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Mechanisms of addition of organolithium compounds to quinoline and isoquinoline

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NOTE TO USERS

MECHANISMS OF ADDITION OF ORGANOLITHIUM COMPOUNDS TO QUINOLINE AND ISOQUINOLINE

by

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Iowa State College

1946

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I. INTRODUCTION

Of all organometallic compounds, the organoalkali compounds are the most reactive types known, the order of increasing reactivity being RLi, RNa, RK, RRb and RCs. Of these the organolithium compounds are the most useful in synthetic organic chemistry due to their ease of preparation and handling, as well as their freedom from toxicity. Furthermore, the organolithium compounds are not spontaneously inflammable when exposed to the atmosphere and may be obtained satisfactorily by procedures similar to those used for the preparation of Grignard reagents. From the preparative point of view RLi and RMgX compounds admirably supplement each other in the sense that RX compounds which will not form Grignard reagents frequently yield the corresponding organolithium compounds in good yield, and vice versa.

Certain very highly reactive types of organolithium compounds are capable of the halogen-metal interconversion reaction. The application of this reaction has led to the preparation of some reactive organometallic compounds which either could not be prepared by previously known methods, or heretofore could only be prepared with difficulty in highly unsatisfactory yields. Of greatest significance is the formation of RLi compounds from structures having otherwise reactive functional groups like -OH, -SH, NH_2, COOH, and >C=N-.

Broadly speaking, organolithium compounds show all the reactions of Grignard reagents. They differ, however, in their action toward an olefinic linkage. Certain organo-alkali compounds are capable of addition to this linkage while Grignard reagents are not. A second difference is brought out in the relative reactivity of Grignard reagents and organo-lithium compounds toward the cyclic ammono aldehyde ethers, pyridine, quinoline and isoquinoline; for Grignard reagents either do not add at all to the azomethine linkage of these heterocycles, or add with difficulty. Organolithium compounds, on the other hand, have been found to react with facility.

We have attempted to extend the applicability of these addition reactions to quinoline and isoquinoline by use of typical organolithium compounds, and organolithium compounds having otherwise reactive groups like $-NH_2$ and -SH. An effort has been made to throw some light on the possible course of these addition reactions. Because of the structural relation-ships to known antimalarial and antituberculous compounds, the series of compounds which were prepared was examined for pharmacological activity.

The preparation of derivatives of quinoline and isoquin-oline as therapeutic agents is of interest for several reasons. (1) The molecular structure of drugs now useful may be altered so as to become even more beneficial. Molecular structures designed after the pattern of useful or active drugs may lead to an improved chemotherapeutic agent. (2) Methods of prep-

aration of these compounds may be adapted by analogy to other types of syntheses. (3) The synthetic sequence involved in the preparation of a possible therapeutic agent may have theoretical value and other chemical applications. (4) Viewed from a theoretical aspect, such new compounds increase our knowledge concerning the complex relationship between molecular structure and physiological activity. (5) Incidental to specific testing for antimalarial and antituberculous activity, new chemotherapeutic agents showing activity toward other diseases may be evolved.

The investigations in this thesis describe the preparation of nitrogen- and sulfur-containing derivatives of quinoline and isoquinoline which may be useful in the manner outlined, especially in the treatment of malaria and tuberculosis.

These syntheses have been effected through the introduction of nitrogen- and sulfur-containing groups into (a) molecular structures possessed of pharmacological activity, and (b) molecular structures which as yet are not known to have any pharmacological activity, but which contain chemically active groups which are known by analogy to confer certain specific activity to given molecular structures.

In the course of these studies a new synthesis was developed which consisted of the addition of organolithium compounds to a cyclic ammono ketone ether such as 2-phenylquinoline. This resulted in the preparation of hitherto unknown types of compounds, namely, the 2,2-disubstituted-1,2-dihydroquinoline

derivatives. The mechanism of this reaction is discussed in the light of our experimental findings.

It is therefore the purpose of this dissertation to examine the mechanisms involved in the interaction of organolithium compounds with quinoline and isoquinoline examples of the cyclic ammono aldehyde and ketone ethers.

II. HISTORICAL

A. Relationship of Pyridine, Quinoline and Isoquinoline to the Ammonia System of Compounds

It soon becomes apparent upon perusal of the chemical literature that many theories which have long before been devised, or have in other ways acquired common acceptance as the result of the investigations of many workers, may be expressed in different terms. Thus, the explanation of the reactions of many nitrogen-containing compounds such as pyridine, quinoline and isoquinoline in terms of the ammonia system in many respects constitutes a restatement of fundamental theories pertaining to the aquo system of chemistry.

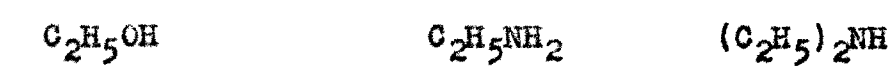
The similarity of the reactions of α- and γ-methylpyridines and α- and γ-methylquinolines to those of methyl ketones was recognized as long ago as 1901 in the work of Koenigs.[1] Since that time several workers, including Chichibabin,[2] and Mills and Smith,[3] have had occasion to remark on Koenigs' concepts. In several instances, pyridine, quinoline and isoquinoline have been referred to as cyclic Schiff bases

1. Koenigs, Ber., 34, 4322 (1901).
2. Chichibabin, ibid., 60, 1607 (1927).
3. Mills and Smith, J. Chem. Soc., 121, 2724 (1922).

with the implication that, like the latter, certain chemical properties may be found in common with the aldehydes and ketones of the aquo system.

A proper understanding of this viewpoint necessitates a brief explanation of the nitrogen or ammonia system of compounds as applied to this work.

The alkylamines may be considered to be alcohols of the ammonia system, for they are produced by the substitution of one or both hydrogen atoms of ammonia by an alkyl group, thus:



C_2H_5OH $C_2H_5NH_2$ $(C_2H_5)_2NH$

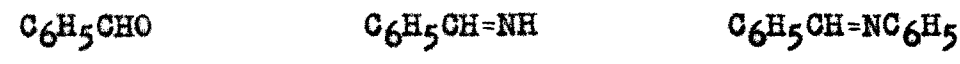
Primary aquo alcohol Primary ammono alcohols

When both hydrogen atoms of water are replaced by groups, an ether is formed; when all three hydrogens of ammonia are replaced, an ammono ether is obtained as follows:

$C_2H_5OC_2H_5$ $\begin{matrix} CH_3 & CH_3 \\ & N \\ & CH_3 \end{matrix}$

Aquo ether Ammono ether

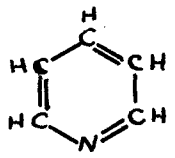
Since nitrogen is trivalent, whereas oxygen is divalent, then all aldehydes of the ammonia system are mixed compounds, as indicated below.



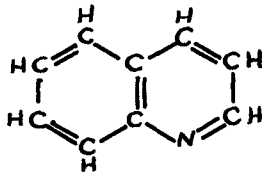
C_6H_5CHO $C_6H_5CH{=}NH$ $C_6H_5CH{=}NC_6H_5$

Aquo aldehyde Ammono aldehyde alcohol (benzylidenimine) Ammono aldehyde ether (benzalaniline)

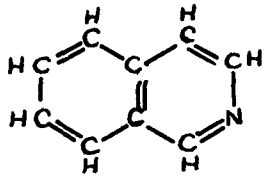
Many cyclic nitrogen compounds including pyridine, quinoline and isoquinoline may be regarded as cyclic ammono aldehyde ethers.



Pyridine



Quinoline



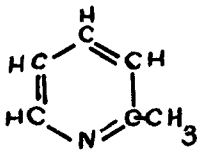
Isoquinoline

Ketones of the ammonia system arise as follows:

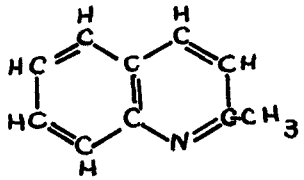
$(CH_3)_2CO$ $(C_6H_5)_2C{=}NH$ $(C_6H_5)_2C{=}NC_6H_5$

Aquo ketone (acetone)	Ammono ketone alcohol (benzophenonimine)	Ammono ketone ether (benzophenone anil)

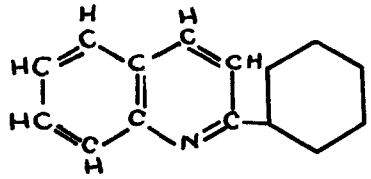
The following formulae are indicative of typical cyclic ammono ketone ethers.



2-Picoline



Quinaldine



2-Phenylquinoline

Of these three compounds, 2-picoline and quinaldine illustrate nitrogen analogs of a methyl ketone of the water system; while 2-phenylquinoline illustrates a phenyl ketone.

The action of a given organometallic compound toward pyridine, quinoline and isoquinoline (samples of cyclic ammono aldehyde ethers) would then appear to be comparable to its action on either open-chain ammono or aquo aldehydes. However,

these nitrogen heterocycles have the bond system of benzene and its homologs, with considerable attendant resonance energy.

Table 1

Resonance Energy

	Kilocalories per mole	
	[4a]	[4b]
Benzene	39	(56)
Pyridine	43	(54)
Naphthalene	75	(103)
Quinoline	69	(91)

4. (a) Pauling, "The Nature of the Chemical Bond", Cornell University Press, Ithaca, New York, 1939, pp. 128-131; (b) Wrinch, Science, 92, 79 (1940).

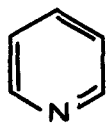
The first set of values in Table 1 have been taken from Pauling[4a] and those in parentheses from Miss Wrinch.[4b]

It will be seen from Table 1 that the resonance energy of a nitrogen heterocycle parallels rather closely that of its nearest carbocyclic analog. It would appear that pyridine, quinoline and isoquinoline would have a reactivity much less than that of the open-chain analogs of either the water or ammonia system where benzenoid resonance is absent.

B. The Action of Grignard Reagents on Pyridine, Quinoline and Isoquinoline

As a logical result of the known similarities between water and ammonia, Franklin[5a] and Strain[5b] have suggested that substances containing the azomethine grouping, -CH=N-, may be regarded as aldehydes of an ammonia system, comparable with aldehydes of the water system which contain the analogous grouping -CHO. The simplest aromatic representatives are the Schiff bases of which benzalaniline, $C_6H_5CH=NC_6H_5$, is an example. These are found to possess very distinct aldehydic properties.[5b,6]

If the Körner formula be correct for pyridine (I), there



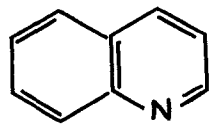
(I)

occurs the same -CH=N- group that is present in the Schiff bases, and that is characteristic of aldehydes of the ammonia system. Furthermore, all compounds containing a pyridine nucleus also partake of the nature of ammono aldehydes. Because of the remarkable stability of the six-membered ring

5. (a) Franklin, J. Am. Chem. Soc., 46, 2150 (1924); (b) Strain, ibid., 49, 1558 (1927).

6. (a) Busch, Ber., 37, 2691 (1904); ibid., 38, 1761 (1905); (b) Miller and Plöchl, ibid., 25, 2020 (1892).

with alternate double and single bonds, the aldehydic properties which one might expect these substances to demonstrate are suppressed. A comparison of the divergent properties of the stable and relatively saturated benzene and the typically unsaturated cyclohexadiene is in order. Further evidence of the stability of pyridine is indicated by the fact that pyridine is not appreciably attacked by hot concentrated sulfuric or nitric acid. Quinoline (II), however, may be oxidized to quinolinic acid by permanganate in alkaline solution resulting in destruction of the benzene ring, but retention of the more stable pyridine ring.



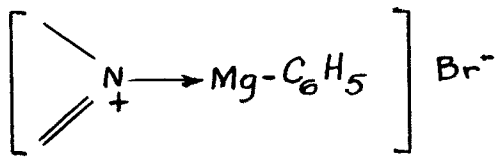
(II)

Because of these relationships it is possible that many of the familiar reactions of an aquo aldehyde may have their partially suppressed counterpart in the corresponding reactions of a cyclic ammono aldehyde such as pyridine, quinoline or isoquinoline.

The smooth addition of organometallic compounds to most aquo aldehydes and ketones is familiar. Evidence to be presented on the addition of organometallic compounds to ammono aldehydes and ketones supports this analogy. Furthermore, the idea of subordinated aldehydic properties due to stability of

the pyridine ring is emphasized by the action of Grignard reagents on these cyclic ammono aldehydes.

The first evidence of the interaction of an organometallic compound and a cyclic ammono aldehyde ether is that attributed to Oddo[7] who studied the action of the Grignard reagent on pyridine and quinoline in ether under ordinary conditions. Oddo found that addition compounds of low solubility were formed. His concept of these complexes with pyridine took the form $(2C_5H_5N + CH_3MgI + (C_2H_5)_2O)$ and $(2C_5H_5N + C_6H_5MgBr + (C_2H_5)_2O)$. According to Bergstrom[8] it is probable that the complexes take the following form, as in the partial formula (III).



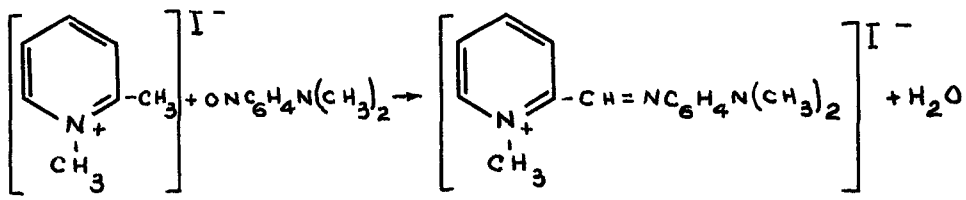
(III)

At least one pyridine molecule becomes attached to the Grignard reagent through the heterocyclic nitrogen by a coördinate bond. Thus it is seen that the nitrogen will bear a positive charge, and it is probable that this may exert some

7. (a) Oddo, Atti accad. Lincei, [V] 16, I, 538 (1907); (b) Oddo, Gazz. chim. ital., 34, II, 422 (1904); ibid., 37, I, 514 (1907); ibid., 37, I, 568 (1907); Reale accad. Lincei, [5] 13, II, 101 (1904).

8. Bergstrom, Chem. Rev., 35, 111 (1944).

activating effect on the reactions that follow in the same manner that the ketonic reactivity of 2-methylpyridine is increased by the formation of a quaternary salt of the type of the methiodide. For example, p-nitrosodimethylaniline will not condense with 2-methylpyridine under any conditions that have been tried. Despite this fact, in the presence of piperidine the compound will react with 2-methylpyridine methiodide with difficulty to form the methiodide of the p-dimethylaminophenyl anil of pyridine-2-aldehyde[9] thus:



Further evidence of the activating effect of quaternary salt formation is found in the work of Freund,[10] who studied the addition of Grignard reagents to pyridine methiodide, and other similar compounds. This reaction will be discussed later (see p. 15).

Oddo[7] found that under ordinary conditions the complex addition compounds were precipitated from the ether solution

9. Kaufmann and Vallette, Ber., 45, 1737 (1912); ibid., 46, 49 (1913).

10. Freund, ibid., 37, 4666 (1904); ibid., 42, 1101 (1909).

and that, on hydrolysis, the pyridine (or quinoline) was regenerated, together with the hydrocarbon corresponding to the Grignard reagent.

In another study the same author discovered that these Grignard reagent-pyridine complexes were capable of reaction with aldehydes of the aquo system, quite analogous to the reaction of the Grignard reagent alone.[11] Thus, in a typical experiment, benzaldehyde was added to a methylmagnesium iodide-pyridine complex to yield ∝-methylbenzyl alcohol upon hydrolysis. In this manner it was found that pyridine, while not undergoing any addition reaction, could form complexes of a type which would act as "carriers" of the Grignard reagent.

As a further outcome of his study, Oddo found that 2-phenylquinoline was formed by heating quinoline with benzene, phenyl bromide and magnesium.[7a] The yield was low. Because of this fact, and because he was not primarily concerned with the preparation of 2-arylquinoline types, this phase of the work was dropped. However, the reaction constituted the first addition of an organometallic compound to a cyclic ammono aldehyde ether.

Almost simultaneously Sachs and Sachs[12] reported addition compounds of quinoline and phenylmagnesium bromide, or ethylmagnesium bromide, of the type $C_9H_7N.RMgX$. The analyses did

11. Oddo, Gazz. chim. ital., 37 /2/, 356 (1907).

12. Sachs and Sachs, Ber., 37, 3091 (1904); ibid., 38, 1087 (1905).

not conform too well to the formulae suggested by them. As with Oddo,[7] quinoline was regenerated on hydrolysis.

In continuation of his work with Grignard reagents and their action on pyridine, Oddo prepared pyrrylmagnesium iodide which was obtained by the addition of pyrrole to methylmagnesium iodide. The magnesium compound so obtained formed an addition compound with pyridine, to which Oddo[13] assigned the following structure.

$$C_4H_4NMg{-}NC_5H_5$$
$$/\,INC_5H_5$$

(IV)

On carbonation, the complex yielded pyrrole-α-carboxylic acid in 25-30% yield.

A point of interest in connection with the action of the Grignard reagent on pyridine is found in Tanberg's study[14] of the use of pyridine as a solvent in the estimation of hydroxyl groups by means of alkylmagnesium halides, as recommended by Zerewitinoff.[15] Tanberg obtained over twice the theoretical volume of gas from α-naphthol and methylmagnesium iodide in pyridine. In investigating the action of carefully purified pyridine alone on methylmagnesium iodide, Tanberg found that

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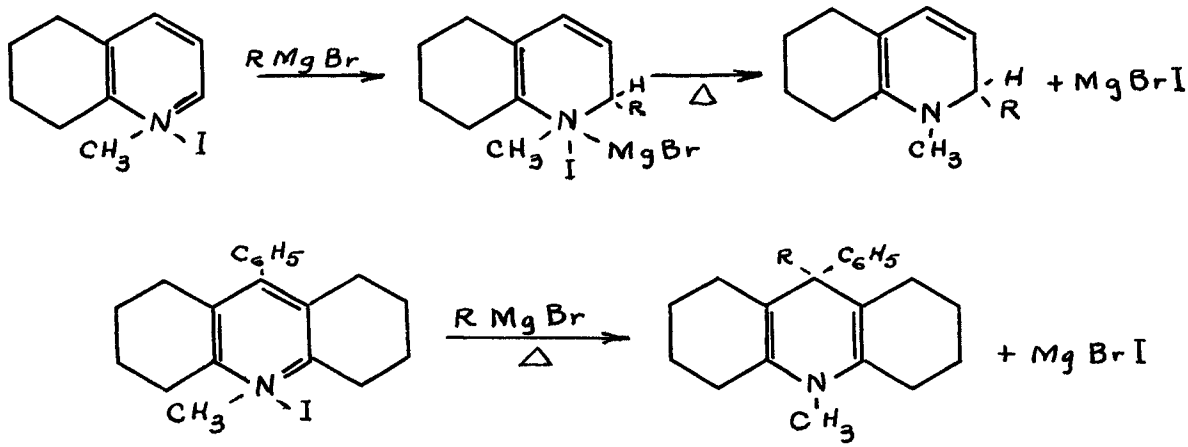
13. Oddo, Gazz. chim. ital., 39, I, 649 (1909).

14. Tanberg, J. Am. Chem. Soc., 36, 335 (1914).

15. Zerewitinoff, Ber., 40, 2023 (1907); ibid., 41, 2233 (1908); ibid., 43, 3590 (1910); ibid., 45, 2384 (1912).

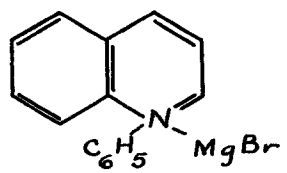
a considerable amount of gas, which was presumed to be methane, was evolved. For this reason he disparaged the use of pyridine in this determination, no further examination of the reaction being made. The gas which Tanberg[14] observed to be evolved was probably hydrogen and the phenomenon will be understood in the light of the work of subsequent investigators.

Another early evidence of RMgX addition to a cyclic ammono aldehyde ether is recorded in the works of Freund,[10] who showed that the methiodides of quinoline, isoquinoline and acridine were capable of addition of the Grignard reagent. With all but acridine, 1,2-addition occurred to produce, upon heating, 1,2-dialkyl-1,2-dihydroquinolines or isoquinolines. With acridine, reaction could only take place at the end of the conjugated system, resulting in 1,4-addition. According to Freund the reactions took the following course.



The compounds so obtained are dihydro derivatives which cannot be converted into the aromatic systems.

In 1930 Bergstrom and McAllister[16] succeeded in preparing 2-alkyl- and 2-aryl- pyridines and quinolines, as well as 1-ethylisoquinoline through interaction of the appropriate Grignard reagent and cyclic ammono aldehyde ether such as pyridine, quinoline, or isoquinoline. It will be recalled that Oddo[7a] obtained a poor yield of 2-phenylquinoline on heating a mixture of quinoline with benzene, phenyl bromide and magnesium. In the work of Bergstrom and McAllister, quinoline (or an analog) and the required Grignard reagent were brought together to form the complex of Oddo. The complex was autoclaved in diethyl ether solution at 150-160° in a special pressure vessel to form the 2-alkyl- or 2-aryl- quinoline (or analog) in yields varying between 44% and 66%. The addition complexes were thought to have the structure of a substituted ammonium salt (V).

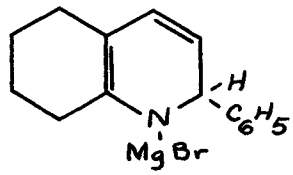


(V)

Upon heating the complex, the phenyl group of (V)

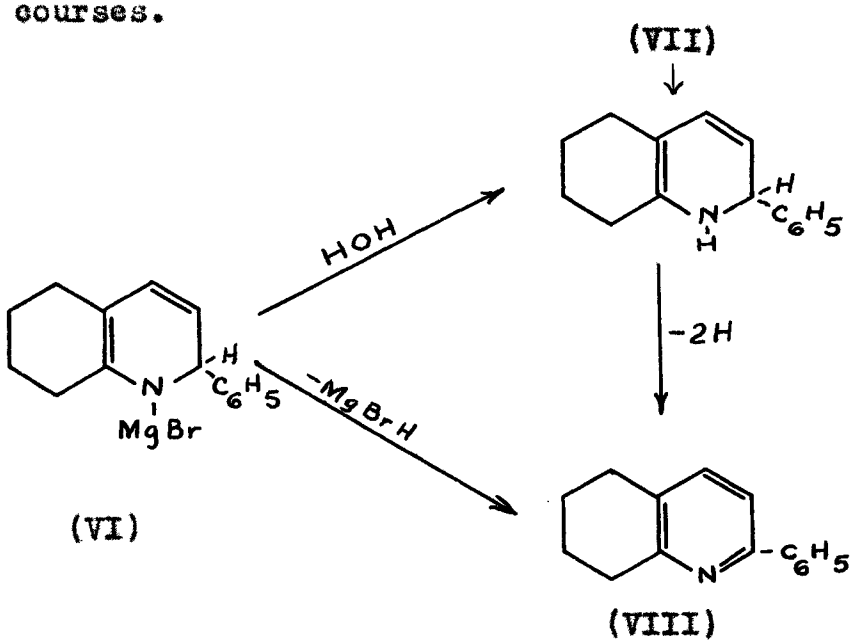
16. Bergstrom and McAllister, J. Am. Chem. Soc., 52, 2847 (1930).

migrates to the adjacent carbon atom to give (VI).



(VI)

As a final result, the Grignard reagent was added to the -CH=N- group, the -MgBr radical accepting the nitrogen of the ammono aldehyde group exactly as it accepts the oxygen in an aquo aldehyde. In the further course of the reaction the conversion of (VI) to 2-phenylquinoline (VIII) may take either of two courses.



(VI) (VII) (VIII)

The view that compound (VII) loses hydrogen finds its counterpart in the loss of hydrogen from the intermediates in the Döbner-Miller synthesis[17] of quinaldine. The loss of MgBrH

17. Döbner and Miller, Ber., 16, 2465 (1883).

(or $MgBr_2$ and MgH_2) from compound (VI) to form compound (VIII) is in agreement with the proposed mechanism for the reaction of organolithium compounds with the -CH=N- group, which will be discussed later. Certainly, magnesium bromohydride or magnesium hydride have never been isolated in these reactions because under the conditions of high temperatures employed in these reactions, according to Bergstrom and McAllister,[16] they doubtless reduce "organic matter" that is present. In support of this idea it was found that the evolution of hydrogen always fell considerably below the theoretical amount.

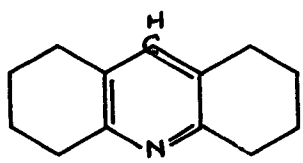
Shortly after Bergstrom and McAllister had demonstrated the addition of Grignard reagents to the pyridine nucleus under forced conditions, and following the classical work of Ziegler and Zeiser[18] on the use of organolithium compounds under normal conditions, Bergmann and Rosenthal[19] published a paper on the alkylation of azomethine compounds by use of benzylmagnesium chloride. In their work, quinoline and benzylmagnesium chloride were shaken for two days in an ether-dioxane medium. On hydrolysis 2-benzyl-1,2-dihydroquinoline was obtained which, according to Bergmann and Rosenthal, underwent spontaneous dehydrogenation to form 2-benzylquinoline. They further maintained that in the case of quinoline, although

18. Ziegler and Zeiser, Ann., 485, 174 (1931).

19. Bergmann and Rosenthal, J. prakt. Chem., [2] 135, 274 (1932).

not in all experiments, some 4-benzylquinoline was isolated as the picrate. The 4-benzylquinoline picrate was not identified by a mixed melting point determination. However, the melting point was in agreement with that given in the literature. In addition, they reported some 2,4-dibenzylquinoline. These authors explained the formation of the latter by the primary addition of benzylmagnesium chloride to quinoline. The primary addition product then presumably split off MgBrH (or $MgBr_2$ and MgH_2), to form 2-benzylquinoline, which was then further attacked in the 4-position by benzylmagnesium chloride through 1,4-addition. The compound, however, was obtained in an exceedingly small amount. Furthermore, the 2,4-dibenzylquinoline had not been previously reported in the literature and no structure proof was performed to characterize the compound. Moreover, Bergmann and Rosenthal[19] made no attempt to support their view of the reaction mechanism by the addition of benzylmagnesium chloride to 2-benzylquinoline.

It is of interest at this point to note the action of the Grignard reagent on acridine (IX) which also contains the



(IX)

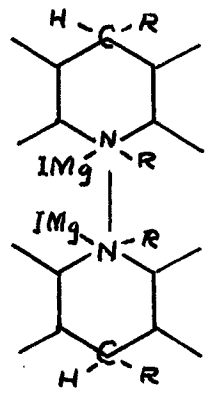
pyridine nucleus. Senier, Austin, and Clarke[20] studied the addition of alkylmagnesium halides to acridine and attempted to extend the reaction by substituting calcium for magnesium in the organometallic reagent. With the organomagnesium compounds they were successful to the extent that well-defined crystalline additive compounds were obtained, but their attempt to prepare organocalcium compounds failed, due to chemical reactions analogous to the Fittig reaction.

The magnesium-containing complexes, which were readily formed and difficult to purify, possessed no definite melting points. Analyses became their only method of characterization. The compounds were insoluble in inert solvents and were decomposed in solvents containing functional groups. Alcohol, for example, decomposed a given complex to regenerate the original acridine and the hydrocarbon corresponding to the Grignard reagent.

