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

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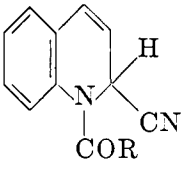
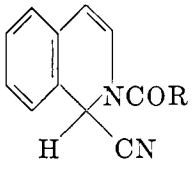
I. Introduction

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.

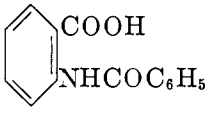


I

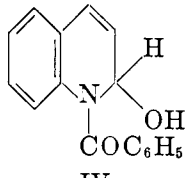


II

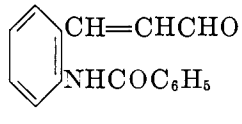
In 1905, after repeated failures in attempts to introduce the benzoyl group into the benzothiazole ring, Arnold Reissert began a systematic study of the benzoylation of cyclic tertiary amines. Upon treatment of a mixture of quinoline and benzoyl chloride with an aqueous solution of sodium hydroxide,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



III



IV



V

The reaction of benzoyl chloride with quinoline in aqueous potassium cyanide solution was tried next and yielded a crystalline compound, $C_{17}H_{12}N_2O$. This compound was found to undergo a remarkable acid-catalyzed cleavage to benzal-

dehyde, 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 the 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 *via* these compounds, the preparative scope has been extended to include several substituted quinolines and isoquinolines.

A. Preparation in aqueous medium

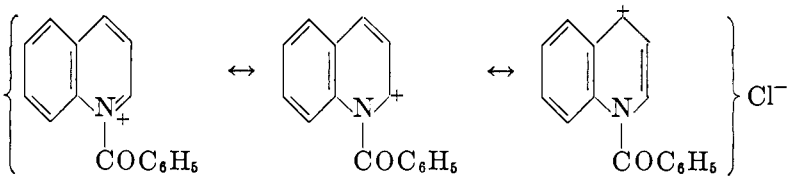
As would be expected, the preparation of Reissert compounds in an aqueous medium has been limited to the use of relatively inactive acid chlorides, specifically the less reactive aroyl chlorides. Aliphatic acid chlorides and reactive aroyl chlorides, such as the nitrobenzoyl chlorides, react much too 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 2 moles of benzoyl chloride to a suspension of 1 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 per cent of the theoretical (42, 60, 61, 87). Application of efficient mechanical stirring increases the ease of operation but does not necessarily increase the yields of the 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-dihydroquinaldo-

nitrile (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 MEDIA

In order to prevent the 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). The 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, 1-benzoyl-1,2-dihydroquinaldonitrile (I: R = C_6H_5) and 1-cinnamoyl-1,2-dihydroquinaldonitrile (I: R = $C_6H_5CH{=}CH{-}$) were obtained in 80 per cent and 76 per cent 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 1 mole of acid chloride, 1 mole of anhydrous hydrogen cyanide, and 2 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 (page 526).

C. EFFECT OF STRUCTURE ON THE REACTIVITY OF THE 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.

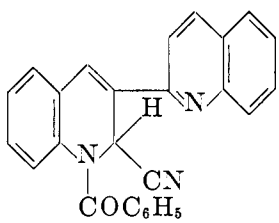
There is abundant evidence that pyridine reacts readily with acid chlorides to form acylpyridinium chlorides (for leading references, see footnote 2, reference 90). Therefore the failure of pyridine to form compounds analogous to I must be due to the fact that practically all of the resonance energy 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.

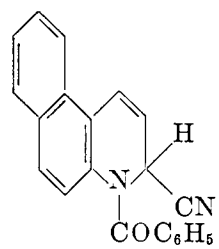
It is also significant that treatment of an acid chloride with hydrogen cyanide in the presence of anhydrous pyridine and an inert solvent affords acyl cyanides (15). In the preparation of compounds of structure I from quinoline under similar conditions, acyl cyanides are also formed, but only as minor products (43). Thus resonance energy considerations appear to tip the balance of the two possible reactions in favor of acyl cyanide formation, rather than adduct formation, in the case of pyridine but not in the case of quinoline.

1. Quinolines

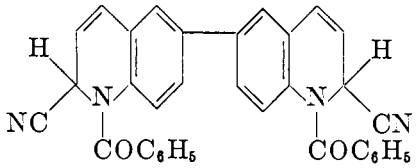
The ability of quinoline to react with an acid chloride and a source of cyanide ion to form I is greatly affected by substituents present on the ring. 6-Methoxyquinoline (37), 6-chloroquinoline (35), 6-methylquinoline (35), and 7-methoxyquinoline (86) readily undergo reaction with benzoyl chloride and 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 inhibits the formation of compounds of the general structure I.



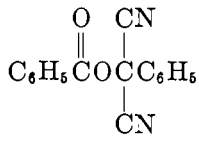
VII



IX



VIII



X

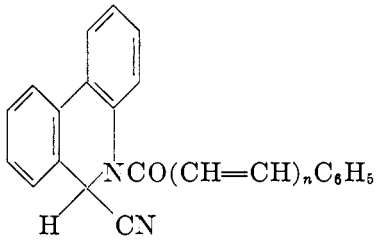
An unusual side reaction has been observed on treatment of 6-methoxyquinoline with benzoyl chloride and aqueous potassium cyanide solution. A significant amount of 6-methoxyquinaldonitrile was obtained in addition to 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (37).

2. Isoquinoline

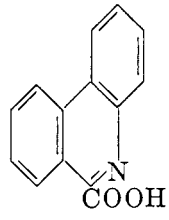
Little is known about the effect of substituents on the reactivity of the isoquinoline ring in the formation of substituted 2-acyl-1,2-dihydroisoquinaldonitriles (II). The formation of Reissert compounds from 6,7-dimethoxyisoquinoline with benzoyl chloride and 2,3-dimethoxybenzoyl chloride has been reported (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 the 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 (page 526).



XI



XII

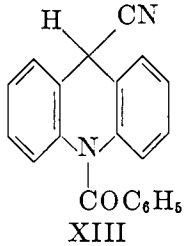
4. Acridine

Inasmuch as hydrogen, hydrogen cyanide, dienophiles, and organometallic compounds readily add across the 9,10-positions of acridine (X), 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).

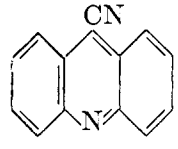
More recently, the preparation of 10-benzoyl-9,10-dihydro-9-acridinecarbo-

nitrile (XIII) has again been attempted (4). From the 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 the 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.

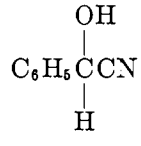
In view of subsequent work (29), the argument that 9-acridinecarbonitrile (XIV) arises from a rearrangement of initially formed 10-benzoyl-9,10-dihydro-9-acridinecarbonitrile (XIII) seems to have little validity. It has been found that benzoyl chloride is not needed in the preparation of XIV, as a reaction of acridine with potassium cyanide in aqueous ethanol gives XIV in 60 per cent yield. There is good reason to believe that XIII is incapable of existence, since the attempted benzoylation of 9,10-dihydro-9-acridinecarbonitrile (XVI), a known compound (56), failed to give XIII (19).



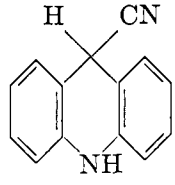
XIII



XIV



XV



XVI

D. REACTIVITY OF THE 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 per cent 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 the general structure $C_6H_5(CH{=}CH)_nCOCl$, which are very sensitive to many reagents, have been converted to Reissert compounds of the phenanthridine series (95).

