THE REACTION

OF

REISSERT COMPOUNDS

WITH

GRIGNARD REAGENTS

by

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HISTORICAL BACKGROUND

Benzoylation of Cyclic Tertiary Amines

As an outgrowth of his attempt to prepare a ketone of
the benzthiazole series by the benzoylation of benzthiazole,
Arnold Reissert[1,2] in 1905 undertook a more thorough investi-
gation of the benzoylation of tertiary cyclic amines.

Dry quinoline, when mixed with dry benzoyl chloride,
apparently undergoes no reaction at room temperature. However,
if a trace of moisture is present, partial crystallization of
quinoline hydrochloride occurs with the simultaneous formation
of benzoic anhydride or benzoic acid. By heating the mixture
to a high temperature, a diquinolyl[3] can be obtained but no
benzoylquinolinium chloride. From a mixture of quinoline and
benzoyl chloride, shaken vigorously with very dilute sodium
hydroxide solution under Schotten-Baumann conditions, A.
Reissert[1] isolated a compound which he at first took to be
1-benzoyl-1,2-dihydro-2-hydroxyquinoline. Further investi-
gation,[2] however, showed that the pyridine ring had been
opened and that the product was o-benzoylaminocinnamaldehyde.
It is possible that the two substances are actually tautomers.

When an aqueous solution of potassium cyanide is used[1]

in place of the sodium hydroxide in the above reaction, a
nearly quantitative yield of 1-benzoyl-1,2-dihydroquinaldo-
nitrile (I), now known as Reissert's compound, is obtained.

The reaction of potassium cyanide and benzoyl chloride in
aqueous solution with other tertiary cyclic amines, pyridine,
benzthiazole and acridine, produced no compound analogous to
that from quinoline; but with isoquinoline,2-benzoyl-1,2-di-
hydroisoquinaldonitrile (II), the so-called isoquinoline
Reissert compound, was formed in good yield.[2]
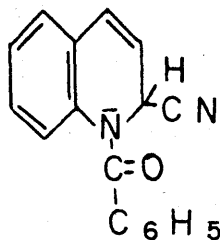
I
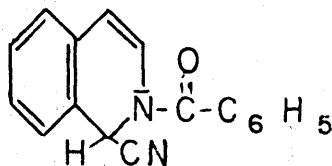
II

Preparation of Reissert Compounds

In aqueous medium. Arnold Reissert[1] formed the original
Reissert compound in nearly quantitative yield by reacting two
moles of benzoyl chloride with one of quinoline in aqueous
potassium cyanide solution. The isoquinoline Reissert compound
was formed[2] by using slightly different proportions of reagents.

Since that time several workers[4,5,6] have made Reissert
compounds from various aromatic acid chlorides in aqueous
medium but rarely in better than 50% yield. With aliphatic

acid chlorides hydrolysis to the acid or conversion to the
acyl cyanide is so rapid that no Reissert compound can be
obtained. Thus Sugasawa and Tsuda[4] prepared the Reissert
compounds given in Table I but failed to get any of the
desired product with enanthyl or phenylacetyl chloride:

Table I

Reissert Compound	Yield
1-Anisoyl-1,2-dihydroquinaldonitrile	50.6%
1-Veratroyl-1,2-dihydroquinaldonitrile	36.2
1-Trimethylgalloyl-1,2-dihydroquinaldonitrile	Trace
1-Cinnamoyl-1,2-dihydroquinaldonitrile	34

The formation of a Reissert compound is greatly influenced
not only by the choice of acid chloride but also by the choice
of quinoline derivative. Gassman and Rupe[5] found that the
following do not form Reissert compounds: quinaldine, 5-nitro-
quinoline, 5-aminoquinoline, 5-acetaminoquinoline, 6-dimethyl-
aminoquinoline, 7-nitroquinoline, 8-hydroxyquinoline, 8-methoxy-
quinoline, 8-benzoyloxyquinoline and 8-acetoxyquinoline. Only
with 6-methoxyquinoline did they obtain the desired product.
The authors gave no explanation for these facts and no consistent
explanation based on electronic considerations can be given.
For example, both the nitro and the amino group, a powerful
electron acceptor and donor substituent, respectively, produce
inactivity when in the 5-position of the quinoline ring.

The authors[5] reported that they frequently obtained con-
siderable quantities of bis-benzoyl cyanide, III.

III
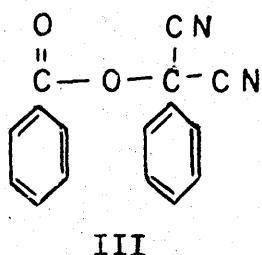
Reissert compounds are probably formed in aqueous
solution by the following mechanism:
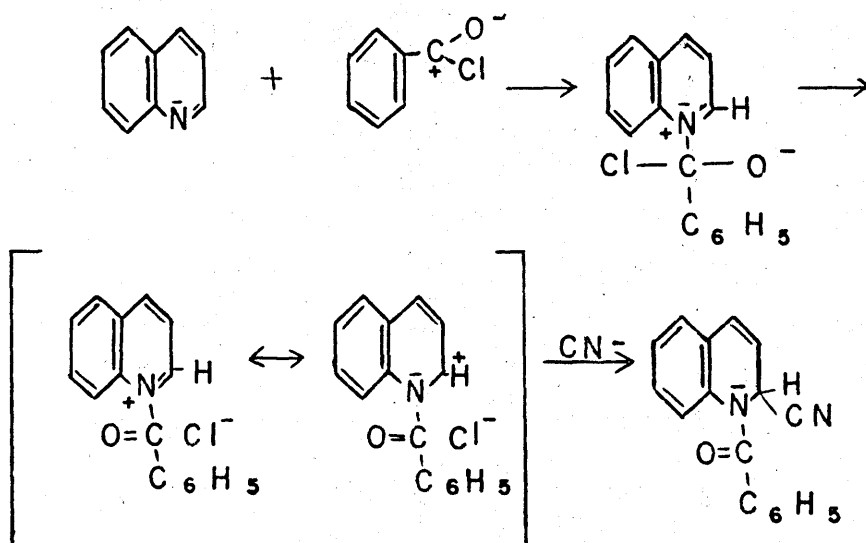
<u>In non-aqueous medium</u>. In order to circumvent the
problem of hydrolysis and to make the preparation of Reissert
compounds more general (a matter of interest as the compounds
may be converted nearly quantitatively to aldehydes) the use
of non-aqueous solvents was investigated.

Dieckmann and Kammerer[7] in 1907 observed the formation
of Reissert's compound in unstated amount while investigating
the action of quinoline in place of pyridine in accelerating
the formation of benzoyl cyanide from benzoyl chloride and

hydrocyanic acid in ether solution. The main product, however, was still benzoyl cyanide, the cyanide ion reacting more readily with the acid chloride than the quinoline.

In 1940 Woodward[8] extended this work and found acyl cyanide formation to be largely preponderant when benzoyl chloride was used. Acyl cyanide formation was exclusive with acetyl chloride when ether or other inert solvents were used or when quinoline was used as its own solvent. No reaction was observed when acetonitrile, benzonitrile, ether, dioxane, acetone or chloroform was substituted in the original procedure of Reissert.

Woodward, however, was able to prepare both the original Reissert compound and 1-cinnamoyl-1,2-dihydroquinaldonitrile in good yield by use of liquid sulfur dioxide as a solvent. Acetyl chloride under these conditions gave negative results. The striking success resulting from use of the more polar liquid sulfur dioxide further indicates the ionic nature of the reaction.

Grosheintz and Fischer[9] have developed a general method for the preparation of Reissert compounds derived not only from aromatic acid chlorides, but also, for the first time, from aliphatic acid chlorides. They reacted freshly distilled quinoline in liquid anhydrous hydrocyanic acid with various acid chlorides dissolved in absolute benzene. In this manner they prepared twelve Reissert compounds from the acid chloride as listed in Table II.

Buchanan, Cook and Loudon[10] used this method to prepare four more of the compounds listed in Table II but failed to

obtain the expected product from p-nitrobenzoyl,3,5-dinitro-
benzoyl and 2,4-dinitrobenzoyl chlorides.

Table II

Acid Chloride	Yield of		
	Reissert Compound	Aldehyde or Derivative	Reference
Acetyl-	74	99	9
Propionyl-	10	92	9
Butyryl-	64	97	9
Isobutyryl-	28	98	9
n-Valeryl-	-	42	9
Isovaleryl-	64	98	9
2-Methoxybenzoyl-	66	97	9
4-Methoxybenzoyl-	88	98	9
o-Chlorobenzoyl-	80	94	9
m-Chlorobenzoyl-	28	96	9
p-Chlorobenzoyl-	77	92	9
Cinnamoyl-	91	82	9
Benzoyl-	96	98	9
o-Nitrobenzoyl-	80	73	10
m-Nitrobenzoyl-	-	-	10
3,4,5-Trimethoxybenzoyl-	-	-	10
2-Nitro-3,4,5-trimethoxybenzoyl-	80	60-70	10

This method of Grosheintz and Fischer[9] has made the
reduction of acids to aldehydes, via their acid chlorides and the
corresponding Reissert compounds, a general method. Unfortunate-
ly, however, it is not nearly as convenient as the original pro-
cedure of Reissert as it involves the use of liquid hydrocyanic

acid and anhydrous conditions.

Reactions of Reissert Compounds

Reaction with phosphorus pentachloride, thionyl chloride, or sulfuryl chloride. 1-Cyanoisoquinoline was unknown and 2-cyanoquinoline obtainable only by fairly roundabout methods when in 1913 Kaufmann and Dandliker[11] made attempts to prepare them from Reissert compounds. They noted that 4-cyanoquinoline was obtainable from 1-alkyl-4-cyano-1,4-dihydroquinolines by oxidation with alcoholic iodine solution followed by vacuum distillation.
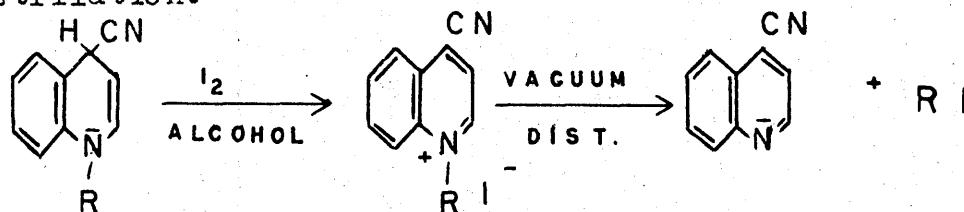
The attempt to oxidize the original Reissert compound in similar fashion to 2-cyanoquinoline either did not go at all or went in a different direction. The treatment of Reissert's compound with a 25 mole % excess of phosphorus pentachloride, however, gave a very vigorous reaction with formation of hydrogen chloride, benzoyl chloride and 2-cyanoquinoline. Use of dry chloroform as a solvent made the reaction milder and more controllable. Yields of 55-70% were reported. Thionyl chloride and sulfuryl chloride were also used successfully. Hamer,[12] however, who repeated the work with phosphorus pentachloride in 1939, was unable to get better than a 24-29% yield.

$$\text{(quinoline Reissert compound)} \xrightarrow[\text{HCCl}_3]{\text{PCl}_5} \text{(2-cyanoquinoline)} + HCl + PCl_3 + C_6H_5\overset{O}{\overset{\|}{C}}\text{-Cl}$$
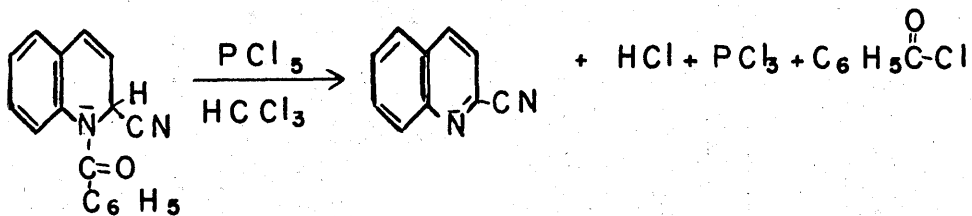
The isoquinoline Reissert compound barely reacted at all with phosphorus pentachloride in chloroform solution, but without a solvent it reacted slowly to give an 84% yield of 1-cyanoisoquinoline. Padbury and Lindwall[13] used this procedure in making derivatives of 1-cyanoisoquinoline but obtained that compound in only 53% yield.

Catalytic hydrogenation. Rupe and coworkers have investigated the catalytic hydrogenation of both the original Reissert compound[14] and the isoquinoline Reissert compound[15] in their study of the reduction of cyano compounds with hydrogen over nickel. They found that sodium and alcohol split the pyridine ring[14] and did not investigate this reaction further. With palladium black, reduction was incomplete and both a secondary and a primary base were formed. When nickel was used as a catalyst, reduction was complete.

With a nickel catalyst, at 70-90°C., under 100 atmospheres pressure of hydrogen, the reaction proceeded as follows:
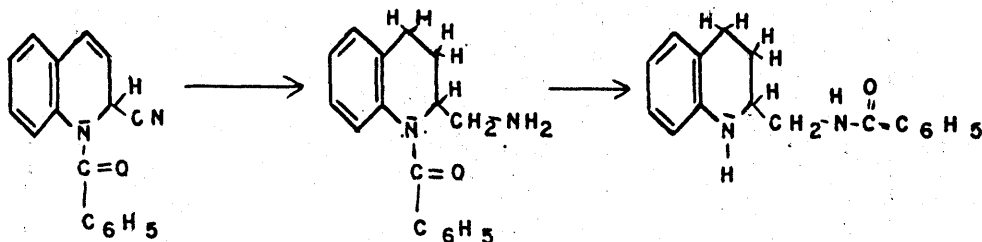
Alcoholic hydrochloric acid was used to hydrolyze the final benzoylated product. The free base was obtained on making the hydrolysis mixture alkaline.
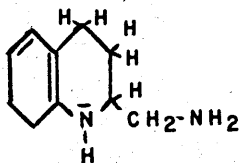
The isoquinoline Reissert compound[15] is similarly hydrogenated to a benzoylated amino compound, although a somewhat higher temperature and pressure, 90-110°C. and 140 atmospheres, are required. Hydrolysis again yields the free base. Similar results are obtained with the Reissert compound derived from 6-methoxyquinoline.[5]
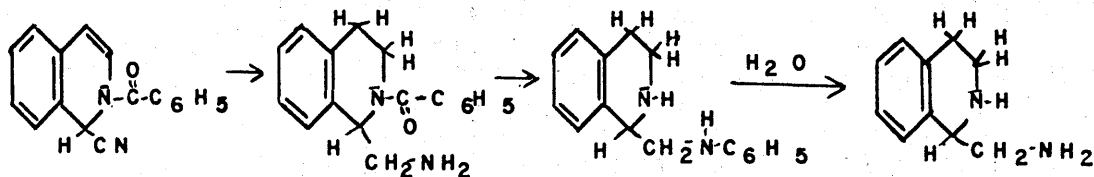
A series of compounds which display some pharmacological activity were prepared[5] from the tetrahydroquinolines and tetrahydroisoquinolines described above.

Reaction with mineral acids. One of the most interesting and probably the most important reaction of Reissert compounds is their ready cleavage, usually in good yield, to the aldehyde corresponding to the original acid chloride and to quinaldo-nitrile, which is further hydrolyzed in the reaction to quinaldic acid or the corresponding amide.[1,2] It thus serves as a convenient means for reducing acids, via their acid chlorides,

to aldehydes, and is limited only by the difficulty of preparation of many Reissert compounds. A partial list of acid chlorides reduced by this method is given in Table II. A. Reissert, who discovered this reaction, also noted a small amount of benzoin quinaldate formed as a by-product.

An analogous reaction occurs with the isoquinoline Reissert compound to give, besides the expected benzaldehyde and isoquinaldic acid, small amounts of benzoin and an unidentified yellow compound, which as a result of combustion analysis was assigned the empirical formula $C_{34}H_{23}N_3O$.

McEwen and Hazlett[6] in 1949 proposed a mechanism which accounts for all the products obtained. They proposed that the first step of the reaction is the coordination of a proton with the amide oxygen of the Reissert compound, IV, giving the conjugate acid, V. By simultaneous loss of a proton from the 2-position of the quinoline ring and gain of a proton by the original carbonyl carbon atom, the complex VI is formed, which then dissociates to an aldehyde and quinaldonitrile (VII). Under the conditions of the reaction, the quinaldonitrile is hydrolyzed to quinaldic acid. Doubtless an important driving force in the reaction is the gain in resonance energy attendant on conversion of the dihydroquinoline to a completely aromatic system.
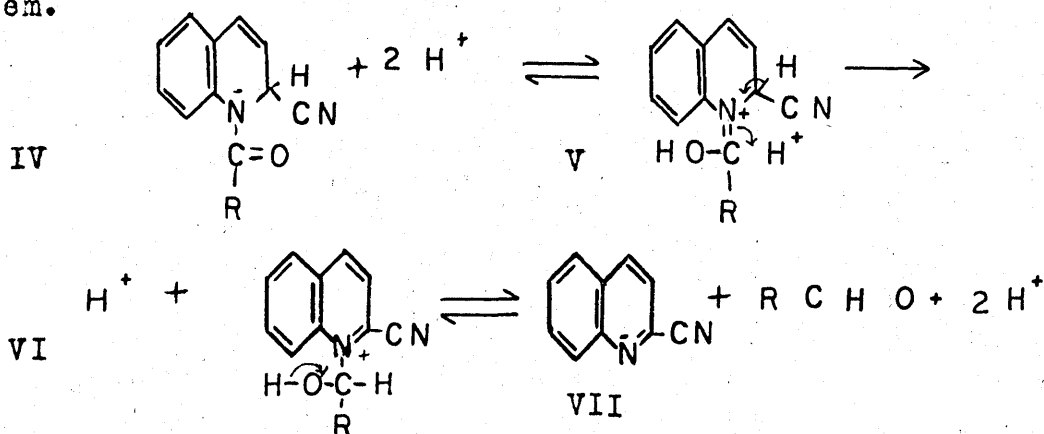
The formation of benzoin quinaldate as a by-product from the hydrolysis of the original Reissert compound can be accounted for by assuming that the conjugate acid of benzaldehyde formed in the reaction competes with the proton in the acceptance of an electron pair to form a new bond with the original carbonyl carbon atom of the Reissert compound, thus forming the complex VIII. This complex then gives the ester, X, via an intra-molecular cyclization to the imino ether complex IX.

VIII   IX   X
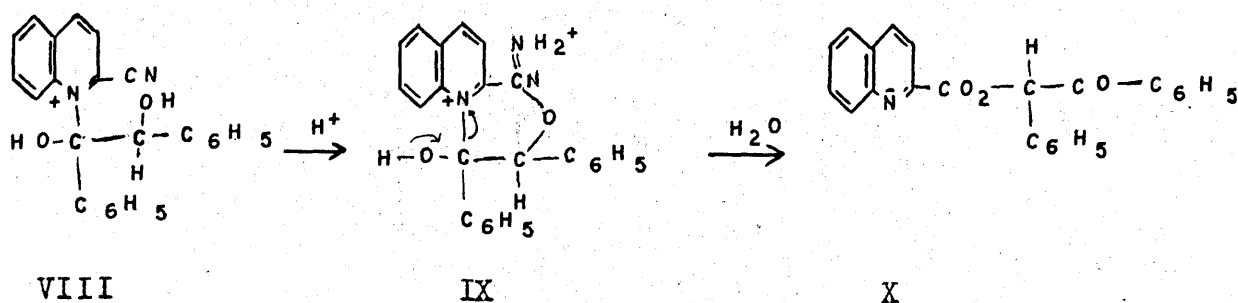
Fairly direct evidence for this intramolecular mechanism was obtained by carrying out a competition reaction involving 1-(p-chlorobenzoyl)-1,2-dihydroquinaldonitrile, 2-benzoyl-1, 2-dihydroisoquinaldonitrile (II), an excess of benzaldehyde and hydrochloric acid. The only products isolated from the reaction mixture, other than benzaldehyde, p-chlorobenzaldehyde, quinaldic acid and isoquinaldic acid, were p-chlorobenzoin quinaldate, benzoin isoquinaldate, a small amount of free benzoin and a yellow product, $C_{24}H_{16}N_2O$. Since the latter three products were also obtained on reaction of the isoquinoline Reissert compound itself with an excess of benzaldehyde and hydrochloric acid, and since no products corresponding to

benzoin quinaldate or p-chlorobenzoin isoquinaldate which would be formed via an intermolecular mechanism were obtained, the intramolecular mechanism is well substantiated.