For these reasons they devised a preparative procedure by which the acridine, dissolved in anisole or phenetole, was added to an ether solution of the previously prepared Grignard reagent. On warming, the insoluble, crystalline, addition compounds were formed. According to these workers the compounds generally consisted of two molecules of the base, combined with three molecules of the Grignard reagent, and took

20. Senier, Austin, and Clarke, J. Chem. Soc., 87, 1469 (1905).

the form:



However, under the mild conditions of preparation which they employed, apparently no alkylation of the acridine system took place, since acridine may be recovered quantitatively from these complexes upon hydrolysis.

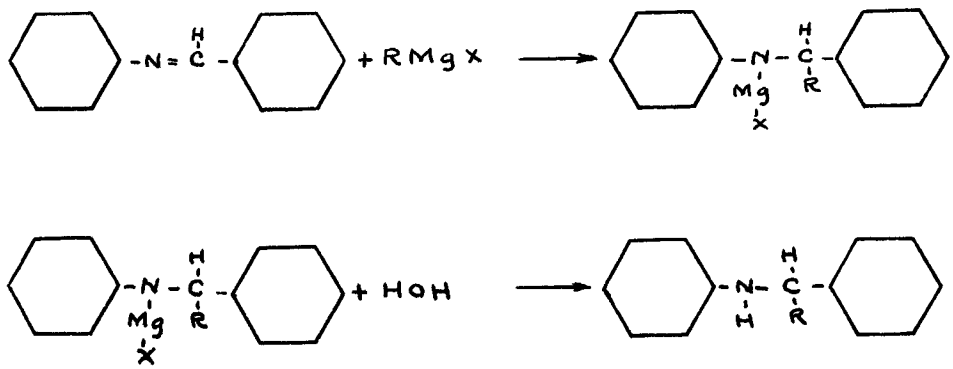
These addition compounds are reminiscent of the complexes of Oddo,[7] and Sachs and Sachs,[12] previously discussed.

Years later, Bergmann and Rosenthal[19] obtained a small yield of 9-benzyl-9,10-dihydroacridine from the addition of benzylmagnesium chloride to acridine. The dihydro derivative so formed resisted all attempts at oxidation to 9-benzyl-acridine.

It will be recalled that substances containing the -CH=N- group may be regarded as aldehydes of the ammonia system comparable to the aldehydes of the water system. These aldehyde properties, insofar as the action of the Grignard reagent is concerned, were not well demonstrated in the case of pyridine, quinoline, isoquinoline and even acridine. This apparent anomaly has been attributed to the remarkable degree

of aromaticity possessed by the pyridine nucleus. In considering other compounds also possessed of the -CH=N- group, but without the attendant complications of inclusion in an aromatic ring, the Schiff bases serve as admirable examples of ammono aldehydes.

The Grignard reagent has been found to add to the -CH=N- linkage with facility in these types, according to the following scheme.[6a]

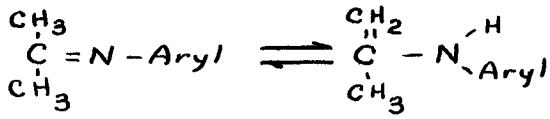


This reaction represents the addition of an organometallic compound to an open-chain ammono aldehyde forming an ammono alcohol, and is analogous to the addition of an organometallic compound to an aquo aldehyde yielding an aquo alcohol. Busch and Leefhelm[21] found that the reaction was generally applicable by a study of the addition of various alkyl- and arylmagnesium halides to N-benzylidenamines.

21. Busch and Leefhelm, J. prakt. Chem., 77, 20 (1907).

Substances which contain the >C=N- group, as has been denoted, may be classified as ammono ketones analogous to the familiar aquo ketones. The aromatic ammono ketones (keto anils) react with the Grignard reagent[22] in the same manner as has been indicated in the case of the ammono aldehydes.

However, the aliphatic keto-anils react, for example, with methylmagnesium iodide in amyl ether solution to give one mole of methane. Practically all of the anil may be recovered by decomposition of the resulting Grignard complex. Short and Watt,[23] in a study of the phenomena, state that these anils must be capable of reacting in the enamic form:



These workers were able to show that the complex obtained by the interaction of acetoneanil and ethylmagnesium bromide reacted with dimethyl sulfate[24] to yield methylisopropenyl-aniline, and thus demonstrated tautomerism in the aliphatic keto-anils. They further investigated the Schiff bases of the type Aryl.CH_2.CH:N.Aryl'. The existence of functional tautomerism of this type has, however, been postulated to

22. Gilman, Kirby, and Kinney, J. Am. Chem. Soc., 51, 2252 (1929).
23. Short and Watt, J. Chem. Soc., 2293 (1930).
24. Gilman and Hoyle, J. Am. Chem. Soc., 44, 2625 (1922).

account for the activity of the γ-methyl groups in pyridine, quinoline and isoquinoline,[3] and will be discussed later.

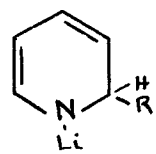
C. The Addition of Organolithium Compounds to Pyridine, Quinoline and Isoquinoline

In contrast to the relatively sluggish action of the Grignard reagents toward the cyclic ammono aldehyde ethers, the organolithium compounds react with facility through addition to the -CH=N- group.

In 1930 Ziegler and Zeiser,[25] incidental to a study of the electrolytic behavior of dimethylphenylmethylpotassium dissolved in pyridine, observed that unlike the alkali metal compounds of triphenylmethane, the deep red color of dimethylphenylmethylpotassium was instantly decolorized by the pyridine solvent. The reaction was so rapid that the two substances could be titrated against each other, one mole of pyridine decolorizing one equivalent of the organoalkali compound. However, all attempts to carry out reactions with the primary product resulted in the formation of intractable oils or resins. For this reason Ziegler and Zeiser substituted aliphatic and aromatic organolithium compounds for the complex dimethylphenylmethylpotassium. They further observed that

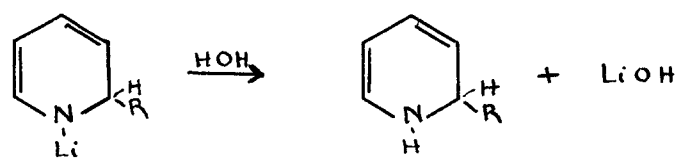
25. Ziegler and Zeiser, Ber., 63, 1847 (1930).

when a one to two normal solution of an alkyllithium compound was added to pyridine, heat was evolved until one mole of the lithium compound had been added. Upon heating to 70-100° the solution became turbid and deposited a powdery precipitate of lithium hydride, which, when the heating was continued long enough, evolved one mole of hydrogen per mole of pyridine, upon hydrolysis with water. The solution was found to contain a 2-alkylpyridine. They also found that the primary addition products, (X) were quite stable in the cold, and in some cases



(X)

could be isolated in crystalline form. With water, they formed 2-alkyl-1,2-dihydropyridines (XI).

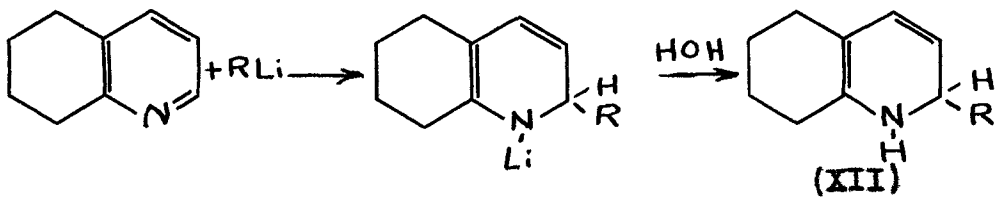


(XI)

Their new reaction thus permitted the smooth, direct substitution of pyridine, and demonstrated a new synthetic field in the application of organoalkali compounds, especially alkyl- and aryllithium compounds.

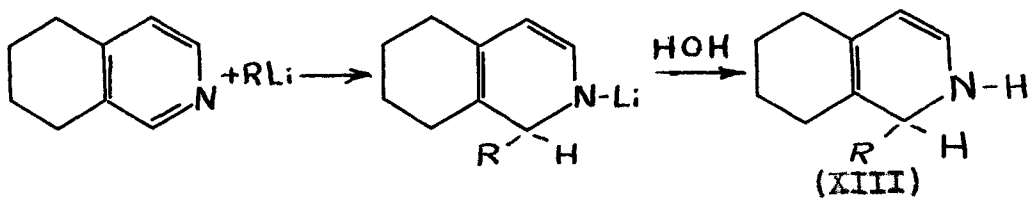
The next year (1931) the same authors, Ziegler and Zeiser,[18] recorded their researches concerning the ramifications of the reaction as applied not only to pyridine, but also to quinoline, and to a lesser extent to isoquinoline and acridine. In their work both aryllithimm and alkyllithium compounds were studied in addition reactions to these heterocycles. The dihydro compounds which were obtained upon hydrolysis were suitably transformed into alkylated or arylated heterocyclic derivatives by a mechanism which is to be discussed later.

Pyridine, quinoline and isoquinoline were found to add the organolithium compound at the -CH=N- linkage, which corresponds to the addition of an organometallic compound to an aquo aldehyde. The dihydro derivatives so formed may be considered to be cyclic ammono alcohols and their formation corresponds to the similar formation of an aquo alcohol from an aquo aldehyde. With quinoline, predominantly, 2-substituted-1,2-dihydro derivatives (XII) were obtained.



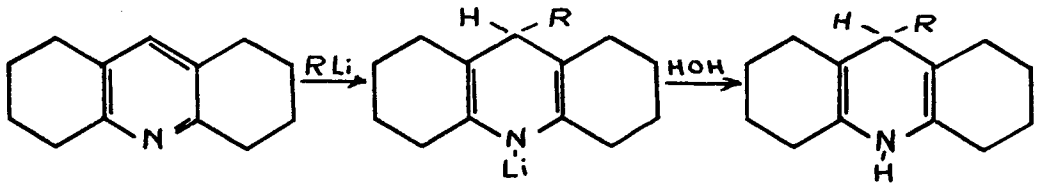
(XII)

Isoquinoline yielded a 1-substituted-1,2-dihydro compound (XIII), thus:



(XIII)

Acridine (XIV) can only undergo addition of organolithium compounds at the termination of the 1,4-conjugated system, that is in the 9,10 positions. Ziegler and Zeiser[18] found that the decomposition products from the addition of butyl- and phenyllithium to acridine, after treatment with water, yielded the corresponding 9-butyl- and 9-phenyl-9,10-dihydroacridine compounds (XV).



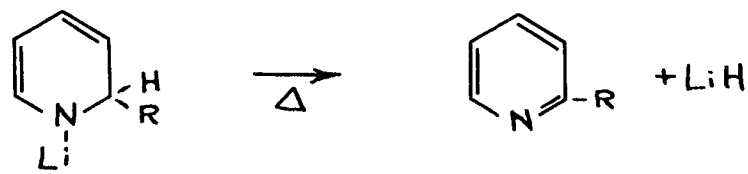
(XIV) (XV)

With regard to the question as to whether pyridine or quinoline is capable of 1,4-addition to form the 4-substituted compounds, after considerable effort Ziegler and Zeiser[18] were unable to supply a conclusive answer. They maintained that the quantity of 4-derivative, if it were present, would only amount to a very small percentage of the total yield. Fractional crystallization of the picrate of their butylquinoline produced a small amount of a uniform product which differed from the picrate of the main product. The amount, however, was insufficient to make possible unquestionable identification.

In contrast to the stability of the 9-substituted-9,10-dihydroacridine compounds, the dihydro derivatives of the other heterocycles were found to have varying degrees of

stability. Ziegler and Zeiser[18] found isolation of the 2-alkyl-1,2-dihydroquinolines, by distillation, to be quite practicable. However, the 2-alkyl-1,2-dihydropyridine compounds were found to be extremely unstable. The corresponding isoquinoline derivatives adopted a middle position.

One of the most outstanding observations which Ziegler and Zeiser made concerning the mechanism of these additions was the thermal splitting of the N-lithio dihydro derivatives of pyridine, to produce lithium hydride and the 2-alkyl- or 2-arylpyridines.



These authors found that the process could be carried out smoothly and without any side reactions, thus restoring the conjugation of the pyridine ring.

Surprisingly, the reaction could not be carried out with the same precision on the previously mentioned higher homologs. Thus, the addition product of butyllithium to quinoline gave, upon heating and hydrolysis of the lithium hydride formed, only about 50% of the theoretical hydrogen. The analogous derivative of isoquinoline yielded 11%, and with the N-lithio-9-n-butyl-9,10-dihydroacridine, lithium hydride formation could not be demonstrated even though the substances were

decomposed by heating. As would be expected with the use of heat, the yields of nuclear alkylated products were moderate with quinoline and poor with isoquinoline and acridine. In the quinoline series it was presumed that the lithium derivative reacted upon the alkylquinoline previously formed. In support of this argument, Ziegler and Zeiser[18] showed that by heating the lithio- derivatives with quinoline, the formation of lithium hydride was completely inhibited. The apparent separate position which the pyridine compounds take is explained in that the aromatic character of the ring is least disturbed subsequent to addition, and its ability to react with lithium hydride is lower in comparison with that of the higher analogs. Furthermore, the temperature at which the splitting of the lithium hydride takes place in pyridine apparently does not induce reaction of lithium hydride on either the N-lithio-2-alkyl-1,2-dihydropyridine or 2-alkylpyridine compounds.

The practical value of the thermal splitting of lithium hydride lay in the possibility of bringing about restoration of the pyridine ring, that is, the conversion of the dihydropyridine system to a nuclear alkylated or arylated pyridine. Splitting of lithium hydride by heat is not practical, except in the case of pyridine. In these researches the heating of the N-lithio- compound was effected in sealed tubes. Later,

Walters and McElvain[26] found it more practical to effect decomposition of the addition product into lithium hydride by displacing the reaction medium (ether) with toluene, and heating to 100° for four hours.

In continuation of their investigation, Ziegler and Zeiser[18] found means of obtaining dehydroalkylated or arylated systems smoothly, and in good yields. The alkyldihydroquinolines or isoquinolines were transformed, by oxidation with boiling nitrobenzene, into the corresponding substituted quinolines or isoquinolines in approximately 80% yield. In their experiments, Ziegler and Zeiser ascertained the completeness of reaction by means of the fact that the dihydro products produce red molecular compounds with picric acid, whereas the dehydrogenated bases produce yellow picrates. The 2-arylquinolines and 1-arylisoquinoline compounds were apparently formed spontaneously to some extent from the dihydroantecedents by dismutation. The dihydro types were never obtained in pure form. Accordingly, to bring about complete dehydrogenation, the compounds were oxidized with nitrobenzene. With the acridine system, however, dehydrogenation of the 9-alkyl-9,10-dihydroacridine was only accomplished by use of mercuric oxide in boiling ethanol.

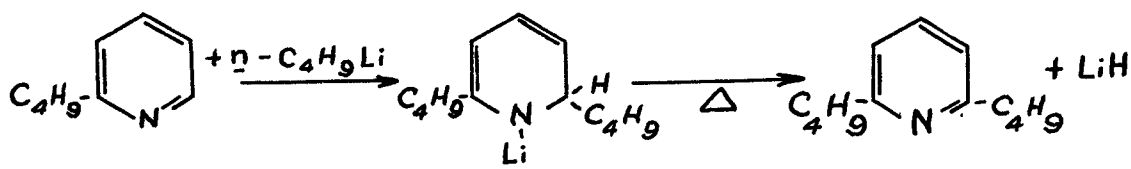
Thus it will be seen that the thermal process as applied to the dehydrogenation in the pyridine series, and the process of oxidation with nitrobenzene as applied to the dehydroquinoline and isoquinolines, complement each other satisfactorily in

26. Walters and McElvain, J. Am. Chem. Soc., 55, 4625 (1933).

the preparation of these nuclear alkylated or arylated heterocyclic systems by the use of organolithium compounds.

The foregoing applications, as compared to the use of the Grignard reagents at high temperatures found in the work of Bergstrom and McAllister,[16] serve to emphasize the high reactivity of organolithium compounds toward the cyclic ammono aldehyde ethers. In this respect the organolithium compounds differ only in degree of reactivity, since both they and the Grignard reagents yield the same products by the same mechanism. The preparative advantages entailed with use of lithium compounds is self-evident.

In continuation of their work on the alkylation of the pyridine nucleus by means of organolithium compounds, Ziegler and Zeiser[18] studied the action of n-butyllithium on a substituted pyridine, namely 2-butylpyridine. According to these workers the reaction took the following course:

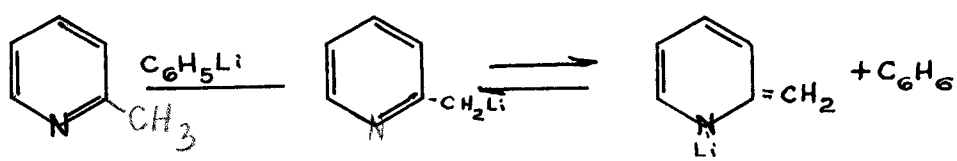


(XVI) (XVII)

As in the case of 2-butylpyridine, heating of the addition product (XVI) split off lithium hydride, with attendant formation of 2,6-dibutylpyridine (XVII). The addition of n-butyllithium to 2-butylpyridine was carried out in benzene medium, required a one-hour reflux period, and the yield of 2,6-di-

butylpyridine was considerably lower than was the case when n-butyllithium reacted with pyridine itself. In the light of the work which is described in the Experimental Section of this dissertation (1,2-addition of an organolithium compound to a 2-substituted quinoline), it is entirely possible that some 2,2-dibutyl-1,2-dihydropyridine might have been formed in this reaction since the position of the azomethine group is not fixed in pyridine, but resonates between the 1,2- and the 1,6- positions (cf. the primary 1,2-addition of n-butyllithium to pyridine, and the secondary "1,6-addition" addition of n-butyllithium to 2-butylpyridine, to form 2,6-dibutylpyridine).

When 2-methylpyridine or 2-methylquinoline was reacted with an organolithium compound, a completely different reaction was observed. These compounds may be considered to be cyclic ammono methyl ketone ethers. Their similarity to methyl ketones of the aquo system has already been pointed out.[1,2,3] Ziegler and Zeiser[18] found that phenyllithium, for example, and 2-methylpyridine yielded 2-picolyllithium (XVIIIa), (XVIIIb) and benzene.



(XVIIIa) (XVIIIb)

2-Methylquinoline exhibited the same phenomenon. This reaction demonstrates lateral metalation in preference to addition to the azomethine linkage. From a study of other examples in the literature, prediction as to the course of reaction with such compounds appears difficult. Later, Tsuda[27] found that 2-n-propylpyridine added n-butyllithium. The metalation of 2-methylpyridine by methyl- and phenyllithium, as discovered by Ziegler and Zeiser,[18] was confirmed in the next year by Bergmann and Rosenthal.[19]

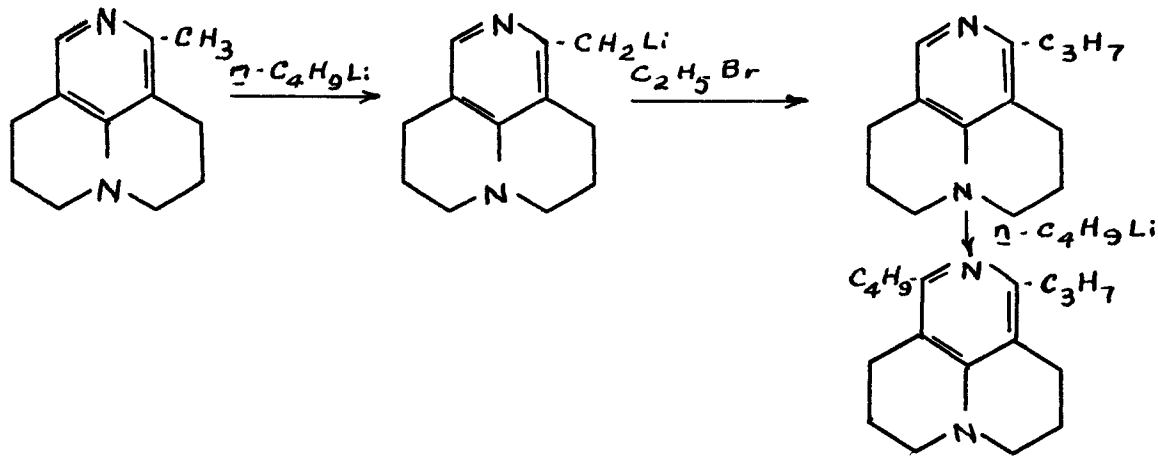
The marked superiority of n-butyllithium over methyl- and phenyllithium in metalation has been unquestionably established in many studies from this laboratory.[28] In the case of 2-n-propylpyridine and 2-n-butylpyridine one might expect lateral metalation rather than anil addition using n-butyllithium. However, as has been pointed out, Ziegler and Zeiser found that with 2-n-butylpyridine, addition of the organometallic compound occurred. Tsuda made the same observation using 2-n-propylpyridine. This apparent anomaly may be explained by the gradient reactivity of alkyl hydrogens, which has been observed in metalation studies of alkyl-aryl sulfides.[29] Methyl phenyl sulfide is capable of lateral metala-

27. Tsuda, Ber., 69, 429 (1936).

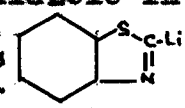
28. (a) Gilman and Jacoby, J. Org. Chem., 3, 108 (1938); (b) Gilman and Moore, J. Am. Chem. Soc., 62, 1843 (1940); (c) Gilman, Moore, and Baine, ibid., 63, 2479 (1941).

29. (a) Gilman and Webb, ibid., 62, 987 (1940); (b) Webb, F. J., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1941.

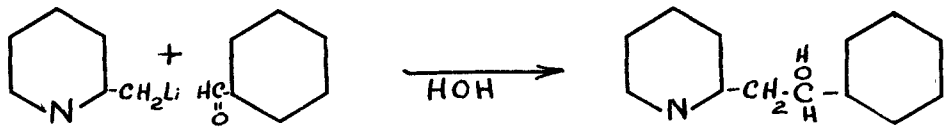
tion, whereas the longer alkyl phenyl sulfides undergo nuclear metalation. Further support of this explanation is found in the studies of Tsuda[27] who obtained metalation of a 2-methyl-group with n-butyllithium, and addition of n-butyllithium when a 2-(n-propyl)- group was present in the same type of molecule, thus:



The organometallic compound obtained in lateral metalation of the 2-methylpyridine type must exert some sort of peculiar deactivating effect upon the azomethine linkage, for it is incapable of intermolecular anil addition.[30] That such com-

30. Recently, Mr. J. A. Beel, of these laboratories, has been able to demonstrate nuclear metalation of benzothiazole in the 2-position, to yield 2-benzothiazolyllithium:  using n-butyllithium at -75 , fifteen minutes, as was shown by carbonation of an aliquot. Furthermore, the benzothiazolyllithium was found to be capable of intermolecular anil addition. However, this organolithium compound is not strictly comparable to the picolyllithium types, since the latter are laterally metalated organometallic compounds and the former is a product of nuclear metalation. Benzothiazolyllithium would be more strictly comparable to the pyridyllithium and quinollithium compounds of Gilman and Spatz, to be discussed later (see pp. 39-40).

pounds are capable of functioning as RLi compounds according to formula (XVIIIa) was shown by Ziegler and Zeiser,[18] who found that the alkyl halides couple with them to alkylate at the methyl group. Thus, from the reaction of quinaldyllithium and propyl bromide, 2-butylquinoline was formed which was identical with that obtained from the addition of n-butyllithium to quinoline, subsequent to oxidation with nitrobenzene. Bergmann and Rosenthal[19] found that 2-picolyllithium and benzoyl chloride yielded 2-phenacylpyridine in an analogous reaction. Noteworthy also is the fact that these authors obtained α-(2-picolyl)-benzyl alcohol (XIX) by the action of 2-picolyllithium on benzaldehyde, thus:

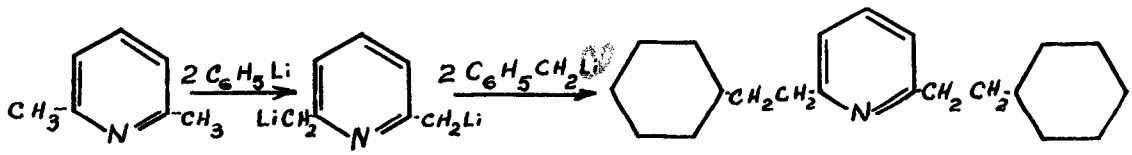


(XIX)

In addition, Ziegler and Zeiser were able to add quinaldyllithium to benzophenone.

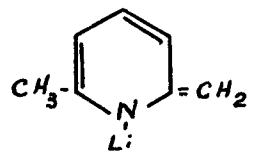
Important, however, are the observations of Bergmann and Rosenthal in their work on 2,6-dimethylpyridine (XX). They were able to decide in favor of a C-Li configuration on the following basis. 2,6-Dimethylpyridine (XX) when treated with two equivalents of phenyllithium, followed by reaction of the resultant laterally metalated product with benzyl chloride,

yielded 2,6-di-(β-phenylethyl)-pyridine (XXI) , thus:



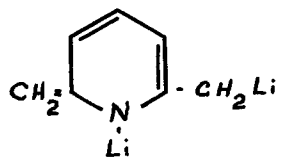
(XX) (XXI)

The authors conclude that metalation of 2,6-dimethylpyridine (XX) could only yield a monolithium compound, if the configuration of formula (XXII) be correct, and thus would be incapable of yielding compound (XXI) , but rather would yield only a monobenzylated product. This reasoning, however, is



(XXII)

based on the assumption that the compound represented by formula (XXII) is incapable of metalation at the remaining α-methyl group, and that the tautomerism is not dynamic in the sense of also being capable of existence in the CH_2Li form, for if it were, conceivably a dilithio- compound of the following type might exist:



From the interaction of one equivalent of phenyllithium and one equivalent of 2,6-dimethylpyridine followed by treatment with benzyl chloride, Bergmann and Rosenthal[19] obtained some 2,6-di-(β-phenylethyl)-pyridine (XXI).

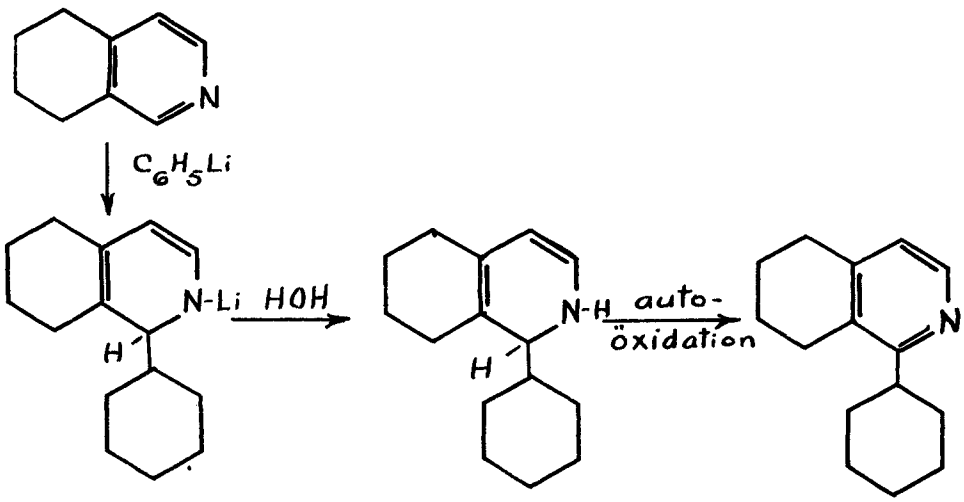
Thus, by use of these types of organolithium compounds and an appropriate reactant, a new means of obtaining 2-substituted pyridines and quinolines is available. Such a procedure admirably supplements the direct introduction of substituents into the pyridine nucleus by means of organolithium compounds.

