the cyano groups, attention was directed to the location of the non-aromatic double bond. It was found that the isomer of lower melting point had an absorption spectrum very similar to that of carbanilonitrile (CXVIII), while the spectrum of the isomer of higher melting point bore a striking resemblance to that of N-methyl-o-vinylcarbanilonitrile (CXIX). On the basis of these results, the isomer of lower melting point was assigned the structure of 1,2(4H)-quinolinedicarbonitrile (CXX), and the isomer of higher melting point was designated as 1,2(2H)-quinolinedicarbonitrile (CXXI).



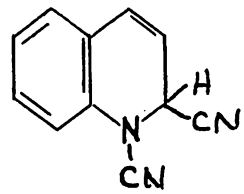
CXVIII



CXIX



CXX



CXXI

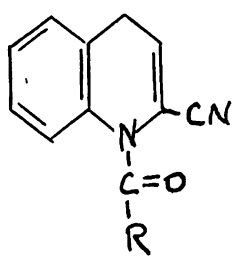
V. Structural Considerations

Although there seems to be no reasonable doubt that I and II represent the correct gross structures of Reissert compounds, there is still some confusion as to the fine structures. These complications arise mainly from examination of the absorption spectra of Reissert compounds.

A. Ultraviolet Absorption Spectra

Although the non-aromatic double bond of II can be located only in the 3,4-position of the isoquinoline ring, the possibility must be considered that the quinoline Reissert compounds may have the structure CXXII, in which the double bond is located in the 2,3-position of the quinoline ring rather than in the 3,4-position, as shown in structure I. The only available argument that structure I is correct lies in the fact that the ultraviolet spectra of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII), 1-benzoyl-4-methyl-1,2-dihydroquinaldonitrile (LXVI) and 1-benzoyl-2,4-dimethyl-1,2-dihydroquinaldonitrile (LXIX) are all

very similar (10). Since LXIX can have the double bond only in the 3,4-position, where it is in conjugation with the benzene ring, it can be argued that XVII and LXVI must also have the double bond in the same position or else their ultraviolet absorption spectra would differ from that of LXIX more than is actually observed. This argument is weakened, however, by the fact that the ultraviolet absorption spectrum of 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XL) is also similar to the spectra of XVII, LXVI and LXIX, although it is true that XL shows absorption at a slightly lower wavelength over the whole absorption region than does XVII, LXVI or LXIX (63).

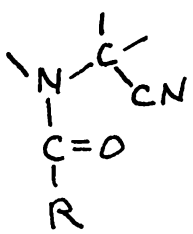


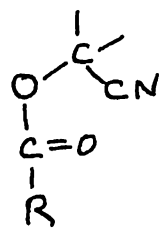
CXXII

B. Infrared Absorption Spectra

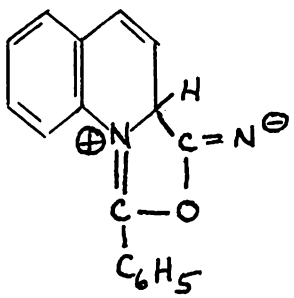
The most striking feature about the infrared spectra of Reissert compounds is the complete lack of absorption in the range 2200-2400 $cm.^{-1}$, the frequency range in which absorption due to a cyano group is observed. It has been found that the intensity of absorption due to the presence of a cyano group is dependent on the structure of the rest of the molecule (54). In a simple nitrile, the band is usually intense,

but its intensity decreases as the molecular weight of the compound increases. Furthermore, the intensity decreases when the cyano group is conjugated with other unsaturated groups or when oxygen-containing functional groups are also present in the molecule. In ketone cyanohydrins, for example, the nitrile band is very weak, but when the cyanohydrin is acylated, the nitrile absorption peak disappears. Since Reissert compounds are nitrogen analogs of acyl derivaties of ketone cyanohydrins, as shown in the partial structures given below, it might have been anticipated that nitrile absorption peaks would also be absent in the infrared spectra of Reissert compounds.





There is some possibility that Reissert compounds may receive a relatively large contribution from resonance structures such as CXXIII. Examination of a Fisher-Hirschfelder model of a Reissert compound reveals that the carbonyl oxygen atom may practically touch the carbon atom of the cyano group. The existence of such an interaction might be the basis for the lack of a cyano group absorption peak in the infrared spectra of Reissert compounds.



CXXIII

C. Physical Properties

While most Reissert compounds can be kept unchanged in the crystalline state for relatively long periods of time, some decomposition nevertheless gradually occurs. For example, a sample of 1-acetyl-1,2-dihydroquinaldonitrile that had been kept in a tightly stoppered bottle for two years was found to give several peaks in the infrared absorption spectrum not found in a freshly purified sample (19). During recrystallization of Reissert compounds from hot solvents, such an ethanol, a yellow color slowly appears and the odor of hydrogen cyanide develops.

Another property possessed by some Reissert compounds is the ability to exist in dimorphic forms. Thus, 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) exists, in the more stable form, as prisms of m. p. 154-155°, but a micro-crystalline form of m. p. 142.5-143.5° has been obtained on rare occasions. On standing, the dimorphic form of

lower melting point gradually reverts to the more stable form. The infrared absorption spectra of both forms are identical. Similarly, 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) has been obtained in two forms, the more stable form having a m. p. of 127-128°, and the less stable form a m. p. of 96-99°. Finally, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) has also been isolated in dimorphic forms, the more stable one having a m. p. of 125-126° and the other a m. p. of 56-57° (19, 42, 96).

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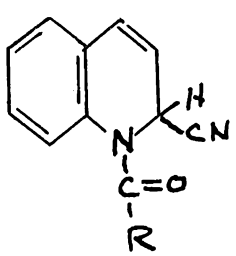
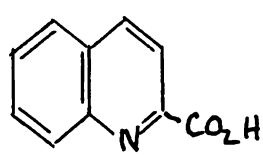
II. THE MECHANISM OF THE ACID-CATALYZED HYDROLYSIS OF REISSERT COMPOUNDS

Aldehydes are formed in excellent yields by the acid-catalyzed hydrolysis of reissert compounds. The Reissert compounds, in turn, are prepared by reaction of acid chlorides with quinoline, isoquinoline or phenanthridine in the presence of potassium cyanide or hydrogen cyanide in a variety of solvents (1-9). A Reissert compound of the quinoline series, a 1-acyl-1,2-dihydroquinaldonitrile (I), gives quinaldic acid (II) and quinaldamide (III) together with the aldehyde in the hydrolysis reaction. Benzoin quinaldate (IV) has also been isolated from the reaction mixture obtained upon hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (V). Analogous by-products are formed from the Reissert compounds derived from the other heterocyclic bases.



I



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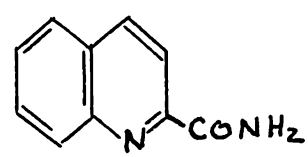

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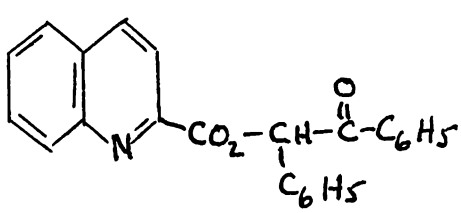

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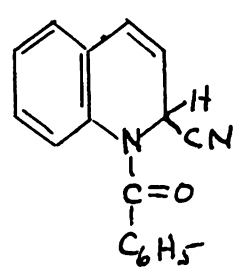
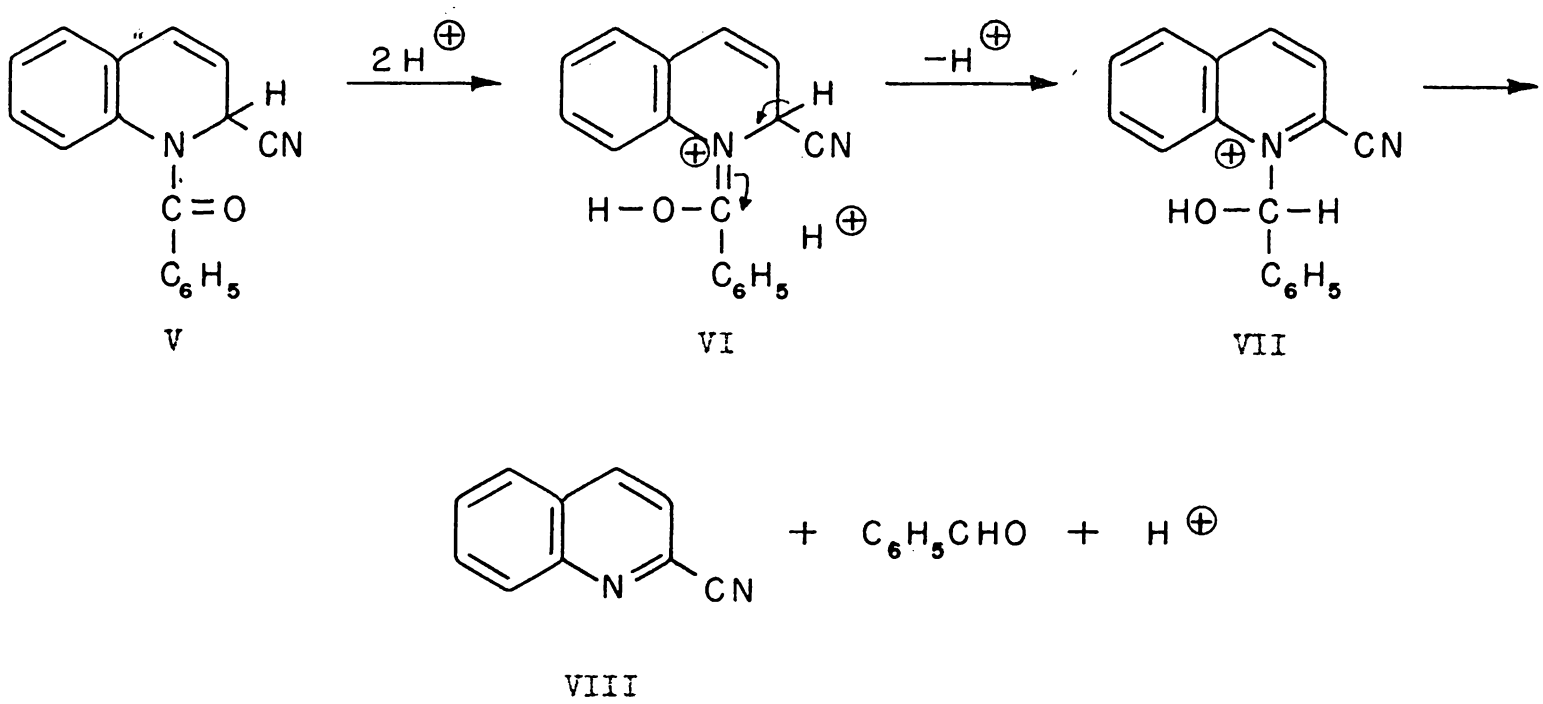


V

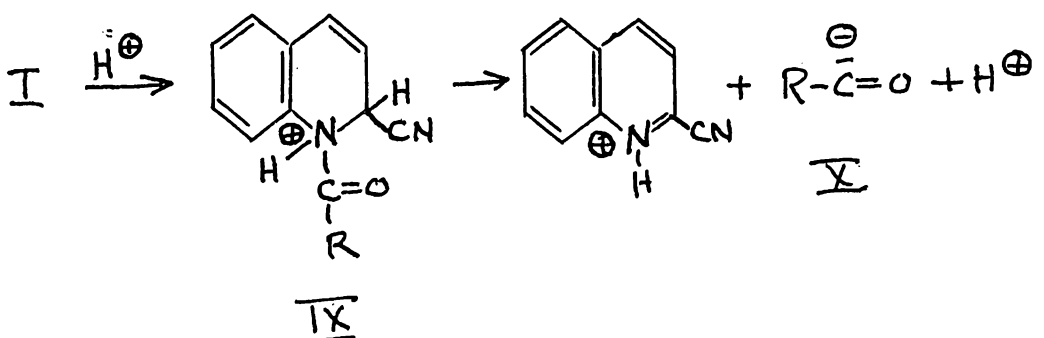


V VI VII

VIII

McEwen and Hazlett (10) recently proposed a mechanism for the formation of aldehydes from Reissert compounds and provided evidence in support of that mechanism. They suggested that the first step involves the formation of the conjugate acid (VI) of the Reissert compound. Then, in a concerted process, a proton is lost from the 2-position of the ring and a second proton is added to the original carbonyl carbon atom to yield VII. Finally, VII collapses to quinaldonitrile (VIII) and the aldehyde. It was assumed that VIII is hydrolyzed to II and III under the conditions of the reaction.

Colonna (11) has disagreed with this interpretation of the reaction. He prefers to consider this cleavage reaction to be very similar in mechanism to some cleavage reactions of acyl derivatives of heterocyclic N-oxides. According to the mechanism he proposed, the first step involves the formation of the conjugate acid of the Reissert compound, IX. Then, simultaneously, a proton is lost from the 2-position of the ring and the transient acyl anion X is formed. Finally the anion combines with a proton from the solution to form the aldehyde.



$\longrightarrow$ VIII + RCHO + $H^{\oplus}$

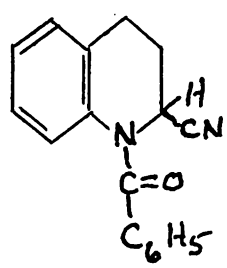
$R-\overset{O}{\overset{\|}{C}}-O^{\ominus}$

XI

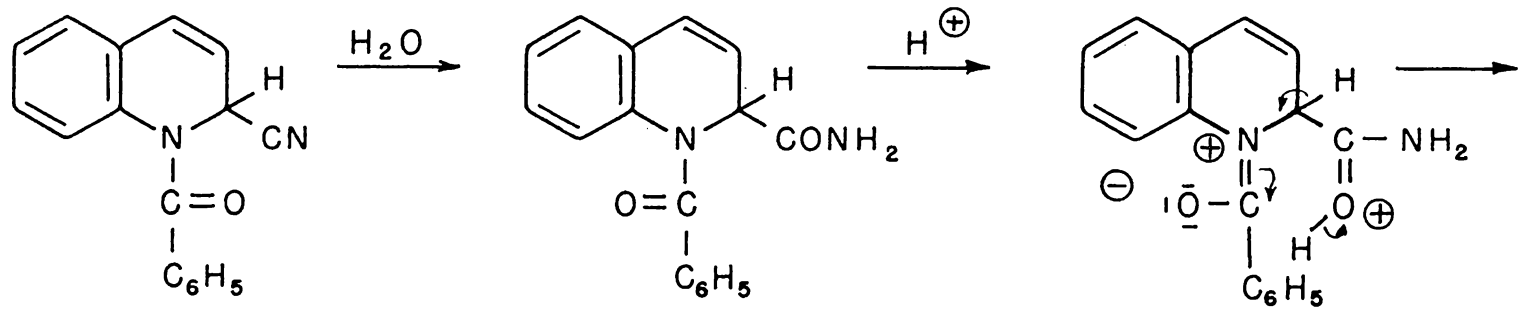
Colonna likened the formation of the acyl anion X to the formation of the acyloxy anion XI, which results from cleavage of the N-oxide group of aromatic heterocyclic N-oxides during reactions such as formation of quinaldonitrile from quinoline-1-oxide by reaction with benzoyl chloride and alkali cyanide. Apart from other difficulties which this mechanism presents in common with that proposed by McEwen and Hazlett (10), the suggestion that there is an analogy between cleavage of an acyl anion and an acyloxy anion seems to have little merit when the lack of similarity, both chemical and electronic, of the two proposed anions is considered. Thus the acyloxy anion XI has been well characterized and has considerable stability, but anion X would not have nearly the same degree of stability.

It was originally thought that the gain in resonance energy in passing from the dihydroquinoline structure to the fully aromatic quinoline derivatives might be an important driving force in the reaction (10). This belief was weakened, however, by certain observations of McEwen, Terss and Elliott (12). These workers described the preparation and acid-catalyzed hydrolysis of 1-benzoyl-1,2,3,4,-tetrahydroquinaldonitrile (XII) and 1-benzoyl-6-methoxy-1,2,3,4-tetra-

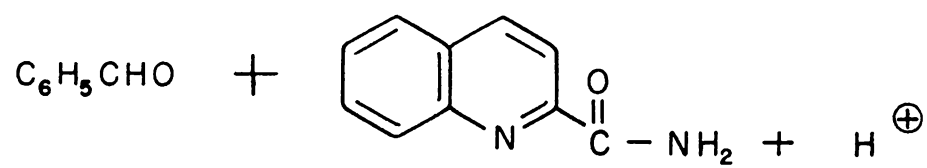
hydroquinaldonitrile. Both of these reduced Reissert compounds gave benzaldehyde upon acid-catalyzed hydrolysis, but only in less than half the yields obtained from the original Reissert compounds themselves. Since the tetrahydroquinaldonitriles would initially give rise to dihydroquinaldonitrile according to the mechanism postulated previously, there would be relatively little gain in resonance energy in the acid-catalyzed hydrolysis of these compounds. Thus this particular "driving force" in these reactions would be absent. Yet benzaldehyde was obtained in moderate yields from XII and its 6-methoxy derivative and at rates roughly comparable to those observed in the case of the original Reissert compounds. It is obvious that some side reaction (or reactions) competes favorably with aldehyde formation in the case of the reduced Reissert compounds, but the nature of the competing reaction was not established by McEwen, Terss and Elliott.



XII



V XIII XIV



III

The above observations strongly suggest that there is no important driving force due to aromatization in the acid-catalyzed formation of aldehydes from Reissert compounds. Consequently it was decided to reinvestigate other phases of the originally proposed mechanism. One obvious point of attack was to determine whether quinaldonitrile (VIII) is indeed an intermediate in the acid catalyzed hydrolysis of V. After a limited solvolysis reaction of 1-benzoyl-1,2-dihydroquinaldonitrile (V) in ethanolic hydrogen chloride solution, the only products isolated were benzaldehyde, quinaldic acid (II), quinaldamide (III) and ethyl quinaldate. Similar reactions in a concentrated aqueous hydrochloric acid mixture yielded only benzaldehyde, quinaldic acid (II) and benzoin quinaldate (IV), together with recovered V. In no case was quinaldonitrile (VIII) isolated. When quinaldonitrile (VIII) itself was treated with hydrochloric acid under the same conditions, however, 39% of it was recovered unchanged; the remainder was converted to quinaldic acid (II) and quinaldamide (III). Thus the rate of acid-catalyzed hydrolysis of quinaldonitrile (VIII) is slower than the rate of acid-catalyzed hydrolysis of V, and this fact excludes quinaldonitrile from further consideration as an intermediate in the hydrolysis of V.

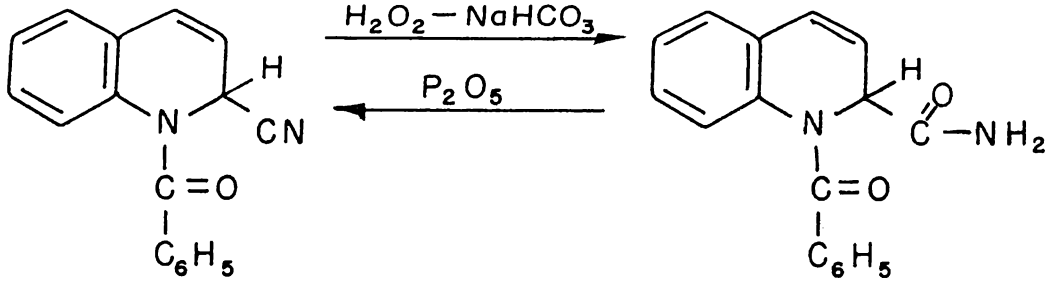
The next mechanism which was taken under consideration involved an initial hydrolysis of V to 1-benzoyl-1,2-dihydroquinaldamide (XIII). It was thought that the conjugate

acid of this amide might give benzaldehyde and quinaldamide *via* the quasi six-membered ring transition state XIV, or some species closely related to it.

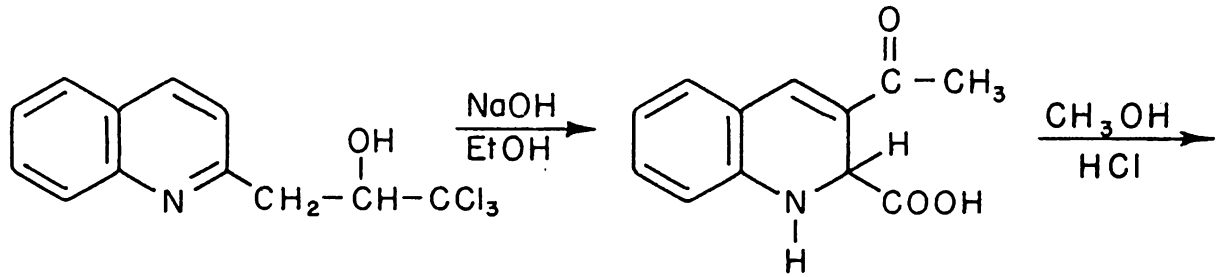
This possibility was rejected when it was shown that authentic 1-benzoyl-1,2-dihydroquinaldamide (XIII) and also 1-benzoyl-3-acetyl-1,2-dihydroquinaldamide (XV) failed to give any benzaldehyde at all on treatment with concentrated hydrochloric acid. The amide XIII was prepared by the action of hydrogen peroxide on V in the presence of sodium bicarbonate. The proof of XIII was based on elemental analysis, the infrared absorption spectrum and the reconversion of XIII to V by dehydration with phosphorus pentoxide in the presence of triethylamine.