Further investigation has revealed that the yellow compound, $C_{24}H_{16}N_2O$, originally reported by A. Reissert as $C_{34}H_{23}N_3O$, is 2-(1-isoquinolyl)-4,5-diphenyloxazole.[16] Combustion analyses do not adequately distinguish between the two formulas. Structure proof was based on the following facts: (1) A molecular weight determination by the Rast method gave a value of 353, as compared with the theoretical value of 348 for a compound with the molecular formula $C_{24}H_{16}N_2O$. (2) The conventional tests of organic qualitative analysis indicate the absence of carbonyl-containing, cyano, hydroxyl or primary or secondary amino groups. (3) The ultraviolet and visible absorption spectrum shows a maximum at 410mμ, which is reasonable for a compound having several aromatic rings in conjugation with each other. (4) The compound is very resistant to both acid and alkaline hydrolysis, but a 6% yield of benzoin and a 5% yield of isoquinaldic acid, together with an 85% recovery of starting material, was obtained after one week of refluxing in 25% sulfuric acid solution. (5) The results of a potassium permanganate oxidation in pyridine solution imply that two moles of benzoic acid are formed per mole of yellow compound oxidized. (6) It is known that benzoin and benzonitrile combine to give 2,4, 5-triphenyloxazole in a reaction catalyzed by concentrated sulfuric acid. This is a combination of reagents somewhat

analogous to that formed in the acid-catalyzed reaction of the isoquinoline Reissert compound, but isoquinaldonitrile and benzoin in sulfuric acid solution do not combine to give the oxazole, XVI.

In considering a mechanism the following facts had to be considered: (1) The addition of excess benzoin to the 2-benzoyl-1,2-dihydroisoquinaldonitrile (II) prior to reaction with the concentrated hydrochloric acid does not increase the yield of the oxazole, XVI. (2) Isoquinaldonitrile does not react with benzoin to give the oxazole, XVI, under the conditions of its preparation from the isoquinoline Reissert compound II. (3) The yield of oxazole, XVI, is markedly increased, although still small, by the addition of excess benzaldehyde to II prior to the reaction with hydrochloric acid.

A mechanism for the formation of the oxazole, XVI, consistent with the known facts, was offered and consists of the formation of the conjugate acid, XI, of II, reaction of this
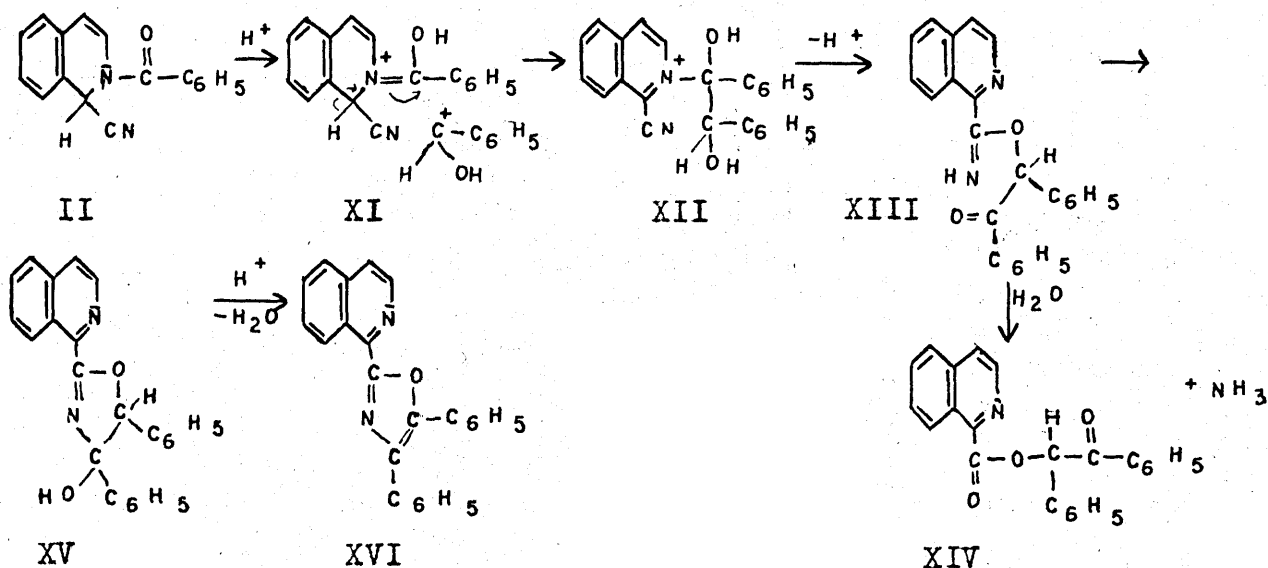
with the conjugate acid of benzaldehyde to give the complex,
XII, which then affords the imino-ether, XIII, by an intra-
molecular rearrangement. All of this is identical with the
mechanism previously proposed for the reaction of the quino-
line Reissert compound with benzaldehyde and hydrochloric acid.
The imino-ether, XIII, then undergoes either a hydrolysis to
benzoin isoquinaldate (XIV) or a cyclization to the hydroxy-
dihydrooxazole, XV. In a simple acid-catalyzed dehydration,
XV then affords 2-(1'-isoquinolyl)-4,5-diphenyloxazole, (XVI).

An independent synthesis of 2-(1'-isoquinolyl)-4,5-di-
phenyloxazole by the method of Davidson, Weiss and Jelling,[17]
to substantiate further the proposed structure, XVI, was
suggested to us by Dr. Marvin Weiss, one of the authors.
They[17] had investigated the action of ammonia in acetic acid
on esters of benzoin and found that good yields of oxazoles
were obtained where R in the equation below was CH_3- or C_6H_5-.
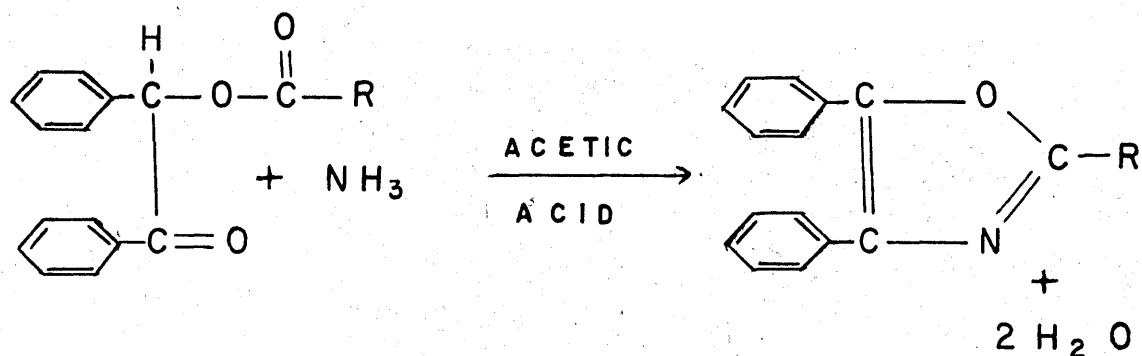
where R = CH_3- or C_6H_5-.

As some of the appropriate benzoin ester (R = 1-isoquinolyl-) was available from the study of the acid catalyzed formation of aldehydes from the isoquinoline Reissert compound, this method of Davidson, Weiss and Jelling[17] was applied to the ester, but none of the desired 2-(1-isoquinolyl)-4,5-diphenyloxazole (XVI) was isolated even though the reaction mixture was exhaustively worked up. Considerable decomposition appeared to have occurred.

As a check of experimental technique one of their[17] reactions, (R = CH$_3$-), was repeated. The desired product was obtained in 51% yield compared with their [17] yield of 82%. This was considered as a sufficiently good check and further attempts to prepare the oxazole , XVI , by this or other methods was abandoned.

Stephen's reduction. Many nitriles, both aliphatic and aromatic, have been reduced to aldehyde imines by a mixture of anhydrous stannous chloride and hydrogen chloride in dry ether.[18] Hydrolysis of the imine hydrochloride thus formed yields the corresponding aldehyde. This method of Stephen is not completely general, but benzaldehyde, β-naphthaldehyde, stearaldehyde and myristaldehyde have been thus prepared.

The successful Stephen's reduction of Reissert's compound, 1-benzoyl-1,2-dihydroquinaldonitrile (I), would give 1-benzoyl-1, 2-dihydroquinoline-2-aldehyde (XVII), or, if hydrolysis occurred in the acid solution, quinoline-2-aldehyde
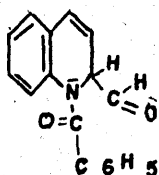
XVII

and benzaldehyde. Kindall[16,19] tried this reaction and isolated and identified only benzaldehyde and unreacted starting material. An acid soluble compound was also obtained, but it was impure and was not identified. It was believed that some, or even most, of the Reissert compound was converted to quinaldinamide or the corresponding imino chloride, since quinaldinamide is obtained in good yield when anhydrous hydrogen chloride alone reacts with the Reissert compound in absolute ether, and the resulting product is hydrolyzed by water.

Alkylation. It has been shown by Boekelheide and Ainsworth[20] that the isoquinoline Reissert compound can be alkylated by certain Mannich bases with the aid of metallic sodium in xylene solution. Alkaline hydrolysis of the resulting product easily gives the corresponding alkylated isoquinoline derivative. The reaction with gramine (R = -H) is given below. 2-Carbethoxy-3-diethylaminomethyl-indole reacted in similar fashion to give 1-(2'-carbethoxy-3-indolyl)-methylisoquinoline (R = -C_3H_5O_2).
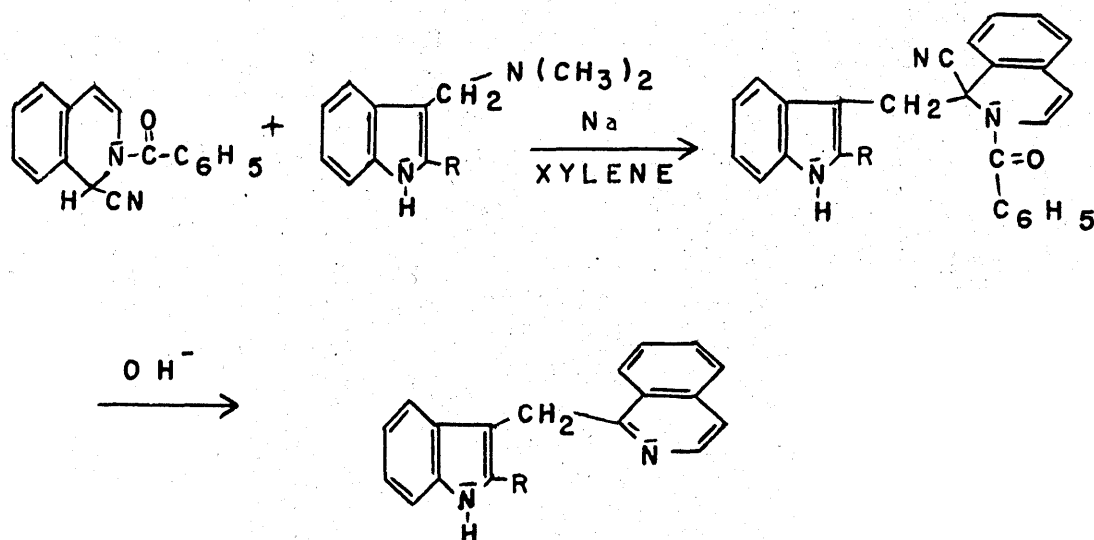
where R = -H or -CO_2C_2H_5

To explain the ease of hydrolysis and the formation of the observed products, Boekelheide and Ainsworth suggested that the hydrolysis proceeds by attack of a hydroxide ion or a water molecule at the amide linkage followed by the shift of a pair of electrons and the loss of a cyanide ion as illustrated below. The driving force for the reaction is probably derived from aromatization of the pyridine ring.
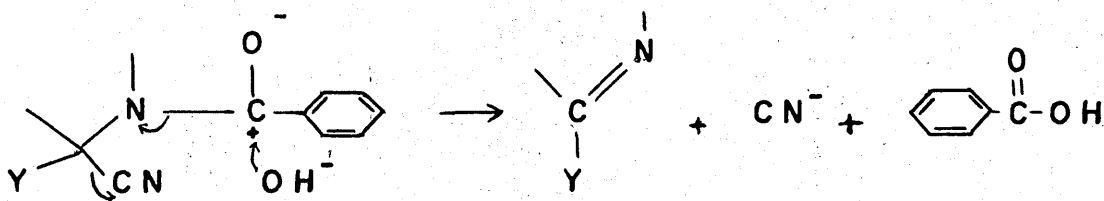
Further work by Boekelheide and Weinstock[21] showed that both the quinoline and isoquinoline Reissert compounds can be alkylated by alkyl halides. Alkaline hydrolysis gave the corresponding alkylated quinolines and isoquinolines. 1-Methyl-, 1-benzyl- and 1-n-butylisoquinoline have been thus prepared. The formation of the anion of the Reissert compound is best carried out under mild conditions in order to avoid rearrangement. Phenyllithium in an ether-dioxane solution proved to be the most satisfactory of the reagents investigated for the alkylation. The over-all procedure appears to have many applications and to be superior to previous methods for preparing such derivatives as 1-methylisoquinoline.
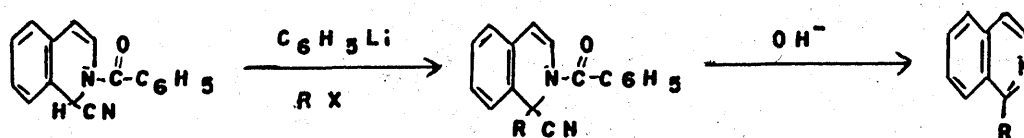
where R = $-CH_3$, $-CH_2 - C_6H_5$ or $-C_4H_9-n$

When the quinoline Reissert compound was subjected to methylation and subsequent alkaline hydrolysis, lepidine was obtained in good yield. No quinaldine, which might have been expected as the product, was isolated. This result raised the question as to whether the intermediate, XVIII, had the 1,2-dihydro structure given or the 1,4-dihydro structure. The same question had never been fully answered even for the original Reissert compound.

Evidence supporting the 1,2-dihydro structures was obtained by subjecting the intermediate, XVIII, to a second methylation. As shown below, the dimethylated product, when subjected to alkaline hydrolysis, gave 2,4-dimethylquinoline (XXI) and must therefore be represented by structure, XX. Since the ultraviolet absorption spectra of XVIII, XX and the quinoline Reissert compound were found to be closely similar, it seems most likely that all are members of the 1,2-dihydroquinoline series.
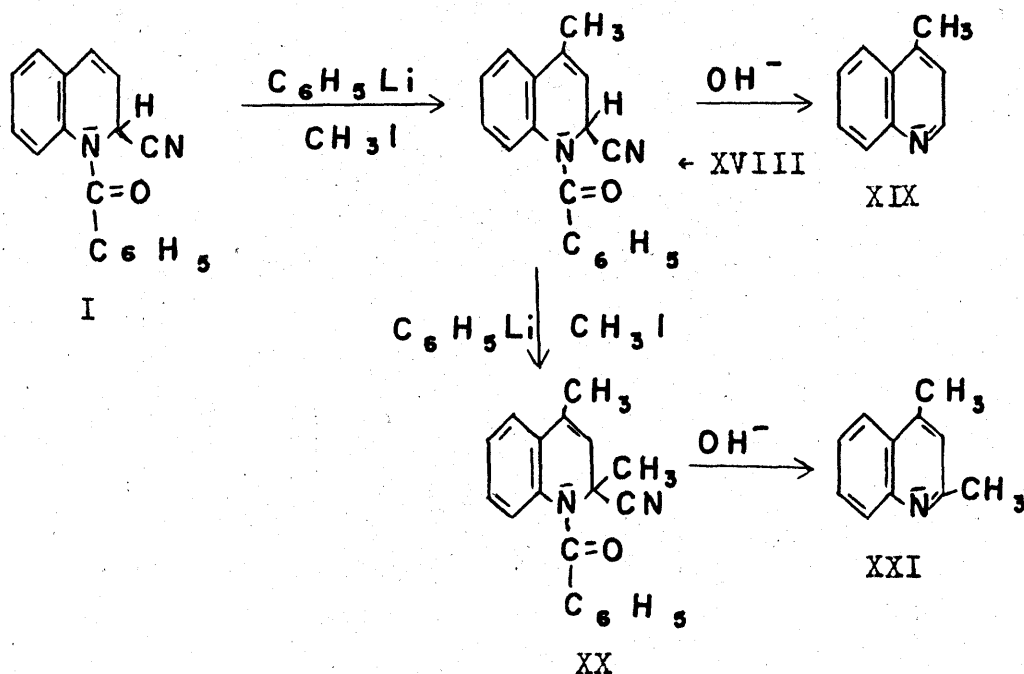
Base catalyzed rearrangement. Certain nitriles react with Grignard reagents to give ketones. As Reissert's compound is a nitrile, Kindall[16, 19] reacted it with methylmagnesium bromide with the expectation of possibly obtaining 1-benzoyl-2-acetyl-1,2-dihydroquinoline (XXII), or 2-acetylquinoline (XXIII) and benzaldehyde if XXII should have been hydrolyzed in working up the reaction mixture.
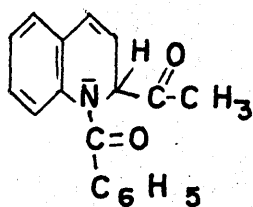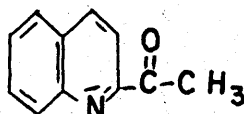
XXII   XXIII

Actually none of these products were obtained as an N to C acyl migration had occurred with the formation of a 50% crude yield of methylphenyl-2-quinolylcarbinol (XXVI). The reaction probably involves the formation of the anion, XXIV, its rearrangement to phenyl-2-quinolyl ketone (XXV) by expulsion of a cyanide ion, and finally, reaction of XXV with methylmagnesium bromide to give the carbinol, XXVI.
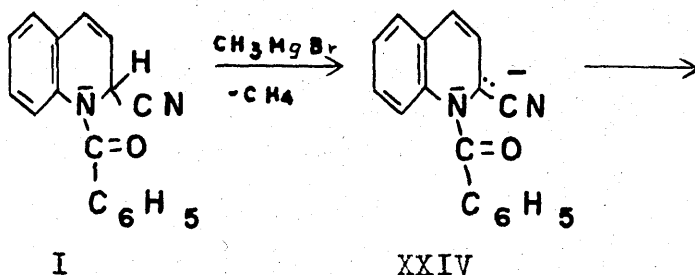
I   XXIV
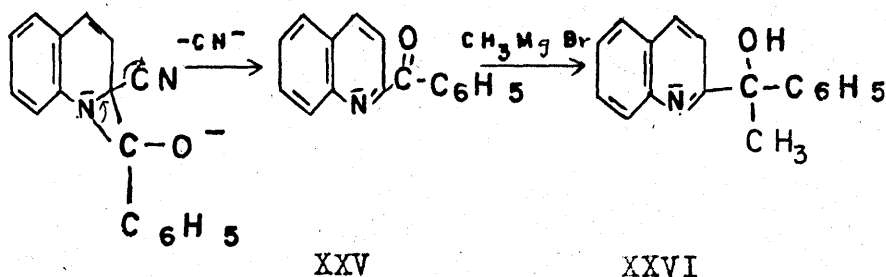
XXV   XXVI

Shortly after publication of the above work, Boekelheide and Weinstock[21] reported that the isoquinoline Reissert compound, when heated with sodium hydride in xylene, rearranged to yield 1-benzoylisoquinoline and sodium cyanide. In a similar manner, 2-acetyl-1,2-dihydroisoquinaldonitrile rearranged to yield 1-acetylisoquinoline. The reaction is
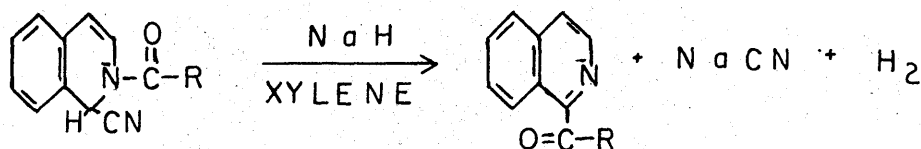
where R = -C_6H_5 or -CH_3

That the rearrangement was of general character was shown by the study of several quinoline Reissert compounds. Thus, 1-acetyl-1,2-dihydroquinaldonitrile and 1-benzoyl-1,2-dihydroquinaldonitrile were readily rearranged to 2-acetyl- and 2-benzoylquinoline, respectively. Results are shown in Table III.