In the interim period between the announcement by Ziegler and Zeiser of the action of organolithium compounds on pyridine[25] and the full publication of their subsequent researches,[18] Bergmann, Blum-Bergmann, and v. Christiani[31] published a paper, a part of which anticipated and confirmed much of the work of Ziegler and Zeiser.

Bergmann and co-workers were able to add phenyl- and p-anisyllithium to isoquinoline, the resultant 1-aryl-1,2-dihydroisoquinoline addition products were presumed to undergo autooxidation to the 1-arylisoquinoline subsequent to hydrolysis. The mechanism of the reaction which they proposed is in agreement with that given in the cases of pyridine and quin-

31. Bergmann, Blum-Bergmann and v. Christiani, Ann., 483, 80 (1930).

oline, and took the following form:



(XXIII) (XXIV)

They established aryl substitution in the 1-position of isoquinoline by the formation of the picrate of their x-phenylisoquinoline, the melting point of which agreed with that given in the literature for the picrate of 1-phenylisoquinoline. The product which they obtained as 1-phenylisoquinoline melted at 80°. The next year, however, Ziegler and Zeiser[18] reported the same compound prepared by the same method, except that the intermediate 1-phenyl-1,2-dihydroisoquinoline (XXIII) was oxidized with nitrobenzene to form 1-phenylisoquinoline (XXIV) which, after repeated crystallizations, melted constantly at 97°. The melting point of their picrate agreed with that of the picrate of Bergmann and co-workers.[31] Ziegler and Zeiser attribute the lower melting free base of the former authors to be due to their assumption of autoöxidation, which

they thought was not well founded.

As has been seen, under ordinary conditions RLi compounds add promptly to the anil linkage. The organolithium compounds formed from compounds like 2-methylpyridine and 2-methylquinoline were exceptions in that they were incapable of addition to themselves. Noteworthy in this regard are the organolithium compounds of pyridine and quinoline. Gilman and Spatz,[32] by proper selection of conditions, were able to prepare 3-quinolyllithium in 52% yield through the halogen-metal interconversion of 3-bromoquinoline with n-butyllithium at -35°. In continuation of their studies in this laboratory, these researchers were able to show halogen-metal interconversion of 2-iodo-4-methylquinoline with n-butyllithium (-5°, five minutes) in preference to either metalation of the methyl group in the 4-position, or addition of the n-butyllithium to the anil linkage.[33] Moderately low temperatures and short-time reaction periods were essential. It was found that under conditions effective for halogen-metal interconversion in a compound such as 3-bromoquinoline (-35°, fifteen minutes), quinoline itself added n-butyllithium promptly to give 93.5% of 2-butylquinoline. The explanations for the preferential halogen-metal interconversion reaction have been discussed by

32. Gilman and Spatz, J. Am. Chem. Soc., 62, 446 (1940).

33. Gilman and Spatz, ibid., 63, 1553 (1941).

Spatz.[34] The most important of these may be mentioned. Firstly, the nuclear halogen may deactivate the anil linkage toward RLi addition, for there is no evidence of either halogen-metal interconversion or addition to the >C=N linkage of 2-chloroquinoline.[33] A chlorine-metal interconversion reaction has been observed only rarely.[35] Secondly, the C-Li linkage that forms subsequent to halogen-metal interconversion may also reduce the activity of the >C=N group. In support of this view are the observations concerning the activity of the C-Li linkage in 2-methylpyridine and 2-methylquinoline.

Further studies on halogen-metal interconversions in the pyridine and quinoline series have resulted in the preparation of a number of hitherto difficultly obtainable, or completely inaccessible, organolithium compounds from the corresponding bromo or iodo compounds.[36] Some of the types reported are: 2-pyridyllithium (62%),[36b] 3-pyridyllithium (70%),[36] and 5-bromo-3-pyridyllithium (41%) from 3,5-dibromopyridine and slightly more than two equivalents of n-butyllithium.[36] Also

34. Spatz, S. M., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1941.

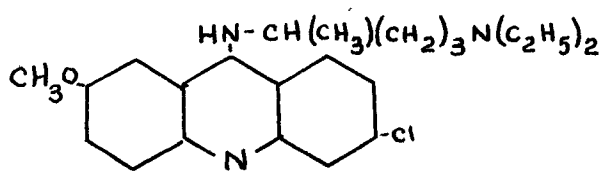
35. (a) Gilman, Langham, and Moore, J. Am. Chem. Soc., 62, 2327 (1940); (b) Wittig, Angew. Chem., 53, 241 (1940).

36. (a) Spatz and Gilman, Proc. Iowa Acad. Sci., 47, 262 (1940); (b) Spatz, Iowa State Coll. J. Sci., 17, 129 (1942); (c) For the preparation of 3,4,6-triphenyl-2-pyridyllithium, see: Gilman and Melstrom, J. Am. Chem. Soc., 68, 103 (1946).

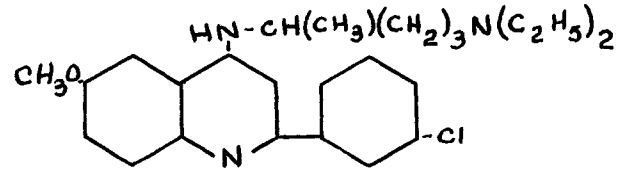
prepared were 6-bromo-2-pyridyllithium (45%),[36b] and 2-lepidyllithium (28-53%).[36b]

It is interesting to note at this point that the γ-quinolyl- chlorine of 4-chloroquinoline and 4-chloro-6-methoxyquinoline, which is sufficiently reactive to undergo condensation with dialkylaminoalkylamines like 1-diethylamino-4-aminopentane but which is unreactive toward an RLi compound, does not show any deactivation of the anil linkage. Gilman and Spatz[37] were able to add m-chlorophenyllithium to these compounds in 35-48% yield.

In recent works from these laboratories the addition of organolithium compounds to cyclic ammono aldehyde ethers, like pyridine and quinoline, has found much practical application in the syntheses of new possible antimalarials.[37] In connection with studies on attempted correlations of constitution with antimalarial action, Gilman and Spatz[37a] prepared "open models" of atebrin (XXV). One of the models was 6-methoxy-2-(3'-chlorophenyl)-4 [(α-methyl-δ-diethylaminobutyl)-amino]-quinoline (XXVI).



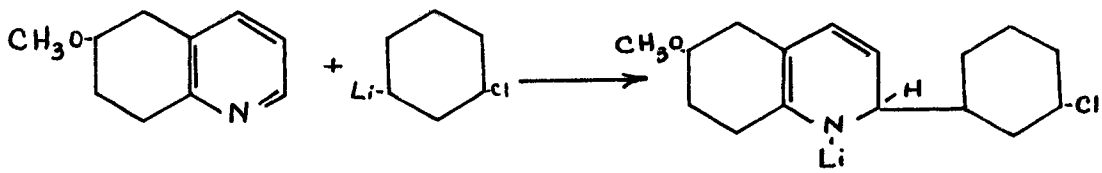
(XXV)



(XXVI)

37. (a) Gilman and Spatz, J. Am. Chem. Soc., 66, 623 (1944). (b) For the preparation of some open quinoline models of atebrin, having a methyl group in place of the methoxyl group, see: Gilman, Christian, and Spatz, ibid., 68, 979 (1946); Gilman, Towle, and Spatz, ibid., 68, 2017 (1946).

In the sequence of reactions required to synthesize the compound, m-chlorophenyllithium (prepared in 70% yield by halogen-metal interconversion of m-bromochlorobenzene with n-butyllithium) was added to the anil linkage of 6-methoxyquinoline, thus:



The intermediate dihydro compound formed upon hydrolysis of the addition product was purified through the picrate, which procedure seemed to effect oxidation to the dehydro compound. 4-Chlorophenyllithium was added by a similar procedure.

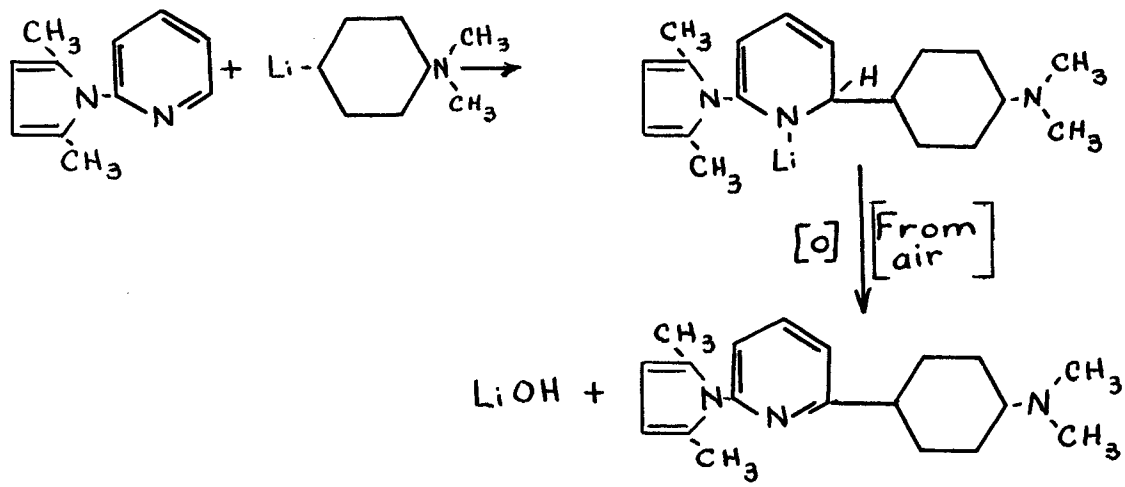
In connection with the pharmacological examination of some fluorine-containing heterocycles, Gilman and Woods[38] had occasion to prepare 2-(m-trifluoromethylphenyl)-quinoline and 2-(m-trifluoromethylphenyl)-8-methylquinoline by the addition of m-trifluoromethyllithium to quinoline and 8-methylquinoline, respectively. Earlier, Gilman and Blume[39] prepared 2-(p-tolyl)-7-trifluoromethylquinoline by a similar reaction involving p-tolyllithium and 7-trifluoromethylquinoline. These

38. Gilman and Woods, J. Am. Chem. Soc., 66, 1981 (1944).

39. Gilman and Blume, ibid., 65, 2467 (1943).

workers favored oxidation of the intermediate dihydro compounds with boiling nitrobenzene.

In a study of antimalarials patterned after plasmochin and atebrin, several pyrryl- derivatives of pyridine and quinoline have been described in the work of Gilman, Stuckwisch, and Nobis.[40] The addition of p-dimethylaminophenyllithium to 2-(2,5-dimethyl-1-pyrryl)-pyridine and 6-methoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline; and the addition of p-(2,5-dimethyl-1-pyrryl)-phenyllithium to quinoline, 8-methylquinoline, and pyridine is described. In oxidation of the dihydro addition products formed with the pyridine compounds and the organolithium compounds, a dry stream of air was used previous to hydrolysis, thus:



40. Gilman, Stuckwisch, and Nobis, J. Am. Chem. Soc., 68, 326 (1946).

This method avoided heating the lithium-containing dihydro addition products to split out lithium hydride, or the alternate oxidation with either nitrobenzene or picric acid to form the dehydrogenated pyridine compound. The dihydroquinoline compounds prepared were oxidized by use of nitrobenzene, the dry air method being unsatisfactory.

The optimum temperature at which a given RLi adds to the anil linkage to give maximum yield of product seems to depend in part upon the specific nature of the RLi compound itself.[38,39,40] Most investigators run the reaction for only a few minutes in the cold.[18,25,26,31,32,33,37,41] Gilman and Spatz[32,33] added n-butyllithium to quinoline at -35° to obtain 93.5% of 2-butylquinoline. With 6-methoxyquinoline and m-chlorophenyllithium the yields of anil addition products were as follows:[37a] 11.1% (-35°), 29.6% (-7 to -5°), 49-54% (0°), and 16.7% (36°). o-Methoxyphenyllithium added in 41% yield at -14°.[38] m-Trifluoromethylphenyllithium[39] and p-tolyllithium in additions to quinoline, 8-methylquinoline, and 7-trifluoromethylquinoline, respectively, were refluxed in ether for three hours prior to hydrolysis and oxidation. In the reaction of p-dimethylaminophenyllithium and 6-methoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline and 2-(2,5-dimethyl-1-pyrryl)-pyridine, a two-hour reflux period was used.[40]

In the work reported in this dissertation, the organo-

41. Oldham and Johns, J. Am. Chem. Soc., 61, 3289 (1939).

lithium compound was refluxed with the cyclic ammono aldehyde ether until a negative color test[42] was obtained.

The necessity of dehydrogenation of the addition product is debatable. In the preparation of 1-phenylisoquinoline, as described by Bergmann and co-workers,[31] an inferior product was obtained when autoöxidation was relied upon. Dehydrogenation has been effected in the majority of cases by means of nitrobenzene. However, mercuric oxide may be necessary, as is the case with the 9-substituted-9,10-dihydroacridine types.[18] Recently zinc dust has been used.[41] In our work, nitrobenzene has been used exclusively.

The possibility of 1,4-addition to the conjugated system of pyridine and quinoline has not been overlooked by early investigators.[16] Bergstrom and McAllister did not isolate 4-phenylpyridine or 4-phenylquinoline from the high temperature reaction of the Grignard reagent with pyridine and quinoline. The 2-isomers were the predominant products. The possibility that 1,4-addition may occur under proper conditions cannot be ruled out. Acridine may be thought of as a dibenzopyridine or a benzoquinoline. When addition of either the Grignard reagent or an organolithium compound occurs to acridine, the 9-position is taken up by the entering group, this entailing 1,4-addition to the conjugated system. No 1,2-addition has been reported. This, however, is a theoretical

42. Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

possibility which is borne out in our 1,2-addition of phenyllithium to 2-phenyl or 2-(p-tolyl)-quinoline, an "open model" of atebrin. With acridine, one would expect there to be a competition between 1,2- and 1,4-addition. Since the 2-position is apparently effectively blocked by the presence of a fused benzenoid system, 1,4-addition would appear to be the natural result.

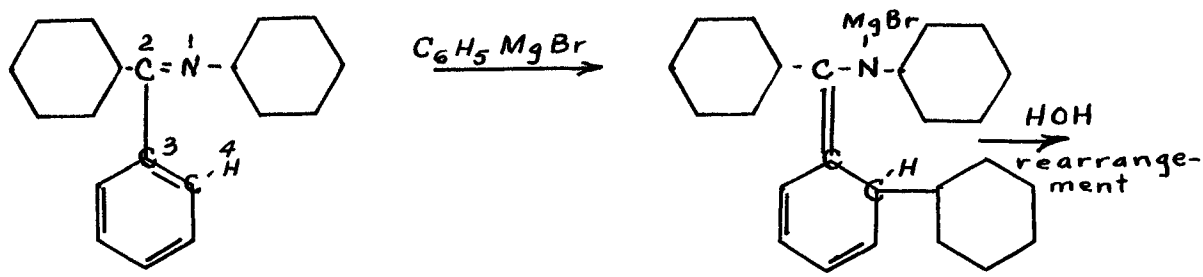
With quinoline, an ammono aldehyde ether, if 1,2-addition is expected by analogy to open-chain ammono aldehyde ethers, and 1,4-addition is possible by analogy to acridine, then some 4-substituted isomers could reasonably be predicted. For instance, from the product of reaction between n-butyllithium and quinoline, Ziegler and Zeiser[18] were able to isolate a uniform picrate differing from the picrate of the main body (2-butylquinoline) by fractional crystallization of the picrate. This they considered to be the 4-butylquinoline isomer. However, in their own words, "the amount was insufficient to make an unquestionable identification".

In the last mother liquor from recrystallization of the product obtained from phenyllithium and quinoline, Ziegler and Zeiser obtained a small amount of a lower melting substance. No further work was done by them on this material. They suggested that the compound might be 4-phenylquinoline.

Although Bergstrom and McAllister[16] did not isolate any isomers in their work with the Grignard reaction, Bergmann and

Rosenthal[19] maintained that some 2,4-dibenzylquinoline was formed in their reaction of benzylmagnesium chloride with quinoline in dioxane. They accounted for this product by postulating the expected 1,2-addition to the anil linkage, followed by some splitting off of MgBrH ($MgBr_2$ and MgH_2) to form 2-benzylquinoline, which was then further attacked by benzylmagnesium chloride through 1,4-addition to yield 2,4-dibenzylquinoline, subsequent to hydrolysis and autoöxidation. These authors, however, made no attempt to add benzylmagnesium chloride to 2-benzylquinoline to support this view.

That 1,4-addition does not occur more readily with quinoline and the Grignard reagent is surprising in view of the evidence for 1,4-addition in other conjugated systems embracing the ammono aldehyde group. Thus, Gilman, Kirby, and Kinney[43] showed that phenylmagnesium bromide reacted with benzophenone-anil (XXVII) through 1,4-addition, to yield o-phenylbenzohydrylaniline (XXVIII) as follows:



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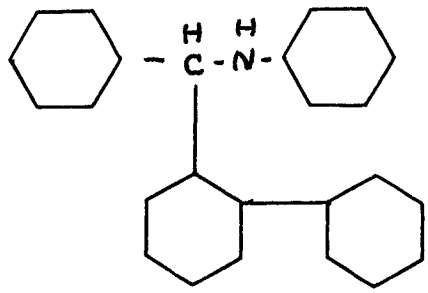
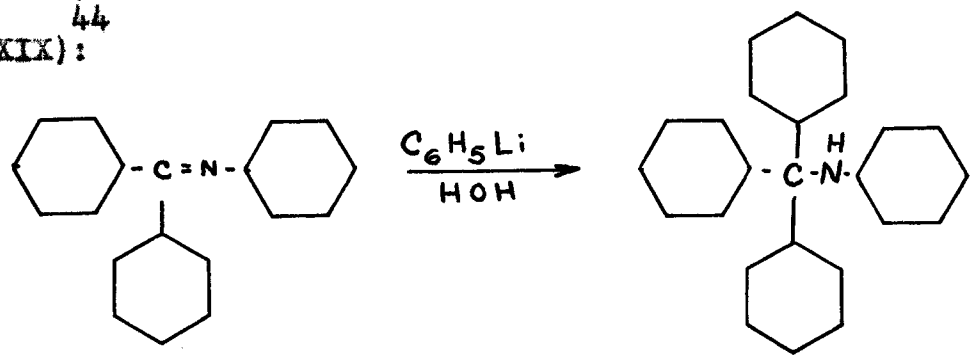
43. Gilman, Kirby, and Kinney, J. Am. Chem. Soc., 51, 2252 (1929).



(XXVIII)

The different reactivities of organolithium compounds and Grignard reagents might lead one to expect that some structures, more especially those with poly-functional groups, will undergo distinctive and different reactions with corresponding members of the organometallic types. Reactions of this type have been observed with benzophenone-anil (XXVII). On the one hand, phenylmagnesium bromide reacts with the former (XXVII) under forced conditions through 1,4-addition to the conjugated system (a conjugation which is partly lateral and partly nuclear). On the other hand, phenyllithium in ether adds 1,2- to the anil linkage yielding triphenylmethylaniline (XXIX):[44]

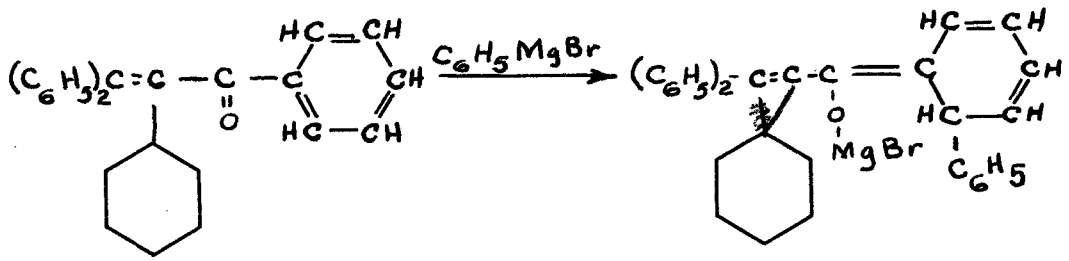


(XXIX)

44. Gilman and Kirby, J. Am. Chem. Soc., 55, 1265 (1933).

As a result of an exhaustive study of addition reactions of organometallic compounds with other conjugated systems, Gilman and Kirby[44] have shown that in general the more reactive RM compounds (for example, organolithium compounds) tend to 1,2-addition and the less reactive RM compounds (for example, organomagnesium compounds) tend to 1,4-addition.

Further evidence of 1,4-addition of the Grignard reagent to a conjugated system involving an aromatic ring and its unsaturated side-chain, is found in the work of Kohler and Nygaard,[45] who demonstrated the addition of phenylmagnesium bromide to tetraphenylpropenone to occur as follows:

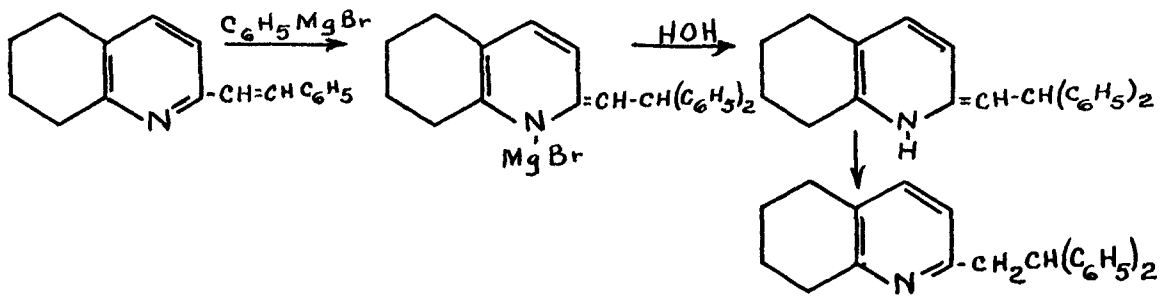


Again (as in the case of 1,4-addition to benzophenoneanil) the ethylenic double bond involved in the addition reaction is situated in a benzene ring.

Of greatest interest, however, is the addition of phenylmagnesium bromide to a compound embracing a similar type of

45. Kohler and Nygaard, J. Am. Chem. Soc., 52, 4128 (1930).

ring-chain conjugation in which an ethylenic double bond is situated in the side-chain, and is conjugated with the nitrogen-carbon double bond (the anil linkage) contained in the pyridine ring of quinoline. Thus, Hoffman, Farlow, and Fuson[46] were able to add phenylmagnesium bromide to benzalquinaldine, which underwent the following transformation to yield α-benzohydrylquinaldine.



As will be observed, 1,4-addition of organometallic compounds to pyridine and its higher homologs has been poorly demonstrated by the low yields of the 4-isomers which have been obtained. Acridine is an exception. The 1,4-addition which occurs with acridine has been explained by the blocking effect of the fused benzenoid structures which are present in the acridine system. If the fine bond structure which has been assigned to isoquinoline be correct, then 1,4-addition cannot occur.

46. Hoffman, Farlow, and Fuson, J. Am. Chem. Soc., 55, 2000 (1933).

III. EXPERIMENTAL

The starting materials used in these preparations were commercial products of the highest purity, unless otherwise indicated, and were used without further purification. All of the melting and boiling points are uncorrected.

Nitrogen was determined by the micro-Dumas method.

Certain of the organolithium compounds to be described were prepared by means of the halogen-metal interconversion reaction. The preparation of the required n-butyllithium is adequately described in the literature.[47] Until recently the latter organometallic compound was generally prepared at room temperature in the conventional three-necked flask, which procedure is relatively time consuming and is limited to small runs because of ether cleavage by n-butyllithium at the reflux temperature of ether.[48] Since halogen-metal interconversions involving one or more active hydrogens require additional equivalents of organometallic compound, a more rapid method of preparation of n-butyllithium, which has recently been described by Gilman and Stuckwisch,[47a] was utilized. The double titration method described by Gilman and Haubein[48] for the

47. (a) Gilman and Stuckwisch, J. Am. Chem. Soc., 65, 1461 (1943); (b) Stuckwisch, C. J., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1943.

48. Gilman and Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

determination of n-butyllithium was used in every case where halogen-metal interconversion products were employed in the preparation of substituted quinoline and isoquinoline compounds.

In all of the reactions involving the active organolithium compounds, the usual three-necked flask equipped with a mechanical stirrer and Hopkins condenser was used. By constantly maintaining a slight positive pressure of dry oxygen-free nitrogen over the reaction, an anhydrous, inert atmosphere was provided. Filtration of the organolithium compounds from unreacted lithium, prior to addition to a reactant, was effected by pouring the organolithium solution through a gas inlet tube, stuffed with glass wool, into a large dropping funnel previously swept out with nitrogen.

2-(p-Aminophenyl)-quinoline. In a three-necked, two liter, round-bottomed flask equipped with a stirrer and condenser having facilities for the introduction of nitrogen, was placed 27.5 g. (0.16 mole) of p-bromoaniline in 200 ml. of anhydrous ether. To this solution was added dropwise, and with vigorous stirring 0.47 mole of filtered n-butyllithium in one liter of ether. After 300 ml. of the organometallic solution had been added, refluxing ceased, and the color of the solution changed from a deep violet to pale yellow. The remaining 700 ml. was added more rapidly, the last 350 ml. being introduced in a rapid stream. The mixture was refluxed

and stirred with external heating for one and one-quarter hours. After approximately fifteen minutes of stirring, a yellow gummy precipitate of the p-N,N-dilithioaminophenyllithium[47,49] was formed. At the end of the heating period, 42 g. (0.32 mole) of freshly distilled quinoline, dissolved in an equal volume of ether, was added dropwise and at such a rate as to maintain reflux. The solution gradually darkened to a deep red color and the organometallic precipitate dissolved very slowly. After the addition was complete, the solution was stirred and refluxed for twelve hours. At the end of this time complete solution had been effected. The ether solution was then hydrolyzed by pouring into an excess of water in a two-liter separatory funnel. After extraction and drying over sodium sulfate, the ether solution was evaporatively distilled. The residual orange colored oil was then heated to 190° for one-half hour with 40 ml. of nitrobenzene to oxidize the intermediate 2-(p-aminophenyl)-1,2-dihydroquinoline. The nitrobenzene and all low boiling material was subsequently removed under vacuum of the water pump and the material boiling up to 120° (0.5 mm.) was discarded. This material consisted chiefly of a small amount of nitrobenzene not removed by the water

49. (a) Gilman and Stuckwisch, J. Am. Chem. Soc., 63, 2844 (1941); (b) Stuckwisch, Iowa State Coll. J. Sci., 18, 92 (1943) [C.A., 38, 728 (1944)]

pump, unreacted quinoline and some 2-butylquinoline. The final product was obtained as an extremely viscous liquid which solidified to an orange glass, after distillation at 165-175° (0.005 mm.) with the aid of a mercury diffusion pump and a metal bath between 225-250°. By this means 17.5 g. (71%) of crude product was obtained, based on 70 percent halogen-metal interconversion. For rectification, the glass was dissolved in benzene and, after charcoaling, set aside to crystallize. Filtration and drying afforded a product melting at 115-120°. In subsequent attempts to crystallize this material, it was found that a pure product could not be obtained even through fractional crystallization, or by attempted use of selective solvents. Isomers of some sort were suspected. Accordingly, all the fractions were combined and the solvents removed. The white crystalline residue weighing 8 g. (0.036 mole) was dissolved in hot 95 percent ethanol and treated with a hot ethanolic solution containing 17 g. (0.072 mole) of dry picric acid. A yellow-orange precipitate immediately formed. After refluxing for ten minutes, the mixture was allowed to cool. Filtration afforded the yellow-orange solid, melting at 170-180°, in quantitative yield. Incidental to an attempt to recrystallize a sample of the picrate from methyl cellosolve, on cooling, it was observed that two picrates separated. One was yellow, and crystallized in very fine feathery needles which appeared to be quite

insoluble in the solvent. The other, an orange picrate, separated simultaneously in the form of hard dense crystals. These two picrates were separated by hand after crystallization appeared to be complete. The yellow picrate melted at 215-217°. The orange picrate melted at 192-196°.