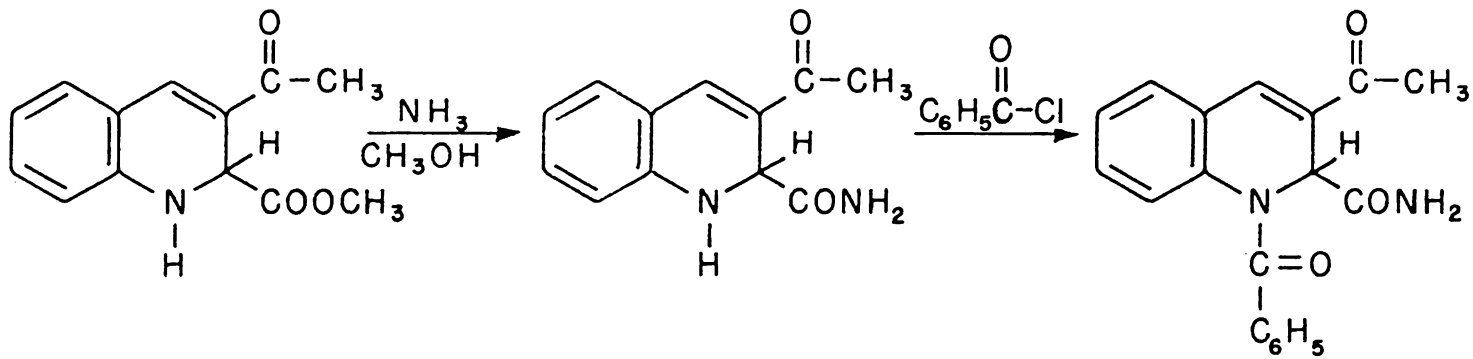
The synthesis of XV was achieved by ammonolysis of methyl 3-acetyl-1,2-dihydroquinaldate (XVI) (13), followed by benzoylation of the amide XVII with benzoyl chloride in hot benzene. Attempts to prepare XV by way of 3-acetyl-1,2-dihydroquinaldoyl chloride failed. Benzoylation of XVI with benzoyl chloride in pyridine solution afforded methyl 1-benzoyl-3-acetyl-1,2-dihydroquinaldate as reported by Woodward and Kornfeld (13), but attempted ammonolysis of this compound resulted in the cleavage of the benzoyl group.

An attempt was next made to gain more precise information on the relative rates of acid-catalyzed formation of benzaldehyde from 1-benzoyl-1,2-dihydroquinaldonitrile (V)


H2O2 — NaHCO3
P2O5
H
CN
N
C=O
C6H5
H
O
C—NH2
N
C=O
C6H5

V XIII


OH
N
CH2—CH—CCl3
NaOH
EtOH
O
C—CH3
H
N
H
COOH
CH3OH
HCl

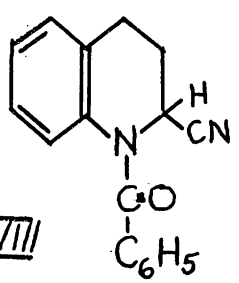

O
C—CH3
H
N
H
COOCH3
NH3
CH3OH
O
C—CH3
H
N
H
CONH2
O
C6H5C—Cl
O
C—CH3
H
N
CONH2
C=O
C6H5

XVI XV

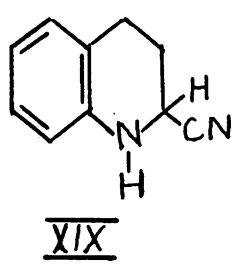
and 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII) and to determine the nature of the acid-catalyzed reaction of XII that successfully competes with formation of benzaldehyde. Qualitative rate comparisons were made at 36° in homogeneous ethanolic hydrogen chloride solutions containing 2,4-dinitrophenylhydrazine. Benzaldehyde-2,4-dinitrophenylhydrazone was collected at various time intervals. Solutions of V became turbid after 18 seconds; after 20 seconds a 63.6% yield of the hydrazone had formed; after 25 seconds the yield was 69.8%; after 60 seconds the yield was 70.3%; with 5 minutes reaction time the yield increased to 89% and gradually increased further to 93% after 3 hours reaction. Solutions of XII became turbid after about 40 seconds; after 45 seconds a 29.3% yield of the hydrazone had formed; after 60 seconds, the yield was 39.6%; after 90 seconds the yield was 40.3%; lengthening the reaction time further did not increase the yield of aldehyde. Although exact values of the relative rates of benzaldehyde formation cannot be given on the basis of the above data, the difference is certainly small, much too small to permit consideration of a special driving force due to a gain in aromaticity for the conversion of V to benzaldehyde plus quinaldic acid and its derivatives. The results indicate that the gain in resonance energy in the reaction of V is important only in determining the yield of benzaldehyde and not in determining the rate of formation of benzaldehyde. In other words, the rate-deter-

mining step in the reaction does not coincide with the product-determining step, and only the latter is influenced by the striving of the system for a greater degree of aromaticity.

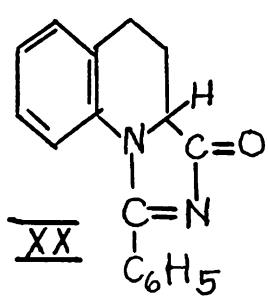
An attempt to determine the nature of the reaction which competes with the formation of benzaldehyde in the case of XII was in large measure successful. After a reaction of limited duration 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII) was obtained in not less than 20% yield. An authentic sample of XV was prepared by the catalytic addition of one molar equivalent of hydrogen to 1-benzoyl-1,2-dihydroquinaldamide (XIII). Further proof of structure of XVIII was its synthesis from 1,2,3,4-tetrahydroquinaldamide (XIX) by treatment with benzoyl chloride in pyridine; however, the major product of this reaction was not XVIII, but a compound, $C_{17}H_{14}N_2O$, which has been assigned the structure XX. Further work dealing with this compound will be presented later. The amide XIX was obtained by ammonolysis of methyl tetrahydroquinaldate; the ester in turn was prepared from tetrahydroquinaldic acid (14). Attempts to prepare the amide XIX from 1,2,3,4-tetrahydroquinaldoyl chloride failed.



XVIII



XIX



XX

The new data clearly require a modification of the previously proposed (10) mechanism for the acid-catalyzed formation of aldehydes from Reissert compounds. We now propose the following modified mechanism: (a) Reaction of V with hydrochloric acid first gives the cyclic intermediate XXI. (b) Rearrangement of XXI affords XXIII, very likely *via* the relatively stable meso-ionic intermediate XXII.[1] It is noteworthy that the reaction mixture always turns a bright yellow after a short period of time. (c) Addition of water to XXIII affords XXIV. (d) Finally, collapse of XXIV gives benzaldehyde plus quinaldamide (III). Since quinaldamide (III) has actually been isolated from the hydrolysis mixture of V there is nothing speculative in regarding it as a primary product of reaction.

In the case of 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII) the assumption can again be made that the first steps involve formation of a cyclic cation XXV and its conversion to a meso-ionic intermediate of structure XXVI. Then XXVI could react in either of two ways: (a) it could accept a proton at the original carbonyl atom to give XXVII, which could then undergo hydrolytic cleavage *via* XXVIII to

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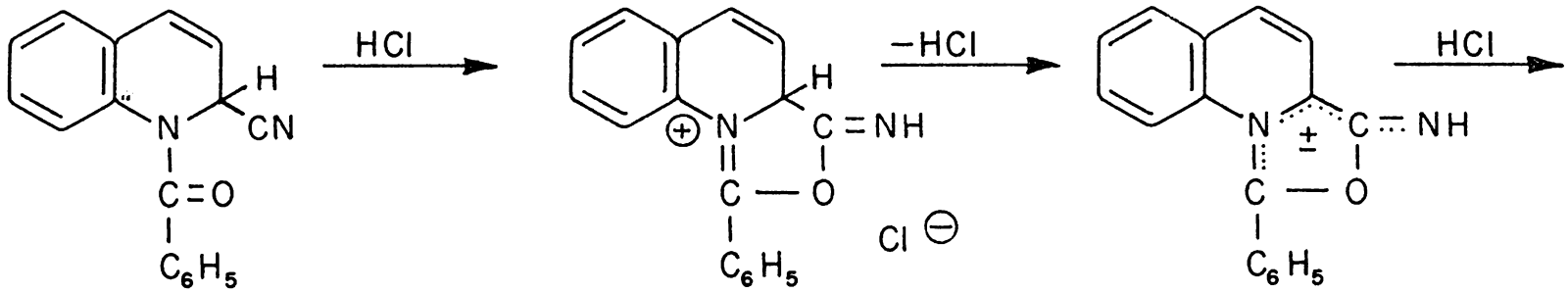
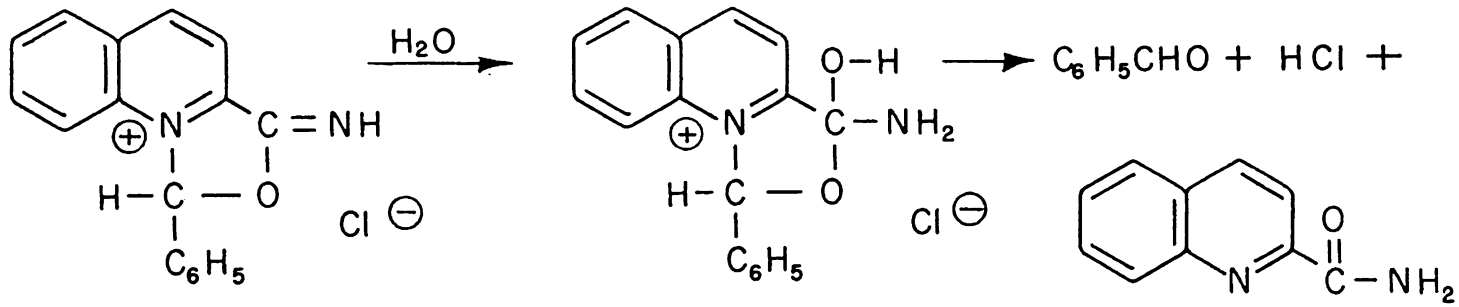
[1]Although it is not symbolized in structure XXII, the π electrons of the 5-membered ring would also enter into resonance interaction with the π electrons of the aromatic rings.



V XXI XXII

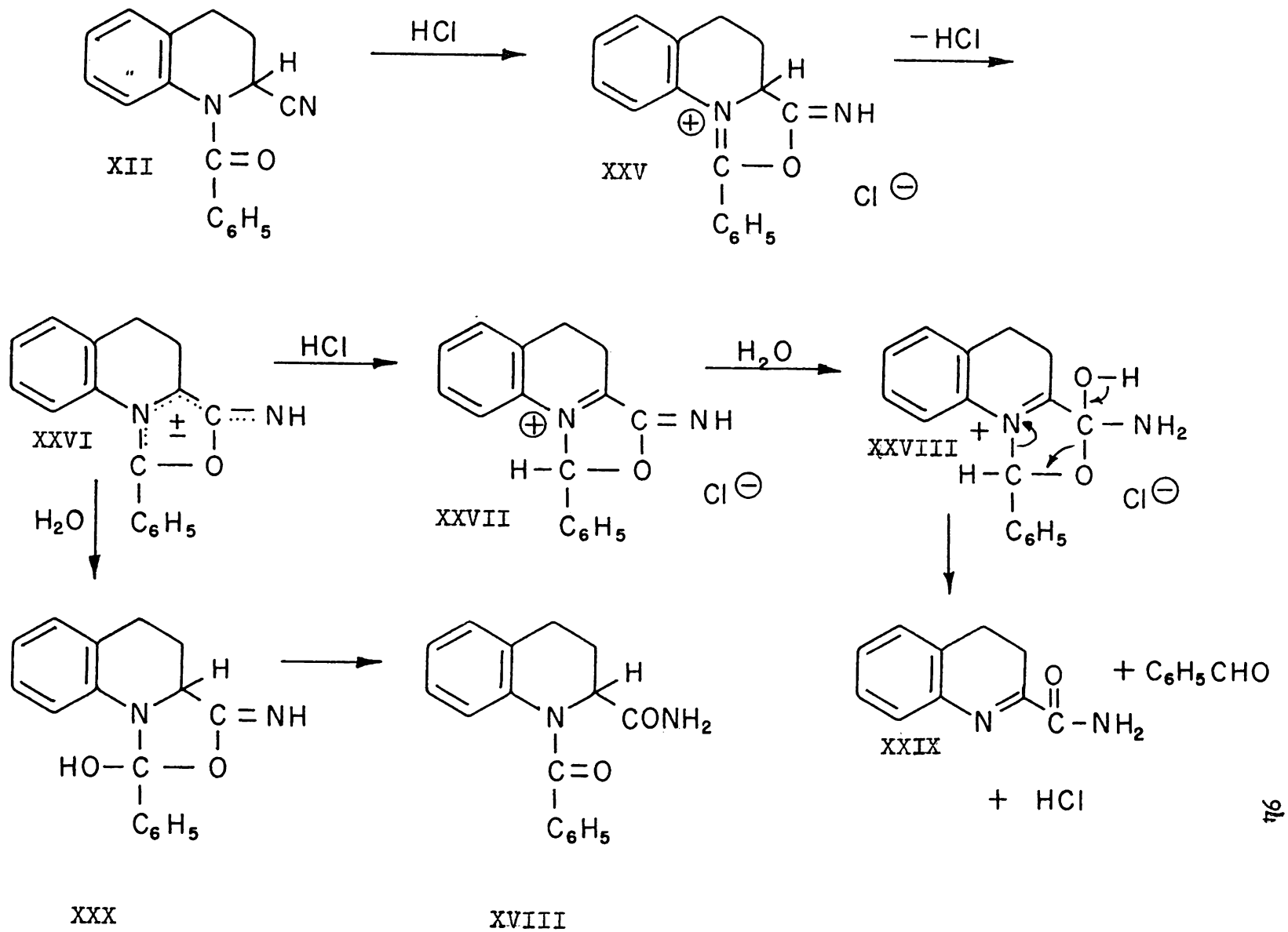


XXIII XXIV III

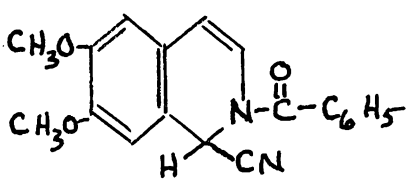
benzaldehyde and 3,4-dihydroquinaldamide (XXIX). (b) Addition of a molecule of water to XXVII would give XXX, which could then collapse to form 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII). It is not particularly surprising that these product-determining sequences of reactions would occur at comparable rates since there is no substantial increase in aromaticity in either sequence.

Further work was carried out in an attempt to isolate the proposed intermediates or to get some evidence for their existence. It was thought that a modification of the reaction conditions might permit isolation of the meso-ionic compound, XXII, or one of its conjugate acids, XXI or XXIII. Attention was turned primarily to the use of hydrogen chloride in an inert, dry solvent, instead of the use of hydrochloric acid in aqueous or alcoholic solution.

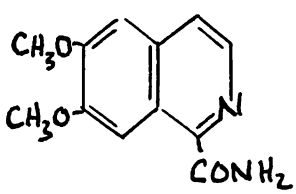
A search of the literature revealed that anhydrous solvents had been used previously as media for the action of dry hydrogen chloride on Reissert compounds. Kaufmann and Dandliker (15), in their attempts to prepare quinaldonitrile from V, observed that action of dry hydrogen chloride on a solution of 1-benzoyl-1,2-dihydroquinaldonitrile (V) in anhydrous benzene, chloroform or ether yielded an unstable yellow compound which had an odor of benzaldehyde. Similarly, McEwen, Kindall, Hazlett and Glazier (16) found that a solution of V in dry ether gave, upon treatment with dry hydrogen chloride, a yellow solid which yielded 45% of quinaldamide


HCl
−HCl
XII
XXV
HCl
H_2O
H_2O
XXVI
XXVII
XXVIII
XXIX
XXX
XVIII
+ C_6H_5CHO
+ HCl

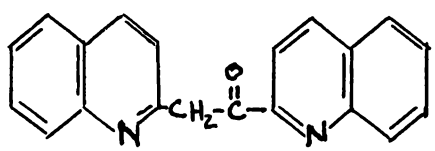
(III) upon hydrolysis. Haworth and Perkin (17) made an observation which is even more significant. These workers reported that passage of dry hydrogen chloride through a cold chloroform solution of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (XXXI) yielded an orange solid which, after being washed with ether, gave benzaldehyde and the amide XXXII upon steam distillation. As any initially formed benzaldehyde would have been removed by the ether wash, its origin by necessity was from action of water upon the orange solid.



XXXI



XXXII



XXXIII

Very similar results have now been obtained by action of dry hydrogen chloride on V in inert solvents. In dry chloroform as a solvent, an odorless, yellow solid resulted. The solid was very sensitive to moist air; it darkened rapidly and the odor of benzaldehyde developed. Even more spectacularly, breathing upon an odorless sample of the

yellow solid caused the odor of benzaldehyde to develop. Hydrolysis of the solid yielded, in addition to benzaldehyde, quinaldamide (III), quinaldic acid (II) (as its copper salt) and a compound thought to be desoxyquinaldoin (XXXIII). Action of strong acid yielded, except for XXXIII, the same products. In each hydrolysis attempt the major product was an intractable tar. Analytical data for the yellow solid would not permit a structural assignment, but indicated rather that it was probably a mixture of two or more components. Lack of homogeneity and of a reliable structural proof prevents a valid comparison of yields of benzaldehyde from this solid and from the parent compound, V.

In anhydrous benzene, action of dry hydrogen chloride on V gave an unstable red-violet colored solid which smelled of benzaldehyde. Hydrolysis of the solid under slightly acidic conditions gave benzaldehyde and quinaldamide (III), but no quinaldic acid. Similarly, basic hydrolysis of some of the solid previously washed free of benzaldehyde with benzene gave essentially the same yield of benzaldehyde, in addition to quinaldamide and an uncharacterized higher melting material. That the solid gave benzaldehyde under basic conditions is particularly significant since it indicates that only water is necessary for completion of the reaction once the necessary intermediate has been formed. Again analytical data would not permit assignment of a definite structure for the colored solid, but the results

were in fair agreement for a compound having the empirical formula required for the monohydrate of XXI or XXIII.

McEwen and Hazlett (10) recently reported that hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (V) in concentrated hydrochloric acid containing an excess of benzaldehyde gave fair yields of benzoin quinaldate (IV). Other Reissert compounds were found to behave similarly. As it was thought that this might be a good synthetic route to such esters and as a continuation of the studies of the action of dry hydrogen chloride on Reissert compounds in anhydrous solvents, dry benzaldehyde was next used as a solvent for the reaction. Reaction of dry hydrogen chloride with the Reissert compound, V, in pure benzaldehyde as a solvent caused an intense orange coloration to develop and precipitation of ammonium chloride. Heating the benzaldehyde solution with small amounts of concentrated hydrochloric acid yielded a brilliant yellow to orange crystalline solid. Conditions had to be varied somewhat in each run to permit isolation of the orange solid, but it was assumed to have nearly the same composition in each case. Acid hydrolysis of the solid yielded as the only isolable products quinaldic acid and, in small yields, a difficulty separable mixture of benzoin quinaldate and a compound thought to be 2-(2-quinolyl)-4,5-diphenyloxazole, XXXIV.[2] No benzaldehyde was

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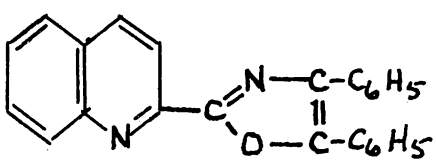
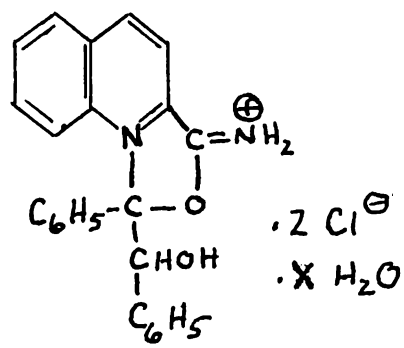
[2] *Cf.* the isoquinoline analog, XXXVII, reference 16.

obtained in any case. Basic hydrolysis of the orange solid yielded quinaldamide and quinaldic acid as the only isolable products.

Analytical results for the orange solid would not permit assignment of a structure, but the available data and the hydrolysis results seems to indicate that it is probably a mixture of at least two components, ammonium chloride and a hydrated compound of the proposed structure XXXV or its decomposition products, the hydrochlorides of benzoin quinaldate (IV), the oxazole XXXIV, quinaldic acid (II) and quinaldamide (III).[3] Attempted purification of the material by recrystallization from C. P. acetone yielded the hydrochlorides of II and III.



XXXIV



XXXV

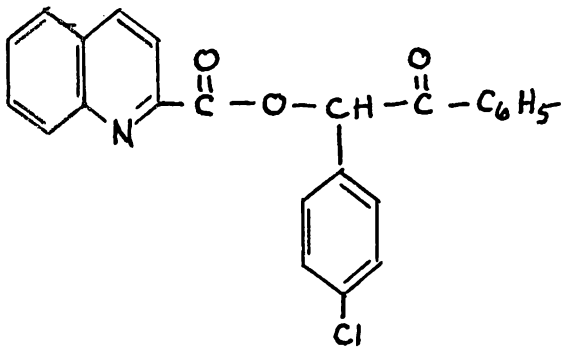
[3]While no absolute evidence is available for the existence of XXXV, it is felt that the color of the compound and the lack of a large melting point range, which would probably be required for a mixture of the decomposition products listed, is some indication that such a compound is present.

Hydrolysis of the benzaldehyde mother liquor after removal of the orange solid gave, in fair yield, a mixture of benzoin quinaldate (IV) and the oxazole XXXIV, in addition to quinaldic acid. Because of the difficulty in handling the reaction mixture and separating the pure components it is not felt that this is a profitable route to the preparation of such benzoin esters.

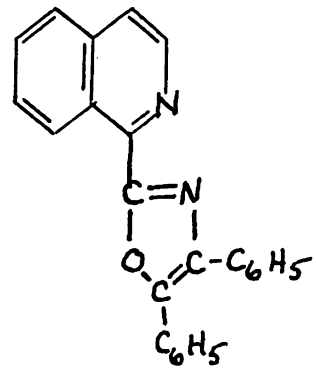
Reaction of dry hydrogen chloride with the Reissert compound V in a solution of C. P. acetone gave, in about 50% yield, a tan solid that was probably mainly quinaldamide hydrochloride. Addition of concentrated hydrochloric acid to the acetone solution after removal of the tan solid and heating yielded a solid which was probably mainly quinaldic acid hydrochloride.

The properties of the compound XXXIV proposed to be 2-(2-quinolyl)-4,5-diphenyloxazole are very similar to those of the isoquinoline analog XXXVII (16). The oxazole XXXIV proved to be very resistant to acid hydrolysis; hydrolysis to benzoin and quinaldic acid occurred to the extent of only about 50% when refluxed for one week with aqueous sulfuric acid. Both the oxazole XXXIV and its isoquinoline analog XXXVII impart a faint fluorescence to their solutions. The oxazole XXXIV, like XXXVII, may be eluted from an alumina column with benzene while contaminant benzoin quinaldate (IV) remains firmly adsorbed.