Table III[21]

Reissert Compound	Yield of Rearranged Product
2-Benzoyl-1,2-dihydroisoquinaldonitrile	70%
2-Acetyl-1,2-dihydroisoquinaldonitrile	30[a]
1-Benzoyl-1,2-dihydroquinaldonitrile	54
1-Acetyl-1,2-dihydroquinaldonitrile	31[a]

a) On the basis of the phenylhydrazone

Experiments designed to determine whether the rearrange-
ment was inter-or intramolecular were inconclusive but tended
to favor the intramolecular mechanism.

REACTION OF REISSERT COMPOUNDS WITH
GRIGNARD REAGENTS

Statement of the Problem

In the course of investigating the chemistry of Reissert's
compound (I), Kindall and Hazlett[16,18] discovered that an inter-
esting rearrangement to produce methylphenyl-2-quinolylcarbinol
(XXVI) takes place on reaction with methylmagnesium bromide in
benzene solution.

I   XXVI
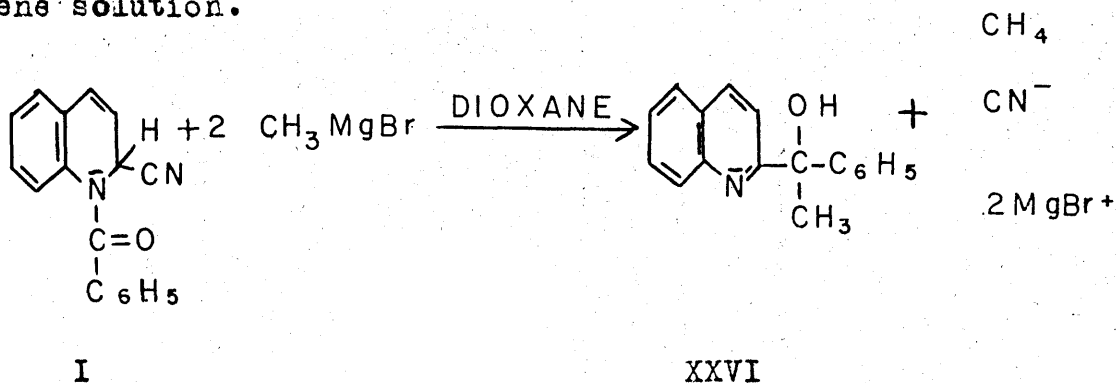
The present work was undertaken to determine (1) the
effect on the rearrangement of variation of structure both in
the Reissert compound and in the Grignard reagent, (2) the
effect of variation of the reaction conditions and (3) the
mechanism of the rearrangement.

The Reaction of Reissert's Compound with

Methylmagnesium Bromide

The reaction between Reissert's compound and methyl-
magnesium bromide was carried out three times in dioxane
solution, and the results are shown in the first part of Table
IV. In the most satisfactory run, the crude yield of methyl-
phenyl-2-quinolylcarbinol (XXVI) amounted to 59%. There was
also obtained a very small amount of 2-benzoylquinoline, which
was identified by combustion analysis and a mixed melting
point test with an authentic sample prepared by the method of
Besthorn[22]. For the significance of the isolation of this
compound see the section on mechanism. Trace amounts of
several other compounds were also isolated from the neutral
fraction of the reaction mixture, but these were not investi-
gated further. One of them appears to be unreacted Reissert
compound (I).

The Effect of Variations in the Reissert Compound

The effect of variations in the quinoline ring. The only
Reissert compound thus far prepared from a substituted quino-
line is 1-benzoyl-1,2-dihydro-6-methoxyquinaldonitrile.(XXVII).
It reacts with methylmagnesium bromide in dioxane solution in
essentially the same way as the unsubstituted Reissert compound
(I). The crude yield of methylphenyl-2-(6-methoxyquinolyl)-
carbinol (XXVIII) was 56.3% and the refined yield 24.3%.
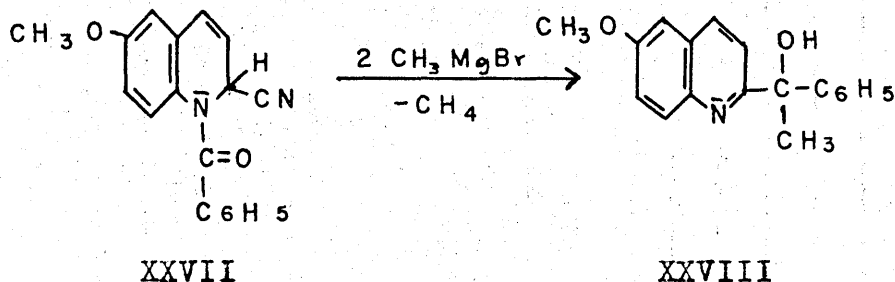
XXVII   XXVIII

The rearranged carbinol, XXVIII, white needles, m.p.
98.5-99-0°, was previously unreported. Its structure was
assumed by analogy with the carbinol, XXVI, produced under
similar conditions from the unsubstituted Reissert compound.
(I). Combustion analyses of the free carbinol and of its
picrate derivative were consistent with structure XXVIII
The dark viscous neutral fraction was not worked up, but it
did not differ greatly in appearance or quantity from that
of the runs reported above.

The only other related variation was the use of the
Reissert compound derived from isoquinoline, II. The results
indicate that the isoquinoline Reissert compound undergoes the
rearrangement in the same fashion as the quinoline analog but
in slightly lower yield. When reacted in the same manner as
in the above reactions, the crude yield of methylphenyl-1-
isoquinolylcarbinol (XXIX) was only 32%, but the refined
yield was 20.2%. There was also a 12% recovery of starting
material.

II   XXIX
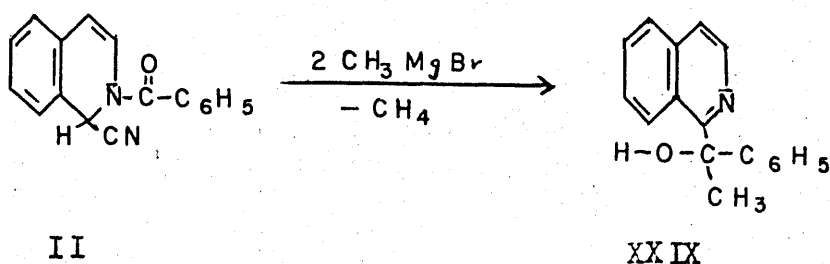
A second trial, using methylmagnesium iodide in place of
methylmagnesium bromide, produced little or no carbinol
XXIX. About half of the initial isoquinoline Reissert
compound (II), was recovered. The procedure differed from
that used in the preceding runs in that the dioxane solution
of the Reissert compound was added to an ether-dioxane sus-
pension of the Grignard reagent. Usually an ether solution
of the Grignard reagent is added to the dioxane solution of
the Reissert compound. The results, therefore, cannot be
directly compared. When this same method, again using methyl-
magnesium iodide, was applied to the quinoline Reissert com-
pound (I), the refined yield was only 12.9% compared with 24-
29% by the standard procedure.

Effect of substituents on the benzoyl group. Three
Reissert compounds, XXX, XXXI and XXXII, derived respectively
from p-chloro-, p-methoxy-, and p-methylbenzoyl chloride, have
been prepared and reacted with methylmagnesium bromide in dio-
xane solution. In each of the three cases the yield of
rearranged product XXXIII, XXXIV and XXXV was markedly lower
than in the same reaction with the unsubstituted Reissert com-
pound. In all but the second reaction with 1-anisoyl-1,2-di-
hydroquinaldonitrile, where more drastic conditions were em-
ployed, about 10% of the starting material was recovered.
The results are summarized in Table IV.

The rearranged carbinol, methyl-p-chlorophenyl-2-quinolyl-
carbinol. (XXXIII), from the reaction with 1-p-chlorobenzoyl-
1,2-dihydroquinaldonitrile (XXX), separated as an oil in 25.9%
crude yield. Attempted recrystallization from various solvents

and long standing failed. The oil was finally converted to
the picrate, m.p. 155.3-156.2°., which, like the carbinol
itself, XXXIII, was previously unreported. Combustion analysis
supported the postulated structure. The refined yield of
rearranged product, XXXIII, calculated from the picrate, was
9.35%. It is possible that the initial oil was contaminated
with quinoline as this product was isolated in other reactions
of this type to be reported later.
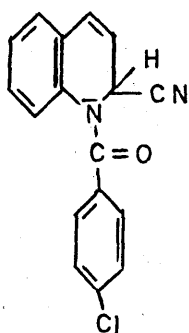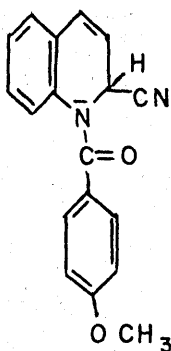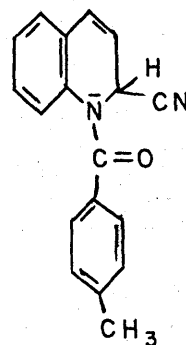
XXX   XXXI   XXXII
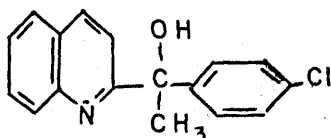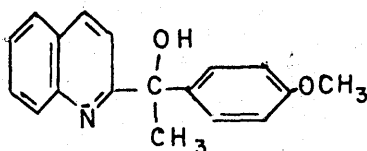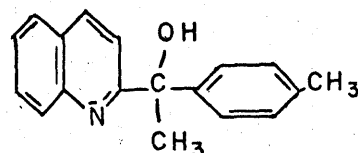
XXXIII   XXXIV   XXXV

The reaction with 1-anisoyl-1,2-dihydroquinaldonitrile
(XXXI) gave only a 4.11% crude and a 1.82% refined yield of

rearranged product, methyl-p-methoxyphenyl-2-quinolylcarbinol (XXXIV). When the reaction was run in xylene under more drastic conditions, the refined yield was 3.84%. The carbinol, m.p.122.2-123.0°, white needles from alcohol, was previously unreported. Combustion analysis supported the proposed structure XXXIV.

Besides an 8.2% recovery of starting material, XXXI, 45mg. of a yellow powder, m.p. 182-188° was isolated from the neutral fraction of the first (normal) run. After the carbinol, XXXI, had been extracted from the second reaction mixture (in xylene) with 5% HCl a second extraction using 6$\underline{N}$ HCl was employed. Upon making this solution alkaline a compound precipitated, which on purification gave 0.3g. fine white needles, m.p.222.2-223.3°. Combustion analysis indicated the empirical formula $C_{12}H_{10}NO$ or possibly $C_{12}H_9NO$. Neither of these two products has been identified.

With 1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII) and methylmagnesium bromide, the amount of rearranged carbinol methyl-p-tolyl-2-quinolylcarbinol (XXXV) was definitely less than 5% and possibly 0%. The dark semi-solid mass was never purified sufficiently for identification. After the carbinol fraction had been extracted with 5% HCl, a 6$\underline{N}$ HCl extraction was made to remove the weakly basic fraction which presumably would contain any 2-p-toluylquinoline that might have been formed. On making the solution alkaline, a very small amount of dark semi-solid oil precipitated. It could not be purified or identified. The initial addition of the 6$\underline{N}$ HCl caused the

precipitation of a considerable quantity of dark semi-solid
material which was insoluble in both the ether and the acid.
It was finally dissolved in ethanol, but it also could not be
purified or identified.

Since 1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII) was new
to the literature, the compound was subjected to acid cleavage
in the presence of 2,4-dinitrophenylhydrazine. On working up
the reaction mixture there was obtained a 96.3% yield of
p-tolualdehyde-2,4-dinitrophenylhydrazone and a 52.7% yield of
quinaldic acid. The structure XXXII was further substantiated
by combustion analysis of a pure sample, m.p.149.5-150.2°.

Since both an electron withdrawing group, p-chloro-, and
electron donating groups, p-methoxy- and p-methyl-, reduce the
amount of rearranged product formed in this reaction, any
simple consistent explanation of the substituent effects on
the basis of electronic theory is difficult if not impossible
to make. This situation undoubtedly arises from the fact that
there are at least three points in a Reissert compound, the
α-hydrogen, the cyano group and the amide carbonyl group, at
which attack by a Grignard reagent can take place. Changes
in the electronic nature of the benzoyl group due to para sub-
stitution obviously effects the reactivity of all three
positions and makes the prediction or explanation of the net
effect at any one position a very complex matter.

Attempts to study further the effects of substitution
on the benzoyl group of the Reissert compound were abandoned
when attempts to prepare quinoline Reissert compounds from

p-fluoro-, and m-fluorobenzoyl chloride by the method of Rupe, Paltzer and Engel[14] failed. The corresponding acids or their potassium salts were formed instead. Similar attempts to prepare isoquinoline Reissert compounds by essentially the method of Rupe and Frey[15] from isoquinoline and p-methyl- and p-chlorobenzoyl chloride were only moderately successful. In the former case little if any of the desired product was formed, the main product being p-toluic anhydride. A crude yield of 10.35% was realized in the preparation of 2-(p-chloro-benzoyl)-1,2-dihydroisoquinaldonitrile (XXXVI), previously unreported. The purified product gave white needles from isopropyl ether or benzene, m.p. 155.2-155.8°. Acid cleavage in the presence of 2,4-dinitrophenylhydrazine resulted in a 50% yield of p-chlorobenzaldehyde-2,4-dinitrophenylhydrazone. Combustion analysis supported the proposed structure, XXXVI. An insufficient quantity was purified to allow a study of its reaction with methylmagnesium bromide. The yield of XXXVI can undoubtedly be improved by further study of reaction conditions.
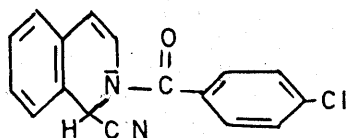
XXXVI

The reaction with Reissert compounds derived from aliphatic acid chlorides. The only Reissert compound derived from an aliphatic acid chloride that was reacted with methyl-magnesium bromide was 1-acetyl-1,2-dihydroquinaldonitrile

(XXXVII). The fraction which supposedly contained the rearranged carbinol, dimethyl-2-quinolylcarbinol (XXXVIII), precipitated as an oil.
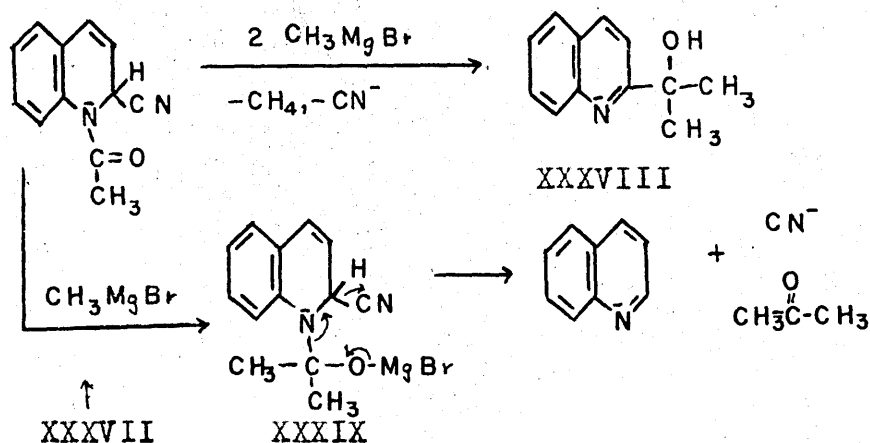
This oil was converted to the picrate and by repeated recrystallization from various solvents separated into two pure compounds. One was identified as quinoline picrate by melting point and an undepressed mixed melting point with an authentic sample. The formation of quinoline (in 1.11% yield) can easily be accounted for if it is assumed that the initial attack of the Grignard reagent is at the amide carbonyl group of the Reissert compound, XXXVII. The resulting complex, XXXIX, yields quinoline, and a cyanide ion.

The other product from the purification of the picrates gave yellow platelets from absolute ethanol and Skelly C solvent and had a m.p. of 150.6-151.4°C. The picrate of dimethyl-2-quinolylcarbinol (XXXVIII), however, is reported[23] as melting at 110°. The combustion analysis of this compound is not available at present.

A small amount of dark viscous oil precipitated when the 6N HCl extracts from this reaction mixture were made alkaline. A very small amount of white crystals m.p.97.6- 102° was finally obtained but never identified. The free carbinol, XXXVIII ,melts at 67° [23], 2-acetylquinoline at 47.5-48°.[24] and the starting Reissert compound, XXXVII, at 96-97° [9] so it could be none of these.

Only a small amount of dark viscous material was obtained from the neutral fraction. Repeated recrystallization from various solvents finally produced a few milligrams of white crystals, m.p.91-92°. A mixed melting point with known 1-acetyl-1,2-dihydroquinaldonitrile (XXXVII) completely melted below 83°, indicating that the two compounds were not the same. The compound has not been identified.

In this experiment the material balance does not appear to have been better than 50%. It rarely has been better than 70% in any of the runs. In this case, as in several others, the inorganic residue resulting from hydrolysis of the Grignard complex was thoroughly extracted with several different solvents, but no organic material was obtained. Possibly the missing material is present in the solvent which is distilled prior to addition of ether and hydrolysis, or perhaps it is present as a water soluble or amphoteric compound in the aqueous mother liquors resulting from the acid extractions.

The Effects of Variation in the Grignard Reagent

The use of different Grignard reagents. On the basis of a fairly extensive study of the influence of structure on the reactions of Grignard reagents with nitriles having α-hydrogens, C.R. Hauser[25] has drawn the following generalizations: (1) For a given Grignard reagent, the fraction of attack at the α-hydrogen increases with increased activity of the α-hydrogen, e.g. C_6H_5-CH_2-CN $>$ CH_3CN $>$ R-CH_2CN. (2) Aromatic Grignard reagents react relatively more at the cyano group and relatively less at the α-hydrogen than aliphatic Grignard reagents. (3) Steric hindrance in the Grignard reagent favors attack at the α-hydrogen. (4) Steric hindrance in the nitrile favors attack at the cyano group.