The yellow picrate was found to be more soluble in 95 percent ethanol than the orange. Nevertheless, separation could not be effected with the latter solvent since the two compounds deposited crystals simultaneously. On testing various solvents for selective solubility toward one of the picrates, it was found that benzene dissolved the yellow picrate slightly to give a yellow solution, while the orange picrate seemed to be unaffected. After evaporation of the benzene, a small amount of the yellow picrate was obtained which melted at 218-219°, after recrystallization from 95 percent ethanol. The orange picrate in the residue, when recrystallized from 95 percent ethanol, melted at 196-197°.

Accordingly, 7 g. of the mixed picrates, after recrystallization once from 95 percent ethanol (to remove any excess of picric acid), was placed in the filter tube of a Soxhlet extractor and continuously extracted for three hours with 500 ml. of benzene. By this time a small amount of the orange picrate had precipitated from the hot yellow benzene solution. The solution was filtered, while still hot, and continuous extraction was resumed for another three-hour period with a

fresh 500 ml. portion of benzene. After filtration, the two benzene extracts were combined and evaporated gently to dryness. During this time small quantities of the orange picrate separated and were removed by successive filtration. The yellow residue from evaporation weighed 0.5 g. When crystallized once from methyl cellosolve, the product melted at 215-217°. A further crystallization raised the melting point to 220-221°.

The orange picrate in the Soxhlet filter melted at 195-196°. On recrystallization to constant melting point from a 95 percent ethanol-methyl cellosolve mixture, the picrate melted at 196-197°.

In another preparation, 17.5 g. (70%) of heavy viscous glass, which distilled at 180-190° (0.003 mm.), was obtained. When this glass, dissolved in hot 95 percent ethanol, was treated with 55 g. of picric acid in boiling ethanol and refluxed for fifteen minutes, there was obtained 30 g. of the mixed picrates which melted at 170-190°. On recrystallization from an acetone-95 percent ethanol mixture, the picrates melted at 188-190°.

Subsequent to continuous extraction of 22 g. of the mixed picrates, as described above, there remained in the Soxhlet filter 20 g. of the insoluble orange picrate, melting at 194-195°. Evaporation of the benzene extract, after filtration of a small amount of the orange picrate, yielded 1.8 g. of the

yellow picrate melting at 200-210°.

The orange picrate in the Soxhlet filter was decomposed by boiling a few minutes in 500 ml. of dilute ammonium hydroxide (1:1). The resultant yellow heterogeneous solution was filtered and washed repeatedly with hot water. Eight grams (25%) of product melting at 115-125° was obtained. Upon charcoaling and crystallization to constant melting point from benzene, the compound melted at 138-138.5° and weighed 4 g. An additional 2 g. melting at 135-136° was obtained by concentration of the mother liquor.

A mixed melting point determination was made with the material melting at 138-138.5°, and an authentic specimen[50] of 2-(p-aminophenyl)-quinoline. There was no depression and hence the compound melting at 138-138.5° is 2-(p-aminophenyl)-quinoline. John[51] reported the melting point of the compound to be 134°. The picrate of the authentic specimen melted at 197-198°. The latter was shown to be identical (mixed melting point) with the orange picrate, which is therefore the picrate of 2-(p-aminophenyl)-quinoline.

x-Butyl-x-(p-aminophenyl)-quinoline. The yellow picrate obtained from the procedure given above was recrystallized from methyl cellosolve and melted at 217-218°. After decomposition

50. Kindly furnished by S. M. Spatz.

51. John, J. prakt. Chem., [2] 133, 13 (1932); ibid., [2] 139, 97 (1934).

with boiling ammonium hydroxide (1:1), filtration and thorough washing with hot water, the compound melted at 143-145°. After charcoaling and crystallizing from benzene, the white crystalline material melted at 148-148.5°.

Anal. Calcd. for $C_{19}H_{20}N_2$: N, 10.10. Found: N, 9.60 and 9.75.

x-Butyl-x-(p-aminophenyl)-quinoline Picrate. The yellow picrate was reformed by treating a 95 percent ethanolic solution of x-butyl-x-(p-aminophenyl)-quinoline, melting at 148-148.5°, with a hot solution of ethanolic picric acid. The resultant yellow insoluble picrate was recrystallized from methyl cellosolve and melted at 220-221°.

Anal. Calcd. for $C_{25}H_{23}O_7N_5$: N, 13.80. Found: N, 13.02 and 13.20.

The analyses obtained from the yellow picrate melting at 220-221°, and those obtained from the free base of the latter, melting at 148-148.5°, would most nearly satisfy a quinoline structure containing the butyl- and p-aminophenyl-groups as substituents.

2-(p-Salicylidenaminophenyl)-quinoline. A mixture of 1 g. (0.0045 mole) of 2-(p-aminophenyl)-quinoline and 0.6 g. (0.149 mole) of salicylaldehyde were heated together in a 50 ml. round-bottomed flask for four hours by means of an oil bath held at 150°. After a few minutes an insoluble, yellow, crystalline mass formed. At the end of the heating stage the

excess salicylaldehyde was removed by washing with 95 percent ethanol. Filtration afforded a quantitative yield of product melting at 185-186°. After recrystallizing to constant melting point from methyl cellosolve, the product for analysis melted at 188-188.5°.

Anal. Calcd. for $C_{22}H_{16}ON_2$: N, 8.65. Found: N, 8.74.

2,2-Diphenyl-1,2-dihydroquinoline. In a three-necked, two-liter, round-bottomed flask equipped with a stirrer and condenser having facilities for the introduction of nitrogen, was placed 40 g. (0.2 mole) of 2-phenylquinoline[18] completely dissolved in 200 ml. of ether. With vigorous stirring, 0.3 mole of phenyllithium[52] in 350 ml. of ether was added at such a rate as to maintain reflux. The ethereal solution immediately turned dark green in color and a very small amount of a yellow precipitate formed. The solution was stirred and refluxed for twelve hours. Hydrolysis of the green-black solution was effected by pouring the latter into a large excess of distilled water in a two-liter separatory funnel. The dark color in the ether was immediately dissipated and gave way to a deep red color which slowly changed to pale yellow. A small amount of insoluble yellow material was removed by filtration. The ether was then evaporatively distilled from a Claisen flask, 50 ml. of nitrobenzene was added, and the solution

52. Gilman, Zoellner, and Selby, J. Am. Chem. Soc., 54, 1957 (1932).

heated for one-half hour by an oil bath at 190-200°. No reaction appeared to occur. The nitrobenzene was distilled under the pressure of the water pump, and all the material which distilled up to 150° (0.5 mm.) was removed. The Claisen flask was then incorporated into the mercury diffusion pump and the material distilled under a high vacuum (0.02-0.03 mm.). Unreacted 2-phenylquinoline began to distill up to 140° and solidified in the receiver. As soon as a thick glassy distillate began to appear in the receiver, the latter was changed and 36 g. of material distilling at 155-165° (0.02-0.03 mm.) was collected. The procedure required a metal bath temperature between 225-250°. All efforts to rectify samples of the glassy distillate by crystallization failed. Moreover, a picrate would not form, but rather deep red oils were obtained in all attempts. It was found that the glass, when treated with dilute hydrochloric acid (1:1) in the presence of a little ethanol, formed an extremely insoluble tan-colored powder. The acid solution was gently warmed to 60° and the lumpy material broken up. Inasmuch as 2-phenylquinoline is soluble in dilute hydrochloric acid (1:1), this medium constituted a separation of the product from unreacted starting material. The balance of the glassy distillate was treated with dilute hydrochloric acid (1:1) (subsequent to removal of the distillate from the receiver with hot 95 percent ethanol, which was evaporated off under vacuum), and the hydrochloride so

formed was filtered off at the pump. At this stage it was necessary that all lumpy material be broken up under the acid reagent. Heating to 60° assisted greatly in the complete conversion. The hydrochloride was thoroughly washed with fresh portions of dilute hydrochloric acid and finally with distilled water. On drying, 22 g. (35%) of crude product melting at 150-168°, with decomposition, was obtained.

The hydrochloride was then decomposed in excess 10 percent sodium hydroxide, the solution finally being warmed to 60° to effect complete reaction. A very viscous brown-colored oil resulted which readily coalesced on cooling; hence the alkaline solution was readily decanted. After washing several times with cold distilled water, the oil had solidified. The solid so obtained was taken up in 95 percent ethanol, charcoaled, filtered and allowed to cool slowly. When the material tended to oil out, crystals (from a test tube crystallization) were added. The product was obtained as white needles weighing 13 g. and melting at 82-84°. The final product for analysis was crystallized to constant melting point from a solution containing a few drops of benzene and a larger quantity of petroleum ether (b.p. 60-68°), and melted at 86-87°.

Anal. Calcd. for $C_{21}H_{17}N$: N, 4.98. Found: N, 5.13.

2-Phenyl-2-(p-tolyl)-1,2-dihydroquinoline. This compound was prepared by two methods. In Method 1, p-tolyllithium was added to 2-phenylquinoline. In Method 2, phenyllithium was

added to 2-(p-tolyl)-quinoline.

Method 1. By a procedure like that used for the preparation of 2,2-diphenyl-1,2-dihydroquinoline, 40 g. (0.2 mole) of 2-phenylquinoline[18] in 500 ml. of anhydrous ether was interacted with 0.3 mole of p-tolyllithium[52] in 375 ml. of ether. The solution immediately turned dark brown to black in color and was refluxed for twelve hours. The pale yellow ethereal solution obtained on hydrolysis was filtered from a small amount of yellow insoluble material and worked up exactly according to the procedure given for 2,2-diphenyl-1,2-dihydroquinoline. By this means 27 g. (45.5%) of a glass which distilled at 172-182° (0.004 mm.), was obtained. A small sample of the glass was converted to the hydrochloride which was extremely insoluble in the dilute hydrochloric acid used (1:1). When a portion was warmed above room temperature, decomposition occurred and a dark red-brown gummy mass resulted. The hydrochloride formed satisfactorily when the temperature was held below 20° and thus separation from any unreacted 2-phenylquinoline was effected. On neutralization with cold 10 percent sodium hydroxide a flocculent, gummy precipitate was formed which was thoroughly washed with water. Filtration, drying and crystallization, after charcoaling in petroleum ether (b.p. 60-68°), yielded white crystals melting at 82-85°. It was found advantageous to add a minute amount (about 5%) of absolute ethanol to the petroleum ether to aid in crystal-

lization by inhibiting the tendancy toward oily precipitation. The main product was crystallized directly without conversion to the hydrochloride. This was accomplished by dissolving the glass in petroleum ether (b.p. 60-68°), charcoaling and filtering twice, adding a trace of absolute ethanol, and chilling and seeding. The product melted at 83-84°. After recrystallization to a constant melting point from absolute ethanol, the compound melted at 85.5-87°.

Method 2. By a procedure like that used for the preparation of 2,2-diphenyl-1,2-dihydroquinoline, 0.15 mole of phenyllithium in 190 ml. of ether was added with vigorous stirring, to 22 g. (0.1 mole) of 2-(p-tolyl)-quinoline[40] in 300 ml. of anhydrous ether. The solution immediately colored dark brown to black and was refluxed for twelve hours. On hydrolysis the ether layer was dark green and in a few minutes turned dark red in color. The red color finally gave way to pale yellow. A small amount of a pale yellow precipitate was deposited on standing overnight. This was removed by filtration. The ethereal solution was worked up exactly according to the procedure given for 2,2-diphenyl-1,2-dihydroquinoline. By this means 15 g. (51%) of a thick viscous glass, which distilled at 175-185° (0.01 mm.), was obtained. The seed required in crystallizing the main product was obtained by purification of a sample of the glass through the hydrochloride, exactly as described in Method 1. The main run was crystallized from

petroleum ether (b.p. 60-68°) (5 percent with respect to absolute ethanol), exactly as recorded under Method 1. Recrystallization from absolute ethanol to constant melting point yielded a white crystalline product which melted at 85-86°.

A mixed melting point involving the products obtained by Methods 1 and 2 was not depressed. The two compounds are therefore identical, indicating that 1,2-addition of the organolithium compound to the 2-substituted quinolines occurred.

A mixed melting point involving the 2-phenyl-2-(p-tolyl)-1,2-dihydroquinoline and 2-phenylquinoline was depressed to melt at 55-60°. A mixed melting point embodying the product and 2-(p-tolyl)-quinoline melted at 60-65°. These depressed melting points indicate that the product was not starting material.

Anal. Calcd. for $C_{22}H_{19}N$: N, 4.72. Found: N, 4.84 and 4.91.

o-Bromobiphenyl. This compound was prepared by modification of the method of Zaheer and Fasich.[53] In our work the diazotization of o-aminobiphenyl was carried out in hydrobromic acid solution, rather than in hydrochloric acid, in order to secure pure o-bromobiphenyl free from possible contamination by any o-chlorobiphenyl.

53. Zaheer and Fasich, J. Ind. Chem. Soc., 21, 27 (1944).

A stirred suspension of 117 g. (0.70 mole) of technical o-aminobiphenyl and 238 g. (1.40 moles) of 48 percent hydrobromic acid in 700 ml. of water was cooled below 5°, and diazotized with a solution of 49 g. (0.70 mole) of sodium nitrite in 100 ml. of water. This required about one-half hour, when the temperature was maintained between 0-5° by means of an efficient ice-salt bath.

A five-liter, round-bottomed flask equipped with a stirrer and containing 100 g. (0.70 mole) of cuprous bromide in a solution made up of 700 ml. of water and 119 g. (0.70 mole) of 48 percent hydrobromic acid, was arranged for steam distillation. After the cuprous bromide solution was heated to boiling, the diazonium solution was gradually added from a separatory funnel while a vigorous current of steam was passed through the reaction mixture. This procedure required approximately two hours.

The small amount of product in the aqueous distillate was taken up in ether and the main reaction mixture exhaustively extracted with ether. The combined ether extracts were then dried, the ether evaporatively distilled, and 106 g. (65%) of the product distilling at 120-130° (0.3 mm.) was collected.

For further purification, the product in ether was extracted with excess 20 percent sodium hydroxide solution. An emulsion formed which separated only with difficulty,

resulting in the formation of three layers. The upper ether layer was removed and dried; the ether evaporatively distilled; and 58 g. (35%) of pure o-bromobiphenyl, distilling at 158-160° (11 mm.), was collected.

2-(o-Biphenylyl)-quinoline. By a procedure like that described for the preparation of 1-(p-dimethylaminophenyl)-isoquinoline, 22 g. (0.095 mole) of redistilled Eastman white label o-bromobiphenyl in 50 ml. of anhydrous ether was reacted with 1.5 g. (0.21 g. atom) of lithium, suspended in 50 ml. of anhydrous ether, to form o-biphenylyllithium in 80% yield, as assayed by titration for total alkali. The filtered organometallic solution (dark brown in color) was added with rapid stirring to 25 g. (0.2 mole) of freshly distilled quinoline in 50 ml. of anhydrous ether. After the first 10 ml. had been added, the solution refluxed vigorously and a yellow meal separated. The solution was refluxed overnight. Subsequent to hydrolysis, the ether was evaporatively distilled, 15 ml. of nitrobenzene was added and the solution heated for one-half hour at 180-190°. After vacuum distillation of excess nitrobenzene and lower boiling excess quinoline, 14 g. (50%) of a thick viscous glass which distilled at 162-166° (0.007 mm.) was collected.

For rectification, the glass was dissolved in hot 95 percent ethanol and filtered from a small amount of insoluble material which melted at 172-175°. Concentration afforded

a second crop of the same material. On charcoaling, filtration and cooling, the ethanolic solution deposited hard, white, dense crystals melting at 98-102°. Recrystallized to constant melting point from 95 percent ethanol, the compound melted at 102-103°.

Anal. Calcd. for $C_{21}H_{15}N$: N, 4.97. Found: N, 5.05.

The high melting material, only slightly soluble in 95 percent ethanol, was recrystallized from methyl cellosolve to melt constantly at 176-177°. This proved to be an isomeric biphenylylquinoline, as was shown by the analysis. Furthermore, the compound was shown to be identical with p-biphenylylquinoline which was subsequently prepared for characterization purposes.

Anal. Calcd. for $C_{21}H_{15}N$: N, 4.97. Found: N, 5.10.

Two repeat runs were made beginning with samples of Eastman white label o-bromobiphenyl obtained from separate purchases. In each, the same two 2-biphenylylquinoline isomers were obtained. Carbonation of an aliquot of the organometallic compound obtained (supposedly o-biphenylyllithium) yielded a crude acid which melted at 115-120°. On recrystallizing once from 95 percent ethanol, the product melted at 190-200°. This material was then extracted three times with hot petroleum ether (b.p. 60-68°) to remove the isomeric o-phenylbenzoic acid. The residue was then recrystallized from ether and melted at 223-225°. A mixed melting

point, using this material and pure p-phenylbenzoic acid, melting at 228-229°, was not depressed. The compound melting at 223-225° is therefore p-phenylbenzoic acid.

The mother liquors from these recrystallizations were combined and the solvents evaporated. The isomeric acids could not be separated by fractional crystallization. Accordingly, various solvents were tried for selective extraction. Of those tried, petroleum ether (b.p. 60-68°) was found to be most satisfactory, having a selective solvent power for the o-phenylbenzoic acid. The p-isomer was almost completely insoluble in the petroleum ether. The product obtained upon crystallization melted at 108-110°. On recrystallization, the melting point was raised to 110-112°. A mixed melting point of this material, with an authentic specimen of o-phenylbenzoic acid, was not depressed.

2-(p-Biphenylyl)-quinoline. By a procedure like that used for the preparation of 1-(p-dimethylaminophenyl)-isoquinoline, 35 g. (0.15 mole) of Eastman white label p-bromobiphenyl dissolved in 150 ml. of anhydrous ether, was reacted with 2.1 g. (0.3 g. atom) of lithium suspended in 75 ml. of anhydrous ether. On completion of the ensuing reaction, titration of an aliquot for total alkali showed an 87% yield of p-biphenylyllithium. A 75 ml. portion of the filtered organolithium compound was added jetwise to a solid carbon dioxide-ether slurry, for carbonation purposes. The balance (150 ml.) of the organometallic solution was added to

50 ml. of an anhydrous ethereal solution containing 13 g. (0.10 mole) of freshly distilled quinoline. Immediately a pale yellow insoluble meal was formed. The mixture was stirred and refluxed for twelve hours. At this point, the ethereal solution was only slightly colored and a copious amount of an insoluble crystalline material was present. The ether was decanted from the residue which, after filtration and drying, weighed 11 g. and melted at 175-178°. Subsequent to hydrolysis and evaporation of the ether solution, there was obtained 10 g. of crude product melting at 150-162°. The total yield was 21 g. (86%). Recrystallized to constant melting point from methyl cellosolve, the compound formed pale yellow platelets which melted at 178-179°. A mixed melting point with this material and the material melting at 176-177° (obtained as an isomer in the preparation of 2-(o-biphenylyl)-quinoline from Eastman white label o-bromobiphenyl) showed no depression.

2-(p-Biphenylyl)-quinoline has been prepared in a different manner by Steinkopf and Petersdorff[54] who give a melting point of 175-177° for the compound. By their method, 2-(p-biphenylyl)-4-carboxyquinoline (prepared from isatin and p-phenylacetophenone in the presence of potassium hydroxide) was decarboxylated by heating to yield the desired 2-(p-biphenylyl)-quinoline.

54. Steinkopf and Petersdorff, Ann., 543, 119 (1940).

The heterogeneous ethereal solution from carbonation, containing the insoluble carbonation product, was treated with distilled water but little solution of the insoluble material was effected. The ether solution was separated and the aqueous layer acidified with hydrochloric acid. Filtering and drying afforded 8 g. (80%) of crude acid melting at 215-219°. Recrystallized to constant melting point from 95 percent ethanol, the p-phenylbenzoic acid so obtained melted at 228-229°. Liebermann and Zsuffa[55] give a melting point of 224° for the acid when prepared by the Fridel and Crafts reaction involving biphenyl and oxalyl chloride.

5-(2,5-Dimethyl-1-pyrryl)-isoquinoline. The 5-aminoisoquinoline required in the preparation of this compound was obtained by the catalytic reduction of 5-nitroisoquinoline in the presence of Raney nickel, as described by Craig and Cass.[56] Nitration of isoquinoline by the method of Le Fevre and Le Fevre[57] yielded the desired 5-nitroisoquinoline. The 5-(2,5-dimethyl-1-pyrryl)-isoquinoline was obtained by condensation of the 5-aminoisoquinoline so obtained with acetonylacetone, by a general method described by Lions and co-workers.[58]

55. Liebermann and Zsuffa, Ber., 44, 857 (1911).

56. Craig and Cass, J. Am. Chem. Soc., 64, 783 (1942).

57. Le Fevre and Le Fevre, J. Chem. Soc., 1470 (1935).

58. (a) Lions and co-workers, J. Proc. Roy. Soc., N. S. Wales, 70, 43 (1936) /C.A., 31, 6653 (1937)/;
(b) ibid., 71, 92 (1937) /C.A., 32, 1695 (1938)/;
(c) ibid., 74, 443 (1940) /C.A., 35, 4771 (1941)/.

In a 500 ml. one-necked flask equipped with a reflux condenser was placed 50 g. (0.35 mole) of 5-aminoisoquinoline, and to the amine was added 39.9 g. (0.35 mole) of acetonylacetone. Two drops of hydrochloric acid (1:1) were added as catalyst to the reaction and the solution actively refluxed for two hours. In subsequent runs on other amines it was found advantageous to use an excess of acetonylacetone over that required by theory. After cooling somewhat, the mixture was poured upon chopped ice. The crude product separated as a brownish-gray crystalline precipitate. After filtration and drying, the product weighed 73 g. (95%), and melted at 78-80°. Upon recrystallization to constant melting point from 95 percent ethanol the yield of product, melting at 83-84°, was 64.5 g. (83%).

Anal. Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.61.

5-(2,5-Dimethyl-1-pyrryl)-isoquinoline Picrate. The picrate was prepared by dissolving 0.5 g. of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline in a minimum amount of 95 percent ethanol. To this solution was added 10 ml. of an ethanolic solution of picric acid, previously saturated at 25°. The resultant mixture was heated to reflux temperature for five minutes, and then allowed to cool slowly, whereupon yellow platelets were deposited. The picrate was recrystallized to constant melting point from 95 percent ethanol and melted at 174-175°.

Anal. Calcd. for $C_{21}H_{17}O_7N_5$: N, 15.58. Found: N, 15.59.

4-Bromoisoquinoline.[59] This compound was most satisfactorily prepared by refinement of the method of Craig and Cass.[56] To a two-liter Claisen flask containing 387 g. (3 moles) of isoquinoline,[60] 350 ml. of 48 percent hydrobromic acid was gradually added with external cooling. After mixing thoroughly, the water and excess hydrobromic acid were removed by distillation under reduced pressure of the water pump, with the use of a boiling water bath. The side-arm of the Claisen flask was then conveniently sealed off with a rubber tube and screw clamp for the subsequent operations. The Claisen flask was fitted with an air reflux condenser in one neck and a dropping funnel in the other neck. To the crystalline hydrobromide, 480 g. (3 moles) of bromine was gradually added from the dropping funnel. The mixture turned a deep red color and slowly began to dissolve in the bromine. At this point the reaction flask was gradually heated to 90-100°, by means of an oil bath, and vigorously shaken until the whole reaction mass had become molten. The dark red liquid melt was then heated for seven hours with the use of the oil bath at 180-190°, until the evolution of hydrogen bromide from the reflux condenser ceased.

59. (a) Edinger and Bossung, J. prakt. Chem., 43, 191 (1891); (b) Bergstrom and Rodda, J. Am. Chem. Soc., 62, 3030 (1940).

60. This material was generously furnished by the Barrett Division, Allied Chemical and Dye Corporation, 40 Rector Street, New York, N. Y.

The 4-bromoisoquinoline hydrobromide, together with any unreacted isoquinoline, was decomposed to the free base by treatment with 150 g. of sodium hydroxide dissolved in 500 ml. of water. The oil thus formed was extracted three times with benzene, one and one-half liters of the solvent being required. The combined extracts were dried over potassium hydroxide.

The benzene was then evaporatively distilled from an oil bath at 120° and the dark red-brown residual oil was rectified by fractional distillation through a modified Claisen flask under the reduced pressure of the oil pump. The material which boiled below 118° (0.3 to 0.4 mm.) was chiefly unreacted isoquinoline (suitable for subsequent preparations). A small amount of liquid, boiling between 118-125° (0.3 to 0.4 mm.), was obtained as a second fraction, and finally the third fraction, pure 4-bromoisoquinoline boiling at 125-127° (0.3 to 0.4 mm.), began to solidify in the water condenser, at which time the water was removed from the condenser. A wide-mouthed receiver was essential. By this means 445 g. (71.5%) of product melting at 39-42° was obtained. A sample of this material was recrystallized from petroleum ether (b.p. 60-68°) and melted at 42-42.5°.

Craig and Cass[56] report a yield of 53% of "fairly pure" 4-bromoisoquinoline in their preparation, while Bergstrom and Rodda[59b] obtained one yield of 73.7%, but state that for some reason in most of their runs the yield was closer to 45%.

This finding was substantiated by our earlier preparations. Subsequently, however, it was found that the yield of 4-bromoisoquinoline was considerably increased over that of earlier preparations by the complete mixing of the molten isoquinoline perbromide hydrobromide prior to the prolonged heating, as indicated above.

4-Aminoisoquinoline. The procedure of Craig and Cass[56] requires a shaking autoclave to effect direct replacement of the bromine group of 4-bromoisoquinoline with the amino group, by use of ammonia under high pressure and temperature, with the aid of a catalyst.

Lacking a shaking autoclave, as such, we resorted to the use of a still-pressure bomb using identical conditions except for the shaking effect. No isolable product was obtained in two attempts. We then resorted to the use of a Parr hydrogenator, which was fitted with a Pyrex glass liner, without the usual hydrogenation connections. By this means we were able to prepare the required 4-aminoisoquinoline.

In the Pyrex glass liner of a shaking Parr hydrogenator, equipped for thermostatic control of temperature, was placed 17 g. (0.082 mole) of 4-bromoisoquinoline, 53 ml. of concentrated aqueous ammonia (density 0.90), and one gram of copper sulfate pentahydrate as catalyst. The whole was heated for 16 hours at 170°, with slow shaking. For rectification, the reaction mixture was treated with dilute sodium hydroxide and

extracted with five successive 100 ml. portions of benzene. The combined benzene extracts were dried over anhydrous potassium carbonate, then the benzene solution subjected to a decolorizing charcoal, followed by filtration of the charcoal. The filtrate was concentrated by distillation to a volume of 70 ml. On cooling, tan microscopic crystals were deposited. The product obtained weighed 7 g. (60%) and melted at 105-108°. Recrystallized from benzene, the compound weighed 6 g. (51%) and melted at 107-108°. Craig and Cass[56] report a yield of 70% of product melting at 107-107.5°, and a melting point of 108.5°, after twice recrystallizing from benzene.