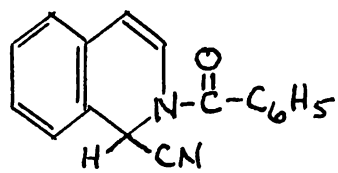
It is necessary, of course, that the new mechanism for the acid-catalyzed hydrolysis of Reissert compounds be capable of explaining the formation of benzoin quinaldate (IV) and 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIV) from 1-benzoyl-1,2-dihydroquinaldonitrile (V). Earlier, McEwen and Hazlett (10) reported that reaction of the Reissert compound V with hydrochloric acid in the presence of an excess of p-chlorobenzaldehyde gave a significant yield of p-chlorobenzoin quinaldate (XXXVI). The isomeric ester, p-chlorobenzoin quinaldate, was obtained by reaction of 1-(p-chlorobenzoyl)-1,2-dihydroquinaldonitrile with hydrochloric acid in the presence of an excess of benzaldehyde. Furthermore, evidence was presented to show that the two esters arose from some intermediate condensation product by way of an intramolecular rearrangement. Later, McEwen, Kindall, Hazlett and Glazier (16) reported that the yield of 2-(1-isoquinolyl)-4,5-diphenyloxazole (XXXVII) from reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXXVIII) with hydrochloric acid was markedly increased by the addition of an excess of benzaldehyde to the reaction mixture; the yield of the oxazole XXXVII was not increased, however, by addition of an excess of benzoin.



XXXVI

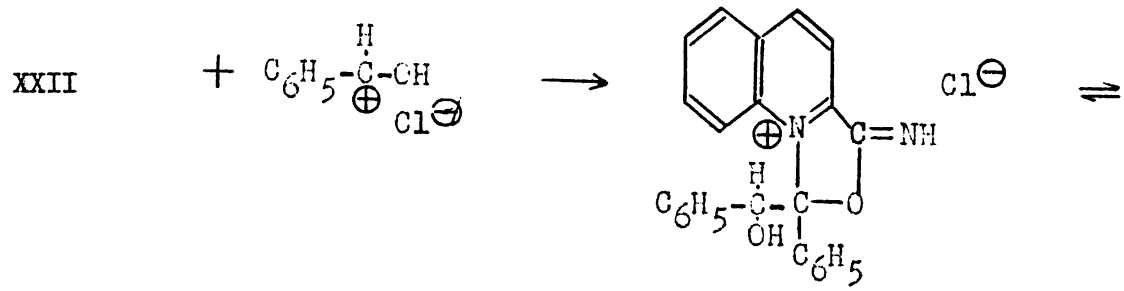


XXXVII

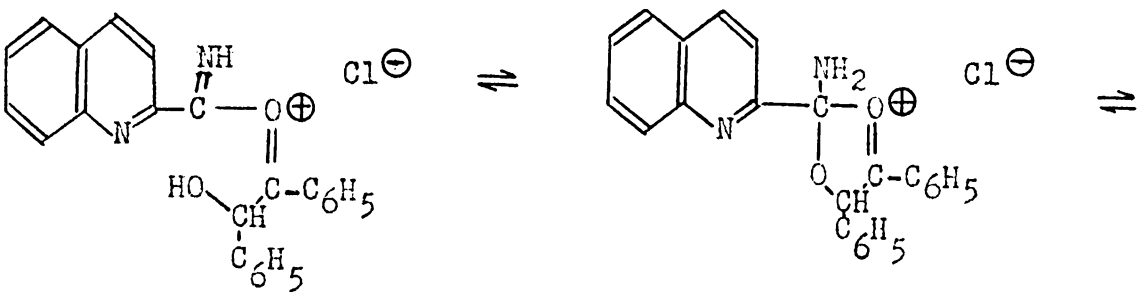


XXXVIII

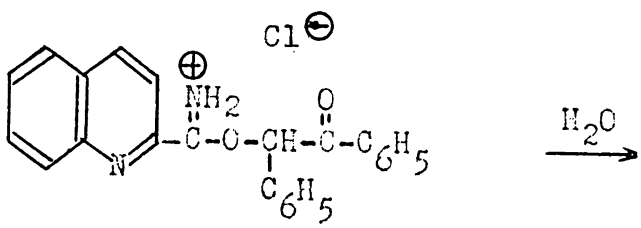
Keeping in mind these experimental facts the new mechanism can readily explain the formation of benzoin quinaldate (IV) and 2-(2 -quinolyl)-4,5-diphenyloxazole (XXXIV) from 1-benzoyl-1,2-dihydroquinaldonitrile (V) as follows: the conjugate acid of benzaldehyde can add to the meso-ionic intermediate XXII to produce XXXIX (cf. XXXV). In turn, XXXIX can rearrange intramolecularly to XLII via XL and XLI, respectively. Then the imino ether XLII could undergo either a hydrolysis to benzoin quinaldate (IV) or a cyclization to the hydroxydihydro-oxazole, XLIII, which affords the oxazole XXXIV in a simple acid-catalyzed dehydration.



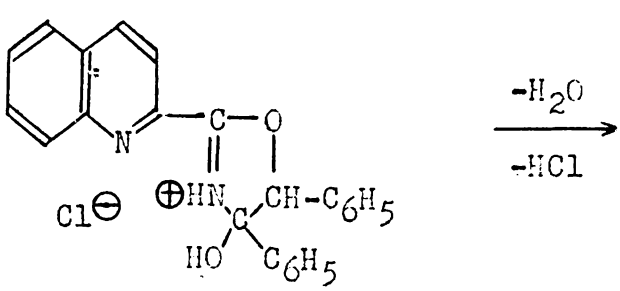
XXXIX



XL XLI



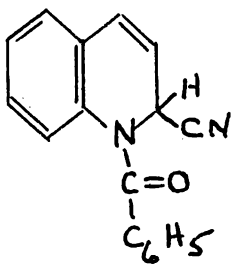
XLII IV



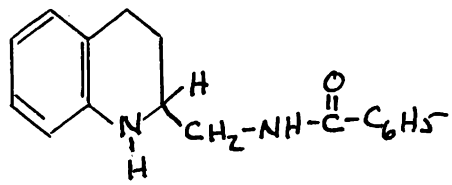
XLIII XXXIV

III. THE HYDROGENATION OF REISSERT COMPOUNDS

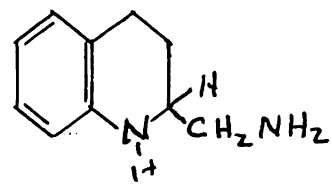
Some time ago, Rupe, Paltzer and Engel (3) reported that hydrogenation of the Reissert compound, 1-benzoyl-1, 2-dihydroquinaldonitrile (V), over a nickel catalyst at 100 atmospheres pressure and at an elevated temperature yielded α-benzamido-1,2,3,4-tetrahydroquinaldine (XLIV). Thus, this treatment resulted not only in reduction of the cyano group and the pyridine portion of the ring system, but also in migration of the benzoyl group to the newly formed aminomethyl group. Acid-catalyzed hydrolysis of the amide, XLIV, yielded α-amino-1,2,3,4-tetrahydroquinaldine (XLV) almost quantitatively. Further proof of structure of the amide, XLIV, other than analytical data, was based on the fact that it gave a crystalline nitrosamine, a derivative characteristic of a secondary amine.



V



XLIV



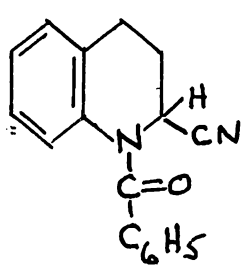
XLV

It was also reported that hydrogenation of the Reissert compound V over a palladium catalyst did not proceed to the same extent as when nickel was used. A compound thought to

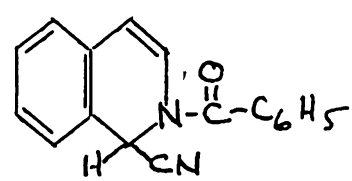
be a bis-amine was a minor product when the catalyst was palladium; the amide XLIV was still the major product. Sodium in hot ethanol was also found to effect reduction, but in this case the pyridine portion of the ring was cleaved.

Subsequent work (4, 5, 18, 19, 20) showed that this rearrangement of the benzoyl group occurred during hydrogenation of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile and the isoquinoline Reissert compound, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXXVIII). In the latter case, hydrogenation occurred only at a somewhat higher pressure.

Catalytic hydrogenation of Reissert compounds at lower pressures was investigated by McEwen, Terss and Elliott (12). Absorption of one molar equivalent of hydrogen at one atmosphere pressure and at room temperature over a platinum catalyst occurred readily with the Reissert compound V and its 6-methoxy derivative to yield the dihydro derivatives, XII and the 6-methoxy analog, respectively, in good yields.



XII



XXXVIII

The isoquinoline Reissert compound, XXXVIII, was found to absorb one molar equivalent of hydrogen under these conditions, but the anticipated dihydro derivative was not obtained. Instead about half the starting material was recovered in addition to an intractable gum. One molar equivalent of hydrogen was again slowly absorbed by XXXVIII over a platinum catalyst when the pressure was increased to about three atmospheres (21), but the results were the same as before.

Unexpected results were obtained when 1-benzoyl-1,2-dihydroquinaldonitrile (V) was subjected to hydrogenation at about three atmospheres pressure (21). In ethanol solution over a platinum catalyst hydrogenation proceeded slowly. The major product was found to be a compound, $C_{17}H_{14}N_2O$ (XX), isomeric with 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII). The latter compound, XII, was also obtained from this hydrogenation reaction mixture, but only in about half the yield of XX. In addition, the completely reduced, rearranged material XLIV was isolated in a small yield.

The compound XX was also obtained (21) in about 70% yield when the hydrogenation period was sufficiently prolonged so that two moles of hydrogen were consumed per mole of Reissert compound, V, at room temperature and atmospheric pressure. Also XX was obtained in unreported yield when 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII) was al-

lowed to absorb one molar equivalent of hydrogen under the same conditions. Furthermore, it was observed that the apparent absorption of three molar equivalents of hydrogen by the Reissert compound V yielded XX, but in smaller yields. The compound XX also absorbed hydrogen under the same conditions, but the only characterized material recovered was the starting compound. Isolated in varying amounts in all reductions was some intractable material. In ethyl acetate as a solvent, absorption of one molar equivalent of hydrogen by V resulted in formation of a mixture of XII and XX. An explanation for these confusing observations will be presented later.

An interesting and very provocative observation was made during oxidation studies on this series of compounds (21). Action of potassium permanganate on the dihydro Reissert compound XII yielded the compound XX. Indeed, this method has been found to be more convenient than further hydrogenation for the preparation of XX from the dihydro Reissert compound, XII. The results of these apparent hydrogenation (reduction) and oxidation reactions seem contradictory in that the same product (XX) is formed from the dihydro Reissert compound, XII, in either case. However, as will be shown later, the permanganate reaction has been interpreted in terms of hydration rather than oxidation and the extended period of contact of XII with the solvent during

further hydrogenation permits a fraction of XII to undergo solvolysis and dehydration to form XX.

Elliott (21) reported that the compound XX gave a 90% yield of benzaldehyde on treatment with mineral acid. On the basis of this information, he thought that the compound XX should be more closely related to the Reissert compound V than its dihydro derivative, XII.[4] He therefore suggested that the compound XX might be 1-benzoyl-1,4-dihydroquinaldonitrile, XLVI. He thought that this compound, along with the isomeric 1,2-dihydro compound, V, would be analogous to the isomeric dicyano-dihydroquinolines.

Mumm and Herrendorfer (22) reported that quinoline reacts easily with cyanogen bromide in the presence of an excess of hydrogen cyanide to yield a dicyanide which is easily converted by ammonia into a lower melting isomer. It was originally thought (23) that these isomers differed stereochemically, and they were assigned the structures of cis- and trans-1,2-dicyano-1,2-dihydroquinoline. Since this would constitute the only known case of a configurationally stable trivalent nitrogen atom which is not linked by a double bond or otherwise part of a rigid ring system, Seeley, Yates and Noller (24) reinvestigated the structures of these isomers. On the basis of molecular refractions and ultra-

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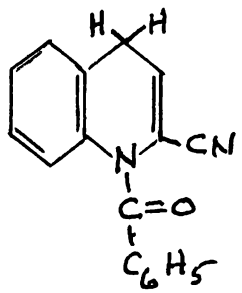
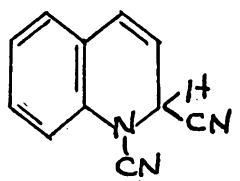
[4] Cf. comparison of yields of aldehyde from V and XII, reference 12.

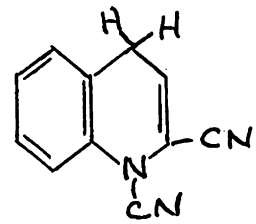
violet absorption spectra, they determined that these compounds were the structurally isomeric 1,2-dicyano-1,2-dihydroquinoline (XLVII) and 1,2-dicyano-1,4-dihydroquinoline (XLVIII).



XLVI



XLVII



XLVIII

In the light of this information, Elliott (21) sought to isomerize the Reissert compound V to the 1,4-dihydro derivative, XLVI,[5] by the use of methanolic ammonia. Although some decomposition occurred under these conditions, only starting material could be recovered. The compound XX was unaffected by alcoholic ammonia. Attempts to isomerize V to XLVI by catalytic action of platinum black also met with no success.

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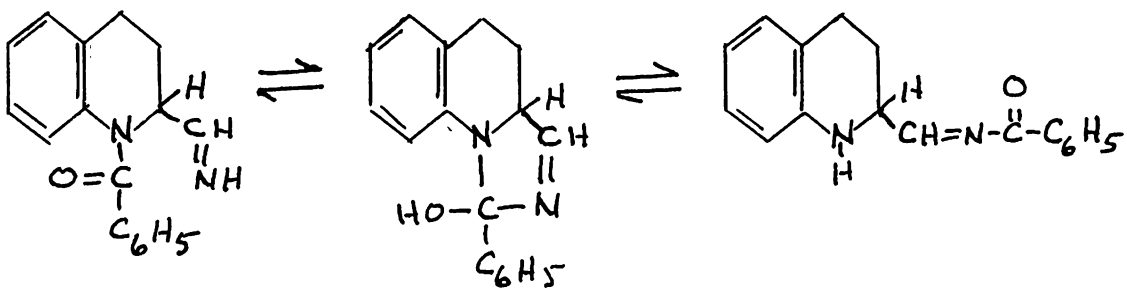
[5] V. Boekelheide and J. Weinstock, J. Am. Chem. Soc., 74, 660 (1952), reported that ultraviolet spectral studies indicate that the quinoline Reissert compounds have the 1,2-dihydro structure, as in V.

Elliott next considered the possibility that the compound XX is actually a "tetrahydro Reissert compound," which might be represented by one, or all, of the tautomeric structures, XLIX a, b and c. However, analytical data would not support such a structure.



XLIX a XLIX b XLIX c

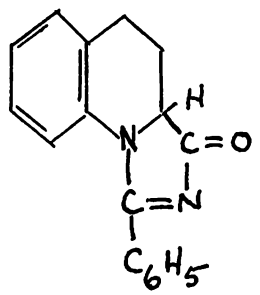
In the course of further investigations on the hydrogenation of Reissert compounds, 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile has been shown to undergo a reaction analogous to that of the Reissert compound V. Absorption of two molar equivalents of hydrogen at one atmosphere pressure over a platinum catalyst yielded a product analogoys to XX. It may also be significant that, in the presence of mercury, absorption of only one molar equivalent of hydrogen by the 6-methoxy analog of V resulted in the formation of the material analogous to XX insteal of 1-benzoyl-6-methoxy-1,2,3,4-tetrahydroquinaldonitrile, which is ob-

tained under normal conditions (12). It was found, however, that the 6-methoxy analog of XX failed to give significant amounts of benzaldehyde on treatment with concentrated hydrochloric acid. Subsequently it was found that, contrary to a previous report (21), the compound XX also fails to give any benzaldehyde by acid-catalyzed hydrolysis; indeed it is much more stable to any type of acid-catalyzed cleavage than is either the Reissert compound V or its dihydro derivative, XII.

Some further hydrogenation studies were made on the Reissert compound V. It was found that frequently, for no apparent reason, absorption of even one molar equivalent of hydrogen occurs extremely slowly in ethanol solution, and additional catalyst must be added to effect complete reduction. It was also found that addition of a trace of acetic acid caused the absorption to go rapidly to the desired point. However, the product in this case proved to be a mixture, assumed to be composed of the normal dihydro Reissert compound XII and the compound XX. There are further indications that the dihydro Reissert compound, XII, as usually obtained is contaminated with some XX.

Any structure proposed for the compound XX must account for the stoichiometry of the reaction, the lack of formation of benzaldehyde by acid-catalyzed hydrolysis and its stability under both oxidizing and reducing conditions. A

structure that is consistent with all the available data is that represented by an imidazolone, XX, 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline. Additional evidence in support of this structure is outlined below.



XX

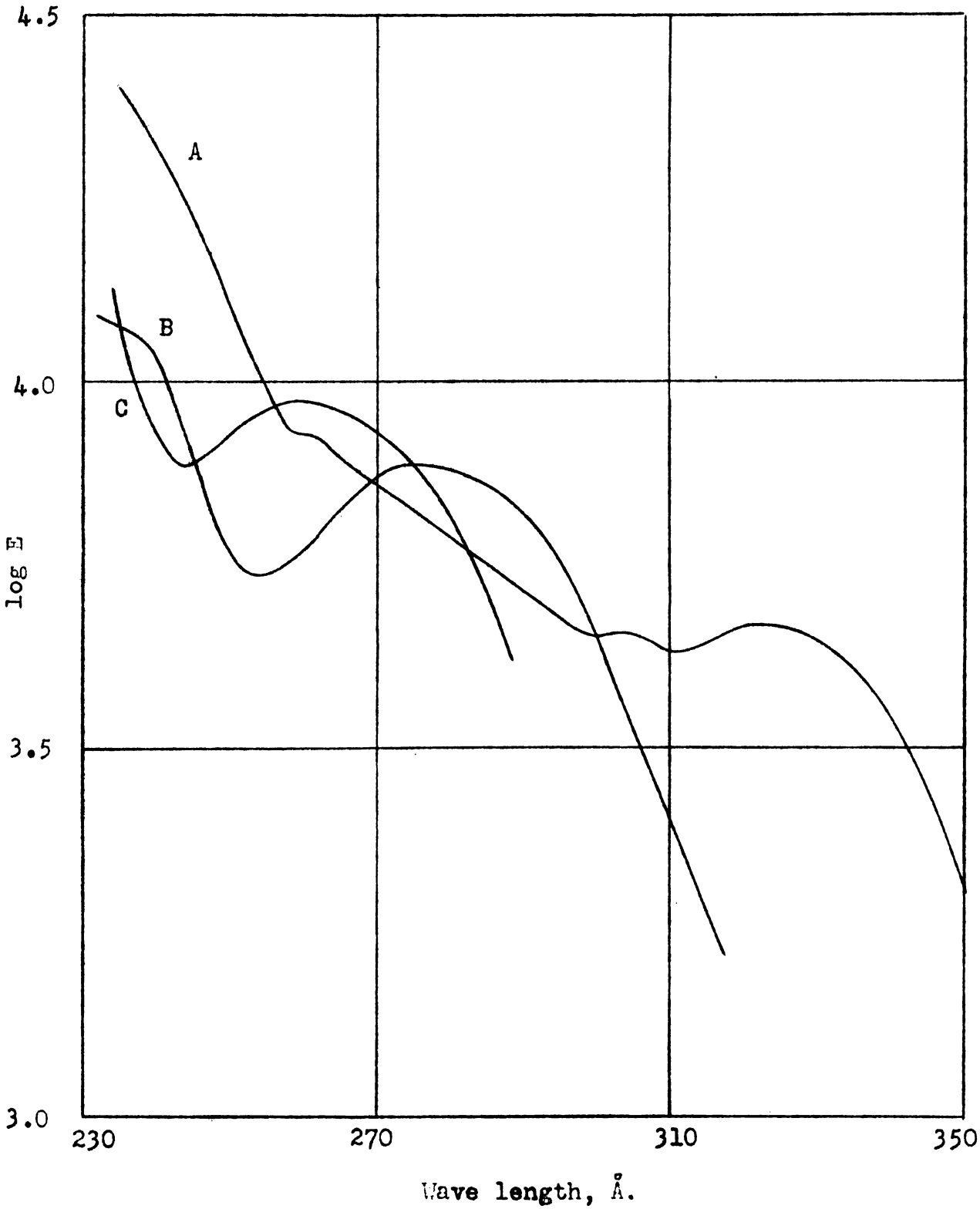
Ultraviolet absorption spectra (Figure I) indicate that the structure of the compound XX and its 6-methoxy analog is greatly different from that of 1-benzoyl-1,2-dihydroquinaldonitrile (V), its dihydroderivative (XII) (12) and their 6-methoxy analogs. The imidazolone XX and its 6-methoxy analog have peaks occurring at about 260 and 280 microns, respectively, while the Reissert compounds V and its 6-methoxy analog and the simple dihydro derivative XII show no peaks above 230 microns in their ultraviolet spectra. There are some differences in the infrared absorption spectra, but no conclusions concerning the structure of XX could be reached on the basis of this data.

Figure 1

A. 1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile

B. 1-Phenyl-3-keto-7-methoxy-3a,4,5,9b-tetrahydroimidazo-[3,4-a]quinoline

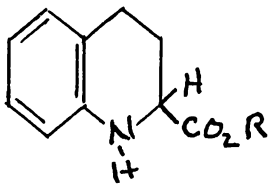
C. 1-Phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline



Failure of XX to give benzaldehyde with concentrated hydrochloric acid is another observation which suggests that its structure bears little resemblance to that of the Reissert compound V; it has been proposed (25) that the general structure as represented in the Reissert compound V is essential for aldehyde formation. The proposed imidazolone XX is very similar structurally to 1-benzoyl-1,2-dihydroquinaldamide (XIII), which also fails to give benzaldehyde on acid-catalyzed hydrolysis (25).