The results of the reaction of a number of Grignard reagents with Reissert's compound, 1-benzoyl-1,2-dihydroquinaldonitrile (I) are listed in the fifth portion of Table IV and are in fairly good agreement with the generalizations of Hauser.[25]

The reaction of ethylmagnesium bromide with Reissert's compound (I) produced less than a 20% crude yield of rearranged carbinol, ethylphenyl-2-quinolylcarbinol (XL). Many attempts were made to purify the dark viscous oil but with little success. A few milligrams of a white compound, m.p.180-181.5°, was isolated, but it would not dissolve in 6N HCl, indicating that the material was a neutral substance present as an impurity or decomposition product. Further

Table IV

1,2-Dihydroquinaldo-nitrile Derivative	Grignard Reagent	Reaction Conditions	Yield of Crude	Rearr.Carbinol Refined
1-Benzoyl-	MeMgBr	Dioxane, 60°	-[1]	-[1]
1-Benzoyl-	MeMgBr	Dioxane, 60°	49.1	24.3
1-Benzoyl-	MeMgBr	Dioxane, 60°	59	29
1-Benzoyl-6-methoxy-	MeMgBr	Dioxane, 60°	56.3	24.3
2-Benzoyl-[2]	MeMgBr	Dioxane, 60°	32	20.2
2-Benzoyl-[2]	MeMgI	Dioxane,[3]60°	0	0
1-p-Chlorobenzoyl-	MeMgBr	Dioxane, 60°	25.9	9.35
1-Anisoyl-	MeMgBr	Dioxane, 60°	4.11	1.82
1-Anisoyl-	MeMgBr	Xylene, 130°	-	3.81
1-p-Toluyl-	MeMgBr	Dioxane, 60°	<5[4]	-
1-Acetyl-	MeMgBr	Dioxane, 60°	-	<2
1-Benzoyl-	EtMgBr	Dioxane, 60°	<20[4]	-
1-Benzoyl-	PhMgBr	Dioxane, 60°	0	0
1-Benzoyl-	PhMgBr	Dioxane,100°	-	12.5[5]
2-Benzoyl-[2]	PhMgBr	Dioxane,100°	49.8	38.8
1-Benzoyl-	MesMgBr	Dioxane, 60°	0[6]	0[6]
1-Benzoyl-	MesMgBr	Xylene, 130°	0[6,7]	0[6]
1-Benzoyl-	MeMgCl	Dioxane, 60°	49.5	30
1-Benzoyl-	MeMgBr	Dioxane, 60°	59	29
1-Benzoyl-	MeMgI	Dioxane,[3]60°	21.4	12.9
2-Benzoyl-[2]	MeMgI	Dioxane,[3]60°	0	0

[1] No accurate yields calculated. [2] A 1,2-dihydroisoquinaldo-nitrile derivative. [3] Different procedure - Grignard reagent precipitated in dioxane. [4] Oil which could not be purified - may not be expected product. [5] 8.5% carbinol, 4.0% ketone. [6] Trace of ketone. [7] A 29% yield of quinoline.

effort produced a few milligrams of another white compound, m.p. 97-102°, which did slowly dissolve in 5% HCl and therefore could be the expected carbinol, XL. No attempt was made to isolate any compounds from the neutral fraction.

Phenylmagnesium bromide when reacted with Reissert's compound under the usual mild temperature conditions produced no isolable diphenyl-2-quinolylcarbinol (XLI). The procedure was slightly different from that normally used, however, in that the dioxane solution of the Reissert compound was added to the Grignard reagent. Also a small amount of unreacted magnesium may have been present. From 20g. of Reissert compound and the Grignard reagent there was obtained from the neutral fraction 5 g. of crystalline solid plus 8.5g of oil. Repeated recrystallization of the solid from various solvents yielded approximately 0.2g. quantities each of unreacted Reissert compound, 2-benzoylquinoline (there was no 6$\underline{N}$ HCl extraction in this particular experiment, thus its isolation from the neutral fraction), and a compound, m.p. 190.2-191.2°, white needles from ethanol. Combustion analysis indicated the empirical formula, $C_{19}H_{14}NO$. No structure has been established.

When this reaction was carried out in the usual manner, except that the reaction mixture in dioxane was refluxed instead of mildly heated, the yield of rearranged products was 12.5%. This included an 8.5% yield of the carbinol, XLI, and a 4.0% yield of the rearranged ketone, 2-benzoylquinoline (XXV). Apparently only 68% of the 2-benzoylquinoline formed reacted with phenylmagnesium bromide to produce the carbinol,

XLI. If the rearrangement involves initial attack at the
α-hydrogen, as seems quite definite from the work of Boekel-
heide and Weinstock[21], and McEwen, Kindall, Hazlett and
Glazier,[16] then these results are in line with the generali-
zations of Hauser.[25] Methylmagnesium bromide gives twice the
yield of products resulting from attack at the α-hydrogen
under mild conditions as phenylmagnesium bromide does even
under more drastic conditions.

A fair amount of biphenyl was the only compound isolated
from the neutral fraction of this second run. Analysis of
another sample of the phenylmagnesium bromide solution showed
that this quantity of biphenyl was present in the original
solution and therefore did not arise from reaction with the
Reissert compound. None of the compound, m.p. 190.2-191.2°.,
reported in the first run, was isolated.
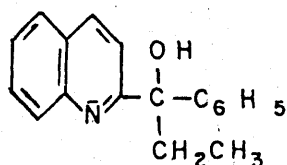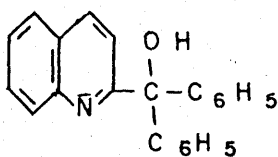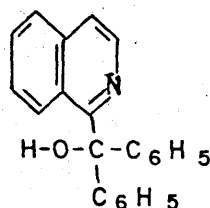
XL   XLI   XLII

The isoquinoline Reissert compound (II) was reacted with
phenylmagnesium bromide under the same vigorous conditions
just described for the quinoline Reissert compound. The yield
of diphenyl-l-isoquinolylcarbinol (XLII) was 49.8% crude and
38.8% refined, the highest refined yield of rearranged product

obtained in any of these reactions. This represents nearly twice the yield of rearranged product that was obtained with methylmagnesium bromide, which does not agree with the postulates of Hauser,[25] but, of course, the conditions were more drastic with the phenylmagnesium bromide. In addition to this large amount of rearranged product, 21% of the starting isoquinoline Reissert compound was recovered.

Diphenyl-1-isoquinolylcarbinol (XLII), white needles from ethanol, m.p.143.2-143.6°, was previously unreported. Combustion analysis supported the proposed structure, XLII.

A small amount of a weakly basic compound was also isolated but could not be identified. It melted 137.5-139.0° and thus could not be 1-benzoylisoquinoline,[26] m.p.76-77°.

The reaction between Reissert's compound and mesitylmagnesium bromide was undertaken in an effort to substantiate further that 2-benzoyl-quinoline is an intermediate in the rearrangement of Reissert compound by Grignard reagents. It was felt that the highly hindered mesitylmagnesium bromide would preferentially attack the $\measuredangle$-hydrogen and would add neither to the cyano group nor to any 2-benzoylquinoline formed. The procedure used was that of addition of a dioxane solution of the Reissert compound to the ether-dioxane mixture of the Grignard reagent. Actually a trace of 2-benzoylquinoline was isolated by purification of the very small precipitate obtained on addition of sodium hydroxide to the 5% HCl extracts of the reaction mixture. No additional ketone could be isolated by use of Girard's "T" reagent on the "neutral" fraction. Repeated attempts at purification of the

large neutral fraction finally resulted in the isolation of
0.2g. of unreacted Reissert compound.

In the second reaction of Reissert's compound and mesityl-
magnesium bromide, the normal method of addition was used, but
the solvent was p-xylene, which was maintained at or near its
boiling point. The major product isolated was quinoline in
29% crude yield and 9.31% refined yield (as the picrate).
Only a trace of 2-benzoylquinoline was obtained from the weak-
ly basic fraction. Apparently steric factors in the mesityl-
magnesium bromide and the Reissert compound (I) are such that
attack at the amide carbonyl carbon is favored. The mechanism
for the formation of quinoline in this case is undoubtedly the
same as that postulated in the case of 1-acetyl-1,2-dihydro-
quinaldonitrile (XXXVII) and methylmagnesium bromide.

Effect of the halide in the Grignard reagent. There is
no marked difference in the action of methylmagnesium chloride,
bromide and iodide in their reactions with Reissert's compound.
The yield of rearranged product does seem to decrease slightly
in the order listed, however, as shown in Table IV.

From methylmagnesium chloride and Reissert's compound a
49.5% crude and 30% refined yield of methylphenyl-2-quinolyl-
carbinol (XXVI) was obtained. The best of three runs with
methylmagnesium bromide gave a 59% crude and 29% refined yield.
When a correction is made for the 27.5% of unreacted Reissert's
compound recovered in the reaction with methylmagnesium iodide,
the crude yield was 29.5% and the refined yield 17.8%. In

this last reaction a dioxane solution of the Reissert compound was added to an ether-dioxane mixture of the Grignard reagent. Lack of reactivity in this case may be attributed to the large amount of Grignard reagent precipitated by the dioxane. The resulting paste may not have been sufficiently well mixed with the Reissert compound for proper reaction.

From the methylmagnesium chloride-Reissert compound reaction mixture, a 2.2% yield of 2-benzoylquinoline was obtained in addition to the 30% yield of rearranged carbinol. A very small amount of a compound, m.p.228-232°, was isolated from the neutral fraction but not identified. A small amount of unreacted Reissert compound was also recovered.

Both methylmagnesium bromide and methylmagnesium iodide have been reacted with the isoquinoline Reissert compound (II). Methylmagnesium bromide and II gave a 52% crude and 20.2% refined yield of methylphenyl-1-isoquinolylcarbinol (XXIX) and a 12% recovery of starting material. The reaction with methylmagnesium iodide was run under the same conditions described above for the methylmagnesium iodide-quinoline Reissert compound reaction and therefore cannot be too rigorously compared with the corresponding methylmagnesium bromide reaction. Using the iodide, the only compound that could be isolated from the reaction mixture, was unreacted isoquinoline Reissert compound (II) in approximately 50% recovery.

The Effects of Reaction Conditions

Effect of the solvent. The reaction between Reissert
compounds and Grignard reagents has been run in three differ-
ent solvents, benzene, dioxane, and xylene. No one reaction
has been carried out in all three solvents under any conditions,
or any two solvents under the same conditions; thus no real
comparison can be made. There does not seem to be any marked
difference, however, as the rearrangement occurs in all three
solvents. The differentiating factor is undoubtedly the
boiling point of the solvent, i.e., the temperature at which
the reaction can be carried out.

Effect of temperature. From the small amount of data
available, (see Table IV), it would appear that the effect
of increased temperature on the amount of rearranged carbinol
obtained from a Reissert compound depended on the Grignard
reagent used. In the reaction of 1-anisoyl-1,2-dihydroquin-
aldonitrile with methylmagnesium bromide a change from di-
oxane and mild heating at 60° to boiling xylene at 130°
increased the yield of carbinol obtained only from 1.82% to
3.81%.

A temperature change from 60° to 100° in dioxane in
the Reissert compound-phenylmagnesium bromide reaction in-
creased the yield of rearranged products from a trace to
12.5%. The analogous reaction with the isoquinoline Reissert
compound in boiling dioxane produced a 38.8% refined yield
of rearranged carbinol. No reaction with mild heating was

carried out for comparison.

The reaction of mesitylmagnesium bromide with Reissert's compound was performed both in dioxane at around 60°C. and in boiling p-xylene at about 135°C. Only a trace of 2-benzoylquinoline was obtained in both cases. At the higher temperature, however, a 29% crude yield of quinoline was isolated compared with none in the former case.

Determination of the Mechanism of the Rearrangement

The rearrangement of Reissert compounds by Grignard reagents seems definitely to involve initial attack at the α-hydrogen and formation of 2-benzoylquinoline as an intermediate as shown below:
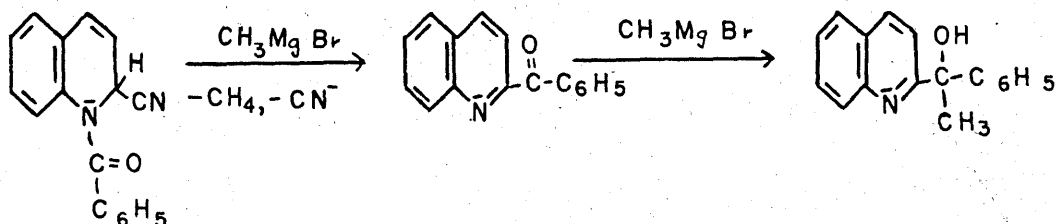
Not only has 2-benzoylquinoline been isolated from several of the reactions reported above, but Boekelheide and Weinstock[21] have isolated this ketone as the main product from the reaction of Reissert's compound with sodium hydride in xylene solution. Sodium hydride would not be expected to attack any functional group other than an active α-hydrogen.

A reaction between Reissert's compound and methylmagnesium bromide in a 1:1 mole ratio was undertaken to deter-

mine if the ketone could be obtained as the major product. It
was felt that with a 1:1 mole ratio there might be insufficient
methylmagnesium bromide present to convert the ketone to the
carbinol. Actually none of either the ketone or the carbinol
was isolated.

The formation of the 2-benzoylquinoline can conceivably
occur by either an intramolecular (A) or an intermolecular
(B) mechanism. The former was originally proposed by McEwen,
Kendall, Hazlett and Glazier[16] and the latter by Boekelheide
and Weinstock.[21]

<u>A</u>

I

XXV

B

I   XLIV

XLIV   XLIV   XXV
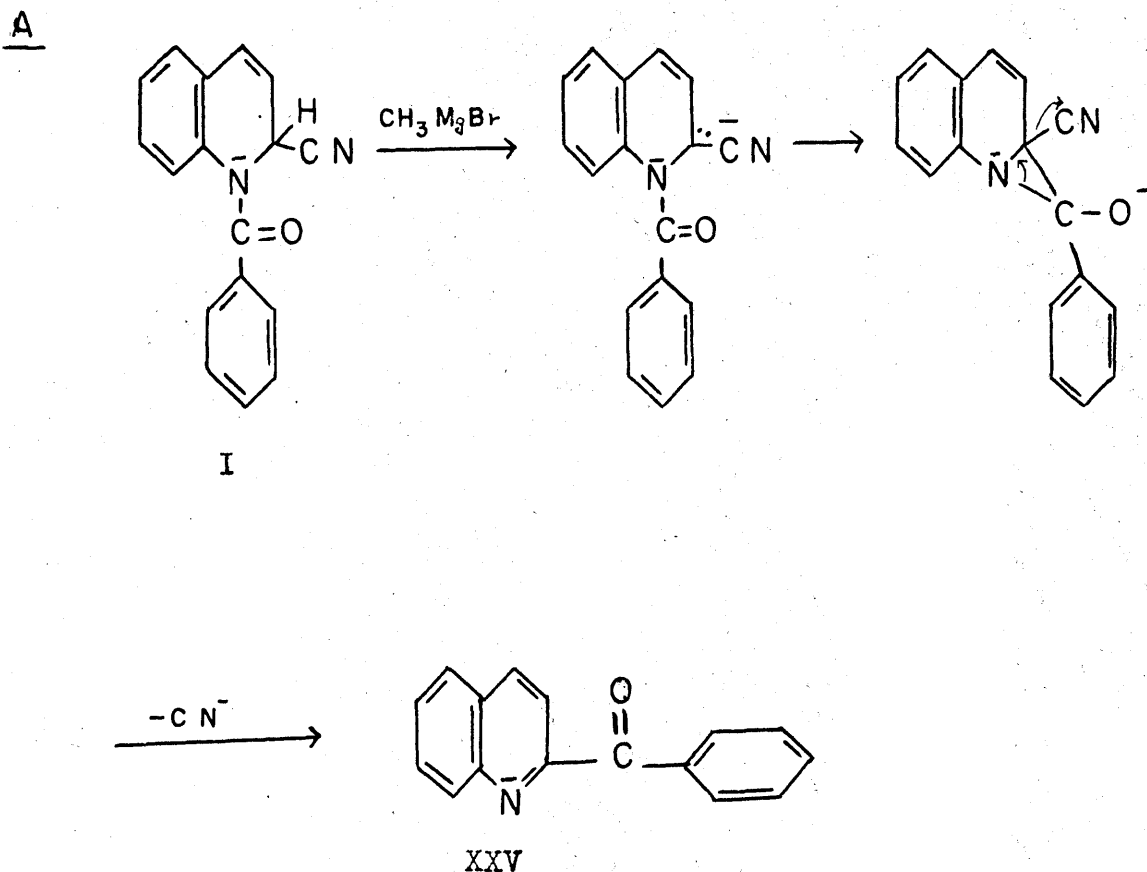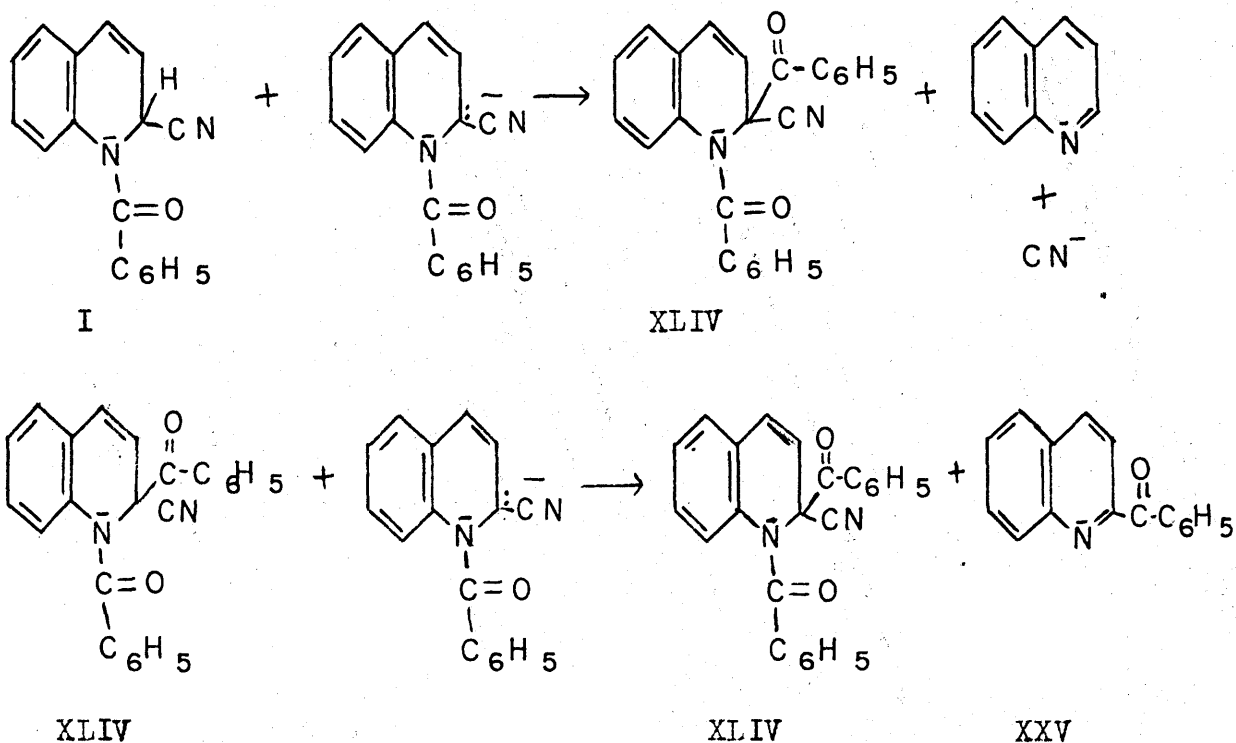
Boekelheide[21] has carried out two experiments designed
to test (A) or (B) as possible mechanisms. His work was in
the isoquinoline Reissert compound series, but the results
would be expected to apply equally well to the quinoline
series.

If (A) were the mechanism of the reaction, it might be
expected that 2-cinnamoyl-1,2-dihydroisoquinaldonitrile.
(XLIII), would undergo cyclization to form a five membered
ring rather than a rearrangement product. Unfortunately,
the reaction proceeded abnormally and neither a cyclization

nor rearrangement product was isolated.