4-(2,5-Dimethyl-1-pyrryl)-isoquinoline. In a 50 ml. one-necked flask was placed 6 g. (0.042 mole) of 4-aminoisoquinoline and 10 g. (0.088 mole) of acetonylacetone. To this mixture was added two drops of 1:1 hydrochloric acid as catalyst and the whole was gently refluxed for three hours. As the reaction proceeded the color of the solution changed from deep red to dark brown. After the period of reflux had elapsed the solution was cooled, whereupon two layers became evident. The whole was poured upon 400 g. of chopped ice and the oil which initially formed, solidified and was then broken up into a crystalline crude product which was filtered and dried. The weight of crude product so obtained was 9 g. (97%), and melted at 76-77°. After recrystallization to constant melting point from methanol, the compound melted at 77-78°.

A subsequent recrystallization did not raise the melting point.

Anal. Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.50.

Quinoline Sulfate. This compound was prepared by modification of the method of Hoogewerff and Van Dorp.[61] Two hundred grams (1.55 moles) of quinoline was dissolved in 400 g. of 95 percent ethanol and converted to the acid sulfate by treatment with 168 g. (1.7 moles) of concentrated sulfuric acid (density 1.84). The supporting flask was cooled during the addition by means of an ice bath and was agitated constantly. At the end of several hours, the quinoline sulfate had deposited in crystalline form and was broken up, filtered and washed with cold absolute ethanol. The yield from the first crystallization was 297.5 g. (85%) of product, melting at 164-165°. Krakan[62] reports a melting point of 163.5-164.5° for this compound. An additional quantity of the salt may be obtained by concentration of the mother liquor.

5- and 8-(2,5-Dimethyl-1-pyrryl)-quinoline. These compounds have previously been prepared by Hazelwood, Hughes, and Lions.[58b] No difficulty was encountered in duplicating their yields provided the quinoline amines were pure. The required 5-aminoquinoline and the 8-isomer were prepared by reduction

61. Hoogewerff and Van Dorp, Rec. trav. chim., 4, 125 (1885).

62. Krakan, J. Russ. Phys. Chem. Soc., 17, 364 /Beil., Volume 20, Springer, Berlin, 1935/.

of the corresponding nitro compounds, using Adams' catalyst and exactly the same conditions and solvents as suggested by Fieser and Hershberg.[63] To prepare 5- and 8-nitroquinoline, the method of Meigen[64] was used which required quinoline sulfate. The latter was best prepared as described above.

8-(2,5-Dimethyl-1-pyrryl)-quinoline Picrate. The picrate formed tan microscopic crystals from 95 percent ethanol, melting at 177-178°. A further crystallization failed to raise the melting point. The procedure used was that given under 5-(2,5-dimethyl-1-pyrryl)-isoquinoline picrate.

Anal. Calcd. for $C_{21}H_{17}O_7N_5$: N, 15.59. Found: N, 15.54.

6-(2,5-Dimethyl-1-pyrryl)-quinoline. The 6-aminoquinoline required in the preparation of this compound was prepared by reduction of Eastman 6-nitroquinoline in concentrated hydrochloric acid-stannous chloride medium, as described by Hargreaves, Marshall, and Whorton.[65] The condensation of 6-aminoquinoline with acetonylacetone was carried out by the method previously described under the preparation of 4-(2,5-dimethyl-1-pyrryl)-isoquinoline. In a 0.07 mole run the product was obtained in 93% yield and melted at 96-97°. Recrystallized to

63. Fieser and Hershberg, J. Am. Chem. Soc., 62, 1640 (1940).

64. Meigen, J. prakt. Chem. [2], 77, 472 (1908).

65. Hargreaves, Marshall, and Whorton, J. Am. Pharm. Assoc., 28, 140 (1939).

constant melting point from methanol, the compound melted at 98-99°.

Anal. Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.80.

6-(2,5-Dimethyl-1-pyrryl)-quinoline Picrate. The picrate crystallized as fine yellow needles from 95 percent ethanol and melted at 185-186°. A further crystallization failed to raise the melting point.

Anal. Calcd. for $C_{21}H_{17}O_7N_5$: N, 15.58. Found: N, 15.50.

2-(2,5-Dimethyl-1-pyrryl)-quinoline (attempted). The following attempts were made to prepare 2-(2,5-dimethyl-1-pyrryl)-quinoline.

Method 1. A mixture of 11.3 g. (0.07 mole) of 2-chloroquinoline and 6.7 g. (0.07 mole) of 2,5-dimethylpyrrole was heated in a sealed tube at 150-160° for sixteen hours.[66] The reaction mixture, a thick black oil, was poured into water and resulted in a dark brown precipitate. This product proved intractable toward crystallization.

Method 2. In a second attempt to prepare 2-(2,5-dimethyl-1-pyrryl)-quinoline, 5.86 g. (0.15 g. atom) of potassium was converted to potassium "sand" by agitation in boiling

66. Adapted from a procedure for the preparation of 2-dimethylaminoquinoline, as given by Gilman, Crounse, Massie, Benkesser, and Spatz, J. Am. Chem. Soc., 67, 2107 (1945).

toluene. After cooling, the toluene was decanted and the "sand" washed with ether into a three-necked, one-liter, round-bottomed flask equipped with a stirrer and condenser. To the stirred suspension of potassium "sand" was added, by drops, 13.3 g. (0.14 mole) of 2,5-dimethylpyrrole.[67] The reaction was allowed to go to completion over a period of two hours. Then 50 ml. of sodium-dried dioxane was added to further effect solution of the N-potassium 2,5-dimethylpyrrole. Most of the ether was then evaporated, leaving a dioxane suspension, light brown in color. To the stirred suspension was added, dropwise, a dioxane solution of 22.9 g. (0.14 mole) of 2-chloroquinoline. The mixture darkened considerably and was refluxed for ten hours. The dioxane was removed on the water pump and the residue distilled under vacuum to give 17 g. of a material melting at 34-35°, which proved to be unreacted 2-chloroquinoline. No isolable product could be obtained from the residue of the distillation.

Method 3. A third attempt to prepare 2-(2,5-dimethyl-1-pyrryl)-quinoline was made. In this run, 2-chloroquinoline and 2,5-dimethylpyrrole were heated together under a reflux condenser by an oil bath at 150-160°. The tar so obtained resisted all attempts at crystallization.

67. Young and Allen, Organic Syntheses, Coll. Vol. II, 299 (1944).

Method 4. A solution of 5 g. (0.035 mole) of 2-aminoquinoline, 11.4 g. (0.10 mole) of acetonylacetone, and one drop of hydrochloric acid (1:1) was refluxed for three hours. During this time the solution darkened considerably. The reaction mixture was poured upon chopped ice to yield a thick viscous oil from which no product could be isolated.

1-(p-Dimethylaminophenyl)-isoquinoline. In a three-necked, one-liter, round-bottomed flask equipped with a stirrer and condenser having facilities for the introduction of nitrogen, was placed 35 ml. of anhydrous ether and 1.05 g. (0.15 g. atom) of metallic lithium. In a nitrogen atmosphere 14 g. (0.07 mole) of p-bromodimethylaniline in 12.5 ml. of anhydrous ether was added, by means of a dropping funnel. A liberal portion was added at the start and the reaction hastened by warming. After reaction had begun the remainder of the solution was added, dropwise, with continuous stirring. The mixture was stirred for an hour after the addition was complete.

The solution was then filtered through glass wool, under nitrogen, into a dropping funnel (previously swept out with nitrogen). The clear solution of organometallic compound so obtained was added dropwise, with rapid stirring, to 9 g. (0.07 mole) of freshly distilled isoquinoline in 15 ml. of anhydrous ether contained in a one-liter, three-necked, round-bottomed flask under nitrogen. Refluxing of the ether occur-

red. After the addition was complete the resultant suspension was rapidly stirred for an hour at room temperature.

Hydrolysis of the mixture was then effected by the addition of a large excess of water, with stirring. After hydrolysis was complete the ether layer was separated and the aqueous solution extracted twice with 25 ml. portions of ether. All ether fractions were dried over Drierite, filtered and the ether evaporatively distilled from a Claisen flask. To the residue was added 10 ml. of nitrobenzene and the solution was heated to 180-190° for one-half hour by means of an oil bath. The nitrobenzene was distilled off under reduced pressure of the water pump and discarded. The residue was then subjected to vacuum distillation. The main product distilled at 196-199° (4 mm.) from a metal bath around 230°. By this means there was obtained 9.5 g. (55%) of an orange-red, glassy material which was crystallized to constant melting point from methanol to melt at 114.5-115°.

Anal. Calcd. for $C_{17}H_{16}N_2$: N, 11.29. Found: N, 11.20.

1-(p-Dimethylaminophenyl)-isoquinoline Picrate. The picrate, prepared from a hot dioxane solution of the isoquinoline compound and a hot ethanolic solution of picric acid, formed scarlet-red glistening crystals which melted constantly at 220-221°.

Anal. Calcd. for $C_{23}H_{19}O_7N_5$: N, 14.68. Found: N, 14.95.

1-(p-Tolyl)-isoquinoline. This compound was prepared by the method described above. p-Tolyllithium,[52] prepared in nitrogen in 90% yield from the interaction of 24 g. (0.14 mole) of p-bromotoluene and 2 g. (0.28 g. atom) of lithium, after filtration through glass wool, was added to 16.1 g. (0.125 mole) of isoquinoline in 16 ml. of anhydrous ether. The product distilled at 174-183° (5 mm.) from a metal bath around 220°, and weighed 15 g. (54.6%). The crude product, melting at 65-68°, was recrystallized to constant melting point from a benzene-petroleum ether mixture, (b.p. 60-68°), to melt at 71-72°.

Anal. Calcd. for $C_{16}H_{13}N$: N, 6.40. Found: N, 6.60.

1-[p-(2,5-Dimethyl-1-pyrryl)-phenyl]-isoquinoline. This compound was prepared by the procedure outlined under 1-(p-dimethylaminophenyl)-isoquinoline. From the reaction between 17.5 g. (0.07 mole) of p-(2,5-dimethyl-1-pyrryl)-phenyl bromide[58b] and 1.05 g. (0.15 g. atom) of lithium, p-(2,5-dimethyl-1-pyrryl)-phenyllithium[68] was obtained in 70% yield. The filtered organometallic solution was added to 6.45 g. (0.05 mole) of freshly distilled isoquinoline, in 15 ml. of anhydrous ether. The product distilled at 203-208° (4 mm.) from a metal bath around 255° as a dark red, glassy, viscous liquid which later solidified to a glass and weighed 6.7 g. (45%). This material was crystallized to constant melting point from a

68. Gilman and O'Donnell, J. Am. Chem. Soc., 66, 840 (1944).

benzene-petroleum ether mixture (b.p. 60-68°) and melted at 159-160°.

Anal. Calcd. for $C_{21}H_{19}N_2$: N, 9.36. Found: N, 9.59.

1-(p-Anisyl)-5-(2,5-dimethyl-1-pyrryl)-isoquinoline. This compound was prepared according to the method indicated for 1-(p-dimethylaminophenyl)-isoquinoline. The required p-anisyllithium[52] was prepared in 82% yield. The filtered organometallic solution was added to an ethereal solution of 26.2 g. (0.12 mole) of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline. The product distilled at 222-228° (2 mm.) as a dark red, glassy, viscous oil, from a metal bath between 250° and 265°, and weighed 15 g. (38%). A small amount of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline was recovered in the forerun.

Anal. Calcd. for $C_{22}H_{20}ON_2$: N, 8.53. Found: N, 8.74.

1-[p-(2,5-Dimethyl-1-pyrryl)-phenyl]-5-(2,5-dimethyl-1-pyrryl)-isoquinoline. From the reaction between 0.90 mole of p-(2,5-dimethyl-1-pyrryl)-phenyllithium[68] and 20 g. (0.90 mole) of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline, as outlined under 1-(p-dimethylaminophenyl)-isoquincline, there was obtained on high vacuum distillation 11 g. (31%) of a dark red, brittle glass which distilled over a range of 220-230° (0.05 mm.). The glass was dissolved in benzene and the solution allowed to crystallize as tan microscopic needles, melting at 214-215°. A further crystallization failed to raise the melting point.

Anal. Calcd. for $C_{27}H_{25}N_3$: N, 10.74. Found: N, 10.91.

1-(p-Nitrophenyl)-isoquinoline. This compound was prepared by dehydrogenation of 1-(p-nitrophenyl)-3,4-dihydroisoquinoline, with use of palladium black. The required 1-(p-nitrophenyl)-3,4-dihydroisoquinoline was prepared by the method of Rodinov and Yavorskaya,[69] their yields and melting points being duplicated. For the preparation of palladium black the procedure of Willstätter and Waldschmidt-Leitz[70] was used. In a 25 ml. round-bottomed flask equipped with an air condenser, was placed 2 g. (0.008 mole) of 1-(p-nitrophenyl)-3,4-dihydroisoquinoline and 1 g. of palladium black. The mixture was heated externally by means of a metal bath and held at 190-200° for two hours, with occasional shaking. At the beginning of the heating period some effervescence occurred. After heating was completed the liquid was cooled somewhat and the product exhaustively extracted with boiling acetone. The palladium was recovered by filtration of the combined extracts. The filtrate containing the product was charcoaled, filtered and concentrated to incipient crystallization and yielded, on cooling, 1.2 g. (60%) of product melting at 150-151°. On recrystallization to constant melting point the product melted at 155-156°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2$: N, 11.18. Found: N, 11.10.

69. Rodinov and Yavorskaya, J. Gen. Chem., (U.S.S.R.) 11, 446 (1941) /C.A., 35, 6592 (1941)/

70. Willstätter and Waldschmidt-Leitz, Ber., 54, 123 (1921).

1-(p-Aminophenyl)-isoquinoline. This compound was prepared by two methods. In Method 1 the preparation, through addition of p-N,N-dilithioaminophenyllithium to isoquinoline, is described. Method 2 records the means by which the compound prepared in Method 1 was synthesized by a different method and was thus characterized as 1-(p-aminophenyl)-isoquinoline.

Method 1. In a three-necked, two-liter, round-bottomed flask equipped with a stirrer and condenser having facilities for the introduction of nitrogen, was placed 38 g. (0.22 mole) of p-bromoaniline in 200 ml. of anhydrous ether. To this solution was added dropwise, and with stirring, 0.66 mole of filtered n-butyllithium in one liter of ether. After 300 ml. of the organometallic solution had been added refluxing ceased and the color of the solution changed from a deep violet to pale yellow. The remaining 700 ml. was added more rapidly, the last 350 ml. being introduced in a rapid stream. The mixture was refluxed and stirred, with external heating, for one and one-quarter hours. After approximately fifteen minutes of stirring a yellow, gummy precipitate of the organometallic compound was formed. At the end of the heating period 57 g. (0.44 mole) of freshly distilled isoquinoline, dissolved in an equal volume of anhydrous ether, was added dropwise and at such a rate as to maintain reflux. The solution immediately became deep orange in color and a finely divided granular

precipitate formed. After the addition was complete the mixture was stirred and refluxed for twelve hours. At the end of this time all the material had dissolved. The ether solution was then hydrolyzed by pouring into an excess of water in a two-liter separatory funnel. After extraction and drying over sodium sulfate the ether solution was evaporatively distilled. The residual oil was then distilled to remove all material boiling up to 110° (0.5 mm.) and the orange colored residue then heated at 190° for one-half hour with 40 ml. of nitrobenzene to oxidize the intermediate dihydroisoquinoline compound. The nitrobenzene was subsequently removed under vacuum and the product distilled with the aid of a mercury diffusion pump. The material which distilled at 178-190° (0.02 mm.), using a metal bath around 240-250°, was collected as an extremely viscous liquid and weighed 23 g. (67%), based on 70% halogen-metal interconversion. In a subsequent run a 70% yield of 1-(p-aminophenyl)-isoquinoline was obtained. For rectification the product was twice crystallized from benzene and melted at 191-192°. A further recrystallization failed to raise the melting point.

Anal. Calcd. for $C_{15}H_{12}N_2$: N, 12.70. Found: N, 12.63.

Method 2. In 50 ml. of absolute ethanol, 0.72 g. (0.0029 mole) of 1-(p-nitrophenyl)-isoquinoline was hydrogenated in one hour over Raney nickel under three atmospheres pressure of hydrogen, at a temperature of 95-100°. After

filtration of the nickel catalyst the ethanolic solution was evaporated to syrup stage, taken up with benzene, and diluted slightly with petroleum ether (b.p. 60-68°). The product crystallized as tiny colorless needles and, after filtration and drying, weighed 0.45 g. (70%), and melted at 185-190°. Recrystallized to constant melting point from benzene, the product melted at 191-192°.

A mixed melting point of the 1-(p-aminophenyl)-isoquinoline, prepared by the two methods given, showed no depression.

1-(p-Mercaptophenyl)-isoquinoline. The p-bromotniophenol required in the preparation of this compound was obtained by the method of Backer and Dijkstra.[71]

By a procedure similar to that used in the preparation of 1-(p-aminophenyl)-isoquinoline, 53 g. (0.28 mole) of p-bromothiophenol in 100 ml. of anhydrous ether was interacted with 0.45 mole of n-butyllithium in 500 ml. of ether. After about one-half of the n-butyllithium had been added the vigorous refluxing subsided. During the addition of the second half of the n-butyllithium, refluxing occurred, but at a slower rate. A copious quantity of a dense pure white crystalline precipitate formed. The heterogeneous mixture was stirred and refluxed for one-half hour. A 50 ml. aliquot of the mixture was withdrawn and carbonated, after which a large excess, 50 g. (0.38 mole) of freshly distilled isoquinoline in 50 ml.

71. Backer and Dijkstra, Rec. trav. chim., 52, 701 (1933).

of anhydrous ether was added. After five minutes the solution turned deep orange in color and, at the end of the addition, a small amount of a gummy orange precipitate had formed. The resulting mixture was refluxed for twelve hours. Hydrolysis was carried out in a nitrogen atmosphere, whereupon the orange color of the solution was dissipated. With rapid stirring, an excess of 20 percent sodium hydroxide solution was added to effect solution of the amphoteric product. The yellow aqueous solution, still under nitrogen, was separated from the ether, fresh ether added, and with vigorous stirring the alkaline solution was acidified with acetic acid. The ether layer turned deep pink in color. A small amount of heavy tar also formed which was ether insoluble. This was discarded. The ether extract was dried over sodium sulfate and, after filtration, ethereal hydrogen chloride was added. A pale yellow crystalline solid formed. Filtration and thorough washing with warm absolute alcohol afforded 15 g. (20%) of the dry hydrochloride, which melted at 241-246° with decomposition. Recrystallized to constant melting point from dilute hydrochloric acid (1:1), the compound formed pale yellow needles melting at 271-272° with decomposition.

Anal. Calcd. for $C_{15}H_{12}NClS$: S, 11.62. Found: S, 11.80 and 11.90.

p-Mercaptobenzoic Acid. A 50 ml. aliquot of the product resulting from the halogen-metal interconversion of p-bromo-

thiophenol and n-butyllithium was poured jetwise into a powdered solid carbon dioxide-ether slurry. A vigorous reaction ensued and a copious amount of precipitate was formed. After five hours, distilled water was added, together with a small amount of 20 percent sodium hydroxide. The ether was separated under nitrogen and the aqueous solution, still under nitrogen, was acidified with dilute hydrochloric acid. The last traces of ether were removed under vacuum and the white precipitate was filtered and dried in a vacuum desiccator. The crude product so obtained weighed 3 g. (75%) and melted at 190-195°. Recrystallized twice from absolute ethanol, the product melted at 214-215°. Bramley and Chamberlin[72] report a melting point of 217° for this compound when prepared through reduction of p-carboxybenzenesulfonyl chloride with zinc dust and hydrochloric acid.

p-(γ-Diethylaminopropylamino)-phenyl Bromide. The γ-diethylaminopropyl chloride required for the preparation of this compound was made in essential accordance with the procedure described by Gilman and Shirley.[73]

The p-(γ-diethylaminopropylamino)-phenyl bromide was prepared by two methods. Method 2 is to be preferred, for the yield (62%) of pure product obtained was superior to that

72. Bramley and Chamberlin, J. Chem. Soc., 376 (1942).

73. Gilman and Shirley, J. Am. Chem. Soc., 66, 888 (1944).

of Method 1 by which was obtained a 52% yield.

Method 1. In a 100 ml. round-bottomed flask equipped with a reflux condenser, was placed 34.4 g. (0.2 mole) of p-bromoaniline and 30 g. (0.2 mole) of freshly distilled γ-diethylaminopropyl chloride. The mixture was then gradually warmed by use of an oil bath until the internal temperature of the solution attained 150-160°. The temperature was held at this point for six hours and required an external temperature of 185-195° in the oil bath. The dark brown solution was cooled somewhat and an excess of distilled water was added, whereupon complete solution was effected. The cooled solution was neutralized with 20 percent sodium hydroxide and exhaustively extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate, and the ether evaporatively distilled. Vacuum distillation from a modified Claisen flask yielded a small amount of forerun which distilled up to 159° (0.5 mm.). The fraction which distilled at 159-161° (0.5 mm.), n_D^{20} 1.5480, was collected and weighed 41.2 g. (72.2%). Redistillation gave 30 g. (52%) of a colorless liquid; b.p. 135-137° (0.20 mm.); n_D^{20} 1.5530: d_{20}^{20} 1.1178.

Method 2. In a one-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 200 ml. of 20 percent sodium hydroxide solution. This is equivalent to 40 g. (1 mole) of sodium hydroxide. To the stirred solution was added 86 g. (0.5 mole) of finely ground

p-bromoaniline, followed by the dropwise addition of 89 g. (0.5 mole) of benzenesulfonyl chloride. During the addition the heterogeneous mixture became quite warm. The solution was kept alkaline at all times and was stirred for one hour. To obtain the sulfonamide, the mixture was chilled, carefully neutralized and then made slightly acid to litmus by addition of concentrated hydrochloric acid (density 1.18). A white precipitate formed in a copious amount. Filtration, washing with water, and drying afforded a quantitative yield of N-(p-bromophenyl)-benzenesulfonamide melting at 124-130°. The melting point as given in the literature is 134°.[74] This material was suitable for the next step without further purification.

In a one-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed an intimately ground mixture of 156 g. (0.5 mole) of the crude N-(p-bromophenyl)-benzenesulfonamide and 41.5 g. (0.3 mole) of anhydrous potassium carbonate. The mixture was stirred and melted by application of a hot oil bath, the temperature of which was maintained around 150°. To the melt was cautiously added, through the condenser, 90 g. (0.6 mole) of γ-diethylaminopropyl chloride. A vigorous reaction ensued, accompanied by evolution of carbon dioxide and much foaming. After the

74. v. Braun, Ber., 40, 3926 (1907).

addition was complete, and with constant stirring, the heating was continued for six hours at an internal temperature of 150-160°. This required a bath temperature of 190-200°. At the end of this period, the mixture was cooled somewhat and poured into a large excess of cold water. A dark brown viscous oil appeared. The oil was washed several times with water and transferred to a one-liter, three-necked, round-bottomed flask fitted with stirrer and reflux condenser. The oil dissolved completely upon the addition of 600 ml. of concentrated hydrochloric acid (density 1.18). Hydrolysis of the amide was complete after refluxing for twelve hours. At this stage the solution was cooled and carefully neutralized by addition of 40 percent sodium hydroxide, with external cooling by means of an ice bath. The cold solution was then exhaustively extracted with ether, the ether extracts combined and dried and the ether evaporatively distilled. The product was vacuum distilled from a modified Claisen flask and the material which distilled at 155-157° (0.5 mm.) was collected and weighed 88.5 g. (62%); n_D^{20} 1.5528; d_{20}^{20} 1.1181.

Anal. Calcd. for $C_{13}H_{21}N_2Br$: N, 9.92. Found: N, 10.19.

p-(γ-Diethylaminopropylamino)-phenyl Bromide Dihydrochloride. An anhydrous ethereal solution of p-(γ-diethylaminopropylamino)-phenyl bromide was subjected to an excess of anhydrous ethereal hydrogen chloride. The pure white dihydrochloride so formed was filtered from the ether and melted at

181-182°. The compound was recrystallized to constant melting point from absolute ethanol and melted at 185-186°.

Anal. Calcd. for $C_{13}H_{23}N_2BrCl_2$: N, 7.83. Found: N, 7.72.

1-[p-(γ-Diethylaminopropylamino)-phenyl]-isoquinoline (attempted). By a procedure similar to that used for the preparation of 1-(p-aminophenyl)-isoquinoline, 0.125 mole of n-butyllithium in 160 ml. of ether was added to 35 g. (0.125 mole) of p-(γ-diethylaminopropylamino)-phenyl bromide in 75 ml. of ether, at such a rate as to maintain the reflux. During the addition, a pale yellow turbidity was observed which appeared to be colloidal in nature, no precipitate separating. There was noticeable refluxing of the ether. Then a second portion (0.125 mole) of n-butyllithium in 160 ml. of ether was added. The refluxing ceased and the color changed to a light gray. The mixture was refluxed for one-half hour and a 50 ml. aliquot withdrawn for carbonation. An ethereal solution of 32 g. (0.25 mole) of freshly distilled isoquinoline was then added. Refluxing occurred, and the stirred solution became deep orange in color. The mixture was refluxed for twelve hours. Hydrolysis afforded an orange-red ethereal solution which was dried, the ether evaporatively distilled, and the residual oil subjected to 40 ml. of nitrobenzene at 180-190°. Attempts to rectify portions of the residual oil by crystallization, after vacuum distillation of the nitrobenzene,

failed.

The residual oil could not be distilled even with the aid of the mercury diffusion pump.

No isolable material could be obtained from the product of carbonation.

When the procedure was repeated the same result was obtained. No isolable picrate could be formed from the crude product of hydrolysis.

4-Nitro-4'-acetamidodiphenyl Sulfone.[75] The 4-nitro-4'-aminodiphenyl sulfide and corresponding acetamido compound required in this preparation were obtained by the method of Raiziss and co-workers.[76]

4-Nitro-4'-acetamidodiphenyl sulfone has previously been prepared by the hydrogen peroxide oxidation of the sulfide.[77] Inasmuch as the period of heating and quantities of solvent used were found to be excessive, in large runs, the following procedure was used. In a two-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 50 g. (0.173 mole) of 4-nitro-4'-acetamidodiphenyl

75. The name acetamido is used in accordance with the nomenclature recommended by Chemical Abstracts, (1945). The name, acetamino, however, is more commonly used.

76. Raiziss, Clemence, Severac, and Moetsch, J. Am. Chem. Soc., 61, 2763 (1939).

77. Gabel and Grinberg, J. Applied Chem., (U.S.S.R.) 12, 1481 (1939) [C.A., 34, 6244 (1940)].

sulfide and 500 ml. of glacial acetic acid. Due to the exothermic reaction 23 g. (0.20 mole) of 30 percent hydrogen peroxide was cautiously added at such a rate as to keep the temperature below 60°. An additional 46 g. (0.40 mole) of 30 percent hydrogen peroxide was then added rapidly and the mixture heated on the steam bath. When the hydrogen peroxide began to decompose the heat was removed as the decomposition supplied enough heat to reflux the solution vigorously, whereupon the suspended material dissolved. Ice water was kept on hand in case the reaction became too vigorous. When the refluxing subsided, the solution was heated by the steam bath for two hours, with stirring. Toward the end of this time the product separated as a fine, tan, crystalline precipitate. After heating was complete the reaction mixture was poured upon crushed ice and, after filtration and drying, weighed 50 g. (90%) and melted at 215-220°. Upon recrystallization twice from acetone the product melted at 229-230°.[76] Gabel and Grinberg[77] report a yield of "about 90-96%" of material melting at 215-218°.