5(4H)-Imidazolones, such as XX, have been found (26, 27) to yield an α-amino acid and an ordinary carboxylic acid under either acidic or basic hydrolysis conditions. As applied to the imidazolone XX, the fragments which would be expected are benzoic acid and 1,2,3,4-tetrahydroquinaldic acid (L). Benzoic acid was obtained quantitatively by prolonged action of hot concentrated hydrochloric acid on XX. Instead of the acid L, however, a polymeric amphoteric material was obtained. Hydrolysis of the imidazolone XX under esterification conditions, to block one possible route of polymerization, produced a basic ester which was probably ethyl tetrahydroquinaldate (LI). Alkaline hydrolysis, on the other hand, using only one equivalent of base, yielded a basic fragment having the empirical formula $C_{18}H_{21}N_3O_2$; this compound has not been identified. In addition an unidentified low melting acid fragment was isolated. It was noted also that ammonia was evolved throughout the hydrolysis period.

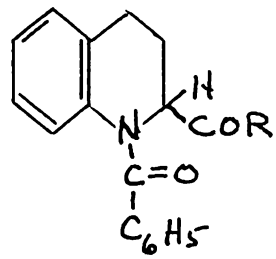
A possible intermediate in the hydrolysis of the imidazolone XX is 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII). It has been shown (14) that the benzoyl group in the corresponding free acid (LII) is cleaved only very slowly under ordinary hydrolysis conditions. Accordingly the imidazolone XX was heated for a short time with excess alkali in the hope that the acid LII could be obtained, but the only material isolated, except for recovered XX, was benzoic acid.[6]



L R = H

LI R = C_2H_5

LIX R = CH_3



XVIII R = NH_2

LII R = OH

Basic hydrolysis of the imidazolone in the presence of hydrogen peroxide provided the best evidence for the proposed structure XX. Treatment of the imidazolone in acetone solution at room temperature with alkaline hydrogen peroxide,

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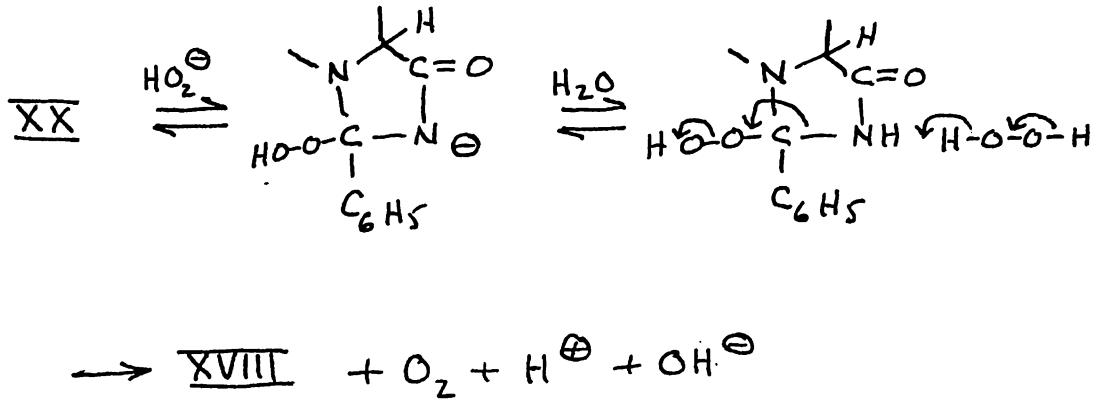
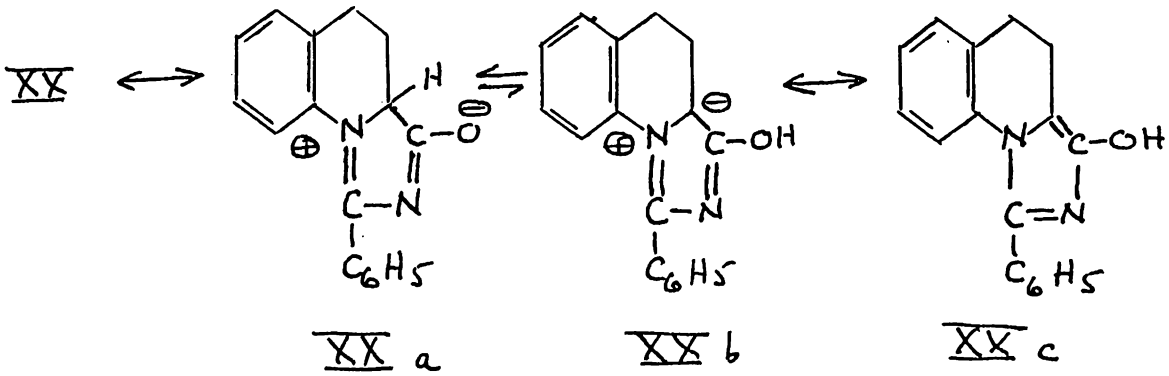
[6]An observation which may have some significance is that either acid or basic hydrolysis of the imidazolone XX appears to yield to some extent hydrogen cyanide or its salt.

as is required for conversion of the Reissert compound I to its amide (25), caused no significant reaction, but when such a mixture was heated under reflux for a short time a 53% yield of the amide XVIII was obtained. It is interesting to speculate on the reason why hydrogen peroxide is required for facile hydrolytic cleavage of this imidazolone ring system. Wiberg (28) has proposed that the primary attack of hydrogen peroxide on nitriles, in their conversion to amides, occurs at the cyano group carbon atom by a peroxide anion. The total mechanism may be adapted to the present case, assuming a similarity between the reactions of nitriles and imidazolones, as follows: the peroxide anion adds at the 2-position of the imidazolone. Then, by action of another molecule of hydrogen peroxide, as shown, the imidazolone ring system is cleaved and the amide XVIII is formed. The driving force in such a reaction would probably be formation of oxygen, which possesses an unusually large heat of formation.



The imidazolone structure given (XX) is only one of a group of contributing tautomeric and resonance structures which may be written, of which the more important are XX a, b and c. In addition, structures could be written involving the π-electrons of the two benzene rings. The stability of the imidazolone XX, then, is not surprising because of the degree of aromatic character which it must have. This proposed aromaticity might explain the necessity of hydrogen peroxide for effecting a facile hydrolytic cleavage reaction.

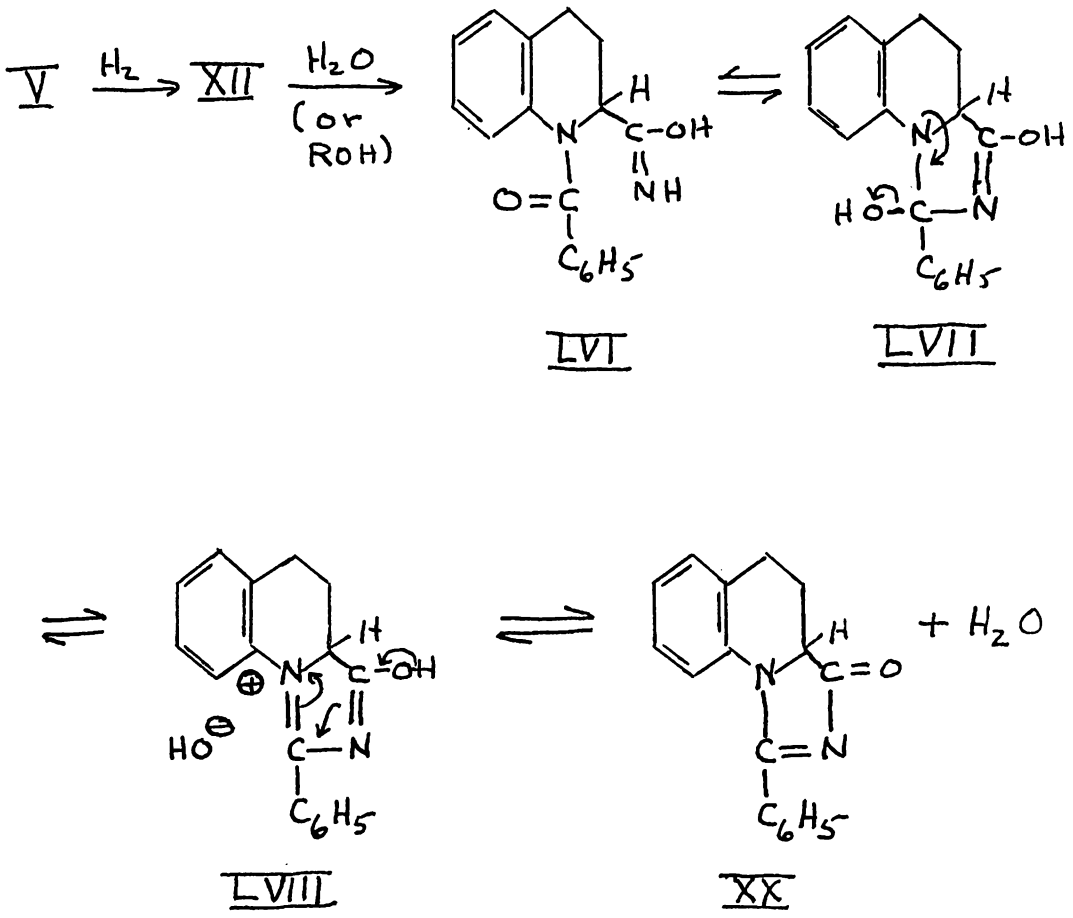


A further indication of the stability of the imidazolone ring system in XX was gained from the results of oxidation studies. It was found that treating the material with potassium permanganate at room temperature had no effect on it; however, when XX was heated for 6 hours with excess potassium permanganate an extremely slow reaction occurred, but about 60% of the starting material was recovered. On

the other hand, the imidazolone XX was less stable to chromic acid oxidation, but no identifiable fragments could be isolated after such a treatment.

The stability of the imidazolone XX lends itself readily to an interpretation of the results obtained on attempts at further reduction. Thus it was found (21) that when XX was allowed to absorb three moles of hydrogen, at least 10% of it was recovered. A reasonable explanation of this is the following: The imidazolone ring is reduced with two moles of hydrogen to yield LIII. This intermediate collapses to give tetrahydroquinaldaldehyde (LIV), benzaldehyde and ammonia. Further reduction yields 2-hydroxymethyltetrahydroquinoline (LV) and toluene. This scheme requires the absorption of 5 moles of hydrogen. The stability of the imidazolone XX is such that the first step of the reduction to form LIII is probably slower than completion of the reduction to LV and toluene. Theoretically, then, at least 5 moles of hydrogen must be absorbed to prevent partial recovery of the imidazolone. Proof for such a hydrogenation scheme as this is lacking, but it has been noted that the odor of ammonia is usually present in the reaction mixture following reduction of the Reissert compound V. It is also of interest that Elliott (21) detected qualitatively the presence of benzaldehyde in the reduction mixture after three moles of hydrogen had been added to XX.

Rearrangement of LVII, probably via LVIII (cf. XX a and b), yields the imidazolone XX.



The stoichiometry of the above reaction requires only one mole of hydrogen, whereas it had been observed in the earlier reactions that two moles were usually absorbed before XX could be isolated. It is proposed that the dihydro Reissert compound XII, under the catalytic action of platinum and in an atmosphere of hydrogen, not only is solvolyzed

to LVI, which is probably the major path of reaction, but is to some small extent further hydrogenated to the imine XLIXa.[7] Then the imine may be further reduced to some unknown end product and this accounts for the anomalous volume of hydrogen absorbed.

The formation of the imidazolone XX from the dihydro Reissert compound XII by action of potassium permanganate need not involve an oxidation as such. Rather the process is probably a hydration of the nitrile group to yield the amide XVIII, followed by condensation to the imidazolone; the latter step may be catalyzed by either permanganate or the small amount of base present, or both.

An attempted independent synthesis of the imidazolone from methyl tetrahydroquinaldate (LIX) and methyl benzimidate, using the method of Finger (26, 29), failed to yield any of the imidazolone XX under a variety of conditions.

What amounts to an independent synthesis of the imidazolone XX was achieved quite by accident. It was found that Schotten-Baumann benzoylation of a product obtained by adding two molar equivalents of hydrogen to quinaldamide hydrochloride over a platinum catalyst yielded XX. Similarly, ammonolysis of methyl tetrahydroquinaldate (LIX) and benzoylation of the resulting product with benzoyl chloride in

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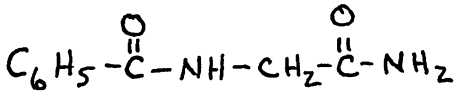
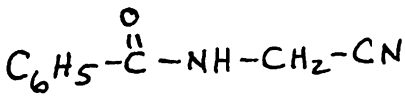
[7]If the rate of hydrogenation were decreased, it would be expected that cyclization to the imidazolone XX would become more apparent. It was found that in those cases where absorption of hydrogen occurred very slowly, significant amounts of XX appeared as a product, even when only one mole of hydrogen was used.

pyridine yielded the imidazolone XX as the major product, in addition to the amide XVIII. It is not too surprising that the imidazolone was obtained in the latter case, since a mixture of benzoyl chloride and pyridine is known to be a good dehydrating agent.

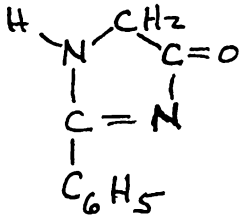
In an attempt to prepare the dihydro Reissert compound XII from the amide XVIII by dehydration with phosphorus pentoxide, the only product obtained was the imidazolone XX. There are only two dehydration products which might conceivably be expected by such treatment, the dihydro Reissert compound XII and the imidazolone XX. This result is another bit of evidence which indicates the validity of the proposed structure for XX. The dehydration of the amide obtained by the alkaline peroxide hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (V) yielded the parent Reissert compound, V (25). In this case dehydration yielded the nitrile, while in the case of the amide XVIII dehydration occurred in the other direction to yield the imidazolone. Thus dehydration of -acylaminonitriles does not appear to be a general method for the preparation of imidazolones. Contrary to earlier reports (30), Kjaer (31) found that dehydration of hippuramide (LX) with phosphorus pentachloride yields hippuronitrile (LXI) rather than the imidazolone, LXII.



LX



LXI



LXII

No attempts have been made to determine whether the imidazolone XX is an intermediate in the formation of the amine XLIV obtained on pressure hydrogenation of the Reissert compound V.

IV. EXPERIMENTAL[8,9]

1-Benzoyl-1,2-dihydroquinaldonitrile (V). - This compound was prepared by the method of Rupe, Paltzer and Engel (3) in 63-89% yield, small white crystals from ethanol, m. p. 153-154.5°, 151-153°; reported m. p. 153-154° (3) and 154-155° (1). The infrared absorption spectrum is recorded on Plate 2.

Controlled Acid-Catalyzed Solvolysis of 1-Benzoyl-1,2-dihydroquinaldonitrile (V) A. In Ethanol. - A suspension of finely-crystalline 1-benzoyl-1,2-dihydroquinaldonitrile (V) was prepared by dissolving 10.00 g. V in 500 cc. of 95% ethanol and allowing the solution to cool to room temperature with vigorous stirring. To this suspension was added 1000 cc. of a saturated ethanolic solution of hydrogen chloride (ca. 10 N); the slightly exothermic reaction was allowed to proceed 3.5 minutes with continued stirring. The reaction mixture was then poured into a large flask externally cooled by an ice bath and containing 850 g. of crushed sodium bicarbonate and 1 kg. of crushed ice. When the evolution of carbon dioxide had ceased, as much of the solvent as possible was removed by distillation under reduced pressure, the temperature being kept below 35-40°. The

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[8] All m. p.'s are corrected.

[9] Analyses by Clark Microanalytical Laboratory, Urbana, Illinois, Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., Weiler and Strauss, Oxford, England and Oakwold Laboratories, Alexandria, Virginia.

distillate, consisting of a mixture of ethanol and benzaldehyde, was treated with a solution of 7.5 g. of 2,4-dinitrophenylhydrazine in 40 cc. of concentrated sulfuric acid and 60 cc. of water. After allowing the mixture to stand overnight, the bright yellow hydrazone was filtered and dried to give 10.26 (93.4%) of benzaldehyde-2,4-dinitrophenylhydrazone, m. p. 220° dec.

The aqueous residue from the distillation was made distinctly acidic by addition of 20 cc. concentrated hydrochloric acid and extracted with six 50 cc. portions of ether. The ether extracts produced only a small amount of a gummy red-brown oil which could not be purified. The aqueous residue was neutralized with solid sodium bicarbonate and then 25 cc. of 10% sodium hydroxide was added. The solution was extracted with three 100 cc. portions of ether. The ether extracts were dried over Drierite and the ether removed by distillation, leaving a red-brown oil which did not solidify on cooling. After attempts at steam distillation, which produced no material of consequence in the distillate, the oil was taken up in a small amount of ether and the solution chilled in a Dry Ice-acetone mixture. Filtering through a pre-chilled funnel produced a low melting solid which was recrystallized from a few cc. of ether, yielding 1.18 g. of a white crystalline material, m. p. 30-33°; reported m. p. for ethyl quinaldate is 36° (32).

The yield, calculated on the basis that the material is this ester, was 15.2%.

The aqueous residue from the ether extraction was filtered and the filtrate acidified with glacial acetic acid. Addition of an aqueous solution of cupric sulfate produced a pale blue precipitate of copper quinaldate dihydrate (33) which was collected and dried; yield, 6.60 g., equivalent to 2.58 g. quinaldic acid (II), 38% yield.

In another run, quinaldamide (III), m. p. 121-123°, was isolated instead of ethyl quinaldate in about the same yield. In no case was quinaldonitrile (VIII) isolated.

B. In Water. - A mixture of 10.00 g. V in 45 cc. of concentrated hydrochloric acid was stirred vigorously for fifteen minutes. The heterogenous reaction mixture, bright yellow in color, was poured into a large flask containing 35 g. of crushed sodium bicarbonate and 150 g. of crushed ice. After the evolution of carbon dioxide had subsided, the misture was filtered and the solid washed with 20 cc. of 10% hydrochloric acid and 50 cc. of cold ether. There resulted 7.46 g. of recovered Reissert compound, V, which on one recrystallization from ethanol gave a m. p. of 153-154.5°.

The aqueous filtrate, combined with the washings, was extracted with ether and the ether extracts were dried over Drierite. Evaporation of the ether left a light colored oil. This was treated with a solution of 4 g. of 2,4-di-

nitrophenylhydrazine in 10 cc. of concentrated sulfuric acid, 20 cc. of water, and 30 cc. of ethanol. The resulting bright yellow solid was too hygroscopic to be weighed or have its m. p. determined; it was probably a mixture of benzaldehyde-2,4-dinitrophenylhydrazone and the hydrazinium sulfate. In another reaction using the same conditions, a 76% net yield of the hydrazone was isolated at this point.

The aqueous residue from the ether extraction was neutralized with sodium bicarbonate to give a pale red-violet colored solution. Extraction of this solution with ether yielded 3 mg. of a compound presumed to be benzoin quinaldate (IV), m. p. 164-166°; reported m. p. 168-168.5° (1).

The aqueous residue was made strongly basic by addition of 5 cc. of 10% sodium hydroxide solution and extracted with ether. The ether extracts yielded nothing. The aqueous solution was then acidified with glacial acetic acid and a solution of cupric sulfate was added. After allowing to stand overnight, the pale blue solid was collected and dried to give 0.96 g. copper quinaldate, equivalent to 0.38 g. quinaldic acid (II), 23% net yield.

In other runs, using slightly different conditions, a small amount of quinaldamide (III) was isolated, m. p. 124.5-126.5° after recrystallizing from ethanol and ligroin; mixed with authentic quinaldamide, m. p. 130-131° (see below). In a reaction which was allowed to proceed 1.5 hours, 9% of benzoin quinaldate (IV) was isolated but none

of the starting Reissert compound, V, was recovered. In no case was there any indication that quinaldonitrile (VIII) was present.

C. In Aqueous Hydrochloric Acid with Added Quinaldonitrile (VIII). - This reaction was run simultaneously, with a suitable time lag to allow working up of the reaction mixture, with an acid-catalyzed hydrolysis of quinaldonitrile (VIII) to insure that the reactants and products in both cases would have equal contact time with the acidic solution.

A mixture of 2.0 g. of V and 1.0 g. of VIII was stirred for 15 minutes in 30 cc. of concentrated hydrochloric acid; the yellow[10] reaction mixture was then poured into a flask, cooled in an ice bath, containing 30 g. of crushed sodium bicarbonate and 60 cc. of water. After 10 minutes, the slightly basic mixture was filtered and the solid washed well with water. The filtrate was immediately extracted with ether, the extracts washed with 4 N hydrochloric acid and the acid wash quickly neutralized with solid sodium bicarbonate. A minute amount of quinaldamide was isolated from this aqueous solution. The ethereal solution after washing with the acid was distilled, and the residual oil was taken up in a few cc. of ethanol. Addition of a solution of 2,4-dinitrophenylhydrazine gave 0.04 g. benzaldehyde-2,4-dinitrophenylhydrazone, m. p. 222-227°.

After extraction with ether, the aqueous residue was

[10]It may be significant that, in the presence of added VIII, the color of the reaction mixture is not nearly as bright as is that with V alone.

acidified with acetic acid. Addition of a solution of copper sulfate gave 0.56 g. of copper quinaldate.

The solid that was filtered after the original reaction mixture was made basic was suspended in water and subjected to steam distillation. 0.11 g. of white, crystalline quinaldonitrile (VIII), m. p. 94.94.5°, appeared in the distillate. The aqueous residue was washed with ether, yielding 1.22 g. of recovered Reissert compound, m. p. 149-151°, after one recrystallization from ethanol. Evaporation of the ether wash gave 0.23 g. quinaldamide (III), m. p. 120-124° after recrystallization from ligroin.

D. In Aqueous Hydrochloric Acid Containing Sufficient Reissert Compound (V) Necessary to Produce A Theoretical Yield of 0.0065 Mole of Quinaldonitrile (VIII) (See Below). - From 3.68 g. 1-benzoyl-1,2-dinydroquinaldonitrile (V) in 30 cc. of concentrated hydrochloric acid, after a reaction identical to those reported previously, was isolated 2.37 g. recovered V, 0.10 g. benzaldehyde-2,4-dinitrophenylhydrazone and 0.29 g. copper quinaldate.

Quinaldonitrile (VIII). - This compound was prepared by the method of Henze (34) from quinoline-1-oxide, benzoyl chloride and potassium cyanide. The yields of crude material, m. p. 85-93°, were practically quantitative. The material was purified by steam distillation and recrystallization from ligroin, m. p. 93°; reported m. p. 93° (34) and 94-95° (35).

Attempts to prepare VIII from quinoline-1-oxide, potassium cyanide and p-toluenesulfonyl chloride, according to the method of Lowman (35), yielded, as the only isolable product, carbostyril, m. p. 189-191°.