On the other hand, it might be expected that evidence regarding mechanism (B) might be obtained by a study of the chemical behavior of compounds of the type of the postulated intermediate, XLIV. The preparation of such a compound in the isoquinoline series, XLV, was accomplished by the benzo-lation of the anion of the isoquinoline Reissert compound (II). Attempts to convert it to 1-benzoylisoquinoline (XLVI) by reaction with the anion of 2-acetyl-1,2-dihydroisoquinaldo-nitrile (XLVII) were unsuccessful. The only product identified from the reaction mixture was the isoquinoline Reissert com-pound (II). Although the results of this experiment are not conclusive, they do offer negative evidence in favor of the intramolecular mechanism (A).
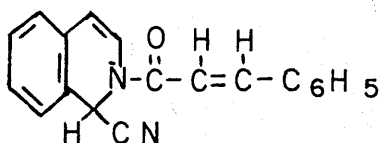
XLIII
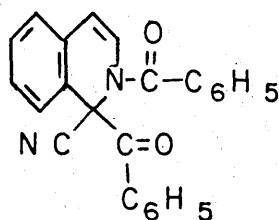
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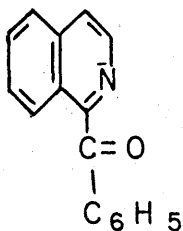
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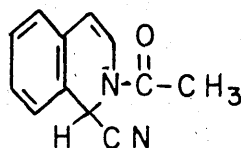
XLVII

The approach taken in the present work toward the solution of this problem was that of a competition reaction between properly substituted Reissert compounds and methylmagnesium bromide. A mixture of 1-benzoyl-1,2-dihydro-6-methoxyquinaldo-nitrile (XXVII) and 1-(p-chlorobenzoyl)-1,2-dihydroquinaldo-nitrile (XXX) was reacted with methylmagnesium bromide in the usual manner. If the mechanism were intramolecular (A) only the two carbinols, XXVIII and XXXIII, which were formed when the reactions were run individually, would be formed. If the mechanism were intermolecular (B) two additional carbinols, XXVI and XLVIII, would also be formed.
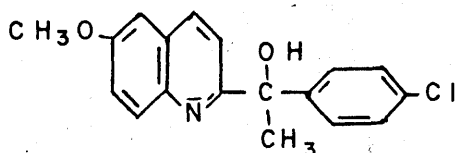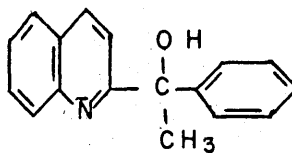
XLVIII   XXVI

The carbinol fraction precipitated as a dark oil and was considerably smaller than expected. The entire fraction was converted to the corresponding picrates and attempts made to separate them by fractional crystallization. Quinoline picrate was the only product positively identified. Another somewhat impure fraction melted at 140.5-141.5° and gave a positive Beilstein test for halogen. A mixed melting point with authentic methyl-p-chlorophenyl-2-quinolylcarbinol picrate, m.p.155.3-156.2°, was 145-146° which suggests they are the same compound. A very small amount of a compound,

m.p.178.5°, which gave a negative Beilstein test for halogen
was also isolated. A mixed melting point with authentic
methylphenyl-2-(6-methoxyquinolyl)-carbinol picrate, m.p.174.5-
175.4°, showed a depression of 10-13°. The compound also
could not be methylphenyl-2-quinolyl-carbinol picrate, m.p.
169°.[27], or 6-methoxyquinoline picrate, m.p. 214-215°.

The weakly basic fraction was purified in the hope that
it might contain some of the rearranged ketones. Two products
were isolated but neither positively identified. The major
one, white needles, m.p.129.8-130.1°, is thought to be
2(p-chlorobenzoyl)-quinoline (XLIX) which would be formed by
the intramolecular process. The combustion data is in fair
agreement with that calculated for a compound of structure
XLIX. The other compound isolated, obtained only in very
small quantity, formed white needles from Skelly C solvent,
m.p. 175-176°.
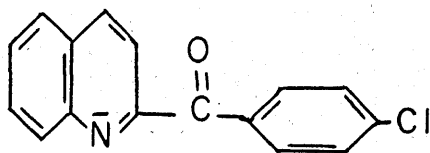
XLIX

Although this evidence is far from conclusive it does
tend to support the intramolecular (A) mechanism. Probably
the most significant item was the failure to isolate any
2-benzoylquinoline, which would have been formed by the

intermolecular process and would, therefore, probably have been present in the weakly basic fraction. It had been found in previous reactions that 2-benzoylquinoline was fairly easy to isolate and identify, even when formed only in very small amounts.

EXPERIMENTAL*

Dioxane. Dow Chemical Co. C.P. dioxane was purified by the method of Fieser.[28]

1-Benzoyl-1,2-dihydroquinaldonitrile (I). The compound was prepared three times by the method of Rupe, Paltzer and Engel,[14] small colorless crystals from alcohol, m.p. 151-153,° and 151.6-152.6°, (lit! m.p. 154-155°).

Reaction of 1-Benzoyl-1, 2-dihydroquinaldonitrile (I) with Methylmagnesium Bromide. A. Into a 1000 cc. three necked flask provided with a sealed mechanical Hershberg stirrer, a dropping funnel (self-compensating), and a reflux condenser connected to a supply of nitrogen, dried by passage through anhydrous calcium chloride, was introduced 20g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) and 154 cc. of dry dioxane. Stirring was commenced and 53 cc. (0.21 mole) of 4M methylmagnesium bromide was slowly added. The first few drops of the Grignard reagent caused the formation of a reddish brown precipitate. The solution eventually became dark brown and very hot and had to be cooled. The dioxane vapors reached

*All melting points corrected unless otherwise indicated. Analyses by Oakwald Laboratories, Alexandria, Va., and Weiler and Strauss, Oxford, England.

the ether solution via the side arm of the dropping funnel and caused some precipitation of the Grignard reagent. The solution was stirred for 20 minutes after the addition of the Grignard reagent and then warmed gently on the steam bath with stirring for another 30 minutes. A considerable quantity of brown precipitate was present in the mixture. The apparatus was modified for distillation of the ether, but no distillate came over at the temperature of the steam bath. Apparently all the ether had been carried off by the nitrogen flow. The dioxane was then distilled under vacuum at 50-55°. A light to medium brown solid cake was left as residue. This was broken up and to it 40 cc. of saturated ammonium chloride solution (160 cc. per mole of magnesium) was added with stirring (as soon as that became possible). A dark red-brown to black suspension resulted. To this, 100 cc. of 2% hydrochloric acid solution was added, and the still alkaline solution was decanted from a solid residue. The solid residue was digested four times with ether. The aqueous solution, with some solid material in suspension, was also extracted with ether, which was combined with the four ether extracts of the solid residue. The aqueous mother liquor was acidified and filtered but no significant residue was obtained. The combined ether extract was extracted four times with 2% hydrochloric acid solution. The combined acid extract, dark red in color, was washed once with ether, which was added to the main ether solution (A). The acid solution was made alkaline with 10% sodium hydroxide solution and the resulting light to dark brown precipitate was filtered with suction; 19g.

of crude methylphenyl-2-quinolylcarbinol(XXVI), m.p. 81-86°.
The material had not been vacuum dried to constant weight so
the crude yield was undoubtedly too high. After two recry-
stallizations from alcohol-water the weight of material was
about half of the original weight. A further recrystallization
from Skelly C solvent gave material of m.p. 91-95°. Another
recrystallization from alcohol-water gave yellow crystals
plus a dark mass. The two fractions were mechanically separated.
Two additional recrystallizations from alcohol-water of the
light yellow portion gave 0.82g. of pure methylphenyl-2-quinolyl-
carbinol (XXVI), m.p. 99-101° (lit.[27] m.p.100°). The dark
portion was recrystallized twice from alcohol-water, twice
from Skelly C solvent and then from alcohol-water (Norit),
o.80g. of pure carbinol being obtained, m.p. 100-101°. Both
products showed no depression in a mixed m.p. test of methyl-
phenyl-2-quinolylcarbinol (XXVI), prepared by the method of
Dyson and Hammick.[27] Considerable quantities of material
appear to have been lost on recrystallization.

Attempts to obtain more pure methylphenyl-2-quinolyl-
carbinol (XXVI) from the residue obtained on evaporation of
the mother liquors, by either sublimation or chromatographic
adsorption on Fisher Adsorption Alumina (80-200 mesh, from dry
benzene, as the solvent) failed.

The main ether solution (A) was filtered to remove some
black residue. The solution was then extracted with three
portions (a total of 200 cc.) of 5% sodium bicarbinate solution.
The slightly turbid yellow alkaline solution was acidified with
5% hydrochloric acid and filtered. The very small amount of

orange-red-brown precipitate which was collected decomposed at 122°. Possibly it was benzoic acid. The acid mother liquor was reduced in volume about 25% by vacuum distillation and extracted three times with ether. Evaporation of the ether solution, dried over anhydrous sodium sulfate, left a small, very dark brown and rather oily residue, which was not further investigated.

The main ether solution from the above alkaline extraction, was distilled, leaving a very dark red brown oil which did not crystallize even in an ice bath. The oil was twice treated with Norit in alcohol solution with no change in the dark color. The solvent was removed under vacuum. The resulting oil was refluxed with Skelly C solvent and the red supernatant liquid decanted. Only a small quantity of the oil had dissolved in the Skelly C solvent. (Attempted purification of the insoluble residue failed and the material was discarded.) After four weeks needle-like crystals appeared in the Skelly C solution together with an oily semi-solid mass. Some of the crystals were mechanically separated with the aid of a spatula and recrystallized from Skelly C solvent. The original solution was suction filtered, more crystals precipitating in the filtrate as a result of the cooling and evaporation. The oily residue on the filter paper was recrystallized from benzene-Skelly C solvent (Norit). A dark solid eventually precipitated. Suction filtration and two washings with Skelly C solvent produced a semi-crystalline solid. All three crops of crystals were combined and recrystallized

from methanol, then from ethyl alcohol, 0.19g. Subsequent
recrystallizations from alcohol, Skelly C solvent (Norit),
Skelly C solvent, and alcohol gave 2-benzolyquinoline in fine
needles, m.p. 108.5-109.0°. (lit.[26] m.p.110-111°).

Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.38, H, 4.75; N, 6.01.
Found: C, 81.83; H, 4.65; N, 6.16.

A mixed m.p. with an authentic sample of 2-benzoyl-
quinoline, prepared by the method of Besthorn,[22] showed no
depression. (2-Benzoyl-quinoline is insoluble in 2-5% hydrochloric
acid and therefore appeared in the neutral rather than the amine
fraction. The use of 6N hydrochloric acid was used in subse-
quent runs with other Reissert compounds for the isolation of
such ketones.)

<u>Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with</u>
<u>Methylmagnesium Bromide. B.</u> Using the apparatus described in
the preceding reaction, 53 cc. (0.21 mole) of 4M methylmagnesium
bromide was added with stirring in ten minutes to a solution of
20g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I)
in 154 cc. of dioxane. The reaction was carried out as before,
but the temperature was controlled so that no dioxane vapor
reached the ether solution to cause precipitation of the Grignard
reagent. After vacuum distillation of the solvent and hydro-
lysis of the resulting dark residue with 40 cc. of saturated
ammonium chloride solution, the mixture was allowed to stand
overnight. To insure complete hydrolysis, 100 cc. of 2%
hydrochloric acid solution was then added and the supernatant

liquid decanted into a separatory funnel. The residue on the
flask was washed with four portions of ether, which was added
to the aqueous solution. About 10 cc. of 5% hydrochloric acid
was added to decrease the basicity of the aqueous layer. An
emulsion formed and broke up slowly. The aqueous layer, still
somewhat emulsified, was withdrawn, made just acid with 2% hydro-
chloric acid solution and then just basic with 5% sodium bicar-
bonate solution. The solution was then extracted with two fresh
portions of ether, which were added to the main ether solution.

The ether solution was extracted twice with 100 cc. portions
of 2% and twice with 100 cc. portions of 5% hydrochloric acid.
The combined acid extract was then washed with a small portion
of ether, which was added to the main ether solution (A). On
making the acid solution basic with 10% sodium hydroxide solution,
a fairly sharp color change from red to yellow was noted at the
end point. Filtration and thorough drying of the resulting pre-
cipitate gave 9.5g. (49.1% crude yield) of methylphenyl-2-
quinolylcarbinol (XXVI). Attempted decolorization of the com-
pound with Norit from both 95% and absolute ethanol failed. On
slow recrystallization from an excess of absolute alcohol, 6g.
of the carbinol, m.p.93-98°, was obtained.

Because of the great losses on recrystallization, another
attempt at a chromatographic adsorption was made under essentially
the same conditions as described in the preceeding reaction.
Again no significant separation was accomplished, but all the
carbinol was recovered.

The 6g. of carbinol was recrystallized from Skelly C solvent, and, combined with some additional crystals obtained from the mother liquors, 4.7g. (24.3% refined yield), of methylphenyl-2-quinolylcarbinol (XXVI), m.p.101.5-102.9°, was obtained.

The alkaline aqueous mother liquor from which the methylphenyl-2-quinolylcarbinal had been obtained was concentrated by vacuum distillation to less than one-third of its original volume. The very small amount of crystals which slowly precipitated was filtered, dried, and washed with hot alcohol, then hot ether to remove organic material. The insoluble portion was washed with water to remove any inorganic salts, and the residue was combined with the residue obtained by evaporation of the solvents used in the initial alcohol-ether washing. The compound was recrystallized from absolute ethanol. The mother liquor subsequently gave additional crystals. All of the nearly white needles were combined. The substance possessed a m.p. of 190-192°. On the basis of the combustion analysis, one can guess that the solid material is a mixture of the acid and amide corresponding to the original Reissert compound (I).

Anal. calcd. for the amide, $C_{17}H_{14}N_2O_2$, and the acid, $C_{17}H_{13}NO_3$:

$C_{17}H_{14}N_2O_2$--C, 73.36; H, 5.07; N, 10.07.

$C_{17}H_{13}NO_3$---C, 73.11; H, 4.69; N, 5.02.

Found ------C, 73.22; H, 4.56; N, 8.09.

The main ether solution (A) was extracted three times with 17cc. portions of 5% sodium bicarbonate solution.

Acidification of the alkaline solution and filtration produced about 0.1g. of brown material which was not further investigated.

Evaporation of the main ether solution, after drying over anhydrous sodium sulfate, gave 5-10 cc. of thick, dark oil. Recrystallization of this oil from benzene-Skelly C solvent left as an insoluble residue 0.04g. of a brown powder, m.p. 303-306°. Attempted purification and identification of this compound failed. A small amount of what is possibly the starting Reissert compound (I), m.p.137-147° after two recrystallizations from Skelly C solvent, was isolated from the benzene-Skelly C solvent mother liquor.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I)
with Methylmagnesium Bromide. C. Into a 1000cc. three necked flask provided with a sealed mechanical Hershberg stirrer, dropping funnel (self-compensating), and a reflux condenser connected through a drying tube filled with sodium hydroxide pellets to a nitrogen supply, was introduced 20g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile(I). After the compound was dissolved in 150 cc. of dry dioxane, 50 cc. (0.20 mole) of 4M methylmagnesium bromide (commercial reagent in dry ether) was added in the course of 10 minutes, with efficient mechanical stirring, the mixture turning a deep red color and becoming quite warm. Stirring was continued for fifty minutes more, the last thirty minutes with mild heating on a steam bath. After standing at room temperature for about an hour, the dioxane and any residual ether were distilled _in vacuo_. The residual dark brown cake was broken up, 100 cc. of ether added, and the

yellow suspension hydrolyzed with 32 cc. of saturated ammonium
chloride solution, stirring being continued through. After the
yellow precipitate had settled, the clear, deep red-brown ether
solution was decanted and the residue washed with three additional
portions of ether. The combined ether solution was filtered
and extracted four times with 100cc. portions of 5% hydrochloric
acid, the first extract being deep red, the others lighter. The
combined acid extracts were washed once with ether, which was
then added to the main ether solution (A), this in turn was
washed with saturated sodium chloride solution, which was added
to the acid extracts. The acid solution, made basic with con-
centrated sodium hydroxide solution, gave, on filtration and
vacuum drying, 11.3g. (59%) of crude methylphenyl-2-quinolyl-
carbinol (XXVI), m.p. 80-102°. Several recrystallizations from
alcohol and Skelly C solvent gave 5.8g. (29%) of XXVI, m.p.102-
103°. Evaporation of the main ether solution (A), after drying
over "Drierite," (anhydrous calcium sulfate) gave 6g. of a dark
viscous oil, which partially crystallized on long standing.
Recrystallization of the crystalline portion from alcohol gave
0.2g. of the starting Reissert compound (I), m.p.149.8-152.0°.
A mixed m.p. with an authentic sample of 1-benzoyl-1,2-dihydro-
quinaldonitrile (I) showed no depression.

1-Benzoyl-1,2-dihydro-6-methoxyquinaldonitrile (XXVII).

The compound was prepared by the method of Gassmann and Rupe[5],
colorless prisms from alcohol, m.p.126-127.5° (lit.[5]m.p.127°).
The compound apparently exhibits dimorphism, as a rapidly ob-
tained m.p. was 96-99°, whereas a slow, careful m.p. determination

showed melting at 93-96°, resolidifying at 96-100°, and remelting at 126-127.5°.

Reaction of 1-Benzoyl-1,2-dihydro-6-methoxyquinaldonitrile (XXVII) with Methylmagnesium Bromide.

When 20g. (0.069 mole) of 1-benzoyl-1,2-dihydro-6-methoxyquinaldonitrile (XXVII) dissolved in 150 cc. of dry dioxane, was reacted with 50 cc. (0.20 mole) of methylmagnesium bromide in the same manner as described for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide, there was obtained 10.43g. (56.3% yield) of methylphenyl-2-(6-methoxyquinolyl)-carbinol (XXVIII), m.p. 74-84°. A recrystallization from Skelly C solvent-benzene (Norit) gave 4.67g. (24.3% refined yield) of the carbinol (XXVIII), m.p. 88.5-95°. Three additional recrystallizations from Skelly C solvent and five from alcohol brought the m.p. to 98.5-99.0°. Combustion analysis supported the proposed structure ,XXVIII .

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.01. Found: C, 77.55, 77.53; H, 6.80, 6.36; N, 5.45, 5.48.

The Picrate of Methylphenyl-2-(6-methoxyquinolyl)-carbinol

was prepared by the general method of Shriner and Fuson[29], yellow needles from alcohol, m.p. 174.5-175.4° after three recrystallizations from alcohol.

Anal. Calcd. for $C_{24}H_{20}N_4O_9$: C, 56.67; H, 3.97; N, 11.02. Found: C, 56.72, 56.80; H, 3.97, 3.93; N, 10.8, 10.7.

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II). The com-
pound was prepared by the method of Rupe and Frey,[15] prisms
from alcohol, m.p.123.5-125.4°, and from a second preparation,
m.p.125.2-126.1°. (lit.[2]m.p.125-126°.)

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II)
with Methylmagnesium Bromide. When 15g. (0.058 mole) of 2-
benzoyl-1,2-dihydroisoquinaldonitrile (II) in 115 ml. of dry
dioxane and 37.5 cc. (0.15 mole) of 4M methylmagnesium bromide
were reacted and the rearranged carbinol isolated in
essentially the manner described for the third reaction (C) of
1-benzoyl-1,2-dihydroquinaldonitrile(I) with methylmagnesium
bromide, an orange brown oil resulted. (Strict exclusion of
moisture and oxygen cannot be claimed here, however, as the
system twice had to be opened to the air briefly and a wire
ram inserted when dioxane vapors from the reaction vessel pre-
cipitated some of a Grignard reagent in the stopcock of the
dropping funnel.) Extraction of the oil with ether, drying of
the solution over "Drierite" and distillation of the ether gave
an oil, which, after 11 days standing, partially crystallized
to give 4.6g. (32% crude yield) of methylphenyl-1-isoquinolyl-
carbinol (XXIX). Recrystallization from alcohol gave 2.9g.
(20% refined yield) of pale yellow crystals, m.p.92.2-93.3°
(lit.[13]m.p. 93-95°).