III. Chemical Properties and Reactions

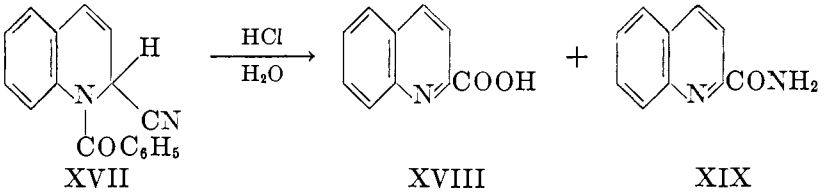
Having a variety of functional groups, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II) may undergo many diverse reactions. For example, there are three sites at which nucleophilic agents may make an initial attack on either I or II: (*a*) the carbonyl carbon atom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

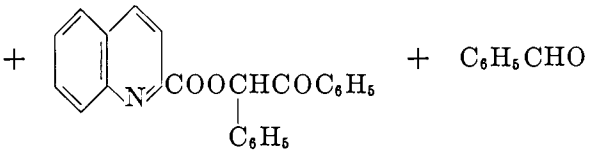
The reaction of Reissert compounds that has probably attracted the greatest attention is the acid-catalyzed hydrolysis to aldehydes plus the corresponding heterocyclic carboxylic acids and their derivatives. In general, this reaction proceeds in good yield and under mild conditions.

1. Scope

The original acid-catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) resulted in the quantitative formation of benzaldehyde. In addition, a good yield of quinaldic acid (XVIII) and smaller amounts of quinaldamide



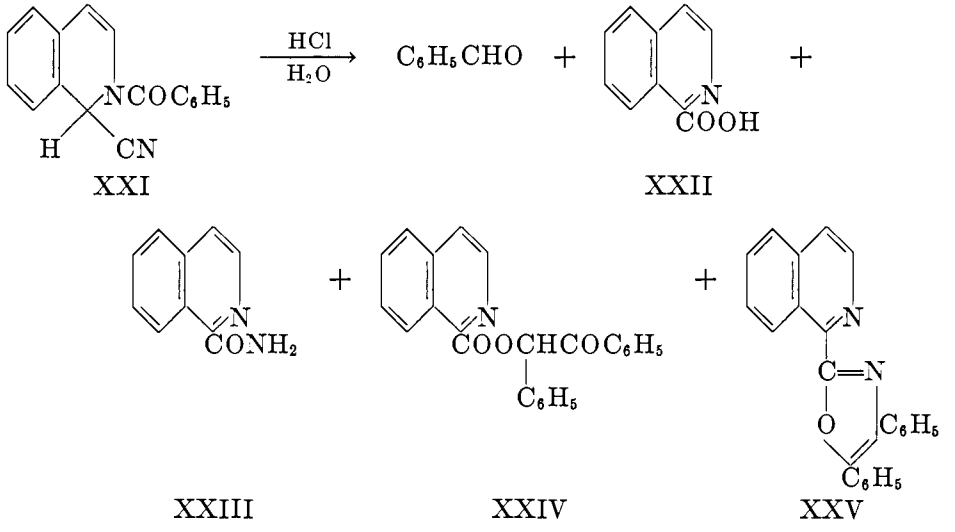
XVII XVIII XIX



XX

(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 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).

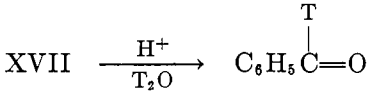


XXI XXII

XXIII XXIV XXV

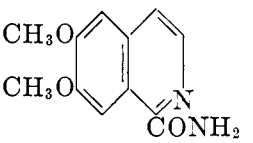
Only phenanthridine-6-carboxylic acid (XII) and the appropriate aldehyde, $C_6H_5(CH{=}CH)_nCHO$, were obtained upon the acid-catalyzed hydrolysis of each of the compounds of general structure XI (95).

A somewhat novel use of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) has been in the preparation of tritium-labeled benzaldehyde. Benzaldehyde-t_1 (XXVI) was obtained in addition to normal benzaldehyde upon the hydrolysis of XVII in mineral acid solution contaning tritium oxide (88). A small isotope effect was observed in the hydrolysis.

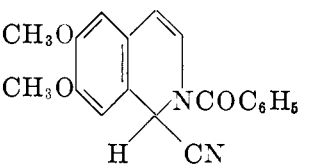


XXVI

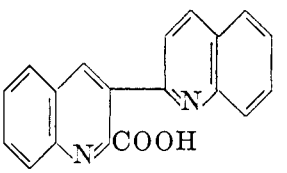
In some cases, the most valuable aspect of the acid-catalyzed hydrolysis of Reissert compounds is in the introduction of the carboxyl group into a heterocyclic nucleus. 2-Benzoyl-1,2-dihydroisoquinaldonitrile (XXI), for example, was found to be a convenient intermediate for the preparation of isoquinaldic 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

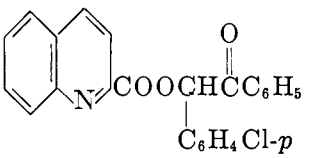


XXVIII

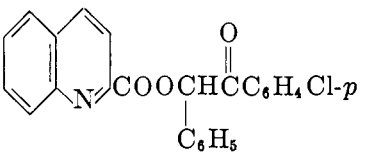


XXIX

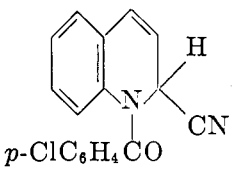
Benzoin quinaldate (XX) and benzoin isoquinaldate (XXIV) are formed in only small amounts upon the acid-catalyzed hydrolysis of XVII and XXI, respectively, in the usual manner. It was found, however, that the yields are markedly increased when the hydrolysis is carried out in the presence of an excess 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 per cent 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 per cent yield upon the acid-catalyzed hydrolysis of 1-(*p*-chlorobenzoyl)-1,2-dihydroquinaldonitrile (XXXII) in the presence of an excess of benzaldehyde (61).



XXX



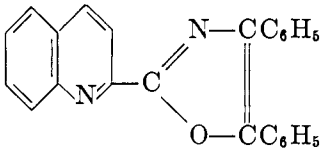
XXXI



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 ob-

tained by the use of aqueous hydrochloric acid, it was difficult to effect an efficient separation of XX and XXXIII (17).

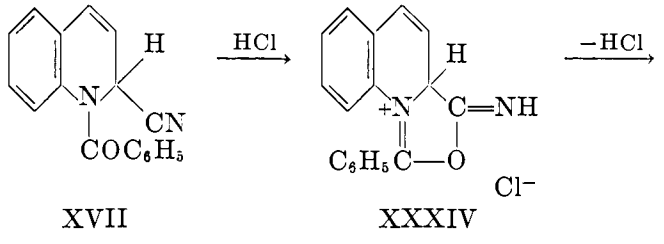


XXXIII

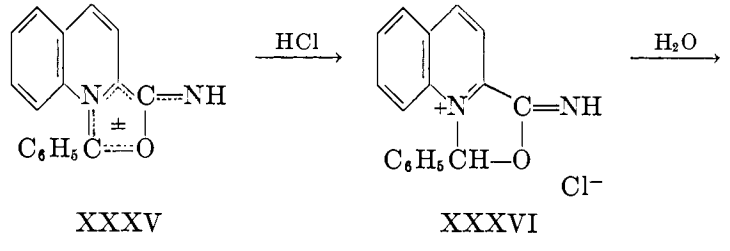
2. Studies of the mechanism

Obviously, the mechanism of the acid-catalyzed hydrolysis of a Reissert compound in which an aldehyde is formed is different from the mechanism of the 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.