Controlled Acid-Catalyzed Hydrolysis of Quinaldonitrile (VIII). - A solution of 1.00 g. of VIII (0.0065 mole) in 30 cc. of concentrated hydrochloric acid was stirred magnetically for 15 minutes. The pale yellow solution was then poured into a flask containing 30 g. of crushed sodium bicarbonate and 50 g. of crushed ice. When the evolution of carbon dioxide had ceased, the white solid which formed was filtered and dried, 1.24 g., m. p. 65-86°. This solid was suspended in 10 cc. of water and steam distilled until no more quinaldonitrile distilled. The distillate, containing the cyano compound, was cooled and filtered to give 0.39 g. of unreacted quinaldonitrile, m. p. 92-93°. The aqueous residue, containing the material that did not steam distill, upon cooling yielded 0.47 g. (68.5% net yield) of quinaldamide (III), m. p. 105-117°.

The filtrate from the original solid was made basic by addition of 2 cc. of 10% sodium hydroxide and extracted with ether. Evaporation of the ether produced nothing. The aqueous residue was acidified with glacial acetic acid and a solution of cupric sulfate was added. After allowing to stand 48 hours, the pale blue copper quinaldate was

filtered and dried; yield 0.63 g. (equivalent to 0.25 g. quinaldic acid, 36% net yield).

In another reaction, using identical conditions, 14% of the quinaldonitrile was recovered unchanged, the remainder being converted, as above, into quinaldamide (III) and quinaldic acid (as the copper salt), in net yields of 52% and 58%, respectively. The apparent total yield is greater than 100%, probably due to the presence of impurities.

1-Benzoyl-1,2-dihydroquinaldamide (XIII). - To a solution of 5.0 g. of 1-benzoyl-1,2-dihydroquinaldonitrile (V) in 500 cc. of acetone was added 2 g. of powdered sodium bicarbonate. The mixture was placed in a bath of cool water and stirred for 10 minutes; 75 cc. of 30% hydrogen peroxide was added dropwise with continued stirring over a period of about an hour. Then 3 cc. of 5% sodium bicarbonate was added and the stirring continued for another hour. The solution was then concentrated to ca. 75 cc. by distillation under reduced pressure; 200 cc. of water was added to the resulting solution and the mixture was cooled in an ice bath. The sticky solid was filtered, washed with water, dried and recrystallized from absolute ethanol to yield 2.53 g. XIII, m. p. 169.5-171°. An additional 0.92 g. of product was recovered from the filtrate to give a total yield of 65%. Recrystallization from 95% ethanol four times gave heavy white crystalline clusters, m. p. 172.8-173.2°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.10; H, 4.80; N, 9.78.

The infrared absorption spectrum is recorded on Plate 3.

In a large scale reaction it is absolutely essential to add the hydrogen peroxide slowly and the temperature must be moderated by water cooling; otherwise there is much decomposition. For example, in one case where 20 cc. of 30% hydrogen peroxide was added at once without stirring to 2 g. of V, the only products isolated were benzoic acid (in minute quantities), quinoline (characterized as the picrate), and 30 mg. of a solid soluble in hot water, m. p. 124.5-126°. Failure to cool in other cases resulted in greatly reduced yields. In one case which could not be repeated, a sizeable amount of a product, m. p. 195-200°, was isolated.

Attempts to hydrolyze the Reissert compound V by means of an alkaline ion exchange resin (IRA-400), according to the method of Galat (36), failed to yield any of the amide XIII; only Reissert compound could be recovered after refluxing in ethanol, benzene and toluene as the solvents.

Dehydration of 1-Benzoyl-1,2-dihydroquinaldamide (XIII). - To a solution of 0.35 g. (0.49 cc.) of triethylamine in 25 cc. of benzene, both dried over phosphorus pentoxide, was added 0.50 g. of 1-benzoyl-1,2-dihydroquinaldamide (XIII). To this olution was added ca. 0.2-0.3 g.

phosphorus pentoxide and the mixture was heated under reflux 30 minutes; then approximately the same quantity of phosphorus pentoxide was added as at first and heating was continued for an additional 30 minutes. The mixture was allowed to stand at room temperature overnight, and then the benzene was decanted from an insoluble sludge. The benzene was removed by distillation and the residue heated on the steam bath under reduced pressure. Recrystallization of the residue from 5 cc. of ethanol produced 0.14 g. (30%) of 1-benzoyl-1,2-dihydroquinaldonitrile (V) as yellow crystals, m. p. 149-152°, and in admixture with authentic V. Recyrstallization once from ethanol gave white needles, m. p. 153-154.5°.

Treatment of 1-Benzoyl-1,2-dihydroquinaldamide (XIII) with Acid. - A mixture of 0.25 g. of the amide, XIII, 0.20 g. 2,4-dinitrophenylhydrazine and 25 cc. of concentrated hydrochloric acid was heated on a steam bath for 15 minutes to give a clear solution. There was absolutely no indication of benzaldehyde formation (a control experiment using V gave immediate precipitation of benzaldehyde-2,4-dinitrophenylhydrazone upon heating on a steam bath). After allowing the mixture to stand 24 hours, a small amount of yellow-brown needles which had formed was collected, m. p. 120-140°. These were not further investigated.

Chloralquinaldine. - This was prepared from quinaldine, anhydrous chloral and dry pyridine according to the procedure

of Alberts and Bachman (37). The crude material was recrystallized from ethanol (Norit) to give 125 g. (61%) of snow white crystals, m. p. 144-146°; reported, m. p. 148° (37).

Sodium Salt of 3-Acetyl-1,2-dihydroquinaldic Acid. - The formation and isolation of this salt was accomplished by a method similar to that described by Einhorn (38) and Dauben and Vaughan (39). A suspension of finely divided chloralquinaldine in ethanol was prepared by pouring 40 cc. of hot water into a solution of 10.0 g. of chloralquinaldine in 35 cc. of coiling absolute ethanol. To this hot solution was added 31 cc. of 23% sodium hydroxide all at once. The immediate reaction was very violent and exothermic, but was over in a few seconds; the deep red colored solution was heated 10 minutes on a steam bath. The solution was cooled to -10° for several days. The red-orange crystals of the sodium salt of 3-acetyl-1,2-dihydroquinaldic acid which formed were filtered, washed with cold ethanol and dried; yield 4.0 g. (40%).

The hydrolysis was repeated several times and yields varied from 30% (on a 25 g. scale) to 40%. After isolation of the above sodium salt, β-(2-quinolyl)-acrylic acid was recovered from the mother liquor (38).

Methyl 3-Acetyl-1,2-dihydroquinaldate (XVI). - This ester was obtained by a method analogous to that described by Woodward and Kornfeld (13) for the preparation of the ethyl ester. A suspension of 4.0 g. of the sodium salt of

3-acetyl-1,2-dihydroquinaldic acid in 40 cc. absolute methanol cooled in an ice bath was saturated with dry hydrogen chloride. The dark violet-colored mixture was allowed to stand overnight in a stoppered flask, during which a yellow solid was deposited. The solvent was removed by distillation under reduced pressure, and a mixture of 50 g. of ice and 50 cc. of water was added to the residue. Then about 5 g. of sodium bicarbonate and 25 cc. of cold 10% sodium hydroxide solution was added. The yellow-orange ester was collected and washed well with distilled water; yield 2.73 g. (87%), m. p. 135-139°; reported m. p. 140-141° (13). The ester was not purified for the next step.

3-Acetyl-1,2-dihydroquinaldamide (XVII). - Dry ammonia was passed through a cold solution of 2.00 g. of methyl 3-acetyl-1,2-dihydroquinaldate (XVI) in 100 cc. of absolute methanol for 1.5 hours. After allowing the solution to stand overnight, the methanol was removed by distillation and the bright orange residue was taken up in hot 95% ethanol. Cooling to -10° overnight gave 0.95 g. of the amide as fine yellow-orange plates, m. p. 174-178°. A second crop of crystals was obtained from the mother liquor; total yield 63.5%. Four recrystallizations from ethanol gave yellow plates, m. p. 181.5-182.5°, soluble in hot water.

1-Benzoyl-3-acetyl-1,2-dihydroquinaldamide (XV). - To a solution of 0.60 g. 3-acetyl-1,2-dihydroquinaldamide

(XVII) in 50 cc. dry benzene was added 0.65 cc. of benzoyl chloride and 0.80 cc. of triethylamine. The mixture was heated under reflux for an hour, an additional 25 cc. of benzene added and then heating was continued for another hour. The mixture was evaporated to dryness and the residue washed with water. The dark colored residue was taken up in 20 cc. of hot ethanol, decolorized and filtered. Concentration of the solution to about 5 cc. and chilling 48 hours at -10° gave 0.14 g. (15.5%) of pale yellow-green pellets, m. p. 190-194°. After four recrystallizations the white crystals start melting at 197°, then resolidify and melt at 230-231°.

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.04; N, 8.75. Found: C, 71.42; H, 5.24; N, 8.97.

The infrared absorption spectrum is recorded on Plate 3.

Attempted benzoylation of the amide XVII under Schotten-Baumann conditions failed; 75% of the amide was recovered. Also the method described by Woodward and Kornfeld (13) for the benzoylation of methyl 3-acetyl-1,2-dihydroquinaldate (XVI) (treatment with benzoyl chloride in pyridine) failed for the amide; about 80% of the amide was recovered.

Treatment of 1-Benzoyl-3-acetyl-1,2-dihydroquinaldamide (XV) with Acid. - To a solution of 0.025 g. 2,4-dinitrophenylhydrazine in 3 cc. concentrated hydrochloric acid was added 0.03 g. XV. The mixture was heated on a steam bath

until solution was complete. There was no indication of benzaldehyde formation after 24 hours.

Methyl 1-Benzoyl-3-acetyl-1,2-dihydroquinaldate. - This compound was prepared by the method of Woodward and Kornfeld (13) in 44% yield, m. p. 141-142°.

Ammonolysis of Methyl 1-Benzoyl-3-acetyl-1,2-dihydroquinaldate. - Dry gaseous ammonia was bubbled into a cold solution of 1.00 g. of methyl 1-benzoyl-3-acetyl-1,2-dihydroquinaldate in 50 cc. of absolute methanol for about 45 minutes. After allowing to stand overnight, the solution was transferred to a sealed glass bomb and heated on a steam bath for 20 minutes. Working up the reaction mixture gave, after crystallization of the resulting solid from methanol, bright yellow plates, m. p. 178-180°, also in admixture with authentic 3-acetyl-1,2-dihydroquinaldamide (XVII).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.42; H, 5.98; N, 12.53; Non-alkaline ash from CH, 1.97.

1-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII). - This compound was prepared from V by hydrogenation over a platinum catalyst using the method of McEwen, Terss and Elliott (12). The infrared absorption spectrum is recorded on Plate 2.

Rate of Benzaldehyde Formation from 1-Benzoyl-1,2-dihydroquinaldonitrile (V) and 1-Benzoyl-1,2,3,4-tetrahydro-

quinaldonitrile (XII). a. An ethanolic solution of the cyano compound was prepared by dissolving 1.00 g. in 50 cc. of hot 95% ethanol. This solution was placed in a reaction chamber surrounded by vapors of boiling ether. When a temperature equilibrium had been reached, a solution of 0.75 g. 2,4-dinitrophenylhydrazine in 100 cc. of a saturated ethanolic solution of hydrogen chloride previously heated to 35-36° was added; the mixture was stirred throughout the course of the reaction. When the time allowed for the reaction was completed, the mixture was immediately filtered through a previously weighed sintered or gooch crucible as rapidly as possible, the flask and the solid washed with two 25 cc. portions of ethanol, and the funnel was then dried in a vacuum dessicator to determine the amount of benzaldehyde-2,4-dinitrophenylhydrazone formed.

It was noted that the reaction mixture became turbid after about 30 seconds with V, but only after 90-120 seconds with XII.

b. The reaction itself was run similarly as above, but only 0.25 g. of the Reissert compound in 25 cc. of ethanol was used; the hydrolysis was carried out with a solution of 0.2 g. of 2,4-dinitrophenylhydrazine in 50 cc. of 8 N ethanolic hydrogen chloride. After the appropriate reaction period, the reaction was quenched by pouring the mixture into 400 cc. ethanol. The 2,4-dinitrophenylhydrazone was collected as above.

Turbidity developed in solutions of V after 18 seconds and in solutions of XII after about 40 seconds.

The results of these studies are recorded in Table 1.

Table 1

Formation of Benzaldehyde by Acid-Catalyzed Hydrolysis of 1-Benzoyl-1,2-dihydroquinaldonitrile (V) and 1-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII)

Compound	Time of Reaction	Method of Isolation[1]	Hydrazone % Yield
V	20 sec.	b	63.6
	25		69.8
	60		70.3
	2 min.		85.5
	3		93.2
	5		93.1
	5	a	89.8
	10		86.4
	20		86.5
	60		91.5
	120		89.4
	180		92.9
XII	45 sec.	b	29.3
	60		39.6
	75		41.4
	90		40.3
	150	a	31.8
	5 min.		32.7
	20		33.9
	30		34.4
	60		34.2
	120		34.8

[1]See experimental details.

Controlled Acid-Catalyzed Hydrolysis of 1-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII). - A mixture of 8.00 g. of the dihydro Reissert compound, XII, (m. p. 130°) in 40 cc.

of concentrated hydrochloric acid was stirred mechanically at room temperature for 30 minutes. After an initial slightly exothermic reaction, the mixture gradually assumed a brown-orange color. It was filtered through a sintered glass funnel to remove a small amount of a crystalline solid; the solid was washed with water, 0.24 g., m. p. 126-131°. After five recrystallizations from ethanol, the resulting white crystals had a m. p. of 146.5-148°; there was no depression when mixed with 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX).

The filtrate, combined with the aqueous washings, was poured into a flask containing a slurry of 24 g. of crushed sodium bicarbonate in 100 cc. of cold water which was in an ice bath. After the evolution of carbon dioxide had ceased, the liquid layer (still acid) was filtered (filtrate A) from a sticky residue. The residue was washed with two 50 cc. portions of ether chilled to ca. -50°, then was taken up on 200 cc. of benzene. The benzene solution was extracted three times with 50 cc. portions of saturated sodium bisulfite solution. After washing well with water, the benzene solution was treated with Norit while hot, filtered and concentrated to about 15 cc. Addition of a few cc. of petroleum ether and cooling gave 1.85 g. of white crystalline 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII), m. p. 187-189° after one recrystallization from ethanol;

there was no m. p. depression when mixed with authentic XVIII.

The benzene-petroleum ether mother liquor was evaporated to dryness and the residue taken up in a hot mixture of 20 cc. of ligroin and 5 cc. of benzene. Slow cooling for 48 hours gave 0.15 g. of a yellow solid, m. p. 140-180°; after four recrystallizations from a mixture of ethyl acetate and absolute ethanol, in which it was very difficultly soluble, small white crystals were isolated, m. p. 258.5-259°.

Anal. Found: C, 74.55; H, 5.22; N, 7.50.

The infrared absorption spectrum of this material in a 1/2% solution in chloroform (saturated) showed peaks of major intensity at 1635 and 1490 $cm.^{-1}$; peaks intermediate in size occurred at 1708, 1360 and 1342 $cm.^{-1}$; less absorption occurred at frequencies of 1762 and 1580 $cm.^{-1}$.

After removal of the above solid, the ligroin-benzene mother liquor was boiled for 30 minutes and then allowed to stand at room temperature for 3 days. A dark colored oil which separated was broken into a solid when the supernatant liquid was heated, yielding 0.03 g. of the above high melting solid. The ligroin mother liquor was evaporated to dryness *in vacuo*, leaving 1.50 g. of a dark tarry oil. This was taken up in 50 cc. of dry benzene and refluxed for 1 hour with 1.25 cc. of benzoyl chloride and ca. 1 cc. of triethylamine. After cooling, the solution was washed with

several portions of dilute sodium hydroxide solution and then with 3 N hydrochloric acid. The only crystalline material that could be isolated by fractional crystallization of the benzene solution was ca. 0.1 g. of the imidazolone, XX, m. p. 148.5-149.5°, undepressed when mixed with authentic XX, and 0.08 g. of an uncharacterized solid, m. p. 70-75°, after recrystallization from ethanol. Most of the tarry material resisted attempts at purification. Attempts to form a picrate from portions of it also failed.

Filtrate A and the ether washes were combined and extracted four times with 50 cc. portions of ether. The ether extracts were dried over Drierite and then the ether was distilled, leaving an oil from which a solid separated. The oil and solid were mixed with 20 cc. of ether, cooled to ca. -50° and filtered, yielding 0.15 of additional XVIII, m. p. 184-186° (total yield, 24%). The ether filtrate was evaporated, leaving an oil which smelled of benzaldehyde. The sodium bisulfite extracts which were made on the benzene solution of the original solid were acidified with hydrochloric acid and extracted five times with 50 cc. portions of ether. The ether extracts were combined, dried over Drierite and then evaporated. The benzaldehyde residue was mixed with 30 cc. ethanol, combined with the benzaldehyde obtained above and added to a solution of 3 g. 2,4-dinitrophenylhydrazine in 8 cc. of concentrated sulfuric acid, 15 cc. of water and 25 cc. of ethanol. After standing

30 minutes, the benzaldehyde-2,4-dinitrophenylhydrazone was collected, m. p. 228-235°, yield 2.21 g. (27%).

The aqueous residue, after the preceding ether extraction, was cooled in an ice bath and neutralized with solid sodium bicarbonate; then a few cc. of 10% sodium hydroxide solution was added. This basic solution was extracted with three 40 cc. portions of ether. The ether extracts were dried over Drierite and then evaporated, leaving a straw-colored oil which deposited a white solid upon standing. After cooling in an ice bath, the mixture was filtered and washed with water, giving 0.53 g. (10%) of a white solid, m. p. 92-113°. The material was dissolved in benzene and refluxed for 1 hour with 2 cc. of benzoyl chloride and 2 cc. of triethylamine. After washing well with dilute sodium hydroxide solution, the benzene solution was extracted three times with 25 cc. portions of 5% hydrochloric acid. Sodium bicarbonate was added to the acid extracts to neutralize them, and then a few cc. of dilute sodium hydroxide solution was added. Extraction with ether gave a small amount of quinaldamide (III), m. p. 124-126° after two recrystallizations from ligroin; mixed with authentic III, m. p. 126-128°. The benzene layer after washing with acid and base was decolorized and then evaporated to dryness. Recrystallization of the residue from ethanol gave 0.30 g. of 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), m. p. 147-148°, also when mixed with authentic XX.

The basic aqueous residue was acidified with glacial acetic acid and then a solution of cupric sulfate was added. After standing 48 hours, the copper salt was collected and dried; yield, 3.20 g. It was suspended in distilled water, heated to about 40° and decomposed with hydrogen sulfide. The mixture was heated to 80° and the copper sulfide removed by filtration. The filtrate was decolorized and allowed to evaporate at room temperature, giving 0.90 g. of a slightly yellow solid, m. p. 180-183° dec. Recrystallization of the material from ethanol afforded two types of crystals, one very soluble in ethanol, tiny white needles, m. p. 163-170° after undergoing a transition at 150°, and the other more difficultly soluble in ethanol, shiny, rose-colored heavy clusters, m. p. 168-180°. The former material, after one recrystallization from ethanol, gave a m. p. of 155-160° (dec.), but there were insufficient quantities to compare with quinaldic acid, m. p. 156-158° (dec.). The identity of the other compound has not been learned; 1,2,3,4-tetrahydroquinaldic acid, the other expected acid, has been reported to melt at 112-113° (14).

1-Benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII).

A. Hydrogenation of XIII. - A suspension of 100 g. of 1-benzoyl-1,2-dihydroquinaldamide (XIII) and 0.1 g. of platinum oxide catalyst in 50 cc. of absolute ethanol was allowed to absorb one molar equivalent of hydrogen at

atmospheric pressure and room temperature. The absorption was extremely rapid; the hydrogenation was complete in 20 minutes. The mixture was heated to boiling and the platinum removed by filtration; the yellow-green filtrate was decolorized, filtered and concentrated to 15 cc. Chilling overnight gave 0.34 g. of white solid, m. p. 188-189°. A second crop of crystals, m. p. 190-192°, was isolated from the mother liquor, total yield, 51%. Four recrystallizations from ethanol gave hard white crystals, m. p. 193.8-194.4°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 10.00. Found: C, 73.01; H, 5.96; N, 9.99.

The infrared absorption spectrum is recorded on Plate 3.

B. From 1,2,3,4-Tetrahydroquinaldamide. - An ice cold solution of 3.0 g. 1,2,3,4-tetrahydroquinaldic acid hydrochloride (L·HCl) (14) in 30 cc. of absolute methanol was saturated with dry hydrogen chloride and allowed to stand at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue (a yellow solid) was mixed with 25 g. of crushed ice and 25 cc. of water. The resulting ice-cold solution was made basic by addition of 5 g. of crushed sodium bicarbonate and 10 cc. of 10% sodium hydroxide solution. The heavy yellow oil which appeared was extracted with ether. The ether extracts were dried over Drierite and evaporated. The product, a heavy

oil (not identified, but probably LIX), was dissolved in 50 cc. absolute methanol; the solution was cooled in an ice bath and saturated with dry ammonia. After allowing the yellow solution to stand 48 hours, the solvent was removed under reduced pressure and the oily residue mixed with a little water. Cooling gave 1.66 g. of a low melting solid. Recrystallization from ethanol gave a white solid, m. p. 105-110° (soft ca. 80°). The product was not characterized, but was probably 1,2,3,4-tetrahydroquinaldamide.[11] It was not purified further for the next step.

A solution of 0.67 g. of the tetrahydroquinaldamide in 25 cc. of dry pyridine was mixed with 0.67 cc. of benzoyl chloride. After allowing to stand at room temperature 10 days, the solvent was removed under reduced pressure. After neutralizing the residue with 5% sodium bicarbonate solution, the mixture was cooled in an ice bath. A solid which formed was filtered from the aqueous solution and recrystallized from ethanol, giving 0.20 g. of 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), m. p. 146-148° after two more recrystallizations from ethanol and when mixed with authentic XX.

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[11]Attempts to prepare the tetrahydroquinaldamide directly from L via the acid chloride met with failure under a variety of conditions. This is not too surprising as it has been reported (14) that 1-benzoyl-1,2,3,4-tetrahydroquinaldic acid (LII) is dehydrogenated by agents that normally yield acid chlorides, as thionyl chloride, to give the completely aromatic quinaldoyl chloride.