Evaporation of the original ether solution, dried over
"Drierite," afforded 15.5g. of a deep orange liquid, which
still had the odor of dioxane. After standing 13 months,

9.5g. remained. Half of this was dissolved in ether and extract-
ed three times with 10 cc. of 6N hydrochloric acid solution. A
pale yellow solid began precipitating with the second extraction
and was filtered and washed with ether. The ether solution was
evaporated to dryness. The residual oil slowly crystallized and
was combined with the other precipitate. The other half of the
original oil treated in the same manner and all the precipitates
recrystallized from alcohol gave 1.8g.(12% recovery) of 2-benzoyl-
1,2-dihydroisoquinaldonitrile (II), m.p. 125.0-125.8°. A mixed
m.p. with an authentic sample of (II) showed no depression.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II)
with Methylmagnesium Iodide. To approximately 0.16 mole of
methylmagnesium iodide prepared from 3.55g. (0.16 mole) of
magnesium and 22.8g. (0.16 mole) of methyl iodide in 43 cc. of
anhydrous ether (dried over sodium), was added 44 cc. of dry
dioxane, a white paste precipitating immediately. A few small
pieces of unreacted magnesium were also present. The same
apparatus was used as in the preceding reaction.

A solution of 20g. (0.077 mole) of 2-benzoyl-1,2-dihydroiso-
quinaldonitrile (II) in 150 cc. of dry dioxane was slowly added
with stirring to the above suspension in 20 minutes. A
beautiful brick red color formed immediately, but no heat was
given off. After another 20 minutes stirring and 15 minutes
standing, the mixture was mildly heated on the steam bath for
about 15 minutes with stirring. It then stood at room tempera-
ture for 3 hours. A white granular solid settled out on the

sides of the flask. The liquid was nearly black. After distillation of the solvent in vacuo at 53-58°, a very dark brown syrup remained. Addition of 100 cc. of ether and a few minutes stirring gave a suspension in a pale yellow solution. The mixture was hydrolyzed by slow addition with stirring of 26 cc. of saturated ammonium chloride solution. A dark red-orange solution and bright yellow paste resulted. No sharp end point was noted. The supernatant ether was decanted and three ether washings of the residual solid added to it. The ether solution was extracted four times with 100 cc. portions of 5% hydrochloric acid solution and a fifth time with a 60 cc. portion. The combined acid extracts were made alkaline with 10% sodium hydroxide solution, a thin film of dark oil rising to the top. During the course of attempted separation in a separatory funnel, about 0.1g. of a dark oily solid precipitated. On ignition it melted but left a white ash; therefore, it was probably mainly inorganic material.

During and after the last acid extraction large amounts of light colored solid precipitated in the ether. Filtration gave 7.5g. of yellow powder, m.p. 115-119°. Evaporation of the ether followed by ice cooling and filtration gave 3g. of light brown powder, which was added to the preceding precipitate and the whole recrystallized from absolute alcohol. A total of 8.9g. of colorless crystals, m.p. 122-124°, was collected and identified as 2-benzoyl-1,2-dihydroisoquinaldonitrile (II), (44.5% recovery) by an undepressed mixed m.p. test.

1-p-Chlorobenzoyl-1,2-dihydroquinaldonitrile (XXX). The
compound was prepared by the method of McEwen and Hazlett,[6]
small prisms from alcohol, m.p. 140.4-142.5° and from a second
preparation, m.p. 140.2-141.4° (lit.[6] m.p.142-144°).

Reaction of 1-p-Chlorobenzoyl-1,2-dihydroquinaldonitrile
(XXX) with Methylmagnesium Bromide. After 15g. (0.051 mole)
of 1-p-chlorobenzoyl-1,2-dihydroquinaldonitrile (XXX) dissolved
in 110 cc. of dry dioxane had been reacted with 30 cc. (0.12
mole) of 4M methylmagnesium bromide in the same manner as in
the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile
(I) and methylmagnesium bromide, an emulsion formed on hydro-
lysis with 36 cc. of saturated ammonium chloride solution.
Neither excess ammonium chloride solution nor saturated sodium
chloride solution broke up the partial emulsion, so the entire
mixture was gravity filtered with considerable difficulty. A
clear ether solution was finally separated.

The deep red ether solution was extracted four times with
80 cc. portions of 5% hydrochloric acid solution. As the
fourth extract still gave heavy clouding on addition of sodium
hydroxide solution, a fifth extraction was made. The combined
acid extracts were washed with ether, which was added to the
main ether solution (A). This was washed with saturated
sodium chloride solution, which in turn was added to the acid
extracts. On making the solution alkaline with 10% sodium
hydroxide solution, a flocculent yellow precipitate appeared.
On standing it became an oil. The mixture was extracted three
times with ether. There was some trouble with an emulsion,

and the mixture was suction filtered, a small amount of inorganic
residue being left on the filter paper. Evaporation of the
ether solution, dried over "Drierite," left 3.73g. (25.9% crude
yield) of an oil containing methyl-p-chlorophenyl-2-quinolyl-
carbinol (XXXIII). There was no crystallization on standing,
even in ice. The oil was dissolved in Skelly C solvent, re-
fluxed for 10-12 minutes with Norit and filtered. On cooling
a red oil came down which did not crystallize even on 10 months
standing. Attempted recrystallization from both carbon tetra-
chloride and absolute ethanol failed.

After 5 months standing the original ether solution (A)
had evaporated, and a semi-solid mass had precipitated.
Suction filtration and washing with alcohol produced 1.4g.
(9.35% recovery) of 1-p-chlorobenzoyl-1,2-dihydroquinaldo-
nitrile (XXX), m.p. 140-142.8° after three recrystallizations
from alcohol. A mixed melting point with an authentic sample
of XXX showed no depression.

Methyl-p-chlorophenyl-2-quinolylcarbinol Picrate. Approxi-
mately 0.3-0.5g. of the red oil, methyl-p-chlorophenyl-2-
quinolylcarbinol (XXX) mentioned above, was converted to the
picrate by the general method of Shriner and Fuson[29]. A large
amount of yellow crystals precipitated together with a dark
solid mass. The entire mass was recrystallized from alcohol
and 1.3g. of product, m.p. 161.5-162° (shrinking and darkening
at 154°), was obtained. The compound was recrystallized twice
more from alcohol, m.p. 154.8-155.7°. The rest of the original

oil was converted to the picrate in the same fashion and again a mixture of yellow crystals,m.p. 150.8-152-6°, and a dark mass resulted. The dark portion formed mainly yellow crystals on one recrystallization from alcohol, m.p. 150-151.4°. A total of 2.45g. of picrate representing a 9.58% refined yield of methyl-p-chlorophenyl-2-quinolylcarbinol (XXXIII) was obtained. After six recrystallizations from Skelly C solvent-absolute ethanol, the m.p. was 155.3-156.2°.

Anal. Calcd. for $C_{23}H_{17}N_4O_8Cl$: C, 53.86; H, 3.34; N, 10.93; Cl, 6.91. Found: C, 54.33; H, 3.23; N, 10.8; Cl, 6.95.

1-Anisoyl-1,2-dihydroquinaldonitrile (XXXI). The compound was prepared by the method of Sugasawa and Tsuda[4], colorless crystals from alcohol, m.p. 106-117 (lit.[4] m.p. 120-120.5°) after four recrystallizations from alcohol. In a second preparation the m.p. was 118.6-119.8° after similar treatment.

Reaction of 1-Anisoyl-1,2-dihydroquinaldonitrile (XXXI) with Methylmagnesium Bromide. When 23g. (0.079 mole) of 1-anisoyl-1,2-dihydroquinaldonitrile (XXXI) dissolved in 160 cc. of dry dioxane was reacted with 50 cc. (0.20 mole) of 4M methylmagnesium bromide and the reaction mixture worked up in the same manner as described for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide, a small amount of dark viscous oil was obtained by gravity filtration of the alkaline amine fraction. After this

oil was recrystallized from alcohol and the inorganic residue
(ignition test left a residue) discarded 0.9g (4.11% crude
yield) of methyl-p-methoxyphenyl-2-quinolylcarbinol (XXXXIV)
remained. The compound was recrystallized from Skelly C solvent
(Norit) and 0.4g. (1.82% refined yield) obtained. Four more
recrystallizations from alcohol brought the m.p. to 122.2-123.0°.

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39, H, 6.14; N, 5.01.
Found: C, 77.16, 77.55; H, 5.74, 5.98; N, 5.95, 5.54.

The main ether solution remaining after the acid extractions
gradually evaporated in the course of three months, leaving a
semi-solid mass. The material was suction filtered, washed with
alcohol and then recrystallized from alcohol. A fine yellow
powder which did not dissolve in the hot alcohol was filtered,
0.045g., m.p. 182-188°. The material which was recrystallized
was combined with additional crystals obtained from the mother
liquor and the total amount recrystallized three times, (once
with Norit) from alcohol; 1.88g. (8.2% recovery) of 1-anisoyl-
1,2-dihydroquinaldonitrile (XXXI), m.p. 118.8-120.2° (lit.[4]
m.p. 120-120.5°), was obtained.

Reaction of 1-Anisoyl-1,2-dihydroquinaldonitrile (XXXI)
with Methylmagnesium Bromide in Boiling Xylene. To 100 cc. of
dry xylene in a 1000 cc. three necked flask equipped with a
sealed mechanical Hershberg stirrer, dropping funnel (self-
compensating) and condenser arranged for distillation was added
28 cc. (0.11 mole) of 4M methylmagnesium bromide (commercial
reagent in dry ether).when the temperature reached 70-80° the

ether began distilling, and the slow addition of 9.5g. (0.033
mole) of 1-anisoyl-1,2-dihydroquinaldonitrile (XXXI), dissolved
in 150 cc. of dry xylene, was commenced. An immediate reaction
took place with the formation of a deep red brown precipitate
and colored solution. The solution was refluxed for an additional
45 minutes after the 25 minutes required for the addition of the
Reissert compound (XXXI). The temperature was then 130°. The
entire reaction was carried out under a nitrogen atmosphere.

After cooling an hour the mixture was hydrolyzed with 27 cc.
of saturated ammonium chloride solution (160 cc. per mole of
magnesium) which was added slowly with stirring and additional
cooling. A clear red solution and a pasty yellow precipitate
formed.

The clear red solution was decanted and 50 cc. of xylene
used to wash the yellow precipitate was added to it. The solution
was extracted with four 100 cc. portions and one 60 cc. portion
of 5% hydrochloric acid solution. The slightly cloudy acid
extracts were filtered, washed with 45 cc. of xylene and filtered
again. The solution was now clear. The xylene solution (A)
was washed with saturated sodium chloride solution, which was
added to the acid extracts, which were now clear red-orange.
The acid solution was made basic with 10% sodium hydroxide
solution and the resulting mixture suction filtered with great
difficulty. The precipitate was washed with water. A total of
1.2g. of granular material (B) was obtained in addition to a
small amount of tarry material. This resinous material on
washing and recrystallization from absolute alcohol gave 0.35g.
(3.84% refined yield) of methyl-p-methoxyphenyl-2-quinolyl-
carbinol (XXXIV), m.p. 120-121° after one recrystallization from
alcohol.

The main xylene solution (A) was extracted twice with 100 cc. portions of 6$\underline{N}$ hydrochloric acid solution. A partially crystalline oil precipitated on making the acid extract alkaline with sodium hydroxide solution. Digestion in boiling absolute alcohol, in which this compound is very sparingly soluble, produced 0.3g. of a fine yellow powder, m.p. 202.5-206°. Two recrystallizations from ethyl acetate and one from benzene gave white crystals, m.p. 222.2-223.2°. The data from combustion analysis would support any of the following empirical formulas: $C_{12}H_{10}NO$, $C_{24}H_{19}N_2O_2$ or $C_{24}H_{20}N_2O_2$.

$\underline{Anal}$. Calcd. for $C_{12}H_{10}NO$, $C_{24}H_{19}N_2O_2$, or $C_{24}H_{20}N_2O_2$:

$C_{12}H_{10}NO$-------------C, 78.24; H, 5.47; N, 7.60.

$C_{24}H_{19}N_2O_2$-----------C, 78.45; H, 5.21; N, 7.62.

$C_{24}H_{20}N_2O_2$-----------C, 78.24; H, 5.47; N, 7.60.

Found----------C, 78.38; H, 5.40; N, 7.71.

Found----------C, 78.19; H, 5.19; N, 7.65.

What appears to be the same compound was also isolated in small quantity by recrystallization of the granular material,B. Recrystallization of the material, once from alcohol, twice from benzene and once from Skelly C solvent, gave a small amount of compound m.p. 218-219°.

Vacuum distillation of the main xylene solution (A) left 2-3 cc. of dark viscous material, which was not further investigated.

$\underline{\text{l-p-Toluyl-1,2-dihydroquinaldonitrile (XXXII)}}$. To 31.3g. (0.48 mole) of potassium cyanide dissolved in 200 cc. of water

and 20.8g. (0.16 mole) of Skraup quinoline in a 500 cc. three
necked flask equipped with a sealed mechanical Hershberg stirrer,
reflux condenser and dropping funnel, was added 49 cc. (0.32 mole)
of freshly distilled p-toluyl chloride in about 5 minutes, with
stirring. After 30 minutes of additional stirring the aqueous
solution was decanted, and the tan, taffy like solid was washed
with dilute hydrochloric acid solution and with water. The pre-
cipitate, now completely solid, was broken up and dried by
suction filtration. Washing with ether removed some of the
yellow color but great quantities of impurities were present
as shown by the abnormal yield (121%) and the wide m.p. range
89-111°.

Washing with ether dissolved nearly half of the material,
and the m.p. of the residue was 107-117°. Recrystallization
of small samples from alcohol and from benzene improved the
m.p. only slightly, but a test recrystallization from carbon
tetrachloride was quite successful. Two recrystallizations of
the entire product from carbon tetrachloride gave 18.5g. (42.3%)
of 1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII), m.p. 148-149.5°.
The melting point after a total of seven recrystallizations from
carbon tetrachloride was 149.5-150.2°.

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21.
Found: C, 78.25, 78.40; H, 5.28, 5.09; N, 10.3, 10.3.

Acid Cleavage of 1-p-Toluyl-1,2-dihydroquinaldonitrile

(XXXII). To a mixture of 4.45g. (0.0162 mole) of 1-p-toluyl-
1,2-dihydroquinaldonitrile (XXXII) and 3.25g. of 2,4-dinitro-

phenylhydrazine (0.0162 mole) in a 250 cc. Erylenmeyer flask
was added 97.5 cc. of 12$\underline{N}$ hydrochloric acid solution. The mix-
ture was heated and then allowed to stand at room temperature
for 52 hours. The mixture was then diluted with approximately
an equal volume of water, heated to boiling, suction filtered
and dried in an oven at 110°. The yield of p-tolualdehyde-2,
4-dinitrophenylhydrazone was 4.72g. (96.3%), m.p. 233-234.2°
(lit.[30] m.p. 235).

Quinaldic acid was isolated from the acid filtrate by
the same method as employed by Padbury and Lindwall[13] for the
isolation of isoquinaldic acid in the acid cleavage of 2-
benzoyl-1,2-dihydroisoquinaldonitrile (II). The yield of
quinaldic acid was 52.7%, m.p. 154° (lit.[1] m.p. 157°). A
mixed m.p. with an authentic sample of quinaldic acid showed
no depression.

Reaction of 1-p-Toluyl-1,2-dihydroquinaldonitrile (XXXII)
with Methylmagnesium Bromide. When 13.6g. (0.050 mole) of
1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII), dissolved in
130 cc. of dry dioxane, was reacted with 30 cc. (0.12 mole)
of 4M methylmagnesium bromide in the same manner as described
for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldo-
nitrile (I) with methylmagnesium bromide, only a very small
amount of dark oil separated from the alkaline amine fraction.
The acid extracts had not been as dark as usual. Unfortunate-
ly, up to two thirds of this product was inadvertently lost

before it could be weighed and the crude yield calculated. The portion saved, at least one third of the total, was very tarry and weighed, at most, 0.1g. An attempted recrystallization from absolute ethanol failed.

The main ether solution, after the dilute acid extraction, was extracted four times with 80 cc. portions of 6$\underline{N}$ hydrochloric acid solution. The initial addition of the 6$\underline{N}$ acid solution caused the precipitation of a large amount of semi-solid material which was insoluble in both excess acid solution and in ether. Attempted recrystallization from alcohol failed. The acid extracts were washed with ether and then made alkaline with sodium hydroxide solution. A small amount of dark resinous material (about 0.1g.) precipitated and was filtered. Recrystallization from absolute alcohol failed to give pure material.

After standing one month the ether had evaporated from the neutral fraction of the reaction mixture, and a semi-solid residue remained. A fairly well defined solid was obtained by filtering the residue with suction. The solid was digested with Skelly C solvent, and the supernatant liquid was decanted. The few crystals which appeared on cooling were not characterized. The insoluble residue was twice recrystallized from alcohol and then once from carbon tetrachloride. A total of 1.4g. (10.3% recovery) of 1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII) m.p. 144-148°, was obtained. A mixed m.p. with an authentic sample of 1-p-toluyl-1,2-dihydroquinaldonitrile (XXXII) showed no depression.

2-p-Chlorobenzoyl-1,2-dihydroisoquinaldonitrile (XXXVI).

To 74g. (1.14 mole) of potassium cyanide dissolved in 500 cc.
of water and 41.6g. (0.32 mole) of isoquinoline in a 1000 cc.
three necked flask equipped with a sealed mechanical Hershberg
stirrer, reflux condenser and dropping funnel, was added 122g.
(0.64 mole) of p-chlorobenzoyl chloride in 28 minutes with
stirring. After 45 minutes the stirring was discontinued and
the light colored granular material immediately suction filtered,
washed with water, then with large quantities of saturated
sodium bicarbonate solution, again with large amounts of water,
and finally suction dried. The dried material was exhaustively
extracted with ether and the solution dried over anhydrous
magnesium sulfate. Distillation of the ether left a brown oily
residue which appeared to contain a large amount of p-chloro-
benzoic acid. The residue was redissolved in ether and ex-
tracted with dilute sodium hydroxide solution. Evaporation of
the ether, after drying over anhydrous magnesium sulfate, left
a dark oil which slowly crystallized in an ice bath. A total
of 10.35g. (11% yield) of crude 2-p-chlorobenzoyl-1,2-dihydro-
isoquinaldonitrile (XXXVI), m.p. 129-134°, was finally obtained.
The compound appears to be very extensively decomposed by re-
crystallization from alcohol. The p-chlorobenzoic acid im-
purity can be removed fairly well by recrystallization from
benzene; the Reissert compound stays in solution and can be
precipitated by addition of Skelly B solvent. Recrystalliza-
tion from diisopropylether is effective, provided only a small

amount of the acid is present. By combining these methods a sample of completely purified 2-p-chlorobenzoyl-1,2-dihydroisoquinaldonitrile (XXXVI) was obtained, m.p. 155.2-155.8°.

<u>Anal</u>. Calcd. for $C_{17}H_{11}N_2OCl$: C, 69.27; H, 3.76; N, 9.51; Cl, 12.03. Found: C, 69.30; H, 3.60; N, 9.50; Cl, 12.04.