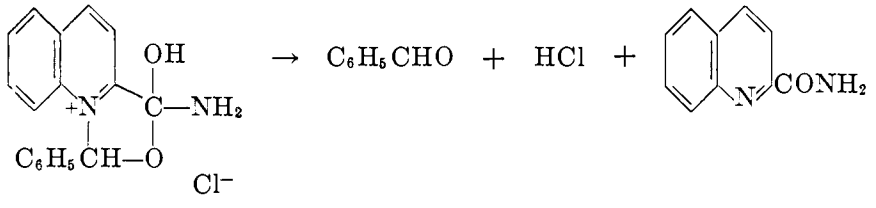
A mechanism has recently been proposed (18) which accounts for all of the products obtained by the acid-catalyzed hydrolysis of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII). It is assumed that the first step in the reaction is formation of the cyclic intermediate XXXIV by the action of hydrochloric acid upon XVII. Then isomerization of XXXIV gives XXXVI, possibly *via* the relatively stable meso-ionic intermediate, XXXV. Addition of water to XXXVI gives XXXVII, which then collapses to form benzaldehyde and quinaldamide (XIX).



XVII XXXIV



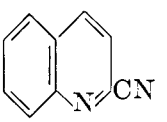
XXXV XXXVI



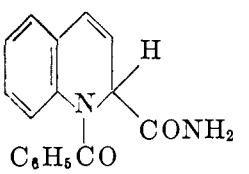
XXXVII XIX

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 mechanisms 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).

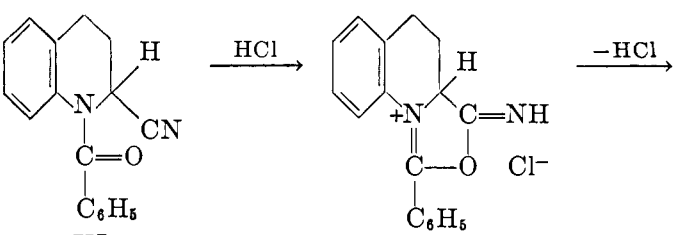


XXXVIII

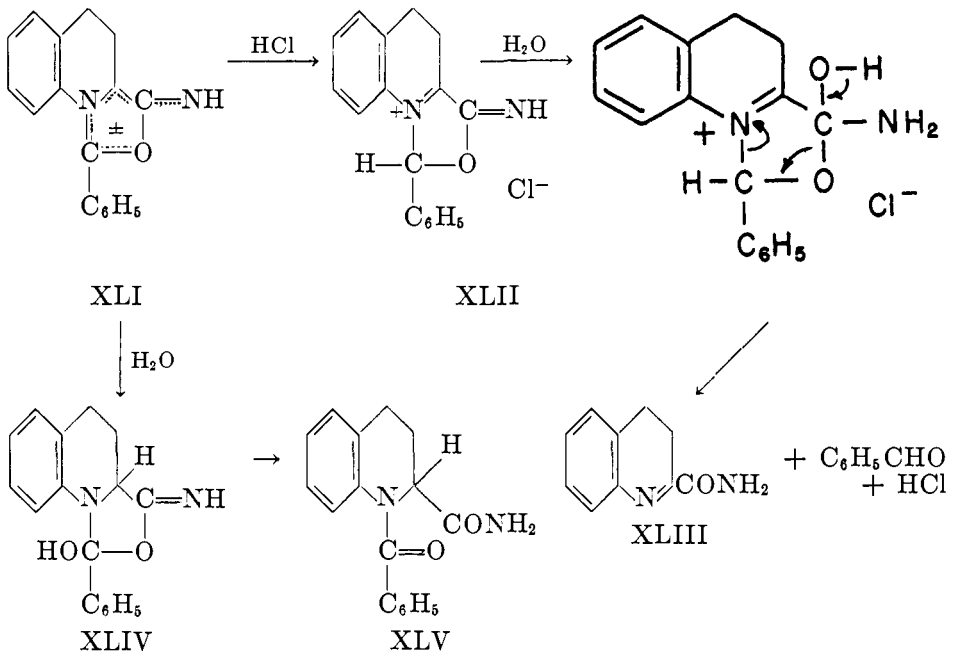


XXXIX

Another fact which must be considered in relation to this mechanism is that the gain in resonance energy derived from the conversion of XVII, with its dihydroquinoline structure, to the fully aromatic quinoline derivatives may not be 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, a low yield of benzaldehyde was obtained from XL (18, 63). The reaction which competes with the formation of benzaldehyde in the acid-catalyzed hydrolysis of XL is the 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 the action of hydrochloric acid on XL may yield 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-



XL

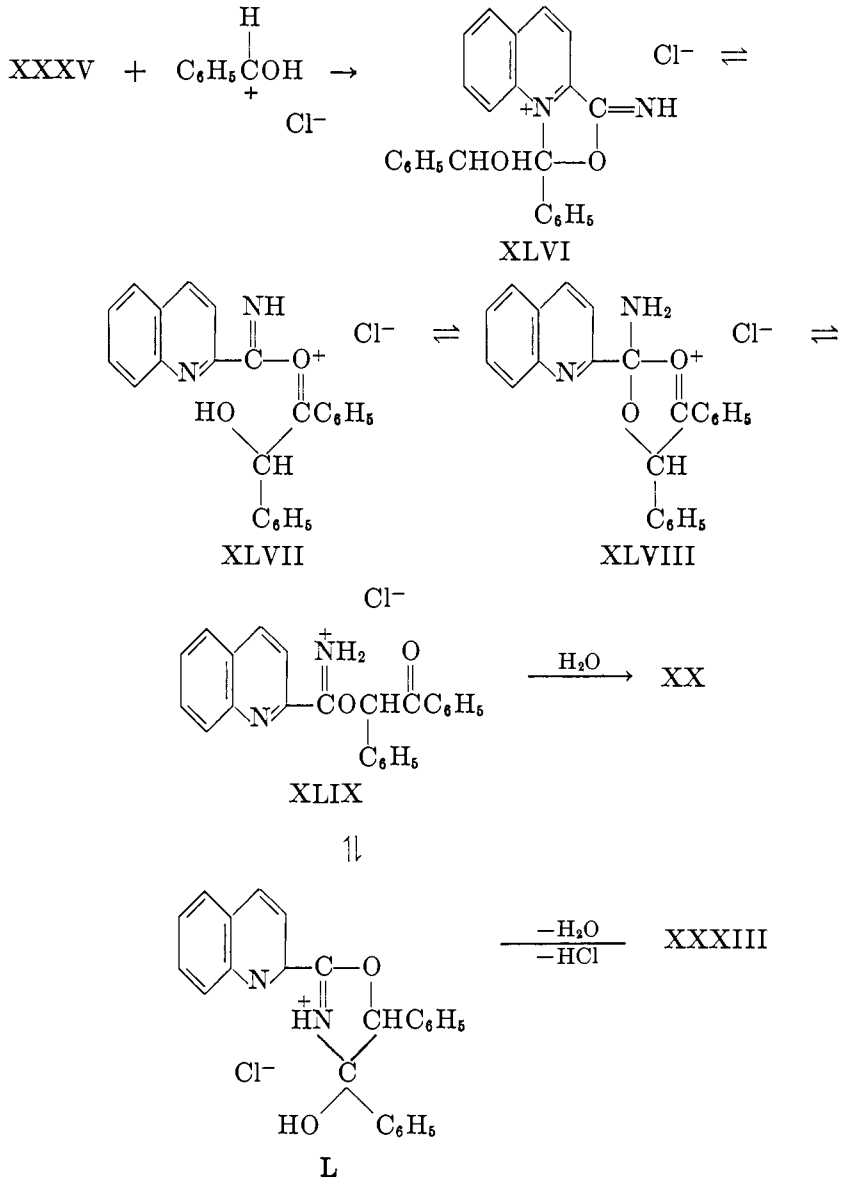


tetrahydroquinaldamide (XLV) (17). Since little gain in resonance energy is available in either case, the two reactions proceed at comparable rates.