The aqueous filtrate upon standing deposited 0.10 g. of XVIII, m. p. 183-188°. Recrystallization from ethanol gave white plates, m. p. 187-190°; mixed with authentic XVIII, m. p. 187-191°.

Action of Hydrogen Chloride on 1-Benzoyl-1,2-dihydroquinaldonitrile (V) in Chloroform as a Solvent. - About 150 cc. of chloroform (C. P.), previously washed with concentrated sulfuric acid and water and then dried over anhydrous calcium chloride, was distilled into a flask, after discarding the first 20-30 cc., containing 10.0 g. of 1-benzoyl-1,2-dihydroquinaldonitrile (V). After the Reissert compound had dissolved, the solution, under an atmosphere of nitrogen (dried and free of oxygen), was placed in an ice bath and hydrogen chloride, dried by passing through sulfuric acid, was introduced. The solution almost immediately became yellow and soon a yellow solid appeared. After about 10 minutes, a solid mass separated. Under a positive pressure of nitrogen, the mass was broken up with a rod, and addition of hydrogen chloride was continued for another 15 minutes. The yellow solid was filtered under a stream of dry nitrogen, washed well with dry ether and dried in a vacuum desicator over anhydrous calcium chloride. Upon standing, it gradually turned to a pale violet color on the surface.

Anal. Found: C, 57.63, 57.38; H, 4.58, 4.83; N, 10.04, 9.88; Cl, 15.00, 15.24.

The solid was very sensitive to the air and moisture; it turned dark quickly in the air. Odorless itself, by breathing across it, the odor of benzaldehyde developed. A water solution gave a qualitative test for benzaldehyde.

The solid was subjected to the following hydrolysis experiments:

a. A mixture of 4.0 g. of the solid and 100 cc. of distilled water was allowed to stand with occasional shaking for about 15 minutes. The reaction mixture, consisting of a dark tar and turbid aqueous solution, was extracted four times with 50 cc. portions of ether; the tar was practically insoluble in the ether. The ether extracts were combined, washed well with 6 N hydrochloric acid and dried over Drierite. Distillation of the ether left an oil which gave 0.58 g. of benzaldehyde-2,4-dinitrophenylhydrazone, m. p. 235-237°, upon mixing with a solution of 2,4-dinitrophenylhydrazine in ethanolic sulfuric acid.

The tar was removed from the aqueous residue. The solution was cooled in ice and made basic by addition of 10% sodium hydroxide solution. The acid washes of the prior ether solution were made basic and combined with this basic mixture. The solid which formed was filtered and washed well with water, giving 0.85 g. of a sticky, yellow-brown solid. The solid was treated with 20 cc. of hot ethanol and the solution was filtered from 0.09 g. of an insoluble residue, m. p. 208-214°. Three recyrstallizations

from a mixture of absolute ethanol and acetone gave small white crystals, m. p. 222.5-223°.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73, N, 9.39. Found: C, 80.23; H, 4.67; N, 9.30.

This material has not been identified with exactness, but it is thought to be desoxyquinaldoin (XXXIII), reported m. p. 221° (40). Attempts to prepare the oxime by the method described in the literature (40) resulted in practically complete recovery of the starting material.

Dilution of the ethanolic solution with water to the cloud point and cooling gave an additional 0.05 g. of this higher melting solid. From the mother liquor was isolated, by concentration to 10 cc. of 0.50 g. quinaldamide (III), m. p. 123-126° after one recrystallization from ligroin.

The basic filtrate, after removal of the solid composed of III and XXXIII, was acidified with glacial acetic acid. Addition of cupric sulfate gave 0.14 g. of copper quinaldate.

The tar which was removed from the original aqueous solution was heated with 20 cc. of ethanol, leaving 0.10 g. of XXXIII, m. p. 219-221°. Evaporation of the ethanol solution yielded 1.01 g. of an intractable tar which could not be purified further.

b. A mixture of 1.2 g. of the solid in 15 cc. of concentrated hydrochloric acid was shaken occasionally for 5-10 minutes. The deep brown-red colored solution was

mixed with 15 cc. of water. Working up the resulting mixture in the same manner as the aqueous hydrolysis mixture afforded 0.51 g. of benzaldehyde-2,4-dinitrophenylhydrazone, 0.35 g. of quinaldamide (III) and 0.65 g. of copper quinaldate. No large quantities of tar were formed.

c. A suspension of 2.8 g. of the solid in 10 cc. of water was subjected to steam distillation. The distillate was run directly into a solution of 2 g. dinitrophenylhydrazine in 20 cc. concentrated sulfuric acid and 20 cc. water, yielding 0.32 g. benzaldehyde-2,4-dinitrophenylhydrazone, m. p. 232-234°.

The aqueous residue afforded 0.50 g. quinaldamide (III), m. p. 127-128°, after two recrystallizations from ligroin-benzene, and 0.80 g. of an intractable tar.

Action of Hydrogen Chloride on 1-Benzoyl-1,2-dihydroquinaldonitrile (V) in Benzene as a Solvent. - Hydrogen chloride, dried by passing through sulfuric acid, was bubbled into 150 cc. of pure benzene, dried over phosphorus pentoxide, through a dispersion tube under an atmosphere of nitrogen, dried and free of oxygen. After the benzene was saturated, 10.0 g. V was added, keeping a positive pressure of nitrogen in the flask, and addition of hydrogen chloride was continued for 15 minutes. The mixture immediately assumed a pale yellow color and after a few minutes a yellow-orange solid appeared. The reaction mixture was allowed to

stand overnight, gradually becoming deep-orange. The material was filtered in a dry-box under a nitrogen atmosphere and washed with dry benzene, giving a bright red-violet colored solid. Drying in a vacuum desiccator gave about 8 g. of a dull brown solid.

Anal.[12] Found: C, 62.11; H, 4.77; N, 8.94, 8.82; Cl, 13.55.

The solid smelled of hydrogen chloride. It was very sensitive to moisture in the air, giving off a continual odor of benzaldehyde. In a closed container, it gradually became a light rust-red color.

The solid was subjected to the following hydrolysis experiments:

a. A mixture of 1.00 g. of the solid in 50 cc. of distilled water was shaken occasionally for 5 minutes. The mixture, consisting of a black tar and a deep red-colored acid solution, was extracted four times with 30 cc. portions of ether. The ether extracts were combined, washed with 6 N hydrochloric acid and dried over Drierite. Distillation of the ether left a yellow oil which was mixed with a solution of 1 g. of 2,4-dinitrophenylhydrazine in 3 cc. concentrated sulfuric acid, 10 cc. of water and 15 cc. of ethanol. The benzaldehyde-2,4-dinitrophenylhydrazone was

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[12] Calcd. for $C_{17}H_{15}N_2O_2Cl$ (monohydrate of XXI or XXIII): C, 64.86; H, 4.80; N, 8.90; Cl, 11.27.

collected and dried; yield, 0.33 g.; m. p. 228-230° (dec.) (37% yield if solid is monohydrate of XXI or XXIII).

The aqueous residue after the ether extraction was combined with the acid washes and made basic with solid sodium bicarbonate, yielding 0.43 g. of a light brown colored solid; recrystallizing once from ligroin-benzene and once from ligroin gave white plates of quinaldamide (III), m. p. 124-126°, also when mixed with authentic III. Extraction of the aqueous filtrate with ether gave an additional 0.03 g. of III, m. p. 124-126°, from ligroin (84% total yield if solid is monchydrate of XXI or XXIII).

The aqueous residue was acidified with glacial acetic acid. Addition of cupric sulfate solution gave no copper quinaldate.

b. About 1.5 g. of the solid was washed well with small portions of dry benzene to remove any adhering benzaldehyde. After drying in a vacuum desiccator, the resulting material (1.32 g.) was added to 50 cc. of cold 5% sodium carbonate solution and shaken occasionally for about 8 minutes. There was an immediate reaction to give a yellow solid and a black tar. The mixture was extracted four times with 40 cc. portions of ether. The ether extracts were combined and washed three times with 20 cc. portions of 6 N hydrochloric acid and then with 20 cc. water. After drying over Drierite, the ether was removed, yielding benzaldehyde. This was con-

verted to the 2,4-dinitrophenylhydrazone in the usual manner, yield, 0.32 g.; m. p. 232-234° (dec.) (represents a yield of 28% if solid is monohydrate of XXI or XXIII).

The acid washes were combined with the original aqueous later and made basic with solid sodium bicarbonate. A solid which formed was filtered, dried and recrystallized from benzene to give 0.31 g. of a material, m. p. 118-145°. The material was heated with several 15 cc. portions of ligroin, the hot ligroin being decanted each time. A trace of insoluble material remained. The libroin extracts, upon slow cooling to room temperature, gave a small amount of an uncharacterized material, m. p. 220-221° after two recrystallizations from benzene.[13] Chilling of the ligroin mother several days gave quinaldamide (III), m. p. 124-126°; there was no depression when mixed with authentic III.

The basic aqueous filtrate was acidified with glacial acetic acid and mixed with a little cupric sulfate solution. A trace of a solid, presumed to be copper quinaldate, settled out.

Action of Hydrogen Chloride on 1-Benzoyl-1,2-dihydroquinaldonitrile (V) in Benzaldehyde as a Solvent.[14] - Gaseous

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[13]This material is probably not desoxyquinaldoin (XXXIII), as the previously isolated solid analyzing for XXXIII was insoluble in both ligroin and benzene.

[14]Conditions had to be varied somewhat in each run to permit isolation of the desired product, but it was assumed that the products had nearly the same composition in each case. Runs using benzaldehyde stabilized with hydroquinone gave large amounts of very high melting materials.

hydrogen chloride was bubbled through a cold suspension of 10.0 g. of 1-benzoyl-1,2-dihydroquinaldonitrile (V) in 50 cc. of dry, freshly distilled benzaldehyde. The mixture rapidly assumed a bright yellow, then an orange color (there was no color change in a blank run, passing hydrogen chloride through benzaldehyde itself); after 15 minutes, the addition of hydrogen chloride was discontinued, and the reaction mixture was allowed to stand at room temperature overnight. A yellow solid was filtered through a sintered glass funnel and washed with ether and chilled ethanol, the latter turning it white; it proved to be ammonium chloride. The benzaldehyde filtrate was mixed with 12 cc. of concentrated hydrochloric acid and heated to 70-75°. Cooling to 2° gave additional ammonium chloride, which was removed. The benzaldehyde solution was mixed with 100 cc. of ether and 20 cc. of absolute ethanol and cooled in an ice bath, yielding 2.48 g. bright orange crystals, m. p. 170-175° dec.

Anal.[15] Found: C, 51.08; H, 4.82; N, 7.31; Cl, 19.07.[16]

The benzaldehyde liquor was extracted with three 100 cc. portions of 3 N hydrochloric acid. Making the acid washes basic with sodium bicarbonate gave 0.32 g. of an unidentified yellow solid, m. p. 100-110° dec. Extraction of the

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[15]The analysis was obtained on a sample prepared in another run.

[16]Calcd. for $C_{24}H_{28}N_2O_6Cl_2$ (XXXV, x = 4): C, 56.37; H, 5.52; N, 5.48; Cl, 13.97. As ammonium chloride was known to be an impurity in the solid, an analysis of XXXV, x = 4, corrected for about 10.5% NH_4Cl is C, 50.46; H, 5.73; N, 7.65; Cl, 19.37.

filtrate with ether gave a trace of organic material. The aqueous residue was acidified with glacial acetic acid. Addition of cupric sulfate gave 3.51 g. of copper quinaldate.

The benzaldehyde-ether layer was washed with sodium bicarbonate; acidification of the washes yielded no benzoic acid. The ether was then removed by distillation and the benzaldehyde by steam distillation. Recrystallization of the yellow residue from absolute ethanol gave 1.78 g. of a white solid, m. p. 100-146°, along with an oil. Upon mixing with a little 95% ethanol, the oil solidified, yielding 1.66 g. additional of the white solid, m. p. ca. 100°. The solid was composed of two components, benzoin quinaldate (IV) and 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIV). The mixture was very difficult to separate and, upon fractional crystallization from 95% ethanol, IV was one time the more soluble fraction and another time XXXIV remained preferentially in solution.[17] Separation could not be effected by use of ligroin or benzene. Dissolving the originally obtained solid (i. e. the 1.78 g.) in 60 cc. of 95% ethanol gave impure IV, m. p. 115-152°. Repetition of this treatment, with slow cooling to room temperature, gave 0.14 g. of pure benzoin quinaldate (IV), m. p. 163-164°; there was no m. p. depression when mixed with authentic IV. From the mother liquor, upon cooling overnight in a refrigerator,

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[17]Benzoin quinaldate (IV), ordinarily difficultly soluble in hot 95% ethanol, was very soluble in ethanol in the presence of the oxazole XXXIV.

was obtained 0.24 g. of a flocculent white solid, m. p. 115-150°. Recrystallization from ethanol gave two types of solids, hard plates of benzoin quinaldate (IV), m. p. 162-163°, and a flocculent white microcrystalline material, m. p. 139-140° after one recrystallization from ligroin, which proved to be the oxazole XXXIV. The 1.66 g. of solid obtained from the oil was dissolved in 30 cc. of hot ethanol. Slow cooling to room temperature gave 0.16 g. of fine white needles, m. p. 128-137°; recrystallization twice from ethanol gave a white solid melting at about 85°, but resolidified material gave a m. p. of 137-139°. Recrystallization of this material from ligroin gave pure 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIV), m. p. 140.5-141.5°.

Anal. Calcd. for $C_{24}H_{16}N_2O$: C, 82.74; H, 4.63; N, 8.04. Found: C, 82.87; H, 5.08; N, 8.29.

Cooling of the ethanolic mother liquor, after removal of the oxazole, to 5° for 10 hours gave 0.70 g. of a white solid, m. p. 130-140°. The solid was heated with three 40 cc. portions of ligroin. Recrystallization of an insoluble residue from benzene gave 0.14 g. of benzoin quinaldate (IV), m. p. 163-165°. Addition of a little benzene to the ligroin extracts and cooling gave an additional 0.16 g. of IV, as the only isolable material.

Properties of the Orange Solid "XXXV". - a. The solid reacted with water, but was not sensitive to atmospheric

moisture as were the materials isolated from the reactions in benzene and chloroform. A mixture of 2.00 g. of the solid in 50 cc. of distilled water was stirred vigorously 30 minutes. A sticky amber-colored solid which formed was filtered and washed well with water; yield, 0.23 g., m. p. 50-110°. Three recrystallizations raised the m. p. to 140.5-151°, after softening at 80°. All the mother liquors were combined and evaporated and the residue combined with the above solid. Heating with a little ligroin gave an insoluble residue of benzoin quinaldate (IV), m. p. 161-163°; mixed with authentic IV, m. p. 162-164°. Cooling the ligroin solution gave a yellow solid, m. p. 124-135°, which on one recrystallization from ligroin gave pure 2-(2-quinolyl)-4, 5-diphenyloxazole (XXXIV), m. p. 139-140°, also upon admixture with authentic XXXIV.

The aqueous filtrate and washes were combined and extracted with ether. Evaporation of the ether gave no benzaldehyde and only a trace of an organic oil. The aqueous residue was made basic with solid sodium bicarbonate and extracted with ether. Evaporation of the ether left a trace of an oil. The aqueous layer was acidified with glacial acetic acid and mixed with copper sulfate, yielding 1.06 g. of copper quinaldate. Decomposition of the copper salt with hydrogen sulfide gave, in the usual manner, 0.42 g. of quinaldic acid (II), m. p. 154-156° dec.; there was no de-

pression when mixed with authentic II.

b. A suspension of 1.0 g. of the orange solid in 10 cc. of concentrated hydrochloric acid was shaken for 15 minutes. After filtering from a small amount of unidentified bright-orange insoluble material, m. p. 189-192° (dec.), the filtrate was about three-fourths neutralized by addition of the theoretical amount of sodium bicarbonate. The solution was extracted with three 30 cc. portions of ether. The ether extracts were dried over sodium sulfate and then evaporated, leaving a brown oil. Recrystallization of the oil from ligroin, with slow cooling to room temperature, gave two types of solid, small yellow pellets, m. p. 148-152° (lost on further recrystallization, but thought to be benzoin quinaldate) and fine white needle-clusters, m. p. 110°. Recrystallization of the latter three times from ligroin gave white crystals, m. p. 112-5-114°. There were insufficient quantities for further purification or characterization.

The aqueous residue, after the ether extraction, was made basic and extracted with ether; the ether extracts yielded no organic material. The aqueous layer was acidified with glacial acetic acid and cupric sulfate solution was added, yielding 0.68 g. of copper quinaldate.

c. Upon heating 75 hours at 120°, some orange solid obtained in another run, but assumed to have nearly the same

composition was gradually converted to quinaldic acid, m. p. 153-156° dec.; after one recrystallization from benzene, m. p. 155-156° and when mixed with authentic II.

d. Some of the orange solid, 1.00 g., was suspended in 50 cc. ethyl acetate and placed in a hydrogen atmosphere over a platinum catalyst. Hydrogenation proceeded very slowly, and after about 2 weeks, about 525 cc. had been absorbed. No hydrogenation products could be isolated, however. An amine was obtained, but attempts to benzoylate this material failed.

Action of Hydrogen Chloride on 1-benzoyl-1,2-dihydroquinaldonitrile (V) in Acetone as a Solvent. - Gaseous hydrogen chloride was bubbled through a cold solution of 10.0 g. of V in 100 cc. of C. P. acetone. The solution gradually turned a deep red color and a bright orange solid appeared. After 15 minutes, the mixture was saturated and addition of hydrogen chloride was discontinued. Upon standing for several hours, the mixture darkened considerably. The mixture was then cooled in an ice bath and filtered through a sintered glass crucible; washing the brown solid with C. P. acetone yielded 4.34 g. of tan crystals, m. p. 192-195°, thought to be quinaldamide hydrochloride. Recrystallization of some of this solid from C. P. acetone gave tan crystalline material, m. p. 195-196°.

Anal. Calcd. for $C_{10}H_{10}N_2O_{3/2}Cl$ (hemihydrate of quinaldamide hydrochloride): C, 55.15; H, 4.63;

N, 12.87; Cl, 16.28. Found: C, 55.40, 55.56; H, 4.73, 4.77; N, 12.8, 12.6; Cl, 16.0, 15.72.

Some of the material was recrystallized twice from absolute methanol, giving flocculent white solid, m. p. 181-189°; from the analytical data, it was thought it might be the hydrate of quinaldimino methyl ether hydrochloride.

Anal.[18] Found: C, 56.98; H, 4.48; N, 11.65; Cl, 13.72.

An aqueous solution of the quinaldamide hydrochloride, upon being made basic, gradually became turbid and crystalline quinaldamide appeared, m. p. 124-126°, also when mixed with authentic III. Quinaldamide was the only isolable organic material, other than a little copper quinaldate. This result (i. e. appearance of solid quinaldamide only slowly) throws some doubt on the validity of the assumption that the above material is simply the hydrochloride of III.

After removal of the quinaldamide hydrochloride, the acetone filtrate was mixed with 200 cc. of dry ether and 10 cc. of concentrated hydrochloric acid. Cooling overnight in a refrigerator yielded 0.30 g. of a brown solid, m. p. 170-180° dec. The filtrate was evaporated on a steam bath and then some mesitylene was removed by heating under reduced pressure. The residue was filtered, leaving 3.86 g.

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[18] Calcd. for $C_{11}H_{13}N_2O_2Cl$: C, 54.88; H, 5.44; N, 11.64; Cl, 14.73.

of a yellow solid, after washing with ether and acetone. Some of the material was recrystallized from C. P. acetone, giving small brown crystals thought to be hydrate of quinaldic acid hydrochloride, m. p. behavior: turns white 120-130°, yellow 150°, dec. with gas evolution 190-193°; reported m. p. 195° (dec.) (41). An aqueous solution of this material gave, quantitatively, quinaldic acid, m. p. 155-156.5° (dec.).

Acid-Catalyzed Hydrolysis of 2-(2-Quinolyl)-4,5-diphenyloxazole (XXXIV). - The oxazole XXXIV was separated from contaminant benzoin quinaldate (IV) by chromatography; the oxazole was eluted from a column of alumina with benzene. A mixture of 0.25 g. of XXXIV and 10 cc. of 25% sulfuric acid was heated under reflux for six days. There was an immediate development of a bright orange color when the acid was added to the oxazole. Some solid which had steam distilled into the condenser was washed down with water. The mixture was extracted with three 30 cc. portions of ether; some solid remained insoluble in either layer. The ether extracts were combined and washed with saturated sodium bicarbonate solution. Acidification of the basic wash and extraction with ether yielded no benzoic acid. The washed ether solution was dried over sodium sulfate and evaporated, leaving 0.07 g. (89% net yield) of benzoin, m. p. 132-133° after two recrystallizations from ethanol; there was no m. p. depression when mixed with authentic benzoin.

The acid aqueous residue, in which was suspended some insoluble material, was made basic with sodium hydroxide and extracted three times with 30 cc. portions of ether. Drying the ether extracts over sodium sulfate and evaporating yielded 0.10 g. of recovered oxazole (XXXIV), m. p. 136-139° after recrystallization from ligroin.

The basic aqueous residue, still containing some insoluble solid, was extracted twice with 20 cc. portions of benzene. Evaporation of the benzene yielded an additional 0.02 g. of recovered XXXIV. The aqueous layer was acidified with glacial acetic acid and mixed with a little copper sulfate solution. Long standing produced a small amount of a blue-green solid which was assumed to be copper quinaldate.

1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile. - This compound was prepared from 6-methoxyquinoline, benzoyl chloride and potassium cyanide by the procedure of Gassman and Rupe (5) in 58% yield, m. p. 122-125°. In two preparations, the Reissert compound was obtained each time as granular crystals with a green tint; the color was not removed by repeated recrystallization, but was removed by the following treatment: A solution of 5 g. of the Reissert compound in 50 cc. of dry benzene was allowed to stand with decolorizing charcoal 10 days at room temperature. The charcoal was then filtered and most of the solvent removed under reduced pressure. Cooling gave a white powder, m. p. 125-

126.2°. After two recrystallizations from ethanol, the m. p. was raised to 127-128°, and the Reissert compound was in the form of pure white granular crystals. Further recrystallization, however, caused the melting point to lower; it gradually decreased to about 112° after several more recrystallizations from ethanol.