<u>Acid Cleavage of 2-p-Chlorobenzoyl-1,2-dihydroisoquinaldonitrile(XXXVI)</u>. To a mixture of 1g. (0.0034 mole) of 2-p-chlorobenzoyl-1,2-dihydroisoquinaldonitrile (XXXVI) and 0.667g. (0.0032 mole) of 2,4-dinitrophenylhydrazine in a 50 cc. Erylenmeyer flask was added 20 cc. of 12<u>N</u> hydrochloric acid solution. The mixture was heated and then allowed to stand at room temperature for 48 hours. The mixture was then diluted with approximately an equal volume of water, heated to boiling, filtered with suction, washed with boiling water and dried. After recrystallization from nitrobenzene there was obtained 0.80g. (50% yield) of p-chlorobenzaldehyde-2,4-dinitrophenylhydrazone, m.p. 267-268° (lit. m.p. 270°[31a], 265°[31b], 264°[31c]). No attempt was made to isolate any quinaldic acid.

<u>Attempted Preparation of 1-p-Toluyl-1,2-dihydroisoquinaldonitrile</u>. An attempt to prepare the compound by the method used by Rupe and Frey[15] for the unsubstituted isoquinoline Reissert compound failed. p-Toluic anhydride was the main product isolated. A very small amount of an impure neutral product was also obtained. It may possibly contain some of the desired isoquinoline Reissert compound.

Attempted Preparation of 1-p-Fluorobenzoyl-1,2-dihydro-
quinaldonitrile. An attempt to prepare the compound by the
method used by Rupe, Paltzer and Engel[14] for the unsubstituted
Reissert compound failed. The only product isolated from the
reaction mixture was potassium p-fluorobenzoate.

Attempted Preparation of 1-m-Fluorobenzoyl-1,2-dihydro-
quinaldonitrile. An attempt to prepare the compound by the
method used by Rupe, Paltzer and Engel[14] for the unsubstituted
Reissert compound failed. The only product isolated from the
reaction mixture was m-fluorobenzoic acid.

1-Acetyl-1,2-dihydroquinaldonitrile (XXXVII). The com-
pound was prepared by the method of Grosheintz and Fischer,[9]
colorless crystals form 50% alcohol, m.p. 94.5-95.5° (lit.[9]
m.p. 96-97°).

Reaction of 1-Acetyl-1,2-dihydroquinaldonitrile (XXXVII)
with Methylmagnesium Bromide. When 10g. (0.0505 mole) of 1-
acetyl-1,2-dihydroquinaldonitrile (XXXVII) dissolved in 74 cc.
of dry dioxane was reacted with 32 cc. (0.13 mole) of 4M methyl-
magnesium bromide (except for the use of a 500 cc. flask in
place of one of 1000 cc. capacity) a dark oil containing some
solid material in suspension was formed on making the dilute
acid extracts alkaline. The deep red to black color which
usually forms with the addition of the Grignard reagent did not
develop until the reaction mixture was heated on the steam
bath. The mixture was colored yellow until that time. The dark
oil which had formed was filtered by suction and the organic

portion dissolved in ether. There was a fair amount of inorganic residue. The aqueous filtrate was extracted with ether, and the two ether solutions were combined, dried over anhydrous magnesium sulfate and the ether evaporated. The dark oil which remained weighed 2.3g. The material did not form a picrate easily from either benzene or alcohol solution, but by dissolving the material in benzene and adding a saturated solution of picric acid in alcohol, following by boiling and then long standing under refrigeration, crystallization occurred. A yellow solid portion was mechanically separated from a dark oily portion and the two were purified separately. The dark portion, after repeated re-crystallization from benzene-absolute alcohol, chloroform-abso-lute alcohol, absolute alcohol, Skelly C solvent-absolute alco-hol, acetic acid and acetic acid-chloroform, finally gave 0.2g. (1.1%) of quinoline picrate, m.p. 201.4-202.4° (lit.[32] m.p. 203°). A mixed m.p. with an authentic sample of quinoline picrate showed no depression. The yellow portion was recrystallized from acetic acid and then from absolute alcohol-Skelly C sol-vent. Concentration of the mother liquor from this second recrystallization gave 0.3g. of a yellow-orange powder, m.p. 150.6-151.4°. (The expected dimethyl-2-quinolylcarbinol picrate melts at 110°[23].)

The ether solution of the reaction mixture remaining after the dilute acid extraction was extracted with four 50 cc. portions of 6$\underline{N}$ hydrochloric acid solution. The deep red acid extracts were washed with ether, which was added to the now

light yellow main ether solution. A small amount of dark oil separated when the acid solution was made alkaline with concentrated sodium hydroxide solution. This oil was extracted with ether, the solution dried over anhydrous magnesium sulfate, and the ether evaporated. The resulting oil, which crystallized on standing, was recrystallized, first from absolute alcohol and then from dilute aqueous alcohol. The few white crystals thus obtained melted at 97.6-102°, and therefore could not be 2-acetylquinoline, m.p. 47.5-48°,[24] 52°,[26] the carbinol, XXXVIII, m.p. 67°[23] or the starting Reissert compound, XXXVII, m.p. 96-97°.[9]

The main ether solution was dried over anhydrous magnesium sulfate and the ether evaporated. The small amount of oil that was left soon crystallized and was treated with Norit in benzene-Skelly C solvent and then filtered and the solvent removed under vacuum. The resulting oil was recrystallized three times from 50% alcohol and once from 95% alcohol. The compound then melted at 90-91°, but it was not impure 1-acetyl-1,2-dihydroquinaldonitrile (XXXVII) as the m.p. was depressed 7° in a mixed m.p. test.

The inorganic residue which was formed in the hydrolysis of the reaction mixture was dried and ground to a fine powder, then digested with benzene. The mixture was filtered and the benzene filtrate evaporated to dryness. Only an insignificant residue was left. The residue on the filter paper was dried and then dissolved in 5% hydrochloric acid solution. This red colored solution was extracted with ether, which was then dried

over anhydrous magnesium sulfate and evaporated to dryness. No

significant residue was left. The clear red acid solution was

made alkaline with sodium hydroxide solution and the resulting

precipitate was extracted with ether, which was dried over an-

hydrous magnesium sulfate and evaporated. No significant

residue was left. The alkaline mixture was then extracted with

benzene, which on evaporation left no significant residue.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with

Ethylmagnesium Bromide. After 20g. (0.077 mole) of 1-benzoyl-

1,2-dihydroquinaldonitrile (I),dissolved in 150 cc. of dry

dioxane, had been reacted with 70 cc. (0.21 mole) of ethyl-

magnesium bromide in the same manner as described for the

third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I)

with methylmagnesium bromide, 2-4g. of a dark oil separated

when the acid extracts were made alkaline with sodium hydroxide

solution. The mixture was filtered and the viscous oil re-

dissolved in ether, again extracted with 5% hydrochloric acid

solution and precipitated with sodium hydroxide solution. The

oil was extracted with benzene, and treated with Norit. The

filtered solution was extracted with 5% hydrochloric acid

solution and the oil precipitated with sodium hydroxide solution.

Only 1.5g. of material remained. Attempted recrystallization

of this material from Skelly C solvent-benzene, acetone and

absolute alcohol failed. Extensive working up of the oil by

digestion, recrystallization and fractional recrystallization

from ether, Skelly C solvent, benzene, Skelly C solvent-benzene

and alcohol, finally produced milligram quantities of two compounds. One appears to be a neutral compound (arising from decomposition or present initially as an impurity) of melting point 178-179.5°. The other compound, which is soluble in 5% hydrochloric acid solution, melts at 96-101°. Neither compound has been identified.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with Phenylmagnesium Bromide. A . To 0.18 mole of phenylmagnesium bromide, made by the method of Allen and Converse,[33] dissolved in 75 cc. of dry ether, was added 20g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I),dissolved in 140 cc. of dry dioxane, in ten minutes with stirring. The apparatus was the same as described for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide. An immediate reaction appeared to take place with the formation of a dark red-brown precipitate. Stirring was continued for 30 minutes without heating and for 30 additional minutes with mild heating on the steam bath. After standing two hours most of the solvent was removed under vacuum. Dry toluene was then added to help remove the last traces of dioxane and to prevent overheating the residue obtained. Severe frothing and bumping occurred when a vacuum was reapplied. The mixture was hydrolyzed with 40 cc. of saturated ammonium chloride solution after the addition of another 100 cc. of toluene. The partially emulsified mixture was gravity filtered and an ether washing of the solid residue was added to the toluene filtrate. The

ether-toluene solution (A) was extracted four times with 100 cc. portions of 5% hydrochloric acid solution. The acid extracts were made alkaline with 10% sodium hydroxide solution, and the aqueous mother liquor was decanted from the precipitated oil. This oil was reextracted with 5% hydrochloric acid solution and again precipitated with sodium hydroxide solution. The precipitate was filtered and digested with ether to remove the organic material. After evaporation of the ether and recrystallization from absolute ethanol, the m.p. of the crystalline material was 186-188.5°. The total amount of material was less than 0.04g.

The ether-toluene solution (A) was extracted with four 75 cc. portions of 5% sodium bicarbonate solution. Acidification of the combined extracts produced no precipitate.

The ether-toluene solution was filtered and distilled under vacuum leaving a thick dark oil as residue. After standing four weeks partial crystallization had occurred, and suction filtration separated 5g. of yellow solid, m.p. 131-170°, from 8.5g. of oil, which was discarded. As a result of multiple fractional crystallizations from alcohol, absolute alcohol and Skelly C solvent, small amounts of recovered Reissert compound (I) and 2-benzoylquinoline were isolated and identified by mixed melting point tests with authentic samples of the two compounds. A small amount of a third compound, white needles from absolute alcohol, m.p. 192-192.3°, was also isolated but not identified. A mixed m.p. with the compound of m.p. 186-188.5° isolated from the amine fraction showed no depression. Combustion analysis indicates an empirical formula of $C_{19}H_{14}NO$.

<u>Anal</u>: Calcd. for $C_{19}H_{14}NO$: C, 83.83; H, 5.18; N, 5.15. Found: C, 83.64; H, 5.12; N, 5.35.

<u>Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with Phenylmagnesium Bromide. B.</u> Using the apparatus described for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide, 55 cc. (0.18 mole) of 3.35 M phenylmagnesium bromide was added in 5 minutes with stirring to 18g. (0.069 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) dissolved in 150 cc. of dry dioxane. The solution became colored black and some heat was evolved. After 3-4 minutes the mixture was vigorously refluxed on a steam bath for one hour. All the ether distilled during the first half hour. After standing for 2 hours, the reaction mixture was worked up in the same manner as described for the third reaction (C) of I with methylmagnesium bromide. The ether solution of the reaction mixture was then extracted with three 100 cc. portions of 6<u>N</u> hydrochloric acid solution. On making the acid solution alkaline, a considerable quantity of oil separated and solidified. The precipitates from both the strong and weak amine fractions were fractionally recrystallized from alcohol, benzene or Skelly C solvent. Diphenyl-2-quinoly-carbinol (XLI) was obtained in 8.5% refined yield, m.p. 188.6-190.4° (lit.[34] m.p. 189°), mainly from the strong amine fraction. 2-Benzoylquinoline (XXV) was obtained in 4.0% refined yield, 107.8-108.4° (lit.[26] m.p. 110-111°), mainly from the weak amine fraction. A mixed m.p. with an authentic

sample of 2-benzoylquinoline prepared by the method of Best-horn[22] showed no depression.

The clear ether solution remaining from the acid extractions was dried over anhydrous calcium chloride and the ether evaporated. The 5.8g. of residual oil slowly crystallized to give, on filtration, 2.6g. of pale red powder. Three recrystallizations from alcohol gave 1.4g. of diphenyl, m.p. 67-68°. A mixed m.p. with an authentic sample of diphenyl showed no depression. That this product was present in the original Grignard solution was shown by hydrolyzing and working up an additional 55 cc. of the original commercial Grignard solution. An equivalent quantity of diphenyl, 2.2g., m.p. 66-67.8°, was obtained. A mixed m.p. with an authentic sample of diphenyl showed no depression.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II) with Phenylmagnesium Bromide. When 20g. (0.077 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II) dissolved in 150 cc. of dry dioxane was reacted with 57.5 cc. (0.193 mole) of phenylmagnesium bromide in the same manner as described for the second reaction (B) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with phenylmagnesium bromide, a crude yield of 11.9g. (49.8%) of diphenyl-1-isoquinolylcarbinol (XLII), m.p. 120-136°, was obtained from the weak amine fraction. The product was recrystallized from alcohol and 9.25g. of material (38.8% refined yield), m.p. 141-143.2°, was obtained. A sample was recrystallized three additional times from 95%

alcohol and once from absolute alcohol. The m.p. of this pure material was 143.2-143.6°.

<u>Anal</u>. Calcd.for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 85.00, 84.94; H, 5.59, 5.56; N, 4.18, 4.29.

On making the 6$\underline{N}$ hydrochloric acid extracts alkaline with sodium hydroxide solution, 2-4g. of oil precipitated. The mixture was filtered, and the oil was digested in ether. The ether solution was filtered, dried over anhydrous magnesium sulfate, and the ether evaporated. The resulting oil would not dissolve in Skelly B solvent, but was recrystallized from Skelly B solvent-absolute alcohol (Norit). The small amount of crystals formed (most of the material was an oil) was improved in appearance by boiling with Skelly B solvent-alcohol, in which it did not dissolve to any appreciable extent. Recrystallization from alcohol produced pale yellow mica-like plates, m.p. 137.5-139.0°. The compound, therefore, cannot be 1-benzoyl-isoquinoline, m.p.[26] 76-77°. A mixed m.p. with diphenyl-1-isoquinolylcarbinol (XVII) was depressed 16°.

The ether solution of the reaction mixture was twice extracted with 50 cc. portions of dilute sodium hydroxide solution and the alkaline extracts acidified. The resulting oil was extracted with ether, the solution dried over anhydrous magnesium sulfate, and the ether evaporated. A small amount of oil was left which had the characteristic odor of phenol and gave a positive ferric chloride test identical with that of a known sample of phenol. The compound was

assumed to be phenol formed by oxygenation of the phenyl-magnesium bromide.

The ether solution of the reaction mixture, on standing, gave 1.78g. of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II). Evaporation of the ether produced 4.5g. of crystals and 4.7g. of oil, which was discarded. The crystalline portion was twice fractionally recrystallized from alcohol and an additional 1.9g. of II was obtained. Another fraction of 0.8g. melted at 56-57°. This fraction was recrystallized from alcohol and the crystals obtained, 0.4g., were allowed to stand for three weeks. The melting point at that time was 122-126°. An additional re-crystallization from alcohol brought the m.p. to 124.2-125.8°. A mixed m.p. with an authentic sample of 2-benzoyl-1,2-dihydro-isoquinaldonitrile (II), showed no depression. Although the evidence is far from conclusive, it appears that the iso-quinoline Reissert compound (II) exists in two crystalline modifications, one melting at 126-127° and the other at 56-57°. None of the other samples of 2-benzoyl-1,2-dihydroisoquinaldo-nitrile (II) showed any depression in mixed m.p. tests with authentic samples of II. A total of 4.14g. (20.7%) of the starting material, II, was recovered.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with Mesitylmagnesium Bromide. To approximately 0.16 mole of mesityl-magnesium bromide, prepared by the method of R. Barnes,[35] in 130 cc. of dry ether, was added 70 cc. of dry dioxane. About

half of the ether was then removed by distillation. The apparatus was the same as that used in the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide. To this thick mixture was added in 38 minutes, with stirring, a solution of 18.8g. (0.072 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) in 160 cc. of dry dioxane, a dark red-brown color forming immediately. The reaction mixture slowly turned to a very dark red-brown solution, but little heat was evolved. Stirring was continued for 20 minutes without heating after the addition of the Reissert compound, and for 45 minutes more with heating by a radiant heater. After standing overnight, the solvent was removed under vacuum and the dark viscous residue hydrolyzed by addition of 40 cc. of saturated ammonium chloride solution with stirring. To insure complete hydrolysis, 70 cc. of 10% hydrochloric acid solution was then added with stirring. After cooling, 200 cc. of ether was added. The entire liquid portion was decanted and several ether washings of the resinous residue were made. All the solutions were combined, and the aqueous phase was separated and neutralized with 10% sodium hydroxide solution. The neutral aqueous solution was extracted four times with ether, which was added to the main ether solution. This ether solution was then extracted five times with 100 cc. portions of 5% hydrochloric acid solution. The combined acid extract was washed with ether, which was added to the main ether solution. Both the ether and the acid solutions were deep red. The acid solution was made alkaline with sodium hydroxide solution.

The small amount of precipitate thus formed was filtered and digested with ether and alcohol, then filtered again. The inorganic residue was discarded. Evaporation of the solvent left approximately 0.1g. of semi-solid material, which, after repeated recrystallization from Skelly C solvent and absolute alcohol, melted at 107.5-109°. A mixed m.p. with an authentic sample of 2-benzoylquinoline showed no depression.

The main ether solution was extracted three times with 75 cc. portions of 5% sodium bicarbonate solution. The combined alkaline extracts were washed with ether and then acidified with 5% hydrochloric acid solution. A clear solution resulted.

The main ether solution was washed with water, dried over anhydrous sodium sulfate, and the ether evaporated. Vacuum distillation of the residual oil gave 4.7g. of colorless mesityline, b.p.$_{30}$ 152-169°. The semi-solid distillation residue was placed under Skelly C solvent and left standing for two months. Filtration with suction of this material gave an oily dark red-brown solid. Repeated attempts at purification by recrystallization from Skelly C solvent-benzene, Skelly C solvent and alcohol gave small amounts of crystalline material. These were combined and recrystallized several times from alcohol. Less than 0.2g. of 1-benzoyl-1,2-dihydroquinaldonitrile (I), m.p. 149-151° was obtained. A mixed m.p. with an authentic sample of 1-benzoyl-1,2-dihydroquinaldonitrile (I) showed no depression.

An attempt to isolate any ketones which might have been

present in the noncrystalline portion of the neutral fraction was made by use of Girard's "T" reagent.[36] The results indicated that no ketones were present.

An attempted chromatographic separation of the compounds present in the mixture, using dry benzene as the solvent and Fisher Adsorption Alumnia, 80-200 mesh, as adsorbent, failed.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with Mesitylmagnesium Bromide in Boiling Xylene. To 20.0g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) dissolved in 250 cc. of p-xylene, dried over sodium, was added 110 cc. (0.138 mole) of filtered 1.25 M mesitylmagnesium bromide, prepared by the method of R. Barnes[35] and analyzed by the method of Fieser,[37] in 13 minutes with stirring. The apparatus was the same as described for the reaction of 1-anisoyl-1,2-dihydroquinaldonitrile (XXXI) with methylmagnesium bromide in boiling xylene. The reaction was carried out under a nitrogen atmosphere. The temperature at the time of the initial addition of the Grignard reagent was 80°. After 45 minutes the temperature was 129°. When the temperature reached 134°, the apparatus was modified for refluxing, which was continued for an hour and 15 minutes. The total time of heating of the reaction mixture was two hours. After cooling the reaction mixture for an hour, the 135 cc. of distillate was added to it together with 400 cc. of ether. The mixture was hydrolyzed with 26 cc. of saturated ammonium chloride solution. The deep red ether-xylene solution was filtered, and several

ether washings of the solid residue were added to this solution.
The solution was extracted with two 100 cc. portions of 5% hydro-
chloric acid solution. The initial addition of the acid caused
the precipitation of a dark oil (A). On making the acid extract
alkaline with sodium hydroxide solution, an oil separated and
was extracted with ether. After drying over anhydrous calcium
sulfate, the ether was evaporated and 2.87g. (29% crude yield)
of quinoline was obtained. The impure product was converted to
the picrate by the general procedure given by Shriner and Fuson[29]
and purified by digestion in hot alcohol and recrystallization
from chloroform. A total of 2.57g. (9.31% refined yield) of
quinoline picrate, m.p. 199.3-200.6° (lit.[32] m.p. 203°) was
obtained. A mixed m.p. with an authentic sample of quinoline
picrate showed no depression.