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

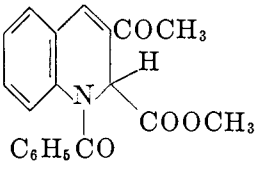
It is also possible for the imino-ether hydrochloride, XLIX, to undergo cyclization to the hydroxydihydroöxazole, L, which can then undergo normal, acid-



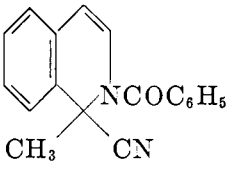
catalyzed dehydration to form 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIII), a product actually obtained under one set of conditions (17). There is convincing evidence available to substantiate the claim that benzoin quinaldate (XX) and 2-(2-quinolyl)-4,5-diphenyloxazole (XXXIII) arise from an intermediate 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 of

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

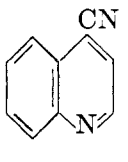
3. General procedure for the preparation of aldehydes

The usual method for the isolation of the aldehyde resulting from the 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 $C_6H_5(CH{=}CH)_nCOCl$, the aldehydes, once formed, would be expected to be sensitive to an acidic environment. It was found that a better yield of aldehyde was obtained by the use of 40 per cent phosphoric acid than by the use of sulfuric acid (95).

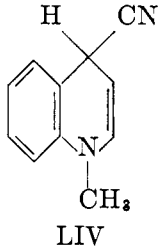
A catalog of all known Reissert compounds, including methods of preparation, yields, and yields of aldehyde produced on acid-catalyzed hydrolysis, is given in table 1.

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 per cent of XXXVIII was reported (51) when the reaction was 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

TABLE 1

Catalog of Reissert compounds and yields of aldehydes obtained upon hydrolysis

Base	Acid Chloride	Method of Preparation*	Yield of Reissert Compound†	Yield of Aldehyde‡	References
			per cent	*per cent*	
Quinoline	Benzoyl	a	94		(43, 75, 81, 97)
		b	96	98	
		c	87		
	Cinnamoyl	a	34		(43, 87, 97)
		b	91	82	
		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, 61)
		b	77		
	o-Methoxybenzoyl	b	66	97	(43)
	Anisoyl	a	51	98	(43, 87)
		b	88		
	Veratroyl	a	36	57	(87)
	3,4,5-Trimethoxybenzoyl	a	Slight	—	(13, 87)
		b	—		
	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)
6-Methoxyquinoline	Benzoyl	a	89	97	(37, 63)
6-Methylquinoline	Benzoyl	a	60	91	(35)
6-Chloroquinoline	Benzoyl	a	48	98	(35)
7-Methoxyquinoline	Benzoyl	a	—	—	(86)
2,3′-Biquinoline	Benzoyl	a	50	—	(48)
6,6′-Biquinoline	Benzoyl	a	—	—	(91)
5,6-Benzoquinoline	Benzoyl	—§	—	—	(22)
Isoquinoline	Benzoyl	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	Benzoyl	a	35	—	(45)
6,7-Dimethoxyisoquinoline	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)

* a, in aqueous medium; b, in anhydrous benzene; c, in liquid sulfur dioxide.

† A dash in this column indicates that the yield has not been reported.

‡ The best yields that have been reported are given. An underscored yield indicates the isolation of the product as a substituted hydrazone or similar derivative. When no yield is given, the aldehyde is known to be formed but in unreported yield.

§ Experimental details lacking in footnote 19 of reference 22.

No reaction occurs upon the treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with phosphorus pentachloride in chloroform solution; upon heating the reagents to a temperature of 125–130°C. in the absence of a solvent however, isoquinaldonitrile (LV) was obtained in a reported 82–85 per cent yield (51). Once again, later workers reported a distinctly lower yield, 53 per cent, in

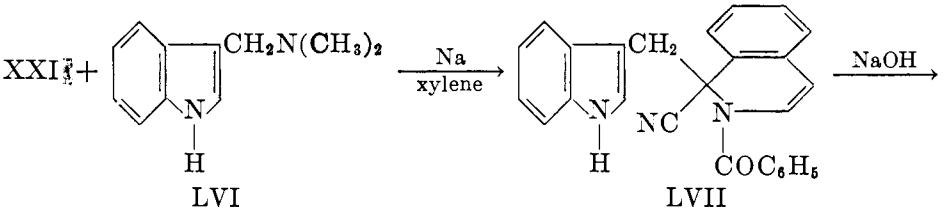
this reaction (74). By use of thionyl chloride in place of phosphorus pentachloride, however, a 72 per cent yield of LV can be obtained (47).

LV

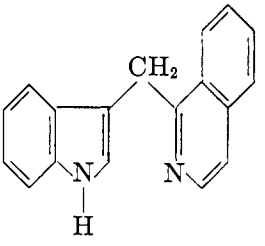
C. ALKYLATION REACTIONS

Reactive anions can be formed by the treatment of Reissert compounds with a variety of bases, inasmuch as the hydrogen bonded to the carbon alpha 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 per cent yield (6, 8). Alkaline hydrolysis of LVII gives 1-skatylisoquinoline (LVIII). It was hoped that the latter compound could be converted to a hexa-

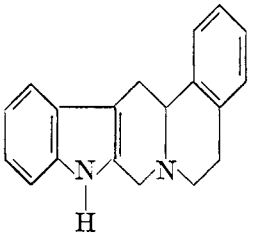


LVI LVII



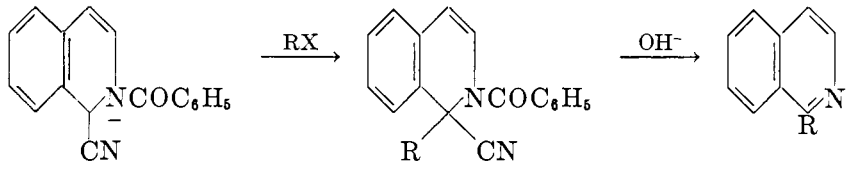
LVIII

hydrobenzoindoloquinolizine (LIX), which was considered to be a possible nucleus for certain of the calabash curare alkaloids.



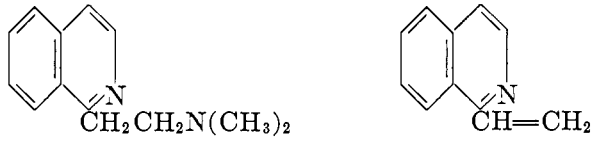
LIX

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.