Hydrogenation of 1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile. A. - A suspension of 2.2 g. of the 6-methoxy Reissert compound and 0.1 g. of platinum oxide catalyst in 50 cc. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature until the theoretical volume of hydrogen corresponding to two molar equivalents had been absorbed. When reduction was about three-quarters complete, an additional 0.1 g. of catalyst was added. The solution was heated to boiling, filtered and the filtrate treated with Norit. The filtrate was concentrated under reduced pressure and the residue cooled, yielding a dark solid. Two crystallizations from absolute ethanol gave yellow crystals, m. p. 148-150°. Pure material was prepared for analysis by four additional recrystallizations from absolute ethanol, m. p. 153-2-154°, long white needles.

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.37. Found: C, 73.82, 73.87: H, 5.47, 5.49; N, 9.65, 9.56.

By analogy with XX, this compound is thought to be 1-phenyl-

3-keto-7-methoxy-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline.

B. The hydrogenation was repeated on 2.00 g. of the 6-methoxy Reissert compound under the same conditions. Before reduction was started, mercury was accidentally spilled into the mixture. After the theoretical volume of hydrogen corresponding to one molar equivalent had been absorbed, the solution was worked up as above, to give dark colored crystals, m. p. 139-143°. After four recrystallizations from ethanol, white needles of the above mentioned compound, $C_{18}H_{16}N_2O_2$, m. p. 152-152.5°, was obtained as the only isolable material, rather than the expected 1-benzoyl-6-methoxy-1,2,3,4-tetrahydroquinaldonitrile (12), also having the formula $C_{18}H_{16}N_2O_2$, m. p. 141-142°.

Another anomalous reduction product was observed in another case. The hydrogenation apparently proceeded normally with the 6-methoxy Reissert compound, except that additional catalyst had to be added to effect absorption of the theoretical volume of hydrogen corresponding to one molar equivalent. The hydrogenation mixture was worked up as above, yielding, after one recrystallization from ethanol, white needles, m. p. 123-124°. After two recrystallizations from absolute ethanol, a completely pure analytical sample was obtained, glistening white needles, m. p. 125.6-126.2°; mixed with 1-benzoyl-6-methoxy-1,

2-dihydroquinaldonitrile, m. p. 109-112°.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.76, 78.90; H, 5.20, 4.97; N, 10.34, 10.54.

The structure of this material has not been proven. Its infrared absorption spectrum was very complex. In a carbon tetrachloride solution, peaks of major intensity occurred at frequencies of 1271, 1230, 1148, 1103 and 693 $cm.^{-1}$; small peaks occurred at 1490, 1467, 1409, 1178, 930 and 905 $cm.^{-1}$.

Action of Mineral Acid on "1-Phenyl-3-keto-7-methoxy-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline". - A mixture of 0.27 g. of the material of m. p. 153-154° and 0.2 g. of 2,4-dinitrophenylhydrazine in 6 cc. of concentrated hydrochloric acid was heated on the steam bath to effect solution and then allowed to stand at room temperature for 2 days. There was no indication of benzaldehyde formation. Addition of 6 cc. water, heating to boiling and filtering gave 0.02 g. of a brown colored solid, m. p. ca. 210°.

Action of Acid on 1-Phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX). - A mixture of 0.1 g. of XX, 0.08 g. of 2,4-dinitrophenylhydrazine and 10 cc. of concentrated hydrochloric acid was heated on the steam bath for 5 minutes to effect solution. There was no indication

of benzaldehyde formation after three days at room temperature.

Hydrogenation Studies of 1-Benzoyl-1,2-dihydroquinaldonitrile (V). - A. In Ethanol as the Solvent. 1. One mole. - Upon addition of one molar equivalent of hydrogen to V in an ethanol solution over a platinum catalyst at one stmosphere pressure, there was usually obtained the normal product, 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII), m. p. about 132°, upon working up the reduction mixture as described above for the 6-methoxy Reissert compound. The rate of reduction at time was rather rapid, being complete in one or two hours, but sometimes reduction was extremely slow, seemingly regardless of the purity of the sample.

When large quantities of the dihydro Reissert compound, XII, were required, reductions were carried out on a three grams scale; after removing the platinum, the ethanol solutions were allowed to stand until up to ten reductions had been completed and then the solutions were combined and worked up. Long standing of the solutions caused separation of beautiful crystals, which, upon recrystallization from ethanol, proved to be the imidazolone, XX, rather than XII. This isomer generally proved to be a minor product, however, but it is believed that most samples of 1-benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII) prepared, except those especially purified by repeated crystallization, contained some XX as an impurity.

2. Two moles. - A suspension of 2.00 g. 1-benzoyl-1,2-dihydroquinaldonitrile (V) and 0.1 g. of platinum oxide catalyst in 100 cc. of 95% ethanol was allowed to absorb two molar equivalents of hydrogen at atmospheric pressure and room temperature. After filtration and concentration of the filtrate, there was obtained 0.75 g. of 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), m. p. 146-148°; reported m. p. 147-148° (21). Additional material was recovered from the mother liquor, to give a total yield of about 60%.

3. Three moles. - Addition of three molar equivalents hydrogen to the Reissert compound V in the above manner (more catalyst was required before absorption was complete) resulted in about a 35% yield of XX, m. p. 144-147°; mixed with authentic XX, m. p. 143-147°. Isolated in about the same quantities was a dark colored, intractable oil.

B. In Ethanol as the Solvent with Added Acetic Acid. - A suspension of 3.00 g. of V and 0.1 g. of platinum oxide in 50 cc. of absolute ethanol was subjected to hydrogenation under the same previously described conditions. About 25% of the theoretical volume of hydrogen (corresponding to one molar equivalent) was absorbed in 10-15 minutes, and the absorption abruptly stopped. An additional 0.1 g. of catalyst and 50 cc. of ethanol was added. Again approximately the same volume of hydrogen was quickly absorbed, and then

reduction stopped. About one cc. glacial acetic acid was introduced; the hydrogenation proceeded smoothly to completion. Upon filtration and concentration of the filtrate under reduced pressure, the solution deposited 1.30 g. of small yellow needles, m. p. 133-138°, after softening at ca. 120°. Two recrystallizations from ethanol failed to improve the melting point. It was assumed that the material was a mixture of XII and XX. Additional solid was obtained from the mother liquor.

Acid-Catalyzed Hydrolysis of the Imidazolone XX. a. - A suspension of 3.0 g. of XX in 50 cc. of 6 N hydrochloric acid was heated under reflux 24 hours. The material gradually dissolved and the solution became yellow. There was a slight odor of hydrogen cyanide. A white crystalline material which had steam distilled into the condenser was washed down with water. Cooling the solution gave a yellow crystalline solid which proved to be benzoic acid; yield, 1.16 g., m. p. 120-123°, also in admixture with authentic benzoic acid.

After removal of the benzoic acid, the acid aqueous solution was extracted twice with 25 cc. portions of ether. After drying over Drierite, the extracts were evaporated, yielding an additional 0.18 g. of benzoic acid, m. p. 119-122° (total yield of benzoic acid was 97%).

The acidic aqueous residue was cooled in an ice bath and made basic with 10% sodium hydroxide solution. Extrac-

tion with ether yielded no basic material. The solution was then barely acidified with glacial acetic acid and 0.65 g. of a gelatinous, pale yellow solid was collected. The material proved to be insoluble in all common organic solvents and in hot water. It was amphoteric, as it dissolved in either excess base or acid and was reprecipitated by the other. It could not be purified or identified.

After removal of this polymeric material, copper sulfate solution was added to the aqueous filtrate, causing 0.89 g. of a dark green solid to settle out. Decomposition of this copper salt with hydrogen sulfide in the usual manner yielded a solid which behaved similarly to the amphoteric material obtained above.

No benzaldehyde was formed on hydrolysis.

b. A mixture of 2.00 g. of XX, 50 cc. of 95% ethanol and 10 cc. of concentrated sulfuric acid was heated under reflux for 24 hours. The reaction mixture quickly assumed a yellow color. After 30 minutes heating, a small portion was removed and tested with 2,4-dinitrophenylhydrazine solution; no hydrazone was formed, indicating the absence of benzaldehyde. After refluxing was completed, the solvent was distilled and the residue mixed with 50 cc. of ice water. The resulting cloudy solution was extracted with ether; evaporation of the ether yielded a sweet smelling oil assumed to be ethyl benzoate. The acidic aqueous residue was made basic with sodium bicarbonate. The resulting solution was

extracted with three 30 cc. portions of ether. Evaporation of the ether extracts after drying over Drierite, yielded a light yellow oil. The oil was mixed with 50 cc. of dry ether and divided into two portions. Methyl iodide was added to one portion, in the hope that a methiodide might be prepared, but this failed. The other ethereal solution was saturated with dry hydrogen chloride, yielding white plates. The solid was recrystallized from a mixture of absolute ethanol and dry ether, to give a flocculent white solid, m. p. 126-127.5°, thought to be ethyl tetrahydroquinaldate hydrochloride (LI·HCl); actually, the analytical data indicates a mixture of the salt and the free basic ester.

Anal. Calcd. for $C_{12}H_{16}NO_2Cl$: C, 59.60; H, 6.67; N, 5.79. Calcd. for $C_{12}H_{15}NO_2$: C, 70.20; H, 7.37; N, 6.82. Found: C, 64.00; H, 7.12; N, 5.95.

No other material could be isolated from the reaction mixture.

Base-Catalyzed Hydrolysis of the Imidazolone XX. a. - A suspension of 3.5 g. (0.014 mole) of XX and 0.56 g. of sodium hydroxide (0.014 mole) in 150 cc. of 75% ethanol was heated under reflux 48 hours. Ammonia was evolved throughout most of the heating; the solution gradually assumed a yellow color. When the heating was discontinued, the solution tested practically neutral to litmus. The solution was concentrated to about 60 cc. and made distinctly

basic by addition of a little 10% sodium hydroxide solution. The basic solution was extracted with three 25 cc. portions of ether. Evaporation of the ether, after drying over potassium carbonate, yielded an oil which solidified to a glass upon cooling; recrystallization from a mixture of ligroin and benzene gave 0.61 g. of a snow white solid, m. p. 85-98°. The material behaved rather oddly on further recrystallization from benzene; the first recrystallization yielded material, m. p. 92-95°, but on subsequent purification, the m. p. jumped to 126-128° (mixed with quinaldamide, m. p. 95-120°). Additional solid was collected from the mother liquors, giving a total yield of 1.00 g. The second and third crop of crystals were combined, dissolved in hot benzene and decolorized. Cooling gave white plates, m. p. 95-98°; two recrystallizations from benzene gave a white microcrystalline solid, m. p. 97.4-98.8°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.50. Found: C, 69.25; H, 6.93; N, 13.57.

(See below for behavior of this material on benzoylation.)

After ether extraction to remove the basic components, the aqueous residue was acidified with hydrochloric acid and extracted with three 25 cc. portions of ether. After drying over calcium chloride, the ether extracts were evaporated and the residue heated under reduced pressure, leaving a dark brown oil which partially solidified on standing. Attempts to recrystallize from ether, benzene, ligroin,

methanol, chloroform, acetone and ethyl acetate failed. The tar was subjected to steam distillation; no benzoic acid was found in the distillate. After this treatment, the water was removed under reduced pressure and the residue mixed with dry benzene. The benzene was distilled off, taking with it the last traces of water. The tar was treated with hot ether. About half the insoluble residue was treated according to the directions for the preparation of a p-bromophenacyl ester (42). An unidentified derivative, m. p. 107.5-108.5°, after four recrystallizations from ethanol, was obtained in amounts too small for an analysis.

No significant material could be isolated from the acidic aqueous residue after the preceding ether extraction.

A solution of 0.1 g. of the agove basic material, $C_{18}H_{21}N_3O_2$, in 20 cc. of dry benzene was mixed with 0.2 cc. of benzoyl chloride and 1 cc. of dry triethylamine. After refluxing 3 hours, the reaction mixture was cooled; 3 cc. of pyridine and 20 cc. of ether were then added. The mixture was washed with dilute sodium bicarbonate, 3 N hydrochloric acid and finally with water. Evaporation of the benzene-ether layer and recrystallization of the residue from ethanol afforded the imidazolone XX, m. p. 146-147°, after one recrystallization from ethanol.

b. A suspension of 1.00 XX in 40 cc. 5% sodium hydroxide was boiled under reflux 45 minutes. The solution gradually assumed a yellow color as the solid partially dissolved.

After cooling to room temperature, some unreacted starting material was filtered and washed with ether, m. p. 145-148°, wt. 0.21 g.

The aqueous filtrate was extracted with ether, yielding a small additional amount of the starting material. The aqueous residue was acidified with hydrochloric acid; fumes of hydrogen cyanide were released. Benzoic acid, 0.13 g., was removed from the acidic solution, m. p. 120-121°.

The acidic filtrate was extracted with three 30 cc. portions of ether. After drying over Drierite, the extracts were evaporated, leaving 0.47 g. of a tar which resisted attempts at purification.

Alkaline Peroxide Hydrolysis of the Imidazolone XX. - Action of hydrogen peroxide on an acetone solution of XX in the presence of sodium bicarbonate at room temperature, as previously described for the conversion of the Reissert compound, V, to its amide, XIII, resulted in no reaction; about 70% of the starting material was recovered.

A solution of 0.70 g. of XX in 75 cc. of acetone was mixed with a solution of 0.2 g. of sodium carbonate in 5 cc. of water. To the resulting cloudy mixture was added 20 cc. of 30% hydrogen peroxide; this addition caused precipitation of a white solid. An additional 75 cc. of acetone was added and the mixture was refluxed 10 minutes. An additional 10 cc. of peroxide was added and heating was continued for 20

minutes more. The hot solution was filtered from some insoluble sodium carbonate; the acetone was distilled from the filtrate and the turbid residue mixed with 200 cc. of water. After standing for about an hour, 0.38 g. (49%) of white, crystalline 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII) was collected, m. p. 187-189°. The solid was recrystallized from ethanol. m. p. 192.5-194° and when mixed with authentic XVIII.

Action of Oxidizing Agents on the Imidazolone XX. A. Potassium Permanganate. - 1. To a solution of 0.2 g. of XX (obtained by a reduction of V) in 10 cc. of pure acetone was added, dropwise, dilute potassium permanganate solution. The solution was swirled after each addition until the purple color was discharged. After a slight excess of the permanganate had been added, a little ferrous sulfate was added and the resulting mixture was acidified with a little hydrochloric acid. Then 30 cc. of water was added; a white, fluffy solid which appeared was filtered, 0.15 g., m. p. 147-148° after one recrystallization from ethanol.

The imidazolone recovered above after the oxidation treatment was dissolved in 10 cc. of pure acetone. The purple color persisted after addition of only one drop of potassium permanganate.

2. The oxidation was repeated using more stringent conditions. A mixture of 0.5 g. of XX, previously freed

from oxidizable impurities by the above process (i. e., treatment of an acetone solution with dilute permanganate), in 50 cc. of water, buffered with 5 g. of ammonium chloride was heated on a steam bath. Small portions of saturated potassium permanganate solution were added intermittently, sufficient time being allowed between additions to permit discharge of the purple color. After about 50 cc. of the permanganate solution had been added (over a period of 6 hours), the hot solution was made distinctly basic with concentrated sodium hydroxide and filtered. The solid was boiled with benzene and filtered. Evaporation of the benzene yielded 0.29 g. recovered XX, m. p. 147-148°.

Acidification of the filtrate gave a small amount of a fluffy white solid, m. p. 230° dec. Nothing else could be isolated.

B. Chromic Acid. - To a cold solution of 0.5 g. of XX in 10 cc. of concentrated sulfuric acid and 20 cc. of glacial acetic acid was slowly added saturated aqueous potassium dichromate solution. After about 5 cc. had been added, a vigorous reaction started with evolution of a gas, but this soon subsided. After about 30 cc. of the oxidizing solution had been added, the mixture was stirred for 30 minutes and then poured over 50 g. of ice. No organic material could be isolated upon working up the reaction mixture in the usual manner.

Attempted Benzoylation of the Imidazolone XX. - A solution of 1.00 g. XX, from reduction of the Reissert compound, in 25 cc. of dry pyridine was mixed with 5 cc. of benzoyl chloride; the resulting mixture was allowed to stand in a closed flask 48 hours. The pyridine was removed from the deep red reaction mixture under reduced pressure; the red-colored residue was neutralized with cold 5% sodium bicarbonate solution and then made basic with cold 5% sodium carbonate solution. After cooling to 5°, a sticky red-colored solid was filtered. Fractional recrystallization of the solid from ethanol by the triangular method allowed an 80% recovery of the starting imidazolone (XX) as the only isolable organic material, other than a little benzoic acid.

Action of Potassium Permanganate on 1-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII). - To a solution of 1.00 g. of the dihydro Reissert compound, XII, in 40 cc. of pure acetone was added intermittently dilute potassium permanganate solution. After addition of the permanganate, the solution was swirled until the purple color was discharged. After sufficient permanganate had been added so that the color persisted, the mixture was heated for a minute on the steam bath. A little ferrous sulfate was added to reduce the excess permanganate and 30 cc. of concentrated hydrochloric acid was added to destroy the man-

ganese dioxide. The precipitated imidazolone (XX) was filtered from the warm solution and washed well with water, m. p. 143-146°; yield, 0.44 g. (44%). The m. p. was raised to 147-149° after one recrystallization from ethanol. The results are the same as those found by Elliott (21).

Attempted Total Synthesis of the Imidazolone XX from Methyl Tetrahydroquinaldate and Methyl Benzimidate (26, 29). - To a solution of 1.25 g. of methyl benzimidate (43, 44) in 15 cc. of dry ether was added slowly a solution of 1.4 g. of methyl tetrahydroquinaldate, prepared as described previously, in 15 cc. of dry ether. There was no apparent reaction. After standing for about 30 minutes, the ether was removed and the residue allowed to stand overnight; no reaction apparently occurred. Then 10 cc. of dry ether and 30 cc. of dry pyridine was added. Again, after three weeks, no reaction had occurred. The solvents were removed under reduced pressure; the residue was taken up in 10 cc. of absolute methanol and mixed with a solution of 1 g. of sodium in 25 cc. absolute methanol. No reaction occurred. The solution was heated under reflux for 30 minutes and then concentrated to about one-half volume. No 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX) could be isolated.

Hydrogenation and Benzoylation of Quinaldamide (III). - A suspension of 3.25 g. of quinaldamide hydrochloride

(III·HCl) (see below) and 0.1 g. of platinum oxide catalyst in 50 cc. of absolute ethanol was placed in a hydrogen atmosphere at one atmosphere pressure and room temperature. The solution turned a blue-green color, due to attack of the acid present on an iron stirring bar. Absorption of hydrogen proceeded slowly; after about 15% of the volume corresponding to two molar equivalents of hydrogen had been absorbed, an additional 25 cc. of ethanol and 0.1 g. of catalyst was added. After about 72 hours, about 53% of the required volume of hydrogen had been absorbed and hydrogen uptake had stopped. A little water was added to the reduction mixture; the mixture was heated to about 40° and the platinum removed. The filtrate was concentrated to a few cc. under reduced pressure. The aqueous residue was made strongly basic by addition of cold 10% sodium hydroxide solution, causing a white solid to appear. Then 6 g. of benzoyl chloride was added, 1 g. at a time, with vigorous shaking. The resulting dark solid was collected, washed well with water and warm 3 N hydrochloric acid and then recrystallized from ethanol. There resulted 0.11 g. of a white powder, m. p. 140-144°; recrystallization five times from ethanol gave beautiful white needles, m. p. 148.5-149°.[19] Admixture with 1-phenyl-

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[19]The material exhibited peculiar behavior upon recrystallization. The first solid which formed was a flocculent white, microcrystalline material; disturbing caused disappearance of this solid and crystallization of the long needles.

3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), obtained by hydrogenation of the Reissert compound V, gave a m. p. 146-148°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.34; N, 10.68. Found: C, 77.99; H, 5.34; N, 10.70.

The infrared absorption spectrum is recorded on Plate 2.

Quinaldamide (III). - The most convenient synthesis of III was from quinaldonitrile (VIII), utilizing the procedure of Lowman (35). A solution was prepared of 3.0 g. of VIII in 20 cc. of concentrated hydrochloric acid. After standing about 30 minutes, heavy prisms of quinaldamide hydrochloride began to separate from the yellow solution. After allowing to stand overnight, the mixture was filtered, yielding 3.25 g. (86%) of the hydrochloride of III, m. p. 198-201° dec.; recrystallization from 3 N hydrochloric acid gave hard yellow prisms, m. p. 204-207° (dec.); reported m. p. 194-200° (dec.) (35). The free base could be generated from the hydrochloride by making basic an aqueous solution of the salt. The quinaldamide exhibits unusual m. p. behavior. Depending on the source, but seemingly regardless of the purity, m. p.'s were observed in a range of 124-126° to 132-133°. Also, the m. p. of a mixture of quinaldamide melting, for example, at 126-127° and quinaldamide melting at 124-126° often was increased to above 130°.

In a single attempt at preparation of III from the

Reissert compound V, the reported (16) yield could not be approached. Quinaldamide was successfully prepared from quinaldoyl chloride.

Dehydration of 1-Benzoyl-,2,3,4-tetrahydroquinaldamide (XVIII). - To a solution of 2.68 g. of 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII) and 2 cc. of triethylamine in 100 cc. of benzene (dried over phosphorus pentoxide) was added about 1.5 g. of phosphorus pentoxide. The mixture was heated under reflux one hour; an additional 1.5 g. of phosphorus pentoxide was added and reflux continued for an hour. After standing at room temperature overnight, the reaction mixture was heated to boiling and the benzene solution decanted from an insoluble sludge. The insoluble material was washed twice with hot benzene. The benzene extracts were combined and concentrated to about 60 cc.; the hot solution was then decolorized and further concentrated to about 30 cc. Addition of an equal volume of ligroin and cooling gave 1.68 g. of hard white pellets, m. p. 133-142°; three recrystallizations from ethanol gave white needles, m. p. 148.5-149.5°; mixed with 1-benzoyl-1,2-dihydroquinaldonitrile (V), m. p. 135-145°; mixed with 1-phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), m. p. 148-149.5°.

Evaporation of the mother liquor gave more imidazolone; total yield, 75-80%.