The ether-xylene solution was extracted five times with
100 cc. portions of 6 N hydrochloric acid solution. The com-
bined acid extract was washed twice with ether saturated with
6N hydrochloric acid solution. The ether was added to the
ether-xylene solution, which was washed with saturated sodium
chloride solution. This solution was added to the acid
extract, which was made alkaline with concentrated sodium
hydroxide solution. The initial addition of base caused an
oil (B) to precipitate and adhere to the sides of the flask.
The mixture was filtered and the tarry residue on the filter
paper recrystallized from absolute alcohol. The small amount
of gray powder thus obtained was digested with ether and filter-
ed. The residue was totally inorganic and was discarded.

Evaporation of the ether from the filtrate and recrystallization of the residue from absolute alcohol gave a very small amount of 2-benzoylquinoline, m.p. 108-108.8°. A mixed m.p. with an authentic sample of 2-benzoylquinoline made by the method of Besthorn[22] showed no depression.

The ether-xylene solution was dried first over anhydrous calcium chloride then over anhydrous calcium sulfate. The solvent was removed under vacuum, and 14g. of dark, viscous, aromatic oil was obtained as a residue. Several months standing in a vacuum desiccator did not produce crystallization.

The precipitate (A) which formed during the initial acid extraction, adhered to the separatory funnel throughout all the extractions and was finally dissolved in chloroform. This solution was extracted with 10 cc. of 6N hydrochloric acid solution, which gave a small amount of inorganic material when made alkaline with sodium hydroxide solution. The chloroform was evaporated and the dark residual oil digested in hot Skelly C solvent. This treatment gave a very dark amorphous solid. Attempts at recrystallization from absolute alcohol, alcohol-water, dioxane, benzene, carbon tetrachloride, ethyl acetate, diisopropylether, diisopropylether-chloroform, nitrobenzene, bromobenzene, acetic anhydride, chloroform-ether, acetone, acetone-water, pyridine and pyridine-water all failed. The material appears to have a melting point of about 134-150°. A portion of the material was refluxed with concentrated hydrochloric acid containing 2,4-dinitrophenylhydrazine for several hours, but only the starting material was isolated from the

reaction mixture. No amines were formed. Similar results were obtained on an attempted alkaline cleavage with sodium hydroxide in 70% alcohol solution, followed by treatment with nitrobenzene.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with Methylmagnesium Chloride.

When 20g. (0.077 mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I), dissolved in 150 cc. of dry dioxane, was reacted with 75 cc. of 2.5M methylmagnesium chloride in the same manner as described for the third reaction (C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium bromide, there was obtained 9.5g. (49.5% crude yield) of thoroughly dried methylphenyl-2-quinolylcarbinol (XXVI), m.p. 89-100°. Two recrystallizations from Skelly C solvent (once with Norit) and two recrystallizations from alcohol gave 5.8g. (30% refined yield) of methylphenyl-2-quinolylcarbinol (XXVI) m.p. 101-103° (lit.[27] m.p. 100°).

After 12 months standing the ether had evaporated from the neutral fraction and a semi-solid residue remained. A portion of this material dissolved on treatment with hot Skelly C solvent, which was decanted and cooled. About 1.5g. of oil came down. Two recrystallizations from Skelly C solvent (once with Norit) and two recrystallizations from alcohol gave 0.4g. of 2-benzoylquinoline, m.p. 104-106.5° (lit.[26] m.p. 110-111°). A mixed m.p. with an authentic sample of 2-benzoylquinoline prepared by the method of Besthorn[22] showed no depression.

That portion of the original semi-solid residue which was insoluble in Skelly C solvent was fractionally recrystallized

from absolute alcohol. Concentration and recrystallization of
the various fractions and their mother liquors from alcohol
finally produced a small amount of Reissert compound (I), m.p.
148-150°. A mixed m.p. with an authentic sample of I showed
no depression. Another compound, m.p. 226-230°, was also iso-
lated but was not investigated further.

Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with
Methylmagnesium Iodide. When 0.16 mole of methylmagnesium
iodide was prepared and reacted with 20g. (0.077 mole) of
1-benzoyl-1,2-dihydroquinaldonitrile (I) in the same manner
as described for the reaction of 2-benzoyl-1,2-dihydroiso-
quinaldonitrile (II) and methylmagnesium iodide, there was
obtained 4g. (21.4% crude yield) of methylphenyl-2-quinolyl-
carbinol (XXVI). Two recrystallizations from Skelly C solvent
(once with Norit) gave 2.47g. (12.9% refined yield) of the
carbinol, XXVI, m.p. 100.5-102.5° (lit.[27] m.p. 100°).

The ether solution of the reaction mixture was extracted
with 60 cc. of 6N hydrochloric acid solution. On making the
solution alkaline with sodium hydroxide solution, 0.1-0.2g.
of tarry material precipitated. An ignition test indicated
that it was mainly inorganic.

Evaporation of the ether solution gave 7.5g. of solid
in addition to 3.5g. of an oil which was discarded. A re-
crystallization from alcohol gave 5.5g. (27.5% recovery) of
impure Reissert compound (I), m.p. 139-148°.

<u>Reaction of 1-Benzoyl-1,2-dihydroquinaldonitrile (I) with</u>

<u>Methylmagnesium Bromide in a 1:1 Mole Ratio.</u> When 20g. (0.077

mole) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) dissolved in

150 cc. of dry dioxane was reacted with 20 cc. (0.08 mole) of

4M methylmagnesium bromide (a 1:1 mole ratio of reactants) in

the same manner as described for the third reaction (C) of 1-

benzoyl-1,2-dihydroquinaldonitrile (I) with methylmagnesium

bromide, there was obtained only about 0.1g. of crude product,

of which a considerable portion was inorganic.

The initial addition of 5% hydrochloric acid solution to

the ether solution of the reaction mixture caused the pre-

cipitation of a dark oil, which later was dissolved in abso-

lute ethanol and benzene. This very dark solution was re-

fluxed with Norit for ten minutes, then filtered and the

solvents removed under vacuum, leaving a few cc. of dark oil.

The oil was treated with dilute sodium hydroxide solution and

extracted with ether, which was dried over "Drierite" and

evaporated. Approximately 1 cc. of dark oil remained. , After

standing six months, partial crystallization had occurred.

The material was filtered with suction and treated with Norit

in benzene solution. It still remained very impure. No

further investigation was made.

The main ether solution, dried over "Drierite", was evapo-

rated, leaving 8-10 cc. of a very dark oil. An attempt was

made, using the method of Girard[36] to separate a ketonic

fraction. Most of the material precipitated when the original

absolute alcohol-acetic acid solution of Girard's "T" reagent
and the neutral oil, after 90 minutes refluxing, was poured into
a mixture of sodium carbonate, ice and water. This dark
material had a m.p. of about 111-119°. It was not further in-
vestigated. Evaporation of the final ether solution of the
ketonic fraction gave no significant residue.

Attempted Chromatographic Separation of Methylphenyl-2-
(6-methoxyquinolyl)-carbinol Picrate and Methyl-p-chlorophenyl-
2-quinolylcarbinol Picrate. A mixture of the two picrates
was dissolved in an excess of chloroform, and attempts were
made to separate them by chromatographic adsorption on Fisher
Adsorption Alumnia, 80-200 mesh, using absolute alcohol as a
developer. Attempts at a chromatographic separation on starch
using chloroform alone and on anhydrous magnesium sulfate
using absolute alcohol as a developer were also without success.

6-Methoxyquinoline Picrate. The compound was prepared from
6-methoxyquinoline by the general method of Shriner and Fuson[29].
The m.p. of the crude material which formed in yellow needles
was 214-215° (uncor.).

Reaction of 1-Benzoyl-1,2-dihydro-2-methoxyquinaldo-
nitrile (XXVII), 1-p-Chlorobenzoyl-1,2-dihydroquinaldonitrile
(XXX) and Methylmagnesium Bromide. After 8.50g. (0.0293
mole) of 1-benzoyl-1,2-dihydro-6-methoxyquinaldonitrile (XXVII)
and 17.07g. (0.0588 mole) of 1-p-chlorobenzoyl-1,2-dihydro-
quinaldonitrile (XXX), dissolved in 200 cc. of dry dioxane,

had been reacted with 60 cc. (0.24 mole) of 4M methylmagnesium
bromide in the same manner as described for the third reaction
(C) of 1-benzoyl-1,2-dihydroquinaldonitrile (I) with methyl-
magnesium bromide, a dark oil precipitated when the 5% acid
extracts were made alkaline with sodium hydroxide solution.
After the oil had been extracted with ether and the ether
evaporated, 5g.of dark oily residue remained. Without
thorough drying, the oil mixture was converted to the corres-
ponding picrates by the general method of Shriner and Fuson.[29]
The resulting oil was recrystallized from alcohol and 1.14g.
of yellow crystals was obtained in addition to a greater
quantity of dark oil. The yellow crystals were digested in
chloroform, and the resulting mixture was filtered. The
chloroform was evaporated from the filtrate and the residual
solid three times recrystallized from alcohol. A very small
amount of dark colored crystals, which gave a negative Beil-
stein test for halogen and melted at 178.5°, was obtained. A
mixed melting point with an authentic sample of methylphenyl-
2-(6-methoxyquinolyl)-carbinol picrate, m.p. $174.5-175.4^{\circ}$,
showed a depression of $10-13^{\circ}$. The compound also could not be
the picrate of methylphenyl-2-quinolylcarbinol (XXVI), m.p.
169°,[27] or of 6-methoxyquinoline, m.p. $214-215^{\circ}$ (uncor.). The
material which did not dissolve during the chloroform digestion
was fractionally recrystallized from alcohol. Recrystalliza-
tion of the first fraction from chloroform gave a small amount
of quinoline picrate, m.p. $195-200^{\circ}$ (lit.[32] m.p. 203°). A

mixed m.p. with an authentic sample of quinoline picrate
showed no depression. Fractional recrystallization of the
second fraction from ligroin-absolute alcohol gave from its
second fraction a material with a m.p. of 140.5-141.5° (un-
cor.). A mixed m.p. with an authentic sample of the picrate
of methyl-p-chlorophenyl-2-quinolylcarbinol (XXXIII), m.p.
155.3-156.2°, melted at 145-146° (uncor.). This suggests that
the two compounds are the same. Attempts at further puri-
fication failed.

The ether solution of the reaction mixture was extracted
twice with 100 cc. portions and once with a 75 cc. portion of
6N hydrochloric acid solution. The initial addition of the
6N acid caused the precipitation of a dark viscous oil, which
did not dissolve in either the ether or the acid during the
rest of the extractions. The combined acid extracts were
washed with ether, which was added to the main ether solution.
This solution was then washed with saturated sodium chloride
solution, which was added to the acid solution. On making this
solution alkaline with concentrated sodium hydroxide solution
and filtering, 1.2g. of slightly oily solid was collected.
Five recrystallizations from alcohol gave a small quantity of
white needles, m.p. 129.8-130.1°, of what may be 2-p-chloro-
benzoylquinoline (XLIX). Data from combustion analysis is in
fair agreement with the proposed structure, XLIX.

Anal. Calcd. for $C_{16}H_{10}NOCl$: C, 71.78; H, 3.77; N, 5.23.
Found: C, 72.55; H, 3.68; N, 5.09.

Multiple fractional recrystallizations of the residual material from alcohol and Skelly C solvent produced, besides additional quantities of the compound m.p. 129.8-130.1°, a very small amount of white needles, m.p. 175-176° (uncor.). The compound has not been identified.

Evaporation of the main ether solution, after drying over anhydrous magnesium sulfate, left 9.25g. of a dark oil, which soon formed a very viscous tar.

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II). Prepared by the method Padbury and Lindwall.[13]

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II), Benzaldehyde and Hydrochloric Acid. From 10.0g. of II, 15g. of benzaldehyde and 50 cc. of concentrated hydrochloric acid, there was obtained 1.34 g. (9.5%) of benzoin isoquinaldate, m.p. 152.8-153.0°, 2.88g. (21.5%) of 2-(1'-isoquinolyl)-4,5-diphenyloxazole (XVI), m.p. 124-125° and 0.30g. (4%) of benzoin.[16]

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II) with Hydrochloric Acid. To 10.00g. of II was added 50 cc. of concentrated hydrochloric acid, with mechanical stirring, in the course of 45 minutes. The stirring was continued another two hours, and then the mixture was allowed to stand 20 hours. The mixture was made neutral by addition of 10% sodium hydroxide solution, then steam-distilled until all the benzaldehyde had been removed. The residual solution was made basic by addition of sodium hydroxide solution, and a red insoluble

oil was taken up in ether, dried over anhydrous sodium sulfate and treated with decolorizing charcoal. Evaporation of the ether afforded 1.43g. of a yellow-brown solid, m.p. 83-115°. Since the components of this mixture have been previously reported,[16,2] no further attempt at purification of the mixture was made.

Reaction of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II), Benzoin and Hydrochloric Acid. To 10,00g. of II, intimately mixed with 10.00g. of benzoin, was added 50 cc. of concentrated hydrochloric acid with mechanical stirring in the course of 45 minutes. The stirring was continued another two hours, and then the mixture was allowed to stand for 20 hours. The mixture was diluted by addition of 100 cc. of water and extracted with 500 cc. of ether. An orange solid, insoluble in either layer, was filtered off. A combination of extraction procedures, using 25% hydrochloric acid and benzene, and a fractional crystallization of the basic fraction, from ethanol, afforded the following substances from the orange solid: 0.60g. of benzoin isoquinaldate (XIV), m.p. 152-153°; 0.70g. of 2-(1ᴸ isoquinolyl)-4,5-diphenyloxazole (XVI), m.p. 124-125°; 0.41g. of isoquinaldamide, m.p. 170-171° (lit.[2] 168-169°); and 0.30g. of an impure amine, m.p. 157-175°. The known substances above, on mixed m.p. determinations with authentic samples, showed no depressions.

From the ether and benzene extracts and also from the fractional crystallization, there was recovered 9.35g. of benzoin. About 1.0g. of gummy material remained after the

various separation procedures had been carried out, and this
resisted further purification.

Properties of 2-(1'-Isoquinolyl)-4,5-diphenyloxazole (XVI).
The substance forms insoluble salts with dilute hydrochloric
and sulfuric acids, the hydrochloride decomposing at 192-195°
and the sulfate at 212-215°. The base is soluble in ethanol
at room temperature to the extent of about 2g./l. The sub-
stance does not absorb hydrogen at one atmosphere pressure over
Adams catalyst at room temperature.

Isoquinaldonitrile. Prepared from II by the method of
Kaufmann and Dandliker.[11]

Reaction of Isoquinaldonitrile, Benzoin and Hydrochloric
Acid. A mixture of 0.70g. of isoquinaldonitrile, 0.97g. of
benzoin, and 30 cc. of concentrated hydrochloric acid was
allowed to stand at room temperature for 20 hours. The mix-
ture was diluted to 125 cc. and filtered, 0.93g. (96%) of
the benzoin being recovered unchanged.

Hydrolysis of 2-(1'-Isoquinolyl)-4,5-diphenyloxazole
(XVI). To 40 cc. of 25% sulfuric acid solution was added
2.00g. of XVI, and the mixture of yellow solid and solution
was refluxed for one week. Some solid material which had
steam-distilled into the condenser was washed down with water,
and the mixture was extracted with ether. Some solid remained
undissolved in either layer. The ether solution was

washed with sodium bicarbonate solution (no organic acid obtained on acidification), then dried over anhydrous sodium sulfate. Evaporation of the ether afforded 0.07g. (6%) of benzoin, m.p. 132-134° after one crystallization from ethanol. A mixed m.p. with an authentic sample of benzoin showed no depression.

The acid layer containing the yellow solid was made basic with sodium hydroxide solution. The mixture of solid and solution was extracted with ether, the solid dissolving in the ether. Evaporation of the ether, dried over anhydrous sodium sulfate, gave 1.70g. (85%) of the starting material, m.p. 124-125° after one crystallization from ethanol.

The alkaline solution was made faintly acid with acetic acid. Addition of a saturated solution of copper acetate with heating on the steam-bath caused a blue-green precipitate to form. This was filtered, washed with distilled water and then decomposed by means of hydrogen sulfide. The copper sulfide was filtered and washed with hot water. Evaporation of the combined filtrate and wash afforded 0.05g. (5%) of isoquinaldic acid, m.p. 161-162° (dec.), also in admixture with an authentic sample of isoquinaldic acid.

Attempted Preparation of 2-(1'-Isoquinolyl)-4,5,diphenyl-oxazole (XVI) from Benzoin Isoquinaldate (XIV). Using the procedure of Davidson, Weiss and Jelling[17] for the preparation of oxazoles, 0.35g. of benzoin isoquinaldate (XIV) m.p. 137-145°, 0.57g. of ammonium acetate hepta-hydrate and 4.75 cc. of glacial acetic acid were placed in a 10 cc. Erylenmeyer flask

equipped with a micro condenser, and the mixture was refluxed at 135° for one hour. The solution quickly turned yellow and considerably more than half of the solid dissolved. The mixture slowly turned dark, and after 30 minutes the entire solution was black. The cooled solution was poured into a small beaker, and 3.8 cc. of distilled water was added. After standing an hour, the mixture was filtered with suction and a small amount of yellow solid collected. (A considerable amount of dark oil was left in the beaker.) The yellow material was digested with hot absolute alcohol, a residue of 0.08g. of yellow solid, m.p. 186-188° (dec.), being left.

This material was mixed with sodium hydroxide solution and extracted with ether. A total of 400 cc. of ether was used, but little of the solid could be extracted. After filtering the aqueous mixture, 0.05 g. of dried solid was collected. The material darkened at 70-80° to such an extent that no accurate m.p. could be determined.

The aqueous mother liquor from the initial working up of the reaction mixture was made alkaline with ammonium hydroxide solution and allowed to stand for some time. A very small amount of a green precipitate came down and adhered to the sides of the flask. An attempted recrystallization from absolute alcohol failed.

The alkaline mother liquor was made just acid with dilute hydrochloric acid solution and heated to boiling. The addition of powdered copper sulfate immediately caused the formation of the characteristic blue color. No precipitate

was formed.

2-Methyl-4,5-diphenyloxazole. The compound was prepared by the method of Davidson, Weiss and Jelling[17] in 51% yield, b.p.$_8$ 193-196.5°, as compared to their 82% yield of product, b.p.$_{18}$ 210-213°.

SUMMARY

The rearrangement of Reissert compounds to quinoline-methanols by the action of Grignard reagents has been investigated. 1-Benzoyl-1,2-dihydroquinaldonitrile, 1-benzoyl-1,2-dihydro-6-methoxyquinaldonitrile and 2-benzoyl-1,2-dihydroisoquinaldonitrile were found to undergo the rearrangement in fair yield. Reissert compounds derived from p-substituted benzoyl chlorides did not undergo the rearrangement in as good yields as the unsubstituted compounds. 1-Acetyl-1,2-dihydroquinaldonitrile either did not undergo the rearrangement at all or went only in very small yield. Methylmagnesium halides appear to be the most satisfactory Grignards in this reaction, but phenylmagnesium bromide worked well at higher temperatures. Mesitylmagnesium bromide gave quinoline as the main product. Increased temperature does not appear to increase the yield of rearranged product in the reaction with methylmagnesium bromide. The effectiveness of the halide in the Grignard reagent appears to be in the order Cl > Br > I. The rearrangement has been observed

in benzene, dioxane and xylene. The mechanism of the rearrangement definitely involves the prior formation of 2-benzoylquinoline and appears to be intramolecular.

The yellow compound obtained in the reaction of 2-benzoyl-1,2-dihydroisoquinaldonitrile with hydrochloric has been investigated. On the basis of a molecular weight determination, the ultraviolet and visible spectra, the hydrolysis products, the oxidation products, and by analogy with other known substances, the compound has been assigned the structure of 2-(1'-isoquinolyl)-4,5-diphenyloxazole. An attempted independent synthesis of 2-(1'-isoquinolyl)-4,5-diphenyloxazole failed.

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