4-Nitro-4'-aminodiphenyl Sulfone. This compound has previously been prepared in 70-75% yield by deacetylation of the corresponding acetamido compound[77] using 18 percent hydrochloric acid. The following procedure, using a more concentrated hydrochloric acid solution and shorter heating period, was found to be more satisfactory. In a two-liter, three-

necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 64 g. (0.20 mole) of 4-nitro-4'-acetamidodiphenyl sulfone and a solution of 660 ml. of concentrated hydrochloric acid (density 1.18) in 340 ml. of water. The suspension was stirred and heated to reflux until all the material dissolved. After cooling, (some 4-nitro-4'-aminodiphenyl sulfone hydrochloride separated during this time), the suspension was neutralized with 40 percent sodium hydroxide. After filtration and drying, the crude 4-nitro-4'-aminodiphenyl sulfone weighed 48 g. (87%) and melted at 155-160°. The material was conveniently crystallized in 72% yield from an acetone-95 percent ethanol mixture and melted at 168-169°. Gabel and Grinberg[77] report a yield of 70-75% of product melting at 167-169°, when crystallized from 50 percent ethanol.

In subsequent runs, where 4-nitro-4'-aminodiphenyl sulfone was desired from 4-nitro-4'-aminodiphenyl sulfide, the compound was prepared in better overall yield by acetylation of the latter according to the procedure given above, followed by hydrogen peroxide oxidation of the resulting 4-nitro-4'-acetamidodiphenyl sulfide, without isolation. Subsequent to deacetylation, a 72% overall yield of 4-nitro-4'-aminodiphenyl sulfone was obtained. In a typical run, 50 g. (0.20 mole) of 4-nitro-4'-aminodiphenyl sulfide was acetylated to obtain the 4-nitro-4'-acetamidodiphenyl sulfide, according to the procedure previously described. Without isolation, and after cooling, the required amount of 30 percent hydrogen

peroxide was added and the oxidation to the sulfone carried out. The resulting 4-nitro-4'-acetamidodiphenyl sulfone was then isolated and subsequently deacetylated, as given above, and crystallized to yield 40 g. (72%) of 4-nitro-4'-aminodiphenyl sulfone, melting at 168-169°.

6-Quinolyl p-Nitrophenyl Sulfone. Application of the method of Skraup to 4-nitro-4'-aminodiphenyl sulfone yielded the desired 6-quinolyl p-nitrophenyl sulfone in good yield. In this work the best procedure was found to include the mass relations suggested by Richter and Smith,[78a] i.e., one mole of the aromatic amine, four moles of glycerol (dried by passing dry air through the liquid at 170-180° for three hours), three-fourths mole of arsenic pentoxide and a weight of sulfuric acid (density 1.84) equal to 55% of the weight of glycerol employed.

A superior product was obtained when the acetylated amine was employed,[78b] in that the amount of tarry by-products was less than when the free amine was used. This procedure also had the advantage of precluding the necessity for deacetylating the 4-nitro-4'-acetamidodiphenyl sulfone.

The Skraup synthesis of 6-quinolyl p-nitrophenyl sulfone, from 4-nitro-4'-aminodiphenyl sulfone was carried out as fol-

78. (a) Richter and Smith, J. Am. Chem. Soc., 66, 397 (1944); (b) Manske, Leger, and Gallagher, Can. J. Research, 19, B, 318 (1941).

lows. In a one-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser fitted with a calcium chloride drying tube, was placed 28 g. (0.10 mole) of 4-nitro-4'-aminodiphenyl sulfone, 37 g. (0.40 mole) of dry glycerol and 17 g. (0.074 mole) of arsenic pentoxide. The flask was equipped with a thermometer dipping into the liquid and the mixture was stirred until a heavy viscous paste was obtained. With vigorous stirring, 21 g. of concentrated sulfuric acid (density 1.84) was added through the condenser at such a rate as to maintain the temperature below 130°. The temperature was then held at 130-135° for one hour and finally the mixture was kept in active reflux for six additional hours.

Without cooling, the reaction mixture was poured upon crushed ice, neutralized in the cold with 40 percent sodium hydroxide, and the yellow-green precipitate recovered by filtration. After drying, the product weighed 31 g. (quantitative yield) and melted over a range of 150-165°. After charcoaling and crystallization from an acetone-95 percent ethanol medium, there was obtained 21 g. (67%) of a yellow crystalline product melting at 181-182°.

When the same procedure was employed, using 32 g. (0.10 mole) of 4-nitro-4'-acetamidodiphenyl sulfone, after charcoaling and crystallizing once from an acetone-95 percent ethanol mixture, 20 g. (64%) of product melting at 179-180° was obtained. The crude product, obtained in

quantitative yield, was found to melt at 170-180° and was almost entirely free of tarry material.

In crystallizing the 6-quinolyl p-nitrophenyl sulfone from the acetone-ethanol mixture, the crude product was dissolved in an excess of acetone, charcoaled and filtered, the filtrate diluted with a volume of 95 percent ethanol equal to one-third that of the acetone, and the resulting solution evaporated to incipient crystallization and then allowed to crystallize. The product for analysis melted constantly at 181-182°.

Anal. Calcd. for $C_{15}H_{10}O_3N_2S$: S, 10.18. Found: S, 10.24.

The following attempt was made in an endeavor to prepare 6-quinolyl p-nitrophenyl sulfone, by oxidation of the corresponding sulfide, (as prepared by the procedure to follow), utilizing hydrogen peroxide as the oxidizing agent.

In a 500 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 7 g. (0.025 mole) of 6-quinolyl p-nitrophenyl sulfide, dissolved in 100 ml. of a (1:1) mixture of acetic anhydride-glacial acetic acid solution. By means of a dropping funnel, and with stirring, 20 ml. of a 30 percent solution of hydrogen peroxide was added gradually to the mixture. After the peroxide had been added, the solution warmed up gradually and began to reflux. After refluxing had subsided the mixture was stirred and heated on

the steam cone for one hour. The reaction mixture was then poured into ice water to form a yellow-brown suspension. After filtration and drying, the product weighed 6.5 g. and melted over 250° with decomposition. No crystalline product could be obtained from this material. On standing, the crude material changed to a brittle dark-brown agglomerate.

6-Quinolyl p-Aminophenyl Sulfone. This compound was prepared by the catalytic reduction of 10 g. (0.032 mole) of p-nitrophenyl 6-quinolyl sulfone, according to the procedure described under 6-quinolyl p-aminophenyl sulfide dihydrochloride (see p. 102). The hot ethanolic solution of 6-quinolyl p-aminophenyl sulfone was filtered off from the Raney nickel and the filtrate concentrated to incipient crystallization. After cooling and crystallization, there was obtained 8 g. (88%) of 6-quinolyl p-aminophenyl sulfone, as colorless white crystals, melting at 170-176°. On recrystallization from an ethanol-acetone mixture the product melted at 178-179°.

Anal. Calcd. for $C_{15}H_{12}O_2N_2S$: N, 9.85. Found: N, 10.05.

6-Quinolyl p-Nitrophenyl Sulfide. This compound was prepared through the Skraup synthesis, exactly according to the procedure previously described (see p. 97). By this means 50 g. (0.20 mole) of 4-nitro-4'-aminodiphenyl sulfide was converted to 54 g. (95%) of crude 6-quinolyl p-nitrophenyl sulfide, melting at 150-155°. After charcoaling and crystal-

lizing from an acetone-95 percent ethanol mixture, there was obtained 31 g. (55%) of product melting at 167-168°. The material for analysis melted at 168.5-169.5°. Since the melting point of 6-quinolyl p-nitrophenyl sulfide is identical with that of 4-nitro-4'-aminodiphenyl sulfone (melting point 168-169°), and since it was considered possible that the oxidizing conditions of the Skraup reaction might have converted the 4-nitro-4'-aminodiphenyl sulfide to the sulfone, a mixed melting point determination was made on 4-nitro-4'-aminodiphenyl sulfone and the product obtained from the Skraup reaction. The melting point of this mixture was depressed to melt at 150-155°, hence the two compounds are not identical.

Anal. Calcd. for $C_{15}H_{10}O_2N_2S$: N, 9.93; S, 11.32. Found: N, 9.87; S, 11.20.

Preliminary to the Skraup synthesis of 6-quinolyl p-nitrophenyl sulfide, an experiment was run in which both 4-nitro-4'-aminodiphenyl sulfide and the corresponding acetamido compound were subjected to the conditions of the Skraup reaction but without the addition of glycerol, i.e., with arsenic pentoxide and concentrated sulfuric acid (density 1.84). It was thought that some sulfone might be formed. A tarry liquid was obtained, after heating and stirring for six hours at 135°. No product could be isolated. The result was the same when stirring and heating was maintained for only one hour.

When the Skraup reaction was attempted on 4-nitro-4'-aminodiphenyl sulfide using boric acid, ferrous sulfate, nitrobenzene (as oxidizing agent), glycerol and concentrated sulfuric acid (density 1.84), according to the method of Cohen,[79] only a 10% yield of crystalline product could be obtained on working up the reaction mixture. The arsenic oxide procedure proved to be the method of choice.

6-Quinolyl p-Aminophenyl Sulfide Dihydrochloride. In a pressure flask equipped with a steam jacket and facilities for the introduction of hydrogen, was placed 8 g. (0.028 mole) of 6-quinolyl p-nitrophenyl sulfide, melting at 168-169°, in 100 ml. of absolute ethanol. To this solution was added 4 g. of Raney nickel. The mixture was subjected to hydrogen, under a pressure of three atmospheres, at a temperature of 95-100° for one hour. The Raney nickel was then filtered off from the ethanol to obtain a colorless solution of 6-quinolyl p-aminophenyl sulfide. The ethanol was evaporated off under reduced pressure until a syrupy residue remained, which resisted all attempts at crystallization. The syrup was dissolved in 25 ml. of a (1:1) mixture of dry benzene and absolute ethanol and the solution evaporated to syrup form. This procedure was twice repeated in order to remove the last traces of water. Ethanolic hydrogen chloride was added and the syrup gradually

79. Cohen, J. Am. Chem. Soc., 52, 3686 (1936).

solidified to form a pale yellow, crystalline powder which was satisfactorily recrystallized from absolute ethanol. After filtration and drying the dihydrochloride weighed 7 g. (78%) and melted at 217-218° with decomposition. A further recrystallization failed to raise the melting point.

Anal. Calcd. for $C_{15}H_{14}N_2Cl_2S$: N, 8.63. Found: N, 8.84.

6-Quinolyl p-Formamidophenyl Sulfone (attempted). In a 250 ml. flask equipped with a reflux condenser was placed 7.5 g. (0.026 mole) of 6-quinolyl p-aminophenyl sulfone and 75 ml. of anhydrous formic acid. The mixture was refluxed for ten hours and then poured into a large excess of cold water to form an oil which gradually solidified. On filtration and drying, the crude product weighed 8.5 g. (quantitative yield) and melted at 191-195°. After crystallization once from 95 percent ethanol as colorless needles, the product melted at 200-201°.

Anal. Calcd. for $C_{16}H_{12}O_3N_2S$: N, 8.95. Found: N, 8.42 and 8.45.

Two subsequent recrystallizations, one from acetone, the other from methyl cellosolve, failed to raise the melting point. The nitrogen analyses given above would check for the monohydrate of the compound. i.e., $C_{16}H_{12}O_3N_2S.H_2O$: N, 8.50.

p-Aminothiophenol. This compound was prepared by refinement of the method of Lantz.[80] In a five-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, with facilities for the introduction of nitrogen, was placed a mixture of 480 g. (2 moles) of sodium sulfide nonahydrate dissolved in two liters of water, and 128 g. (0.81 mole) of p-chloronitrobenzene. The mixture was refluxed for eight hours. After cooling there remained a small amount of an orange colored oil, which was removed by extraction with ether. The aqueous layer was saturated with finely powdered sodium chloride, and then 240 g. (4 moles) of glacial acetic acid was added and the liberated oil extracted several times with ether. After drying over anhydrous sodium sulfate and distillation of the ether, the product was obtained by vacuum distillation. By this means 70 g. (69%) of product distilling at 143-146° (17 mm.) and melting at 43-45° was obtained. The pure compound melts at 46°.[81]

The product, as prepared by Lantz,[80] melted at 30°, no yield being given.

5-Nitro-6-quinolyl p-Aminophenyl Sulfide. The 5-nitro-6-chloroquinoline required in the preparation of this compound was prepared in quantitative yield (crude) by nitration of

80. Lantz, French Patent 714,682 (1931), /Chem. Zentr. I, 1829 (1932)/.

81. Zincke and Jörg, Ber., 42, 3366 (1909).

6-chloroquinoline using the method of Claus and Schedler.[82] After crystallization, an 87% yield of pure material melting at 129° was obtained.

In a 500 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser with facilities for the introduction of nitrogen, was placed 14 ml. of absolute ethanol. Careful addition of 0.64 g. (0.026 g. atom) of sodium afforded an ethanolic solution of sodium ethoxide, to which was added 3 g. (0.026 mole) of 4-aminothiophenol. By means of a dropping funnel, there was added 5 g. (0.024 mole) of 5-nitro-6-chloroquinoline dissolved in 70 ml. of hot absolute ethanol. The reaction mixture was kept at 60° during the addition and the product separated as a crystalline slurry. The reaction flask was then stirred for one-half hour at room temperature and 10 ml. of distilled water was added to dissolve the sodium chloride that had formed. Filtration and washing once with ice-cold absolute ethanol gave 4.5 g. of pure product melting at 137-138°. An additional 2 g. of product melting at 136-137° was obtained by dilution of the filtrate with water to incipient crystallization and subsequent chilling. The total yield of product was 6.5 g. (90%). The product for analysis melted at 137-138°, after crystallization to constant melting point from 95 percent ethanol.

82. Claus and Schedler, J. prakt. Chem., 49, 359 (1894).

In earlier runs the reaction product was refluxed for from one to two hours. This resulted in varying amounts of tarry material, with attendant difficulty in purification, together with greatly decreased yields. In one run an oily residue remained, after evaporating most of the alcohol in vacuum, and the product was rectified in only 60% yield, after hydrochloric acid extraction of the residue, charcoaling and subsequent crystallizations of the liberated free base from 95 percent ethanol.

Anal. Calcd. for $C_{15}H_{11}O_2N_3S$: N, 14.15. Found: N, 14.16.

5-Amino-6-quinolyl p-Aminophenyl Sulfide Trihydrochloride. In a pressure flask, equipped with a steam jacket and facilities for the introduction of hydrogen, was placed 15 g. (0.05 mole) of 5-nitro-6-quinolyl p-aminophenyl sulfide dissolved in 150 ml. of absolute ethanol. To this solution was added 4 g. of Raney nickel catalyst. The mixture was subjected to hydrogen, with shaking, under a pressure of three atmospheres at a temperature of 95-100° for one hour. The Raney nickel was then filtered off from the ethanolic solution, to which was added ethereal hydrogen chloride. The resulting bright orange crystalline precipitate of the trihydrochloride was filtered and weighed 16.5 g. (88%). The compound melted at 251-252° and was found to be very insoluble in absolute ethanol, dioxane and acetone, slightly soluble in methyl

cellosolve, and quite soluble in 95 percent ethanol. To recrystallize the compound, the material was dissolved in the required amount of 95 percent ethanol, concentrated to incipient crystallization, seeded and allowed to cool, whereupon hard, dense, orange crystals, melting at 261-262°, were deposited. A further recrystallization failed to raise the melting point.

Anal. Calcd. for $C_{15}H_{16}N_3Cl_3S$: N, 11.15. Found: N, 11.30.

4-Acetamidothiophenol. This compound was prepared by the method of Gabel and Grinberg.[77] In two runs, satisfactory results were obtained, but in subsequent attempts to prepare the compound by exactly the same procedure, the method failed due to the formation of 4-acetamidodiphenyldisulfide, which was isolated and further reduced to the desired 4-acetamidothiophenol.[83] In a one-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 20 g. (0.086 mole) of 4-acetamidobenzenesulfonyl chloride[84] and 110 ml. of 95 percent ethanol. The reaction vessel was cooled with ice and 25 g. of zinc dust was added, followed by the dropwise addition of 55 ml. of concentrated hydrochloric acid (density 1.19) over a period of fifteen to eighteen minutes. The flask was then heated by the steam bath for one-

83. Hinsberg, Ber., 39, 2430 (1906).

84. Generously supplied by the Monsanto Chemical Company, St. Louis, Missouri.

half hour. A sample was withdrawn shortly after heating and a few drops of lead acetate were added. The formation of a red-brown precipitate indicated the reaction had proceeded in the right direction. When a yellow precipitate was formed in this test, the reaction had gone in another direction (Gabel and Grinberg[77]), resulting, as indicated above, in the formation of 4-acetamidodiphenyldisulfide. After the heating was terminated, the hot reaction mixture was poured into 500 ml. of water containing 15 g. of concentrated hydrochloric acid (density 1.19). The contents of the flask were washed out with 95 percent ethanol, containing hydrochloric acid, and added to the main portion which had formed a pale yellow precipitate. After cooling, filtration and drying in vacuo, there was obtained 12 g. (89%) of product melting at 151-152°. The compound was kept in a desiccator under vacuum until required. Gabel and Grinberg report a yield of 72% of product melting at 149-150°.

5-Nitro-6-quinolyl p-Acetamidophenyl Sulfide. This compound was prepared by two methods. In one, 5-nitro-6-quinolyl p-aminophenyl sulfide was acetylated by use of acetic anhydride in acetic acid medium. In the other, the sodium salt of 4-acetamidothiophenol was condensed with 5-nitro-6-chloroquinoline.

Method 1. To 35 ml. of glacial acetic acid in a three-necked, round-bottomed flask equipped with a stirrer and

reflux condenser, was added 14 g. (0.047 mole) of 5-nitro-6-quinolyl p-aminophenyl sulfide. The solution was stirred and 10 g. (0.1 mole) of acetic anhydride was added, dropwise, by means of a dropping funnel. The mixture was refluxed two hours and poured into 500 ml. of ice water, with rapid stirring. The yellow solid which separated was filtered and washed several times with distilled water. On drying, the crude product weighed 15 g. (94%) and melted at 161-163°. Subsequent to recrystallization to constant melting point from 95 percent ethanol, the product softened at 95-100° and, after this transition melted at 173-174°. Upon drying under vacuum, the product melted without transition at 173-174°.

Method 2. In a 500 ml., three-necked, round-bottomed flask equipped with a stirrer and condenser, was placed 30 ml. of 95 percent ethanol containing 3.25 g. (0.08 mole) of sodium hydroxide. To this solution was added 13.4 g. (0.08 mole) of 4-acetamidothiophenol, followed by the dropwise addition of 16.8 g. (0.08 mole) of 5-nitro-6-chloroquinoline, dissolved in 210 ml. of hot 95 percent ethanol. The solution was stirred and refluxed for one-half hour and then 100 ml. of distilled water was added. After cooling and filtering there was obtained 21.5 g. (80%) of crystalline product, melting at 167-170°. After recrystallization to constant melting point from 95 percent ethanol, and drying in vacuum, the compound melted at 173-174°.

A mixed melting point determination, made on products obtained by each method, was not depressed.

Anal. Calcd. for $C_{17}H_{13}O_3N_3S$: N, 12.42. Found: N, 12.62 and 12.52.

5-Nitro-6-quinolyl p-(2,5-Dimethyl-1-pyrryl)-phenyl Sulfide (attempted). In a 250 ml., round-bottomed flask equipped with a reflux condenser, was placed 3 g. (0.01 mole) of 5-nitro-6-quinolyl p-aminophenyl sulfide and 15 ml. of acetonyl-acetone. The mixture was refluxed for two hours, and the dark brown solution was poured into ice water. Filtration afforded a dark gummy precipitate, from which no product could be isolated.

5-Nitro-6-quinolyl p-Chlorophenyl Sulfide. The 4-chlorothiophenol required for the preparation of this compound was prepared from 4-chloroaniline through reaction of the diazonium salt with potassium ethyl xanthate, and subsequent saponification of the resulting xanthogenic ester, as described by Daccomo.[85]

The 5-nitro-6-quinolyl p-chlorophenyl sulfide was prepared by Method 2 as described under 5-nitro-6-quinolyl p-acetamidophenyl sulfide. Accordingly, 7.2 g. (0.05 mole)

85. Daccomo, Jahresber Fortsche. Chem., 1377 (1891) /Beil., 6, 326, Julius Springer, Berlin, 1923_7; see also, Schwarzenbach and Egli, Helv. Chim. Acta., 17, 1176 (1934) for a good general procedure.

of 4-chlorothiophenol was added to 20 ml. of 95 percent ethanol containing 2 g. (0.05 mole) of sodium hydroxide. To this solution was added 8.6 g. (0.04 mole) of 5-nitro-6-chloroquinoline dissolved in 100 ml. of hot 95 percent ethanol, and the mixture was refluxed one-half hour. After diluting the reaction mixture with 35 ml. of distilled water, the product crystallized from the reaction mixture. On filtration and drying there was obtained 11 g. (88%) of product melting at 115-116°. A recrystallization from 95 percent ethanol did not raise the melting point.

Anal. Calcd. for $C_{15}H_9O_2N_2ClS$: N, 8.84. Found: N, 8.98.

5-Nitro-6-quinolyl p-Acetamidophenyl Sulfone. The required 4-acetamidobenzenesulfinic acid was prepared by the method given in Organic Syntheses.[86] The sodium salt of the acid was conveniently prepared according to the directions given in the latter reference.

In a 500 ml., three-necked, round-bottomed flask fitted with a reflux condenser, mechanical stirrer, and thermometer, was placed 24 g. (0.11 mole) of the sodium salt of 4-acetamidobenzenesulfinic acid and 30 ml. of a mixture of 37.5 ml. of ethylene glycol and 60 ml. of methyl cellosolve. The mixture was stirred and heated by an oil bath until solution was com-

86. Gilman and Blatt, ed., Organic Syntheses. Collective Vol. I, 2nd ed., Wiley, New York, 1941, p. 7.

plete, after which 20.9 g. (0.10 mole) of finely powdered 5-nitro-6-chloroquinoline was added. The mixture was stirred and heated at 125° for three and one-half hours, and after cooling somewhat, 10 ml. of distilled water was added to dissolve the sodium chloride formed. The product formed a thick paste during the course of the reaction. After standing several hours at room temperature the compound was filtered and washed several times, first with 95 percent ethanol, then with distilled water, and finally with 95 percent ethanol. A quantitative yield of colorless, crystalline product, melting at 246-247°, was obtained. When recrystallized to constant melting point from the ethylene glycol-methyl cellosolve mixture, the compound melted at 247-248°.

Anal. Calcd. for $C_{17}H_{13}O_5N_3S$: N, 11.32; S, 8.64. Found: N, 11.36; S, 8.74.

The following attempt was made in an endeavor to prepare the compound by oxidation of 5-nitro-6-quinolyl p-acetamidophenyl sulfide with 30 percent hydrogen peroxide.

To a solution of 9.5 g. (0.028 mole) of 5-nitro-6-quinolyl p-acetamidophenyl sulfide dissolved in 10 ml. of glacial acetic acid, in a 250 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was added 8.6 ml. of 30 percent hydrogen peroxide, the temperature being maintained below 60°. After the addition was completed the solution was stirred and heated on the steam bath for two hours.

During this time a brown-yellow precipitate appeared. The solution was cooled and poured onto ice, yielding a brown precipitate which rapidly formed a gummy mass on exposure to the air. After drying, the gummy material set up to a hard brittle glass which was broken up to a powder for attempted crystallization. None of this product could be resolved as 5-nitro-6-quinolyl p-acetamidophenyl sulfone.

5-Nitro-6-quinolyl p-Aminophenyl Sulfone. In a 500 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 250 ml. of hydrochloric acid (1:1) and 20 g. (0.054 mole) of 5-nitro-6-quinolyl p-acetamido phenyl sulfone. The mixture was refluxed for fifteen minutes and then cooled and neutralized with 20 percent sodium hydroxide solution. After filtration and drying, the product was obtained in quantitative yield and melted at 250-255°. The compound was recrystallized to constant melting point from an ethylene glycol-methyl cellosolve mixture (37.5 ml. of ethylene glycol and 60 ml. of methyl cellosolve), and melted at 258-259°.

Anal. Calcd. for $C_{15}H_{11}O_4N_3S$: S, 9.73. Found: S, 9.88 and 9.76.

8-Nitro-6-quinolyl Phenyl Sulfide (attempted). In a 500 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 10.4 g. (0.05 mole)

of 6-chloro-8-nitroquinoline[87] dissolved in 250 ml. of 95 percent ethanol and 21.7 g. (0.1 mole) of the silver salt of thiophenol (prepared by addition of dilute silver nitrate to an ethanolic solution of thiophenol). The suspension was stirred and refluxed for twelve hours, after which the material was filtered without cooling. The filtrate was concentrated to incipient crystallization and after cooling, the 6-chloro-8-nitroquinoline was recovered, in quantitative yield. When the experiment was repeated, using methyl cellosolve as the solvent, no reaction occurred.

5-Nitro-8-acetamido-6-quinolyl p-Acetamidophenyl Sulfone. This compound was prepared by the interaction of sodium 4-acetamidobenzenesulfinate and 5-nitro-6-chloro-8-acetamidoquinoline. The preparation of the latter by a sequence of reactions, beginning with 6-chloro-8-nitroquinoline, has already been described.[87] To a solution of 9.8 g. (0.044 mole) of the sodium salt of 4-acetamidobenzenesulfinic acid in 60 ml. of a mixture of 37.5 ml. of ethylene glycol and 60 ml. of methyl cellosolve, was added 10.6 g. (0.04 mole) of 5-nitro-6-chloro-8-acetamidoquinoline in a 250 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser. The solution, which was obtained on heating, was

87. Gilman, Benkeser, Gainer, Lindblad, Marshall, Massie, Myers, and Tolman, J. Am. Chem. Soc., 68, 1577 (1946).

refluxed for three and one-half hours. During this time a tan crystalline precipitate formed. At the end of the heating, the solution was cooled somewhat and 6 ml. of water was added to dissolve the sodium chloride formed by the reaction and any excess of the sodium salt of 4-acetamidobenzenesulfinic acid. The mixture was allowed to stand overnight and then filtered. The crystalline precipitate was washed with cold 95 percent ethanol, then with hot water, and finally with 95 percent ethanol. After drying, the crude product so obtained weighed 15 g. (92%) and melted at 306-308°. On recrystallization to constant melting point from methyl cellosolve, the compound melted at 313-314°.

Anal. Calcd. for $C_{19}H_{16}O_6N_4S$: N, 13.10. Found; N, 13.30.

5-Nitro-8-amino-6-quinolyl p-Aminophenyl Sulfone. In a 250 ml., three-necked, round-bottomed flask equipped with a reflux condenser, was placed 7.5 g. (0.0175 mole) of 5-nitro-8-acetamido-6-quinolyl p-acetamidophenyl sulfone and 150 ml. of a solution of hydrochloric acid containing 100 ml. of concentrated hydrochloric acid (density 1.18) and 50 ml. of water. The mixture was refluxed for fifteen minutes, whereupon all the starting material dissolved. On cooling, the product separated in large orange-yellow crystals which were filtered off. The crystalline product was then suspended in water and neutralized with concentrated ammonium hydroxide,

and the resulting yellow precipitate filtered. On drying there was obtained 5.5 g. (91%) of product melting at 240-245°. The compound, when recrystallized to constant melting point from acetone, melted at 247-247.5°.