Preparation of α-Benzamidoquinaldine. - This material

was prepared as it was needed in the proof of structure of XX, since it is isomeric with XII and XX.

2-Aminomethylquinoline was prepared by hydrogenation of quinaldonitrile (VIII) (45). A solution of 1.0 g. VIII in 50 cc. of 95% ethanol and 1.6 cc. of concentrated hydrochloric acid was allowed to absorb the theoretical volume of hydrogen at atmospheric pressure and room temperature corresponding to two molar equivalents over a palladium catalyst. The reduction mixture was heated to boiling, 3 cc. of 3 N hydrochloric acid added, and the palladium filtered off. The clear dark yellow filtrate was concentrated to 10 cc. under reduced pressure; addition of 10 cc. absolute ethanol to the residue and cooling in an ice bath gave 1.20 g. of 2-aminomethylquinoline dihydrochloride, m. p. 227-237°.

A solution of 0.3 g. of the above salt in 3 cc. of water was mixed with 15 cc. of 20% sodium hydroxide solution. Then 2 g. of benzoyl chloride was added, about 0.5 cc. at a time, with vigorous shaking. After cooling the basic reaction mixture to room temperature, the green granular solid was collected and recrystallized from dilute ethanol; this gave 0.17 g. of a white solid, m. p. 85-90° (dec.). Two recrystallizations from a mixture of ligroin and benzene and two more from dilute ethanol gave a flocculent white solid, m. p. 127.5-129°.

Studies of the Structure of Reissert Compounds by Infrared Absorption Spectra. - On Plates 4, 5 and 6 are recorded the infrared absorption spectra of 1-benzoyl-1,2-dihydroquinaldonitrile (V) and 1-acetyl-1,2-dihydroquinaldonitrile in a variety of solvents. A striking observation is that in no case does a peak occur at the frequency (i. e., 2200-2400 cm.$^{-1}$) required for cyano absorption. A discussion of a possible cause of this has been included in the first part of this thesis.

Plate 2

Infrared Absorption Spectra

A. 1-Benzoyl-1,2-dihydroquinaldonitrile (V), 1% solution in CCl_4
B. 1-Benzoyl-1,2,3,4-tetrahydroquinaldonitrile (XII), 1% solution in CCl_4
C. 1-Phenyl-3-keto-3a,4,5,9b-tetrahydroimidazo[3,4-a]quinoline (XX), 1% solution in $CHCl_3$

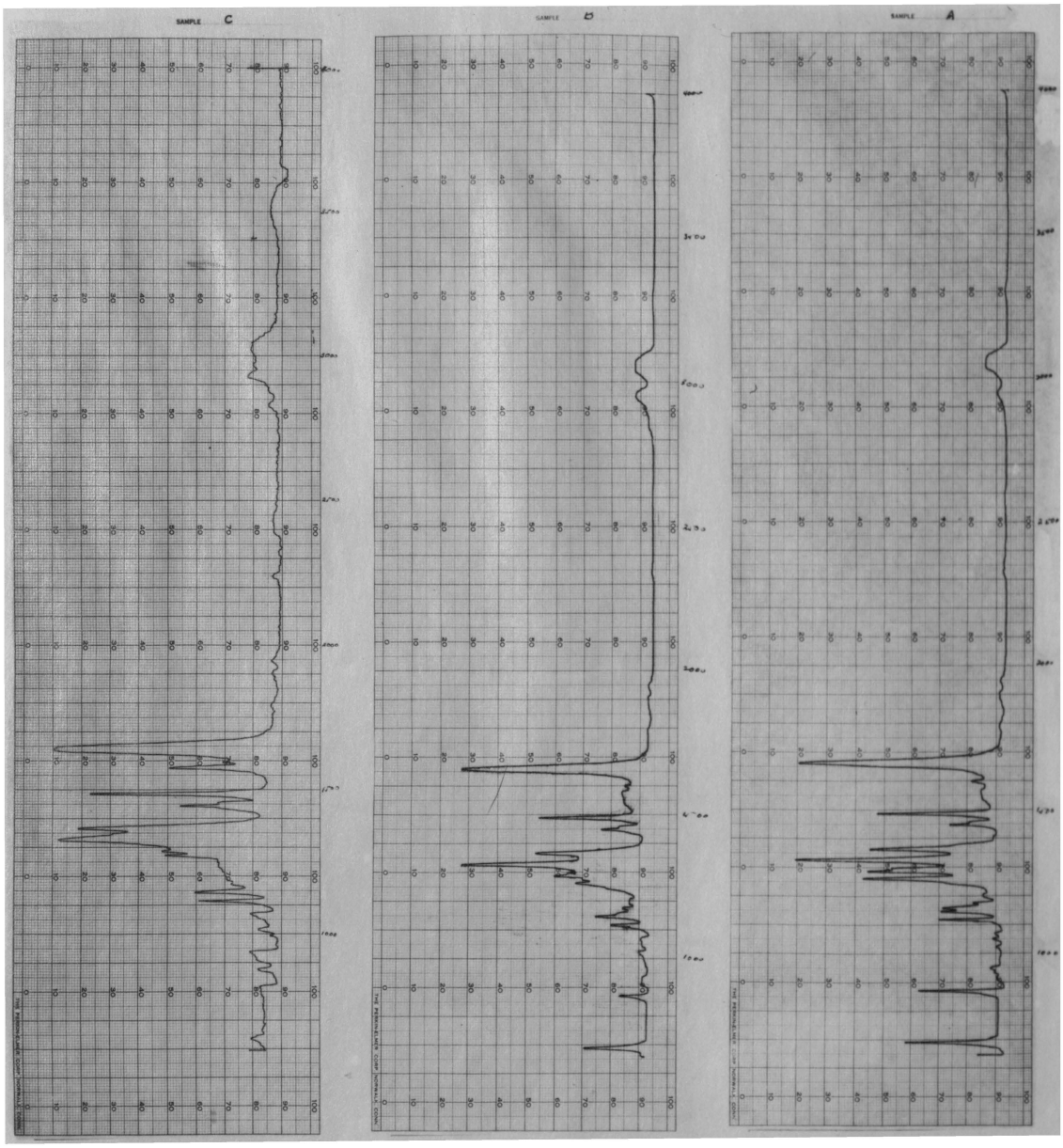


Plate 3

Infrared Absorption Spectra

A. 1-Benzoyl-1,2-dihydroquinaldamide (XIII), 1% solution in $CHCl_3$
B. 1-Benzoyl-3-acetyl-1,2-dihydroquinaldamide (XV), solution in $CHCl_3$
C. 1-Benzoyl-1,2,3,4-tetrahydroquinaldamide (XVIII), 1% solution in $CHCl_3$

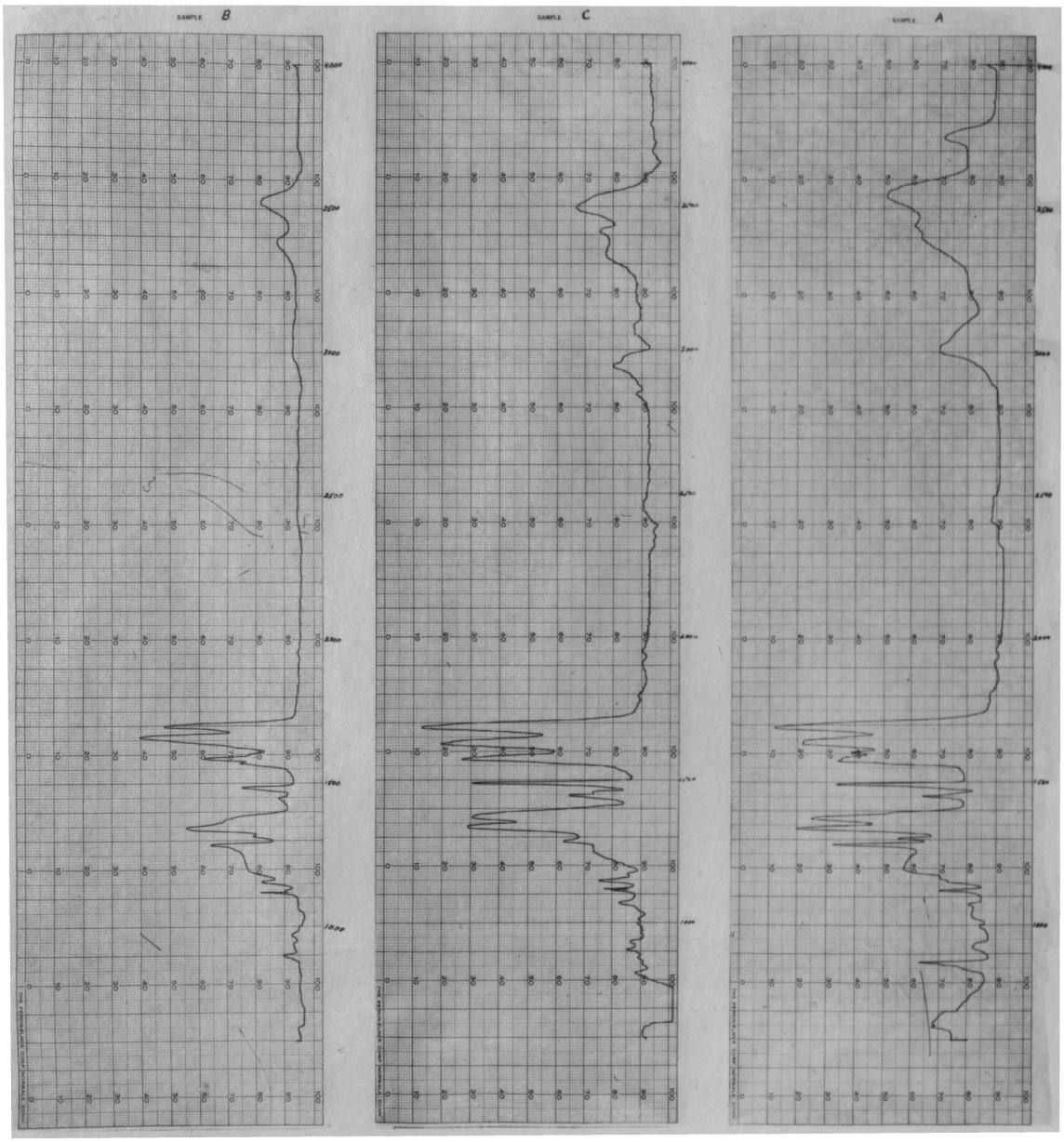


Plate 4

Infrared Absorption Spectra
of 1-Benzoyl-1,2-dihydroquinaldonitrile

A. A Nujol mull
B. A 1% solution in chloroform
C. A 1% solution in acetone

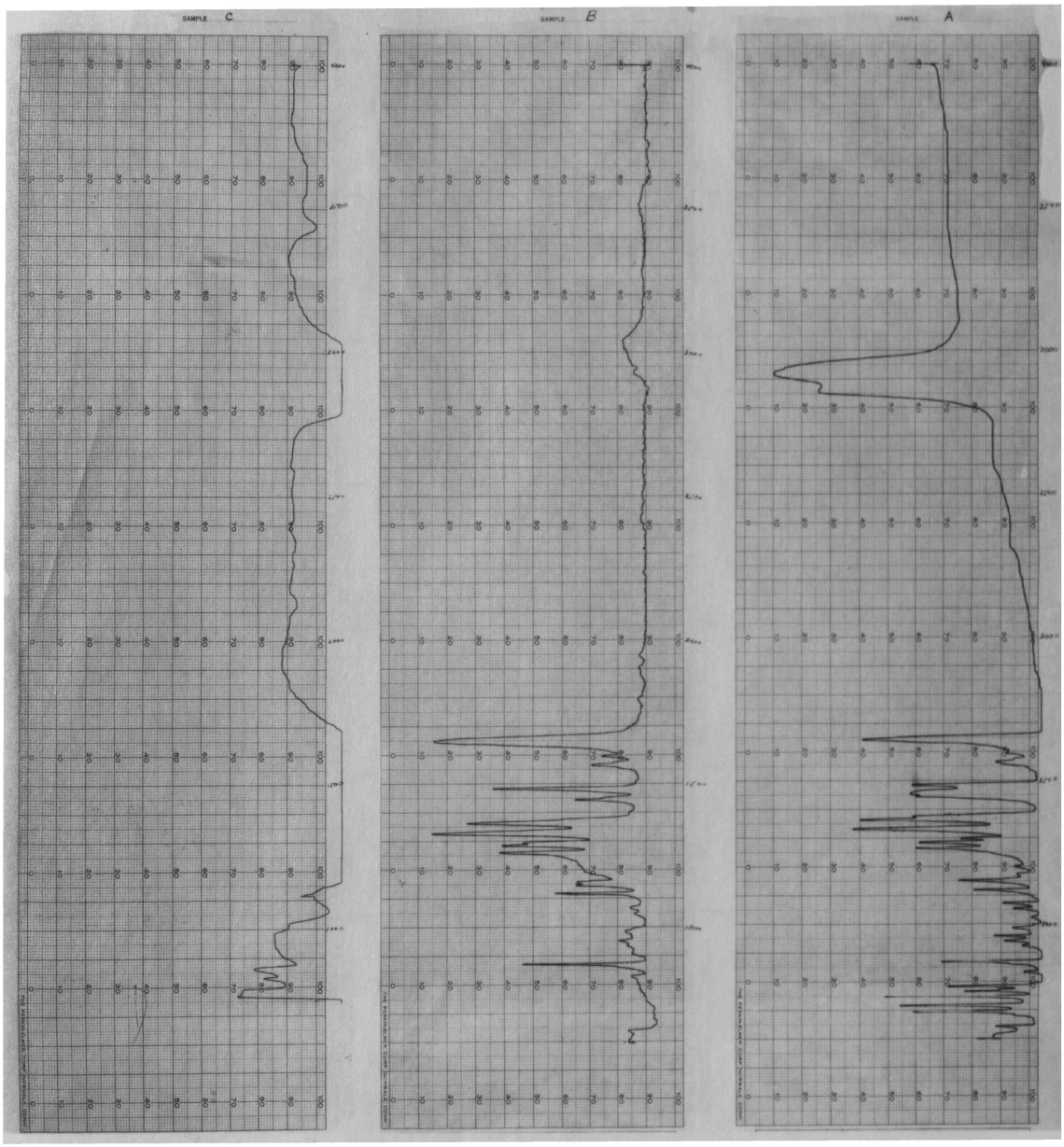


Plate 5

Infrared Absorption Spectra
of 1-Benzoyl-1,2-dihydroquinaldonitrile

A. A saturated solution in benzene
B. A 1% solution in pyridine
C. A saturated solution in 1:1 triethylamine-toluene

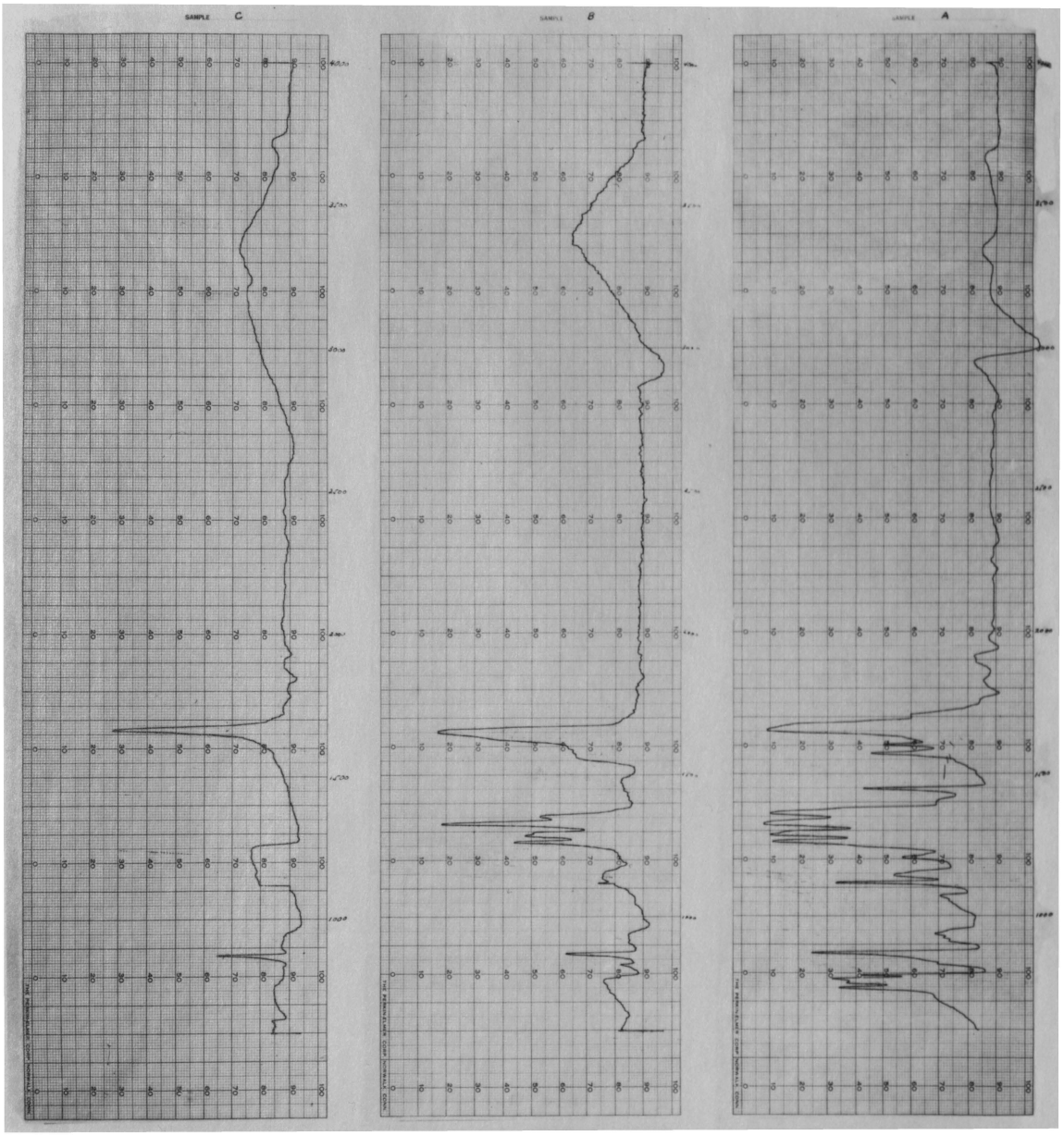
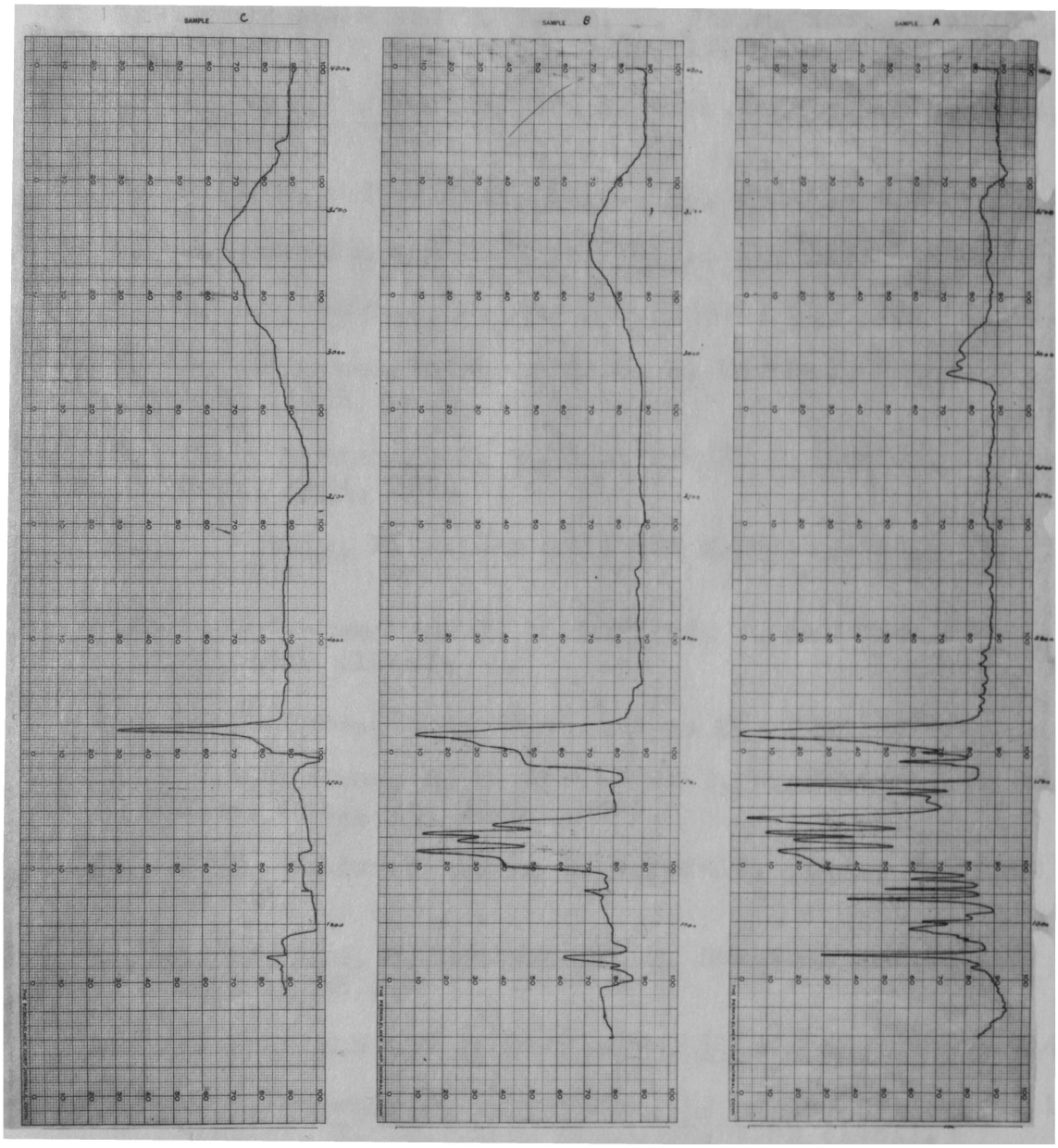


Plate 6

Infrared Absorption Spectra of 1-Acetyl-1,2-dihydroquinaldonitrile

A. A 1% solution in chloroform
B. A 1% solution in pyridine
C. A saturated solution in triethylamine



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