LX LXI LXII

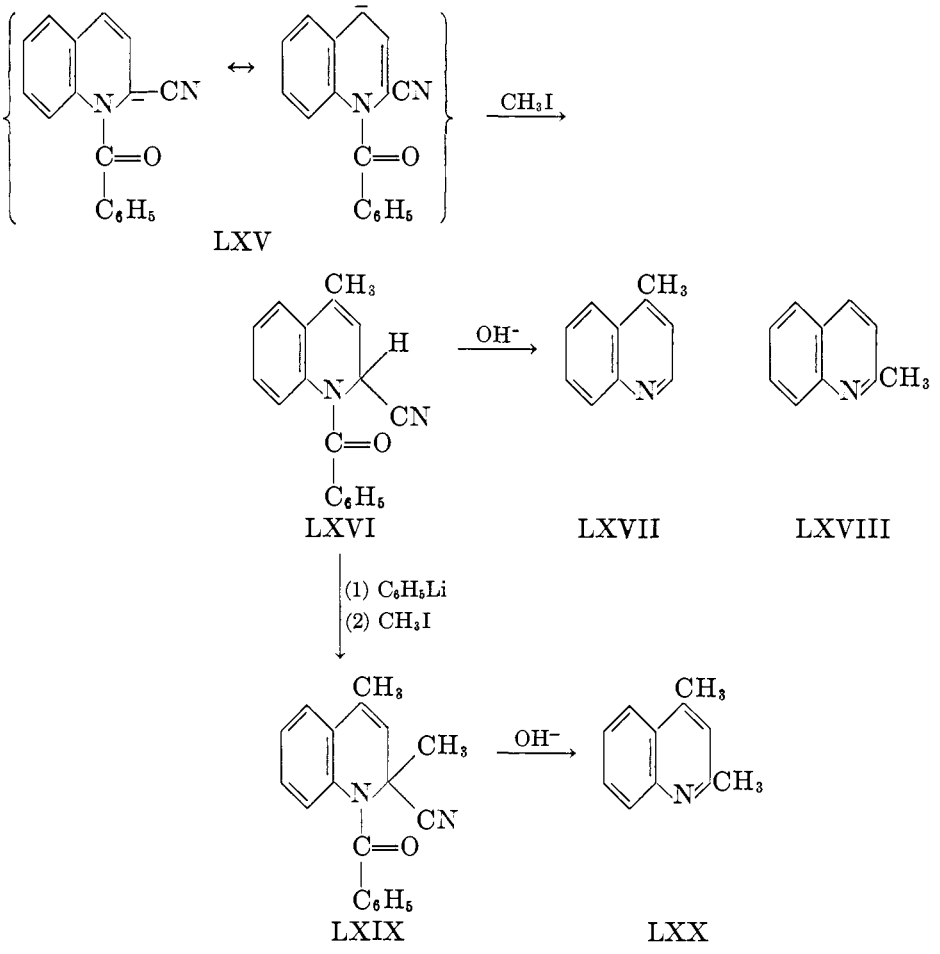
The alkylation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) has been carried out with methyl iodide, benzyl bromide, *n*-butyl bromide, and hydrocinnamyl iodide. The overall yield of the 1-alkylisoquinoline (LXII) in each case was 58 per cent for 1-methylisoquinoline (isoquinaldine), 78 per cent for 1-benzylisoquinoline, 41 per cent for 1-*n*-butylisoquinoline, and 44 per cent 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 per cent yield. 1-Vinylisoquinoline (LXIV) may be prepared from LXIII by distillation of the latter compound over potassium hydroxide (9).



LXIII LXIV

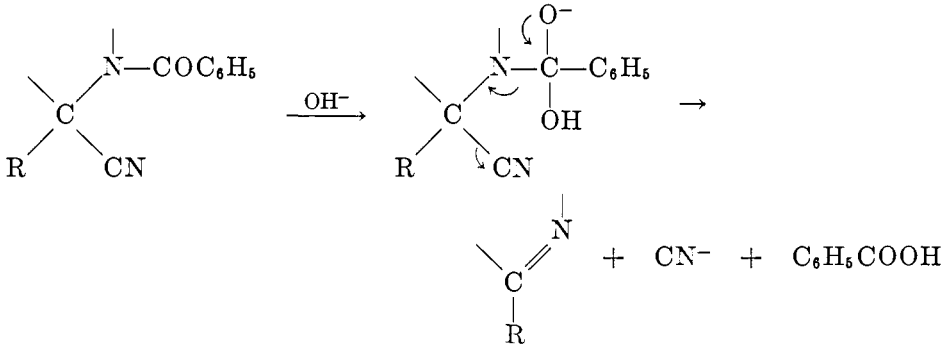
Similarly, 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) is easily converted to its conjugate base, LXV, by treatment with phenyllithium. Reaction of LXV with methyl iodide and subsequent hydrolytic cleavage gives lepidine (LXVII) rather than quinaldine (LXVIII) (10). Inasmuch as stabilization of the anion 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, and then methyl iodide, gives 1-benzoyl-2,4-dimethyl-1,2-dihydroquinaldonitrile (LXIX), which can be converted to 2,4-dimethylquino-



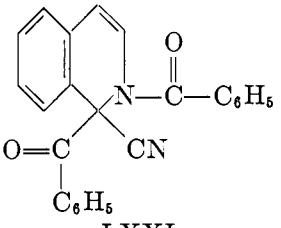
line (LXX) by alkaline hydrolysis (10). The overall yields of LXVII and LXX are much smaller than the yields of the various 1-alkylisoquinolines (LXII).

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 in-



volves 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 per cent yield. Alkaline cleavage of this product gives only a trace of 1-benzoylisoquinoline, the major heterocyclic product being isoquinoline (10).

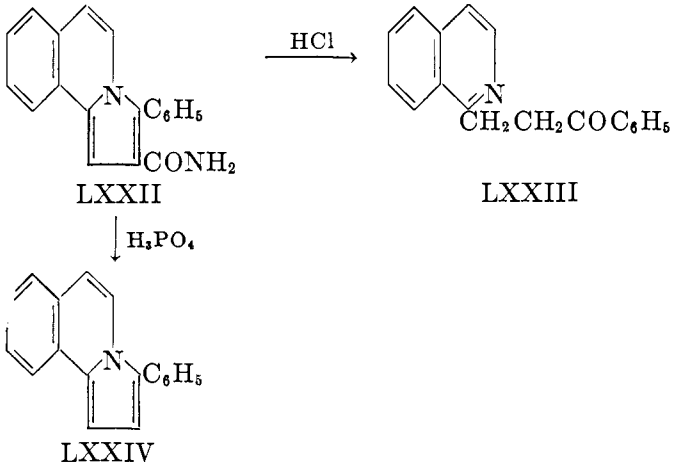


LXXI

D. MICHAEL-TYPE ADDITION REACTIONS

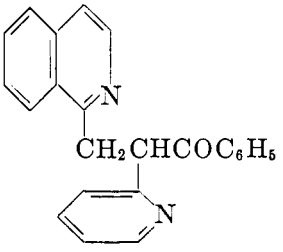
The conjugate bases derived from Reissert compounds have been found to add to acrylonitrile, 2-vinylpyridine, and ethyl acrylate in the Michael manner, but the reactions are complicated owing to the occurrence of subsequent reactions of the original adducts.

Reaction of the conjugate base, LX, of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with acrylonitrile gives 3-phenyl-2-formamido-7,8-benzopyrrocoline (LXXII) in 76 per cent yield (7). The structure was proven by degradation reactions. Action of concentrated hydrochloric acid on LXXII gave a 95 per cent yield of phenyl β-(1-isoquinolyl)ethyl ketone (LXXIII), while action of 100 per cent 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 per cent yield.

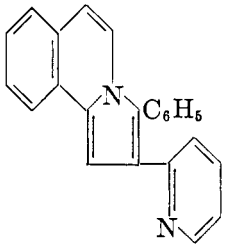


LXXII LXXIII LXXIV

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

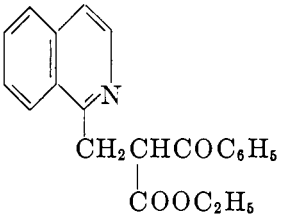


LXXV

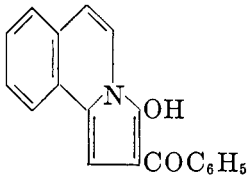


LXXVI

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

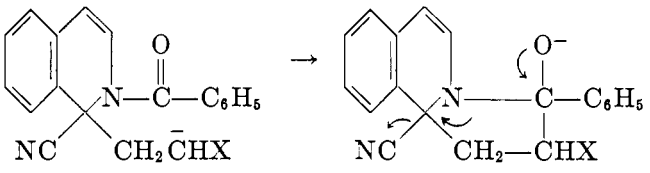


LXXVII

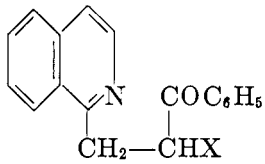


LXXVIII

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).