Anal. Calcd. for $C_{15}H_{12}O_4N_4S$: N, 16.29. Found: N, 16.40.

5-Nitro-8-amino-6-quinolyl p-Acetamidophenyl Sulfone. In a 250 ml., three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, was placed 8.1 g. (0.036 mole) of the sodium salt of 4-acetamidobenzenesulfinic acid dissolved in 50 ml. of a mixture of 37.5 ml. of ethylene glycol and 75 ml. of methyl cellosolve. To the stirred solution was added 7.5 g. (0.0334 mole) of finely powdered 5-nitro-6-chloro-8-aminoquinoline.[87] The mixture was then refluxed for three and one-half hours. During this time the product separated in crystalline form. After the heating was complete, 6 ml. of water was added to dissolve the sodium chloride and excess sodium salt of 4-acetamidobenzenesulfinic acid. The solution was then allowed to stand overnight and the product filtered off and washed with 95 percent ethanol, hot water, and finally 95 percent ethanol. After drying, the product weighed 12.2 g. (95%) and melted at 255-258°. After recrystallizing to constant melting point from methyl cellosolve, the product melted at 261.5-262.5°.

Anal. Calcd. for $C_{17}H_{14}O_5N_4S$: S, 8.30. Found: S, 8.42 and 8.50.

4-Nitro-4'-acetoacetamidodiphenyl Sulfone.[88] In a one-liter, three-necked, round-bottomed flask equipped with a hand stirrer and thermometer, was placed 28 g. (0.216 mole) of ethyl acetoacetate. The system was heated by means of an oil bath to maintain an internal temperature of 160°. To the acetoacetic ester, heated to 160°, was added 15 g. (0.054 mole) of finely powdered 4-nitro-4'-aminodiphenyl sulfone, at such a rate as to maintain the temperature at 160°. The mixture was occasionally stirred to remove any ethanol formed through condensation of the reactants. After heating at 160° for one-half hour, the solution was allowed to cool to room temperature, whereupon the product crystallized in hard, dense, pale yellow needles. After filtration, and washing with 95 percent ethanol, the product weighed 14 g. (72%) and melted at 155-175°. In another run, product melting at 187-188° was obtained. For purification through crystallization, acetone was found to be the most suitable solvent. The following data were obtained when repeated recrystallizations were performed. After the first recrystallization, the compound melted at 179-180°. On recrystallization the product melted at 180-181°. After a third recrystallization the material melted at 183-184°. Subsequent to the fourth recrystallization the product melted at 183-185°. The compound did not appear to melt sharply. A mixed melting point of the material melting at

88. Adapted from procedures employed for the preparation of 2-hydroxy-4-methyl-6-methoxyquinoline, Ainley and King, Proc. Roy. Soc. (London), B125, 60 (1938).

at 183-185° and starting material melting at 170-171°, was depressed to 150-160°. The product is therefore not identical with the starting material. The compound used for analysis melted at 187-188°.

Anal. Calcd. for $C_{16}H_{14}O_6N_2S$: N, 7.74. Found: N, 8.24.

2-Hydroxy-4-methyl-6-quinolyl p-Nitrophenyl Sulfone (attempted). In a one-liter, three-necked, round-bottomed flask equipped with a mechanical stirrer and reflux condenser, and having a thermometer to indicate the internal temperature of the contents, was placed 15 ml. of concentrated sulfuric acid (density 1.84), cooled to 2-5° by means of an ice bath, with rapid stirring. Thirty-six grams (0.10 mole) of supposed 4-nitro-4'-acetoacetamidodiphenyl sulfone ($O_2NC_6H_4SO_2C_6H_4NHCOCH_2COCH_3$), in finely powdered form, was added at such a rate as to keep the temperature below 35°. The ice bath was then replaced by a water bath which was heated to 85-90°. A sudden evolution of heat may occur at this point. The mixture was then heated at 90-100° for two hours. At the end of this time, and while still hot, the mixture was poured, with stirring, into an excess of water. The product which separated was then filtered and washed once with distilled water. The filter cake was then suspended in water in a large beaker and made slightly alkaline to litmus by the addition of dilute ammonium hydroxide. The suspension was filtered and washed several times with distilled water.

For purification the crude product was charcoaled and crystallized from 95 percent ethanol and melted at 160-161°. A further crystallization raised the melting point to 167-169°. A mixed melting point determination on this material and 4-nitro-4'-aminodiphenyl sulfone was made and, since the melting point was not depressed, the product was 4-nitro-4'-aminodiphenyl sulfone, which was regenerated under the conditions employed.

4-Nitro-4'-acetoacetamidodiphenyl Sulfide.[88] When 4-nitro-4'-aminodiphenyl sulfide was reacted with ethyl acetoacetate, under the conditions previously outlined, a quantitative yield of product, supposedly 4-nitro-4'-acetoacetamidodiphenyl sulfide ($O_2NC_6H_4SC_6H_4NHCOCH_2COCH_3$), melting at 133-134°, was obtained. The material for analysis melted at 133.5-134.5°.

Anal. Calcd. for $C_{16}H_{14}O_4N_2S$: N, 8.48. Found: N, 8.75.

On attempted ring closure of this material under the conditions previously given, subsequent to crystallization, a product melting at 142.5-143° was obtained. This was found to be identical with 4-nitro-4'-aminodiphenyl sulfide, by means of melting and mixed melting points. Apparently 4-nitro-4'-aminodiphenyl sulfide was regenerated from the supposed acetoacetamido compound under the conditions employed.

γ-(p-Nitrophenoxy)-propyl β-Hydroxyethyl Sulfone. This compound was prepared by the hydrogen peroxide-oxidation of the corresponding sulfide in glacial acetic acid medium. The

required γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide was prepared by the following sequence of reactions which has recently been described.[89]

$$p\text{-}O_2NC_6H_4ONa + ClCH_2CH_2CH_2OH \longrightarrow p\text{-}O_2NC_6H_4OCH_2CH_2CH_2OH + NaCl$$

$$p\text{-}O_2NC_6H_4OCH_2CH_2CH_2OH + SOCl_2 \longrightarrow p\text{-}O_2NC_6H_4OCH_2CH_2CH_2Cl + SO_2 + HCl$$

$$p\text{-}O_2NC_6H_4OCH_2CH_2CH_2Cl + NaSCH_2CH_2OH \longrightarrow p\text{-}O_2NC_6H_4OCH_2CH_2CH_2SCH_2CH_2OH + NaCl$$

To a stirred solution of 70 g. (0.275 mole) of crude γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide in 275 ml. of glacial acetic acid contained in a one-liter, three-necked, round-bottomed flask equipped with a thermometer, stirrer and dropping funnel, was added 32 g. (0.28 mole) of 30 percent hydrogen peroxide at such a rate as to maintain the temperature below 60°.

Then, after the same cautious addition of 64 g. (0.55 mole) of 30 percent hydrogen peroxide, the dropping funnel was replaced by a reflux condenser and the mixture heated on a steam cone. When the hydrogen peroxide began to decompose, the heat was removed as the decomposition supplied enough heat to reflux the solution vigorously. An ice bath was kept on hand in the event that the decomposition became too violent. When the refluxing had subsided, the mixture was stirred and

89. Gilman and Fullhart, J. Am. Chem. Soc., 67, 1585 (1945).

heated on the steam cone for two hours. At the end of this time the hot reaction mixture was cooled externally and then poured onto a kilogram of chopped ice with stirring, to assist in solidification of the thick, viscous, yellow oil which separated. After working the chilled crude product with a stirring rod the material solidified to a pasty bright yellow solid. Filtration and drying afforded a quantitative yield of the crude material which melted at 88-95°. In the first run, which was made, a tedious fractional crystallization of the crude product from 95 percent ethanol yielded two products, one of which melted constantly at 103-104°, the other constantly at 85-86°. Subsequently, the compound melting at 103-104° was shown to be γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone (the desired product), and the lower melting product proved to be the acetic acid ester of the other, that is γ-(p-nitrophenoxy)-propyl β-acetoxyethyl sulfone. The crude material is thus a mixture of the hydroxy compound and its acetate ester.

For rectification, the crude material in powder form was suspended in two liters of 2N sulfuric acid in a five-liter, three-necked, round-bottomed flask equipped with a stirrer and reflux condenser, and the heterogeneous mass was refluxed for five hours. After cooling, filtration and drying, the brown colored solid weighed 70 g. (85%) and melted with sintering at 88-95°. After charcoaling and recrystallization to constant

melting point, the pale yellow crystalline compound melted at 103-104°. A mixed melting point determination with the above material and the compound melting at 103-104°, obtained directly from the crude material by fractional crystallization, was not depressed. The two compounds are therefore identical.

A small portion of the material melting at 85-86°, presumably γ-(p-nitrophenoxy)-propyl β-acetoxyethyl sulfone, was hydrolyzed with boiling 2N sulfuric acid according to the procedure outlined above. After charcoaling and crystallization from 95 percent ethanol, the pale yellow crystals melted at 103-104°. A further crystallization did not raise the melting point. This material was shown to be identical with the material melting at 103-104°, which was separately isolated from the crude product of oxidation by the method of mixed melting points.

Anal. Calcd. for $C_{11}H_{15}O_6NS$: N, 4.84. Found: N, 5.01.

γ-(p-Nitrophenoxy)-propyl β-Acetoxyethyl Sulfone.

Method 1. A mixture of 10.3 g. (0.04 mole) of crude γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide and 6 g. (0.06 mole) of acetic anhydride was heated to 110° for one hour in a round-bottomed flask, equipped with a reflux condenser. The hot mixture was then cooled to 0°, by means of an ice bath, and 10 ml. of glacial acetic acid was added, followed by the cautious, dropwise addition of 12 g. (0.12 mole) of 30 percent hydrogen peroxide. The mixture was then heated

on a steam cone until the hydrogen peroxide began to decompose. The heat was removed until the violence of the reaction had subsided, after which time the solution was stirred and heated at 95-100° by the steam cone for two hours. At the end of this period the amber solution was poured upon an excess of ice, whereupon a viscous yellow oil separated which, upon washing in cold 10 percent sodium bicarbonate, set up to a yellow solid. Filtration, washing with distilled water, and drying afforded 10.5 g. (80%) of crude product melting at 65-72°. After three recrystallizations from 95 percent ethanol, the product melted constantly at 85-86°.

Method 2. A solution of 2.9 g. (0.01 mole) of γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone, melting at 103-104°, in 10 g. (0.1 mole) of acetic anhydride was gently warmed to 125°, and the temperature held at 125° for one-half hour by means of an oil bath. The mixture was allowed to cool and then poured upon an excess of chopped ice. The material solidified upon stirring and was washed once or twice with 10 percent sodium bicarbonate solution. After filtration and washing with distilled water, followed by vacuum drying, a quantitative yield of product softening at 78° and melting at 81-82° was obtained. After recrystallization to constant melting point from 95 percent ethanol, the pale yellow crystalline material melted at 85-86°.

Both the compounds obtained by either Method 1 or Method

2 were found to be identical with the compound melting at 85-86° which was isolated from the crude product of oxidation of γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide.

Anal. Calcd. for $C_{13}H_{17}O_7NS$: N, 4.23. Found: N, 4.21.

γ-(p-Aminophenoxy)-propyl β-Hydroxyethyl Sulfone. In a pressure flask containing a solution of 135 ml. of acetone and 15 ml. of absolute ethanol, 9.7 g. (0.034 mole) of γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone, melting at 103-104°, was hydrogenated, over Raney nickel as catalyst, under three atmospheres pressure of hydrogen. The pressure flask was steam-jacketed and heated to 95-100° during the course of the reaction. After shaking for one hour the Raney nickel was filtered off and the water-white filtrate evaporated to dryness under vacuum. Filtration and drying afforded 8.7 g. (92%) of the white crystalline product which melted at 131-132°. Upon recrystallization to constant melting point from 95 percent ethanol, the compound melted at 133.5-134°.

Anal. Calcd. for $C_{11}H_{17}O_4NS$: N, 5.40. Found: N, 5.53.

γ-[p-(2,5-Dimethyl-1-pyrryl)-phenoxy]-propyl β-Hydroxyethyl Sulfone (attempted). Method 1. This preparation followed the general procedure of Hazelwood, Hughes, and Lions.[58b] A mixture of 4.5 g. (0.0173 mole) of γ-(p-aminophenoxy)-propyl β-hydroxyethyl sulfone, melting at 132-133°, and 5 g. (0.044 mole) of acetonylacetone was placed in a 50 ml. flask, which was fitted with a condenser. Approximately two drops of

dilute hydrochloric acid (1:1) was added and a faint red color formed in the solution. The mixture was then heated to 100° for one hour, whereupon all the material in the flask dissolved. At this stage the solution was refluxed for two hours by means of an oil bath. After cooling, the dark brown solution was poured, with stirring, upon an excess of chopped ice. After standing for several hours and upon working the heavy gummy material, a dark brown solid was obtained. Attempts to recrystallize the solid from methanol, ethanol, benzene, chloroform and petroleum ether (b.p. 60-68°) were unsuccessful. The crude solid darkened considerably on standing and formed a shiny, black, brittle, amorphous mass which could not be rectified.

Method 2. A mixture of 3.42 g. (0.03 mole) of acetonylacetone, 5.2 g. (0.02 mole) of γ-(p-aminophenoxy)-propyl β-hydroxyethyl sulfone, melting at 132-133°, 15 ml. of absolute ethanol, and 5 ml. of glacial acetic acid were refluxed for four hours. At the end of the heating period the mixture was chilled for several hours by means of an ice-salt bath. No crystallization occurred. On pouring upon excess ice, a viscous oil was obtained which gradually solidified after standing. Attempts to crystallize this material failed. On repeated extraction of the solid with petroleum ether (b.p. 60-68°), a minute amount of starting material was obtained which, upon subsequent recrystallization from 95 per-

cent ethanol, melted at 129-131°. A mixed melting point determination using this product and the starting material showed no depression.

γ-(p-Aminophenoxy)-propyl β-Chloroethyl Sulfone Hydrochloride. One hundred grams (0.93 mole) of Eastman white label thionyl chloride was placed in a 250 ml., round-bottomed flask and the liquid cooled to 0° by means of an ice-salt bath. With continued cooling and vigorous shaking, 11 g. (0.043 mole) of finely powdered γ-(p-aminophenoxy)-propyl β-hydroxyethyl sulfone was dusted into the thionyl chloride. An immediate reaction took place and the thionyl chloride colored to a deep yellow. When the addition was complete a lumpy mass had formed. A reflux condenser was fitted to the flask and the heterogeneous mixture was gently warmed, beginning with a cold water bath. Shaking was continued. As the mixture warmed, solution of the amine was effected and a gaseous evolution occurred. The solution, yellow to orange in color, was gently refluxed for one hour with the water bath held at 80-90°. At this stage the flask was equipped for downward distillation and the bulk of the excess thionyl chloride was distilled off under the vacuum of the water pump. The excess thionyl chloride was then effectively and completely removed by the dropwise addition of absolute ethanol, with shaking, to the ice-cold liquid remaining in the flask. A vigorous exothermic reaction occurred, the ethanol being con-

verted to gaseous ethyl chloride with evolution of hydrogen chloride gas and sulfur dioxide. It was found essential that the addition of absolute ethanol be dropwise, and that the reaction mixture be constantly cooled by an efficient ice-salt bath. After excess absolute ethanol had been added, the semi-solid mass was gently warmed by means of a water bath to complete the reaction. Continuous gas evolution occurred and the crystalline hydrochloride precipitated out immediately in well-formed yellow needles. Sufficient absolute ethanol was added to dissolve the material. In the first run a few crystals were reserved for seeding purposes. A small amount of charcoal was added to the clear solution and after hot filtration, cooling and seeding, the material was set aside to crystallize. Filtering and drying in a vacuum desiccator yielded 10.5 g. (78%) of pale yellow crystals of the hydrochloride which melted at 175-176°. The product for analysis melted constantly at 179-180°, when recrystallized from absolute ethanol.

Anal. Calcd. for $C_{11}H_{17}O_3NCl_2S$: N, 4.46; Cl, 22.44. Found: N, 4.47; Cl, 22.48.

β-(6-Methoxy-8-quinolylamino)-ethyl γ-(p-Aminophenoxy)-propyl Sulfone (attempted). A mixture of 1.95 g. (0.0112 mole) of 6-methoxy-8-aminoquinoline,[90] 3.5 g. (0.0112 mole) of

90. Kindly supplied by Parke-Davis and Company, Detroit, Michigan.

γ-(p-aminophenoxy)-propyl β-chloroethyl sulfone hydrochloride, and 1.5 ml. of absolute ethanol were mixed and heated by a boiling water bath for one hour. The solution turned dark red-brown in color. At this stage the mixture was heated for six hours by an oil bath held at 120-130°. During the heating period the mixture reverted to a dark yellow crystalline mass. After cooling the solid was dissolved in 60 ml. of distilled water. Twenty percent sodium hydroxide solution was then added until the mixture was basic to litmus, whereupon a dark gray precipitate formed. This material was insoluble in ether. The heterogeneous mixture was then exhaustively extracted with ether. The ether extracts were combined and dried over anhydrous sodium sulfate. Filtering and drying of the precipitate gave 3.5 g. of the dark material. This product was found to be insoluble in 95 percent ethanol, dioxane and methyl cellosolve, and could not be rectified by crystallization.

The dried ether extract was subjected to ethanolic hydrogen chloride. A pale buff-colored precipitate resulted. When recrystallized from absolute ethanol, the compound melted at 220-222°. A qualitative analysis for sulfur was negative. A mixed melting point determination involving this material, and an authentic specimen of 6-methoxy-8-aminoquinoline hydrochloride, was not depressed. The compounds are therefore identical. For this reason it was concluded that the condensation failed. Further attempts to effect reaction by varying

the temperature and time of reaction gave the same result.

The condensation also failed when morpholine was substituted for 6-methoxy-8-aminoquinoline.

γ-(6-Methoxy-8-quinolylamino)-propyl Mercaptan Hydrochloride. The γ-chloropropyl mercaptan required in the preparation of this compound was synthesized in essential accordance with the procedure given by Sjorberg.[91] In brief, thioacetic acid was added to the ethylenic double bond of allyl chloride to obtain α-acetyl γ-chloropropyl mercaptan in 83.5% yield. The thioester so obtained was cleaved through use of an excess of one percent methanolic hydrogen chloride to yield γ-chloropropyl mercaptan in 81% yield.

A mixture of 17.5 g. (0.1 mole) of 6-methoxy-8-aminoquinoline[90] and 12.6 g. (0.115 mole) of γ-chloropropyl mercaptan was placed in a 100 ml., three-necked, round-bottomed flask equipped with a condenser and facilities for the introduction of nitrogen. The mixture was heated by an oil bath at 100° for three-quarters of an hour. The temperature was slowly raised to 130° over a period of one and one-half hours, at the end of which time the temperature of the oil bath was held at 135° for fifteen hours. Subsequent to cooling, 100 ml. of distilled water was added, together with 5 ml. of concentrated hydrochloric acid (density 1.18). Complete

91. Sjorberg, Ber., 74, 64 (1941).

solution was effected except for a small amount of remaining insoluble crystalline hydrochloride. An excess of 20 percent sodium hydroxide was added to the aqueous solution and the crystalline material broken up to aid in solution. The alkaline solution so obtained was then exhaustively extracted with ether to remove any unreacted 6-methoxy-8-aminoquinoline. The aqueous solution was made acid with hydrochloric acid to liberate the amphoteric base, and then made alkaline with ammonium hydroxide. The oily ammoniacal solution was then exhaustively extracted with ether, the ether extracts combined and dried, and the ether evaporatively distilled. The crude red oil so obtained weighed 10 g. On vacuum distillation 8 g. (32%) of a pale yellow viscous oil boiling at 174-178° (0.5 mm.) was collected. Conversion to the hydrochloride was effected by solution of the oil in anhydrous ether, followed by addition of methanolic hydrogen chloride. The compound so formed was bright orange in color and melted at 168-170°. Recrystallized to constant melting point from absolute methanol, the compound sintered at 171° and melted at 172-173.5°.

Anal. Calcd. for $C_{13}H_{17}ON_2ClS$: N, 9.83; S, 11.22. Found: N, 9.83 and 9.82; S, 11.25, 11.20 and 11.10.

4-Hydroxyisoquinoline. A mixture of 10.5 g. (0.05 mole) of 4-bromoisoquinoline, 5 g. (0.02 mole) of copper sulfate pentahydrate, and 4.1 g. (0.06 g. atom) of copper bronze

powder as catalyst, was intimately ground in a mortar. The resulting powder was then added to a solution of 31.3 g. (0.78 mole) of sodium hydroxide dissolved in 17 ml. of water, and thoroughly mixed. The mixture was then transferred to a copper beaker, placed in a sealed bomb chamber and electrically heated to 210° for twelve hours.

After cooling, the dark brown residue in the copper beaker was taken up with hot water and the suspension filtered. The aqueous filtrate was treated with excess Dry Ice in pebble form, whereupon the crude light brown 4-hydroxyisoquinoline precipitated. Filtration afforded 4.5 g. (61%) of product melting at 210-214°. A small portion of the product was sublimed against a cold finger under a vacuum of 0.15 mm., and the sublimate melted at 218-220°.

The crude material was suitably crystallized as long slender needles from a mixture of one volume of glacial acetic acid and two volumes of diethyl ether, after complete solution in the acetic acid. When the crystalline product was thoroughly dried in a vacuum desiccator, an amorphous tan powder was obtained, which melted at 223°. Further recrystallizing and vacuum drying did not raise the melting point.

In another run, using double the quantities outlined, the yield of crude 4-hydroxyisoquinoline checked at 60%. For unknown reasons, in some subsequent runs poor yields and large amounts of tar were obtained when the size of run was further

increased. It is possible that use of a suitable shaking autoclave might overcome this difficulty.

Anal. Calcd. for C_9H_7ON: N, 9.65. Found: N, 9.67.

4-Hydroxyisoquinoline Picrate. A sample of the base, dissolved in hot 95 percent ethanol, was treated with a hot 95 percent ethanolic solution of picric acid. On cooling, a yellow crystalline picrate formed which melted constantly at 243-244°, after repeated recrystallization from 95 percent ethanol.

Anal. Calcd. for $C_{15}H_{10}O_8N_4$: N, 14.97. Found: N, 15.20.

IV. DISCUSSION

Following the isolation of quinine and cinchonine by Pelletier and Caventou in 1820, and the demonstration of the activity which these compounds possessed as antipyretics, especially in combating malarial fever, the attention of chemists of the entire world has been directed to the syntheses of new compounds possessing superior pharmacological properties. The discovery by Gerhard in 1842 that cinchonine, when fused with potassium hydroxide, yielded quinoline and quinoline derivatives served to stimulate greatly the interest of research workers in the quinoline nucleus. The attention which chemists and clinicians have devoted to studies of the therapeutic properties of quinoline and its derivatives has contributed greatly to our present knowledge of the chemistry relating to quinoline and its analogs.[92]

A. The Addition of Organolithium Compounds to Quinoline

The use of organometallic compounds as an adjunct to the syntheses of aryl- and alkylquinolines is relatively new. The present status of such reactions has been discussed in the Historical Section of this dissertation. The preparation of

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92. v. Oettingen, "The Therapeutic Agents of the Quinoline Group", the Chemical Catalog Company, Inc., New York, N.Y. (1933).

several organolithium compounds used in this study--and particularly those with otherwise reactive functional groups--was effected through application of the halogen-metal interconversion reaction using n-butyllithium. This reaction[28a,b,32,33,35a,47b,49a,93] is a method of choice for the preparation of organolithium compounds inaccessible through other more direct methods. Noteworthy is the fact that by this means aryllithium compounds containing nuclear hydroxyl,[93f] primary amino,[47b,49a,93e] and carboxyl[93f] substituents have been obtained. To date these organolithium compounds have either been used for the direct introduction of organic substituents (containing functional groups) into other organometallic compounds, or converted into the corresponding organomagnesium compounds by means of anhydrous magnesium bromide prior to reaction with an organometallic halide. These findings lent hope to the possibility that the direct introduction of substituents containing otherwise reactive functional groups might be effected by the addition of such organolithium compounds to quinoline and isoquinoline.

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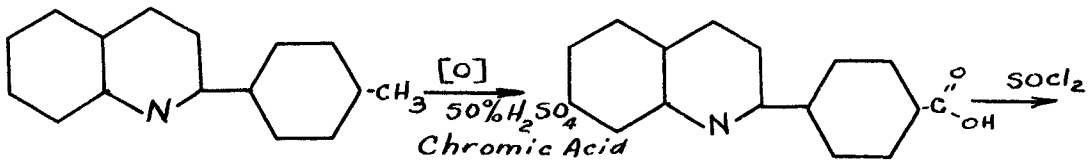
93. (a) Wittig, Pockels, and Dröge, Ber., 71, 1903 (1938); (b) Gilman, Langham, and Jacoby, J. Am. Chem. Soc., 61, 106 (1939); (c) Wittig and Pockels, Ber., 72, 89 (1939); Wittig and co-workers, ibid., 73, 1197 (1940); (d) Gilman and Jones, J. Am. Chem. Soc., 63, 1439, 1441, 1443 (1941); (e) Gilman and Stuckwisch, ibid., 64, 1007 (1942); (f) Arntzen, C. E., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1942.

Further extension of the applicability of this type of organometallic compound by demonstration of such an addition reaction seemed inviting. In addition, the preparation of such compounds seemed more desirable due to the rather high tuberculocidal activity of 2-(p-aminophenyl)-pyridine and related types.[94] As a result, the syntheses of similar homologs in the quinoline and isoquinoline series were undertaken in the hope that an even more active type might be found.

In the quinoline series the particular higher homolog is 2-(p-aminophenyl)-quinoline. Corresponding types in the isoquinoline series are the 1-(p-substituted-phenyl)-isoquinoline compounds.

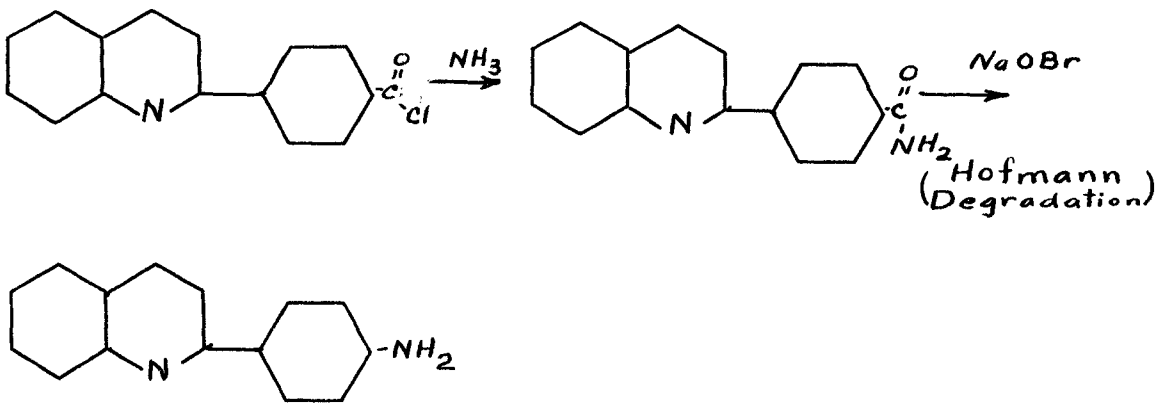
Heretofore the most practical syntheses of 2-(p-aminophenyl)-quinoline were accomplished by John.[95,96] By one means, this worker obtained the compound by the following series of reactions:[95]



94. Unpublished studies by J. T. Edwards and R. Clark of these laboratories.

95. John, J. prakt. Chem., [2] 133, 13 (1932).

96. John, ibid., [2] 139, 97 (1934).



By a second method,[96] the compound was obtained through the decarboxylation of 2-(p-aminophenyl)-4-carboxyquinoline. The latter was obtained by the interaction of isatin and p-aminoacetophenone in a strongly alkaline medium.