LXXIX LXXX



LXXXI

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=CHX (where X = CN, $COOC_2H_5$, 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).

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

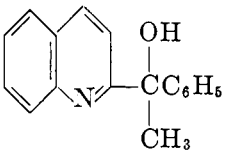
TABLE 2

Reaction of Reissert compounds with Grignard reagents

Reissert Compound	Grignard	Product	Yield	References
			per cent	
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	8.5	(42, 60)
		2-Benzoylquinoline	4	
	MesMgBr*	2-Benzoylquinoline	Trace	(42, 60)
		Quinoline	29	
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)
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-$CH_3OC_6H_4MgBr$	Phenyl-*p*-anisyl-1-isoquinolylcarbinol	34	(77)

* 2,4,6-Trimethylphenylmagnesium bromide.

reaction of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) with methylmagnesium bromide gives a 59 per cent 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°C. for alkylmagnesium halides and about 100°C. or more for arylmagnesium halides. The results of a number of these reactions are summarized in table 2.



LXXXII

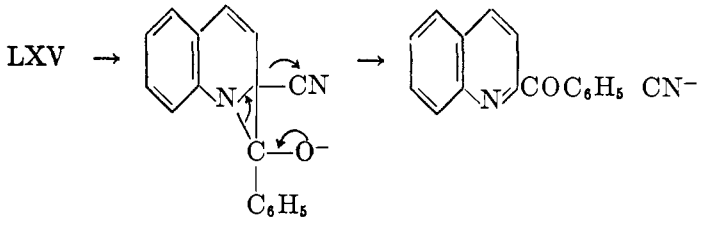
A similar rearrangement occurs upon treatment of a Reissert compound with sodium hydride in boiling xylene. 1-Benzoylisoquinoline may be obtained in 70 per cent yield, together with sodium cyanide and hydrogen, upon treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) with sodium hydride under these conditions (10). 1-Acetylisoquinoline is obtained in 30 per cent yield from 2-acetyl-1,2-dihydroisoquinaldonitrile, 2-benzoylquinoline in 54 per cent yield from 1-benzoyl-1,2-dihydroquinaldonitrile (XVII), and 2-acetylquinoline in 31 per cent yield from 1-acetyl-1,2-dihydroquinaldonitrile in similar reactions.

(b) Studies of the mechanism

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.

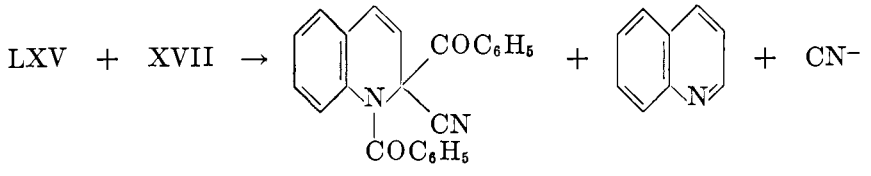
Two possible mechanisms have been considered whereby the conjugate base of a Reissert compound rearranges to the α-acyl derivative, with expulsion of a cyanide ion. For example, it has been proposed (62) that 2-benzoylquinoline

arises from the anion LXV, by way of the ethylenimine intermediate, LXXXIII, by an intramolecular process.

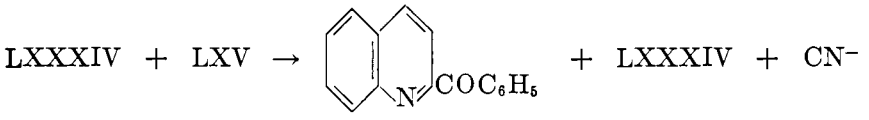


LXXXIII

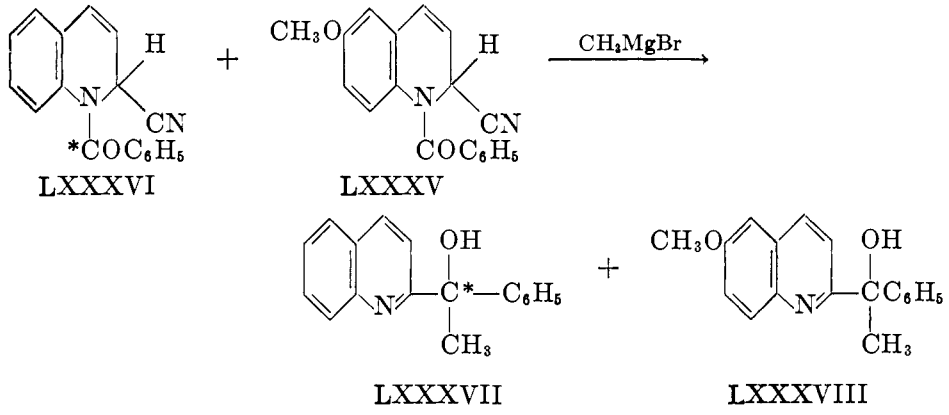
The other mechanism which has been considered involves a two-step intermolecular process, actually an ionic chain reaction, involving the formation of 1,2-dibenzoyl-1,2-dihydroquinaldonitrile (LXXXIV) as an intermediate (10).



LXXXIV



More recently, a convincing proof that the rearrangement is intramolecular has been provided (96). Reaction of methylmagnesium bromide with a mixture of 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) and 1-benzoyl-carbonyl-C_1^{14}-1,2-dihydroquinaldonitrile (LXXXVI) gave active methylphenyl-2-quinolylcarbinol (LXXXVII) and unlabeled methylphenyl-2-(6-methoxyquinolyl)carbinol (LXXXVIII). When competing reactions do not give mixed products the result is not highly significant, unless it is known that the rates of



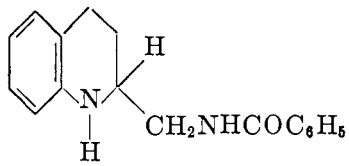
LXXXVI LXXXV

LXXXVII LXXXVIII

the two reactions are of the same order of magnitude. This condition has been satisfied in the competition reaction under consideration here, since it has been determined that both 1-benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXXV) and 1-benzoyl-1,2-dihydroquinaldonitrile (XVII) undergo the rearrangement-condensation reaction with methylmagnesium bromide at nearly identical rates.

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°C. and at a hydrogen pressure of 100 atm., for example, gives α-benzamido-1,2,3,4-tetrahydroquinaldine (LXXXIX).



LXXXIX

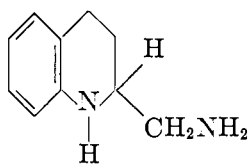
F. REDUCTIONS

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 the cyano groups.

1. Catalytic hydrogenation

(a) High-pressure reductions

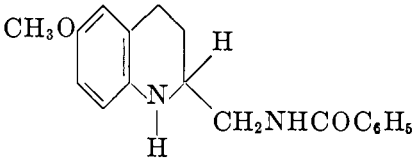
It has already been mentioned that catalytic hydrogenation of XVII gives LXXXIX. The latter compound can be hydrolyzed to α-amino-1,2,3,4-tetrahydroquinaldine (XC) in almost quantitative yield under acidic conditions (81).



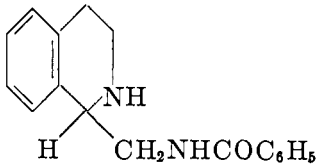
XC

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 (XCII), respectively, being formed (5, 37, 57, 80, 82). Reduction of

XXI, however, required a hydrogen pressure of 140 atm. and a temperature of 90–100°C.



XCI



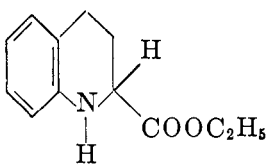
XCII

By use of palladium as the catalyst instead of nickel, an 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 1 atm. 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 per cent yield (63). 1-Benzoyl-6-methoxy-1,2-dihydroquinaldonitrile (LXXV) behaves in the same manner, yielding 62 per cent 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 of the starting material is recovered unchanged, and the reduction product (or products) cannot be isolated in crystalline form (33, 63).

The proof of structure of XL was based mainly on the demonstration that the compound can also be prepared by the dehydration of 1-benzoyl-1,2,3,4-tetrahydroquinaldamide (XLV) with phosphorus pentoxide and by the fact that XL may be reconverted to XLV upon treatment with hydrogen peroxide and sodium bicarbonate solution. Furthermore, XL may also be prepared by treatment of tetrahydroquinaldamide with benzoyl chloride in pyridine solution. Benzoic acid is obtained upon either acid- or base-catalyzed hydrolysis of XL, and ethyl tetrahydroquinaldate (XCIII) by ethanolysis of XL, catalyzed by sulfuric acid (17).

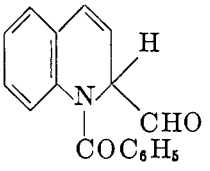


XCIII

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 was obtained upon treatment of XVII with stannous chloride and hydrogen chloride, but benzaldehyde was formed (53, 62).



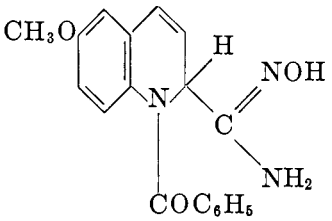
XCIV

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 XVII with 30 per cent hydrogen peroxide in acetone solution in the presence of sodium bicarbonate gives a 65 per cent 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).



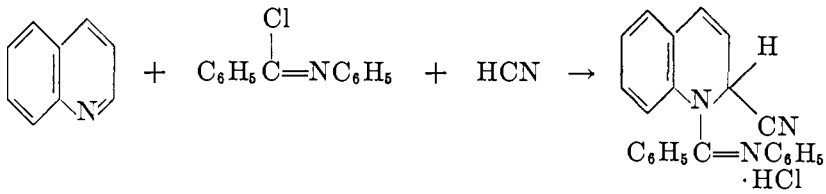
XCV

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).

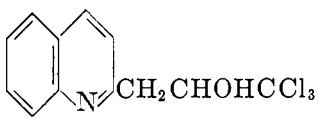


XCVI

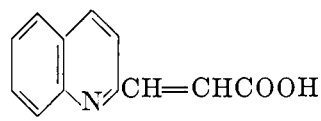
This compound (XCVI) is a nitrogen analog of a Reissert compound, and the analogy is strengthened by the fact that the odor of benzaldehyde develops upon heating XCVI with dilute hydrochloric acid. Pyridine, but not acridine, was reported to form an addition product similar to XCVI, but its properties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

B. METHYL 3-ACETYL-1,2-DIHYDROQUINALDATE

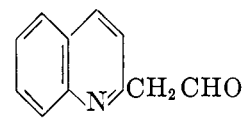
It was reported in 1886 that alkaline hydrolysis of α-(trichloromethyl)-2-quinolineëthanol (XCVII), better known as chloral quinaldine (1, 30), gives two amphoteric compounds, β-(2-quinolyl)acrylic acid (XCVIII) and a compound of the empirical formula $C_{12}H_{11}NO_3$ (30, 31). Upon decarboxylation, 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

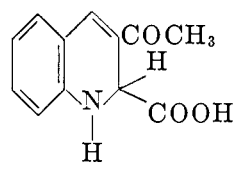


XCVIII



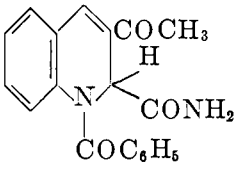
XCIX

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



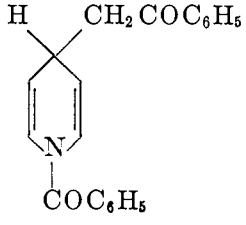
CI

C. OTHER *N*-ACYLDIHYDRO AROMATIC HETEROCYCLIC NITROGEN DERIVATIVES

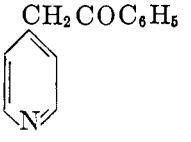
In many cases, compounds analogous to Reissert compounds are formed when the cyanide ion is replaced by other nucleophilic agents in the reaction with quinoline and an acid chloride. Furthermore, reactions of this type have been observed with pyridine also. No attempt will be made to describe all such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

1. Pyridine derivatives

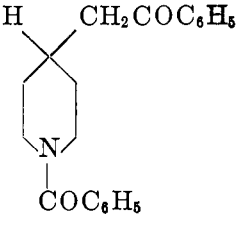
1-Benzoyl-4-phenacyl-1,4-dihydropyridine (CII), or the isomeric compound having the 1,2-dihydro structure, is formed by reaction of acetophenone, pyridine, and benzoyl chloride for a prolonged period of time at room temperature (16, 28). Air oxidation of CII gives 4-phenacylpyridine (CIII), and addition of one molar equivalent of hydrogen to CII over a platinum catalyst gives 1-benzoyl-4-phenacylpiperidine (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



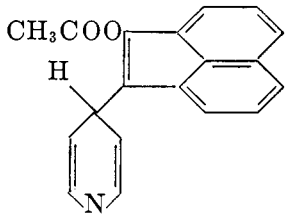
CIII



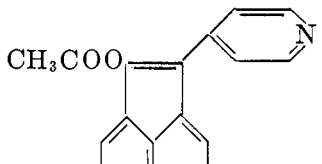
CIV

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).

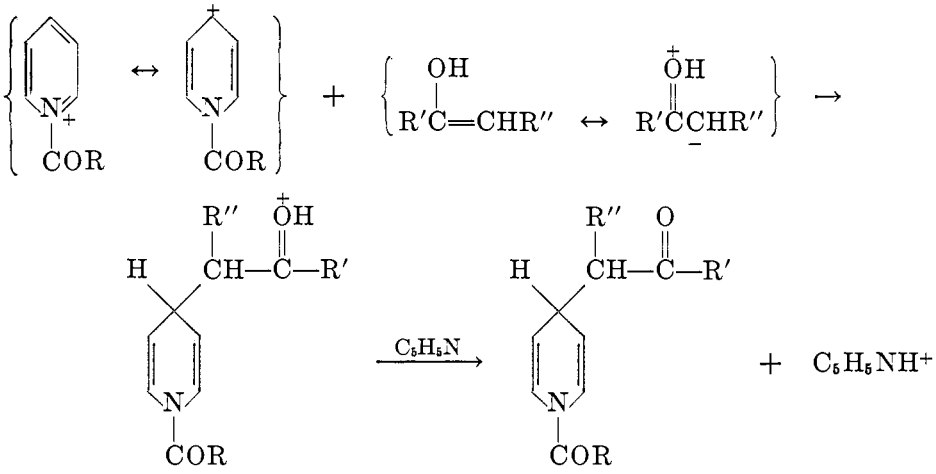


CV



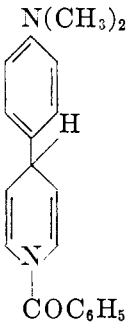
CVI

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.

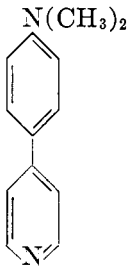


A dialkylaniline may serve as the nucleophilic agent in the condensation reaction with an acylpyridinium salt. For example, a reaction of dimethylaniline, benzoyl chloride, and pyridine in the presence of a copper-bronze catalyst was found to give a 67 per cent yield of 4-(*p*-dimethylaminophenyl)pyridine (CVIII). This product was assumed to have arisen from initially formed 1-benzoyl-4-(*p*-dimethylaminophenyl)-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

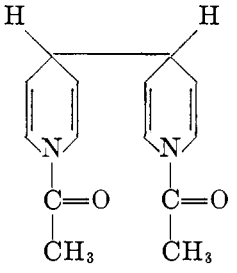


CVIII

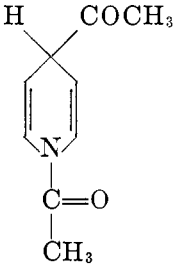
Other dialkylanilines were found to give products analogous to CVIII on reaction with benzoyl chloride and pyridine, but the yields gradually dropped as the size of the alkyl groups was increased. From a reaction mixture of *m*-dimethylaminotoluene, benzoyl chloride, and pyridine there was obtained a 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 per cent 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 per cent yield. Similarly, *sec*-butylmagnesium bromide condensed with benzoylpyridinium chloride to give a small yield of 2-(4-pyridyl)butane, but no product corresponding in properties to the probable dihydropyridine intermediate could be isolated.

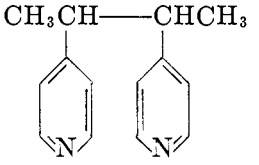
In a somewhat different type of condensation reaction, a reductive acylation, 1,1′-diacetyl-1,4,1′,4′-tetrahydro-4,4′-bipyridine (CIX) was isolated after reaction of pyridine with zinc dust and acetic anhydride (26, 27). Further investigation revealed that 4-ethylpyridine and 1,4-diacetyl-1,4-dihydropyridine (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-ethyl-



CIX



CX



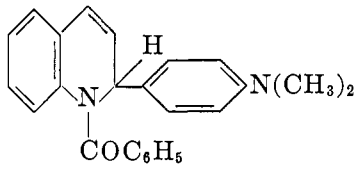
CXI

pyridine 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).

The yield of 4-ethylpyridine can be raised to 60–70 per cent 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). Although it was originally reported that no analogous reaction occurs with certain homologs and other derivatives of pyridine (84), later workers reported that 12–13 per cent yields of 2-methyl-4-ethylpyridine and 3-methyl-4-ethylpyridine may be obtained from 2-picoline and 3-picoline, respectively (93a).

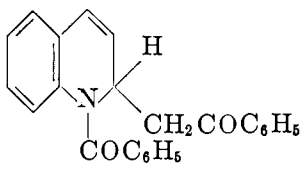
2. Quinoline derivatives

1-Benzoyl-2-(*p*-dimethylaminophenyl)-1,2-dihydroquinoline (CXII) has been obtained in 43 per cent 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).



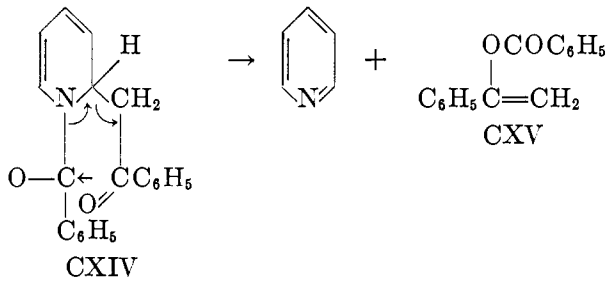
CXII

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 per cent yield (99). Products probably similar in structure to CXII and CXIII have also been obtained in the 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, the 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

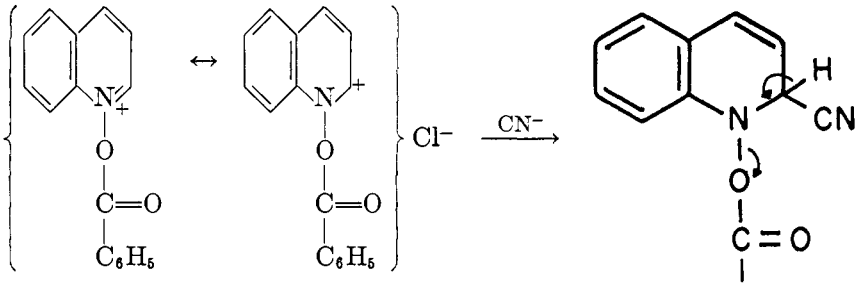
D. "REISSERT REACTION" WITH QUINOLINE-1-OXIDE

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 per cent (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), al-

though 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

C_6H_5COOH + 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 per cent yield of 1-methyl-1,4-dihydrocinchoninonitrile (LIV) was obtained upon the 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 per cent yield of cinchoninonitrile (LIII) (49, 52). An overall yield of LIII of 56–65 per cent has been obtained by this method (44).

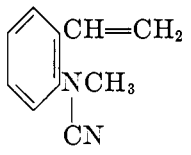
There has been some controversy over the 1,4-dihydro structure proposed for LIV. The argument has been raised (see private communication from C. K. Ingold given in footnote 19, reference 22) that the most thermodynamically stable product, as far as the degree of conjugation is concerned, would be 1-methyl-1,2-dihydrocinchoninonitrile.

F. 1,2-DICYANODIHYDROQUINOLINES

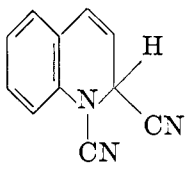
When quinoline is treated with cyanogen bromide and hydrogen cyanide, a quinoline dicyanide is formed (66). This compound is converted to an isomer of

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 *cis*- and *trans*-1,2-dicyano-1,2-dihydroquinoline (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(4*H*)-quinolinedicarbonitrile (CXXI), and the isomer of higher melting point was designated as 1,2-(2*H*)-quinolinedicarbonitrile (CXX).

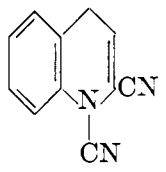
CXVIII



CXIX



CXX



CXXI

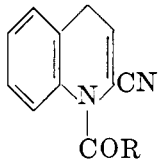
V. Structural Considerations

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

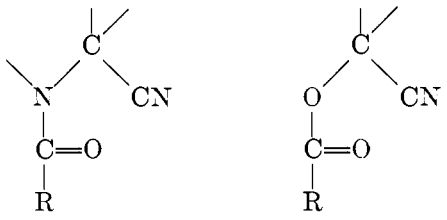
double bond is located in the 2,3-position of the quinoline ring rather than in the 3,4-position, as shown in structure I. The only available argument that structure I is correct lies in the fact that the ultraviolet spectra of 1-benzoyl-1,2-dihydroquinaldonitrile (XVII), 1-benzoyl-4-methyl-1,2-dihydroquinaldonitrile (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 wave length over the whole absorption region than does XVII, LXVI, or LXIX (63).



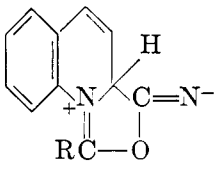
CXXII

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 bond is very weak, but when the cyanohydrin is acylated, the nitrile absorption peak disappears. Since Reissert compounds are nitrogen analogs of acyl derivatives 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 an absorption peak for the cyano group 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 the recrystallization of Reissert compounds from hot solvents, such as 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°C., but a microcrystalline form melting at 142.5–143.5°C. 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 melting point of 127–128°C., and the less stable form a melting point of 96–99°C. Finally, 2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) has also been isolated in dimorphic forms, the more stable one having a melting point of 125–126°C. and the other a melting point of 56–57°C. (19, 42, 96).

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