The relative inaccessibility of 2-(p-aminophenyl)-quinoline makes desirable a more direct means of obtaining the compound. Therefore, the possible use of an organolithium compound was considered as a means of obtaining direct substitution in the quinoline and isoquinoline heterocycle in the 2- and 1-positions, respectively. In the case of 2-(p-aminophenyl)-quinoline and 1-(p-aminophenyl)-isoquinoline, the required organometallic compound would be p-aminophenyllithium. The syntheses were accomplished through the preparation of the supposed p-N,N-dilithioaminophenyllithium[47b] by halogen-metal interconversion of p-bromoaniline with n-butyllithium, and addition of the resultant insoluble organo-

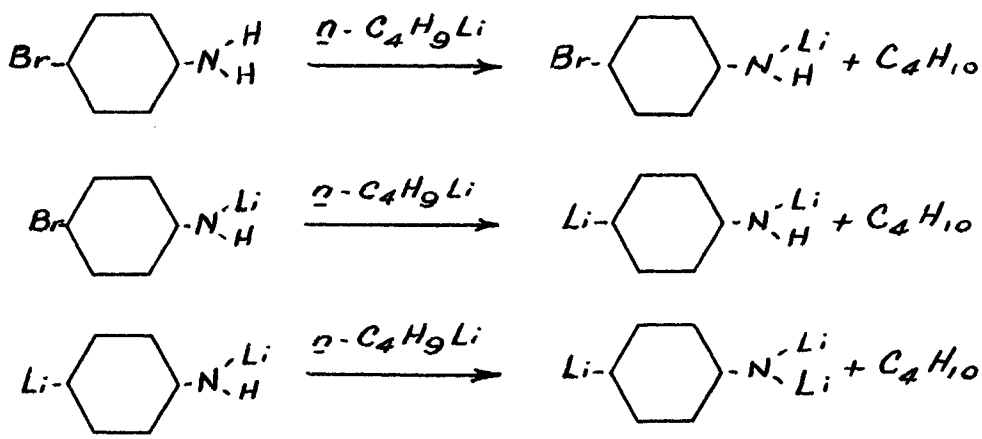
metallic compound to the ammono aldehyde group of quinoline or isoquinoline to obtain, subsequent to hydrolysis and oxidation, 2-(p-aminophenyl)-quinoline, and 1-(p-aminophenyl)-isoquinoline, respectively.

Recently, Gilman and Stuckwisch[49a,93e] had occasion to prepare this particular organometallic compound incidental to an extension of procedures for the introduction of water-solubilizing groups to organometalloidal compounds. The organometallic compound was prepared by the halogen-metal interconversion of p-bromoaniline with n-butyllithium (-60°, nine minutes) in 68% yield.[49a] In subsequent work in this connection, halogen-metal interconversion was effected by addition of n-butyllithium to p-bromoaniline at the reflux temperature of ether.[93e]

In our first attempts to prepare 2-(p-aminophenyl)-quinoline, quinoline was added to the organometallic solution subsequent to attempted halogen-metal interconversion of p-bromoaniline with n-butyllithium (-60°, nine minutes). This resulted in the formation of 2-butylquinoline and recovery of most of the p-bromoaniline. For this reason it was concluded that halogen-metal interconversion was incomplete under the conditions employed, and that the n-butyllithium reacted with the quinoline, resulting in the formation of 2-butylquinoline.

The p-N,N-dilithioaminophenyllithium was prepared most satisfactorily through addition of n-butyllithium (three

equivalents) to p-bromoaniline (one equivalent), prior to refluxing for one hour, during which time the organometallic compound separated as a yellow, gummy, crystalline precipitate. According to Stuckwisch[47b] the apparent course of the reaction is as follows:



The usual procedures involving the addition of an organometallic compound to a cyclic ammono aldehyde ether require equivalent amounts of the organometallic compound and pyridine derivative. In our preparation of 2-(p-aminophenyl)-quinoline, using the above organolithium compound, two equivalents of quinoline were added for each equivalent of p-bromoaniline (subsequent to halogen-metal interconversion) since color tests[97] indicated that there was present an excess of n-butyl-

97. Gilman and Swiss, J. Am. Chem. Soc., 62, 1847 (1940).

lithium due to incomplete replacement of the active hydrogens of p-bromoaniline, or incomplete halogen-metal interconversion. The excess quinoline added any unchanged n-butyllithium, thus permitting the much slower reaction of addition to quinoline of p-N,N-dilithioaminophenyllithium (which is insoluble in the ether medium) to occur. This reasoning was supported by the isolation of varying quantities of 2-butylquinoline from the reaction mixture. The orange-red product, N-lithio-2-(p-aminophenyl)-1,2-dihydroquinoline is relatively insoluble in ether and formed a layer over the yellow insoluble organometallic compound. As a result, reaction was retarded considerably. For this reason, stirring and refluxing was maintained for a twelve-hour period after which time all the insoluble organometallic compound had disappeared, leaving only the partially soluble orange-red addition product.

In isolating the product, nitrobenzene oxidation together with high vacuum distillation were found to be the only procedures by which the material could be freed from secondary products. Attempts at direct isolation of any product through the picrate were abortive. This will be understood upon consideration of the complexity of the crude reaction product which may contain the following materials: unreacted p-bromoaniline, n-butyl bromide (from halogen-metal interconversion of p-bromoaniline and n-butyllithium), aniline (from hydrolysis of any unreacted p-N,N-dilithioaminophenyllithium),

unreacted quinoline, 2-butylquinoline, and finally 2-(p-aminophenyl)-quinoline, together with a secondary product [x-butyl-x-(p-aminophenyl)-quinoline] of reaction and the corresponding dihydro derivatives of several of the above.

The best procedure was found to include (1) evaporative distillation of the ether, (2) oxidation of the 1,2-dihydro-addition products with nitrobenzene, (3) vacuum distillation, firstly, under the vacuum of the water pump, secondly, distillation of all material boiling up to 150° (0.5 mm.) under the vacuum of the oil pump, and thirdly, the final distillation of the product (with the aid of a mercury diffusion pump) as an extremely viscous oil which solidified to a glass on cooling.

The viscous glass was best rectified by conversion to the picrate, continuous extraction of the picrate with benzene to remove a secondary reaction product, and final decomposition of the picrate to the free base.

In its final form the preparation of 2-(p-aminophenyl)-quinoline through the direct introduction of the p-aminophenyl group to the quinoline nucleus, by addition of the appropriate organometallic compound to quinoline, provides a rapid and relatively simple means of obtaining the compound. In contrast are the methods heretofore available which involve complex ring closures. These procedures, already discussed, require expensive starting materials and multiple stage reac-

tions, and are time-consuming.

The identity of our 2-(p-aminophenyl)-quinoline was established by comparison with an authentic specimen using the mixed melting point procedure. The picrate obtained from 2-(p-aminophenyl)-quinoline (either that prepared from our compound, or that prepared from the authentic specimen) melted at 197-198°. John[95] recorded the melting point of the picrate as 181°, no analysis or data on recrystallization of the compound to constant melting point being given.

Incidental to the preparation of 2-(p-aminophenyl)-quinoline, a small amount of the picrate of a secondary product of reaction was isolated from the picrate of the main product. Its separation, due to a selective solubility of the picrate in benzene, has been described in detail in the Experimental Section of this dissertation. In accounting for the formation of the secondary product the possibility of 1,4-addition to the quinoline nucleus (see pp. 27, 45-50) was considered. This, we reasoned, could result in the formation of any of three different compounds; 4-(p-aminophenyl)-quinoline melting at 150°[98] (no picrate is described in the literature), 2-butyl-4-(p-aminophenyl)-quinoline (not described in the literature), or 2-(p-aminophenyl)-4-butylquinoline (similarly not described in the literature). The formation of the latter compound is extremely inprobable, for under the con-

98. Koenigs and Nef, Ber., 20, 627 (1887).

ditions employed (excess of quinoline) it is unlikely that any n-butyllithium would remain in the reaction mixture for more than a few minutes. The addition of n-butyllithium to quinoline is extremely rapid. Moreover, the addition of insoluble p-N,N-dilithioaminophenyllithium to quinoline is much slower. We thought it altogether more likely that the latter organometallic compound would react with the 2-butylquinoline already formed in the reaction mixture.

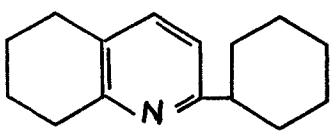
These considerations make necessary the assumption that LiH is split off (at least to some extent) from the N-lithio-x-substituted-1,x-dihydroquinoline addition product. Such reactions are known to occur and have already been discussed (see pp. 28-30). Moreover, this was demonstrated in our work in the preparation of 2-(p-biphenylyl)-quinoline (see pp. 68-69). Under the same conditions as were employed in the addition of p-N,N-dilithioaminophenyllithium to quinoline (that is a twelve-hour reflux period), p-biphenylyllithium added to quinoline, and the resultant N-lithio-2-(p-biphenylyl)-1,2-dihydro addition product split out lithium hydride. This was shown by the formation of almost pure ether-insoluble 2-(p-biphenylyl)-quinoline which was easily removed and characterized prior to hydrolysis of the reaction mixture.

Furthermore, Gilman and Spatz[33] treated quinoline with a slight excess of n-butyllithium in ether at -35° for fifteen minutes. On hydrolysis 2-butylquinoline was obtained in

93.5% yield without the isolation of 2-butyl-1,2-dihydroquinoline.

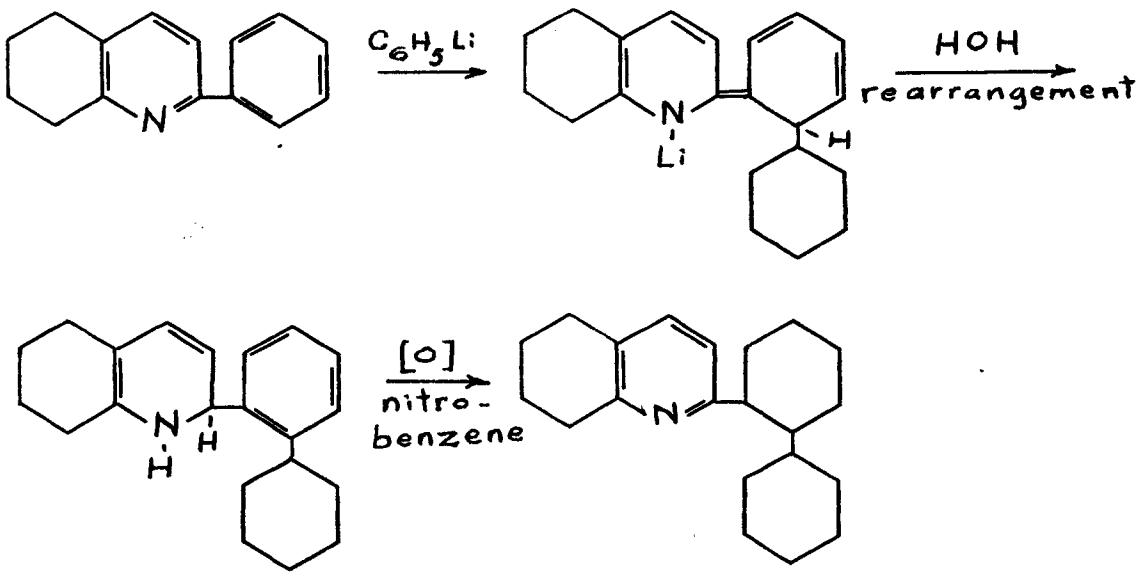
The analyses of the picrate and free base of the small amount of secondary reaction product were in closest agreement with those for an x-butyl-x-(p-aminophenyl)-quinoline (or picrate). Therefore, 1,4-addition of the p-N,N-dilithioaminophenyllithium to quinoline was ruled out. Consequently it is possible that the compound may be 2-butyl-4-(p-aminophenyl)-quinoline, or less likely, 4-butyl-2-(p-aminophenyl)-quinoline. Later studies which were pointed at elucidation of this structure, suggest the possibility that the compound may be 2-butyl-2-(p-aminophenyl)-1,2-dihydroquinoline.

In our endeavor to prove or disprove the possibility of 1,4-addition to a quinoline nucleus, we chose 2-phenylquinoline, an "open model" of acridine.



It was thought that the quinoline nucleus, already substituted in the 2-position (at which point anil addition readily occurs), should present a structure closely resembling acridine--the classical example of 1,4-addition in this series. In 2-phenylquinoline, the 2-position is supposedly blocked. Therefore further addition, we reasoned, could not occur at

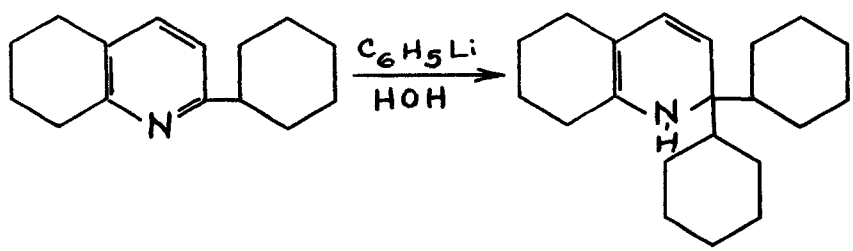
this point. If 1,4-addition be possible, then 2,4-diphenylquinoline (m.p. 112°), which has been described in the literature,[99] should result upon interaction of phenyllithium with 2-phenylquinoline. The compound which we obtained from this reaction melted at 86-87°, and therefore could not be 2,4-diphenylquinoline, even though the analysis showed the compound to have a molecular formula agreeing with that of a diphenylquinoline. The possibility of our having obtained 2-(o-biphenylyl)-quinoline was considered. It is easy to understand, from what has already been said concerning additions to compounds having terminal cumulated unsaturated groups (see pp. 47-50), how 2-(o-biphenylyl)-quinoline might have been formed by the following reaction.



99. Beyer, Ber., 20, 1772 (1887).

Our confusion was increased following the synthesis of 2-(o-biphenylyl)-quinoline by the addition of o-biphenylyllithium to the anil linkage of quinoline. The compound which was obtained subsequent to hydrolysis and nitrobenzene oxidation did not melt at 86-87°, but rather at 102-103°. In addition, the compounds were shown to be different by the mixed melting point method. Surprisingly enough, lateral 1,4-addition or nuclear 1,4-addition could not have taken place.

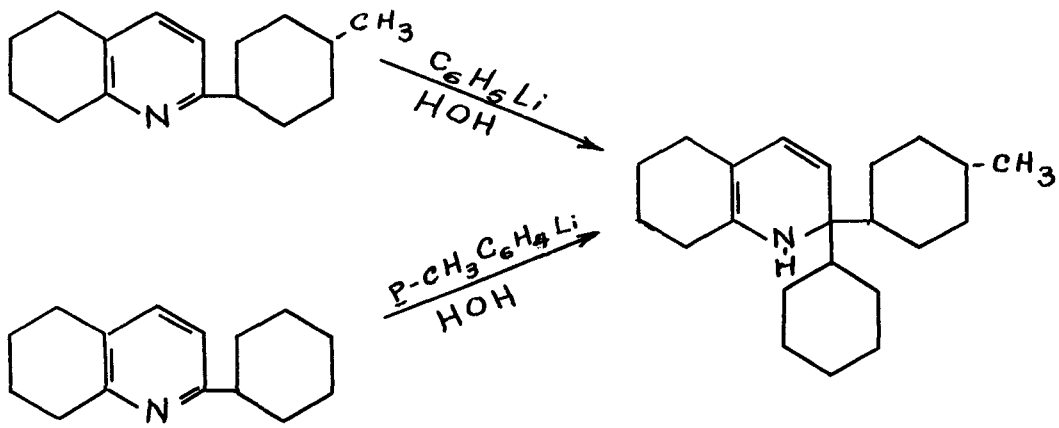
The only other reasonable possibility was that of 1,2-addition of phenyllithium to 2-phenylquinoline. So far as we know, there is no record of the 1,2-addition of an organometallic compound to a 2-substituted quinoline or 2,6-disubstituted pyridine. This would constitute addition of an organolithium compound to a cyclic ammono phenyl ketone ether, thus:



(XXX)

Compound (XXX) is a 2,2-disubstituted-1,2-dihydroquinoline, or specifically, 2,2-diphenyl-1,2-dihydroquinoline. This reaction has its counterpart in the 1,2-addition of phenyllithium to benzophenone-anil,[44] (see p. 48), an example of an open-chain ammono phenyl ketone ether.

Proof that the addition must have taken the course outlined above was supplied by our synthesis of a different homolog of the same type, by the same reaction but with different starting materials. Thus, 2-phenyl-2-(p-tolyl)-1,2-dihydroquinoline (XXXI) was synthesized either (1) by the addition of phenyllithium to 2-(p-tolyl)-quinoline, or (2) by the addition of p-tolyllithium to 2-phenylquinoline, as follows:

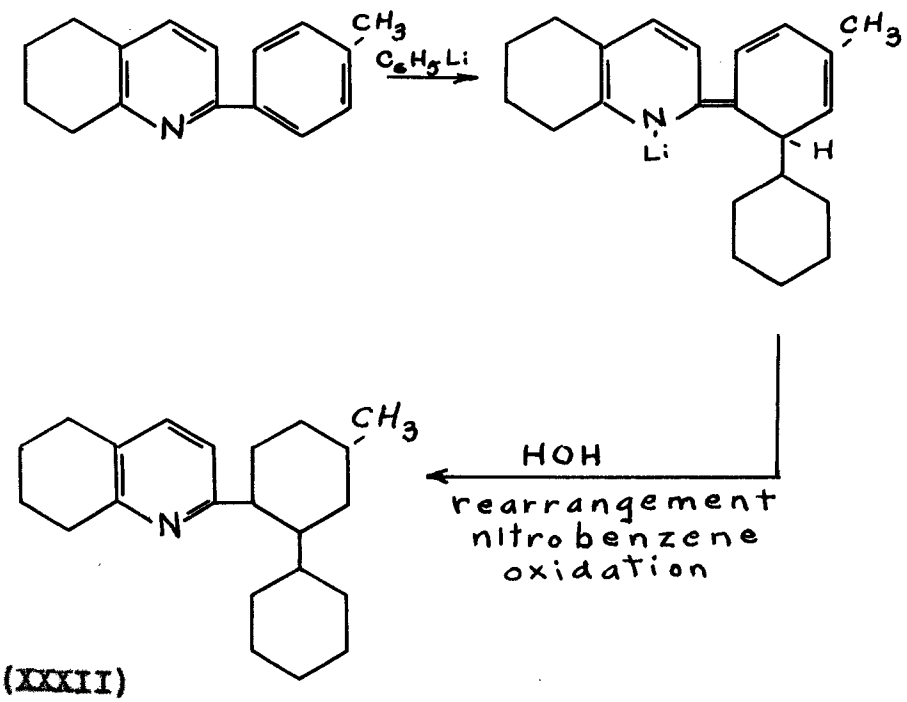


(XXXI)

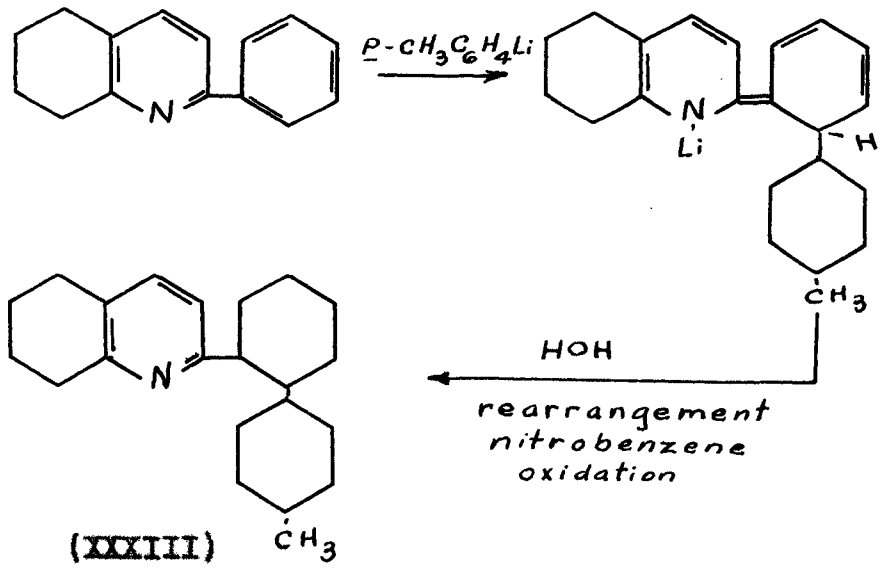
The compounds obtained from both synthetic routes were shown to be identical by the mixed melting point method. If nuclear 1,4-addition had occurred to the 2-substituted

quinoline compound, then in the first case 2-(p-tolyl)-4-phenylquinoline would have resulted. In the second example nuclear 1,4-addition would have resulted in formation of 2-phenyl-4-(p-tolyl)-quinoline; and the compounds, even though they conceivably might have had the same melting points, would have shown a depression in a mixed melting point determination.

Furthermore, if lateral 1,4-addition had occurred, the first reaction would have resulted in the formation of 2-(2-quinolyl)-5-methylbiphenyl (XXXII), and the second reaction would have yielded 2-(2-quinolyl)-4'-methylbiphenyl (XXXIII), thus:



(XXXII)



(XXXIII)

The melting point of the mixed compounds would also be depressed in this case.

In the preparation of these compounds one and one-half equivalents of a filtered solution of organolithium compound was added to one equivalent of the 2-arylquinoline in ether. The mixture was stirred and refluxed for twelve hours. All efforts to crystallize the reaction products directly, failed. Consequently resort was made to vacuum distillation with the aid of a mercury diffusion pump. By this means viscous glasses were obtained. Direct crystallization from a suitable solvent, without previously seeding the solution, was found to be impossible. Moreover, the products as distilled were contaminated by the presence of starting material. Since the hydrochlorides of the reaction products were found to be exceedingly insoluble in dilute hydrochloric acid, whereas

the 2-substituted quinolines were soluble, a means of purification was hereby obtained. Subsequent to liberation of the purified hydrochlorides, the free bases crystallized nicely.

Analytical samples of the free bases failed to yield a picrate; intractable oils resulted. Pure 2,2-diphenyl-1,2-dihydroquinoline formed a pure white hydrochloride, which softened at 172°, and melted with decomposition at 175-178°. On standing, however, the hydrochloride decomposed to a black gum. Further, our experience with 2-phenyl-2-(p-tolyl)-1,2-dihydroquinoline also indicated the hydrochloride of this compound to be unstable. In the latter case purification through the hydrochloride was effected only as a means of obtaining seed for the crystallization of the main product.

Incidental to the preparation of 2-(o-biphenylyl)-quinoline (prepared from Eastman white label o-bromobiphenyl) for the structure proof of our compound melting at 86-87°, an isomeric biphenylylquinoline melting at 176-177° was isolated in small amount. 2-(p-Biphenylyl)-quinoline has been prepared by a different method,[54] the melting point being given as 175-177°. It was suspected that the isomer may have been the above compound which might have arisen from (1) impure o-bromobiphenyl containing some of the para- isomer, or (2) rearrangement of the o-biphenylyllithium. The latter possibility was ruled out and the former shown to be the case,

by the following means.

Authentic o-bromobiphenyl was prepared by diazotization of o-aminobiphenyl with cuprous bromide in hydrobromic acid medium. Subsequent to preparation of o-biphenylyllithium from the authentic compound, carbonation of an aliquot yielded pure o-phenylbenzoic acid. Thus no rearrangement of the organometallic compound could have occurred. The main portion of the organometallic compound, on interaction with quinoline and rectification in the usual manner, yielded a compound identical with the o-biphenylylquinoline derived from Eastman white label o-bromobiphenyl, but no high melting isomer was found.

Carbonation of the o-biphenylyllithium obtained from Eastman white label o-bromobiphenyl yielded a mixture of acids. Petroleum ether (b.p. 60-68°) was found to have a selective solvent action for o-phenylbenzoic acid. Separation of the isomers was effected by use of this fact. p-Phenylbenzoic acid was obtained by ethanolic crystallization of the residue subsequent to petroleum ether extraction. Thus it was shown that Eastman white label 'o-bromobiphenyl' gave rise to o-biphenylyllithium and a smaller amount of p-biphenylyllithium.

To characterize the isomer melting at 176-177°, 2-(p-biphenylyl)-quinoline was prepared from p-biphenylyllithium and quinoline. The compounds were found to be

identical by the mixed melting point method. Carbonation of an aliquot of the p-biphenyllithium yielded p-phenylbenzoic acid which was identical with the p-phenylbenzoic acid obtained in small amount from carbonation of the Eastman-derived 'o-biphenylyllithium'.

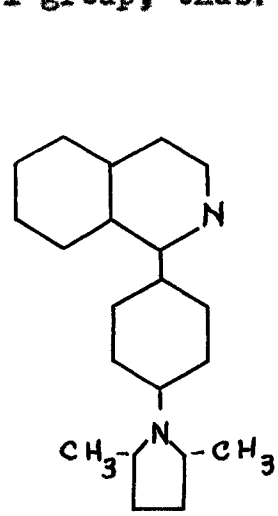
Incidental to the preparation of 2-(p-biphenylyl)-quinoline from the interaction of p-biphenylyllithium and quinoline, it was found that the N-lithio-1,2-dihydro-2-(p-biphenylyl)-quinoline addition product spontaneously split off lithium hydride to form 2-(p-biphenylyl)-quinoline upon refluxing the solution overnight prior to hydrolysis. The latter compound is extremely insoluble in the common organic solvents such as diethyl ether and 95 percent ethanol. As a result, the compound separated in crystalline form from the ethereal reaction mixture. A portion of this material was removed directly from the reaction flask without prior hydrolysis and was found to melt at 175-178°. The pure compound melts at 178-179°. Hence, nitrobenzene oxidation was omitted in this preparation. The yield in the reaction amounted to 86% of that required by theory.

B. The Addition of Organolithium Compounds to Isoquinoline

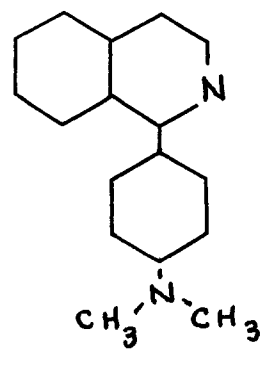
Prior to a study of the possible addition to isoquinoline of organolithium compounds having otherwise reactive function-

al groups, it seemed desirable to establish the generality of the reaction. This was done by the addition of a variety of substituted organolithium compounds such as p-dimethylaminophenyllithium, p-(2,5-dimethyl-1-pyrryl)-phenyllithium, p-tolyllithium, and p-anisyllithium to the ammono aldehyde linkages of isoquinoline and a substituted isoquinoline derivative, namely 5-(2,5-dimethyl-1-pyrryl)-isoquinoline.

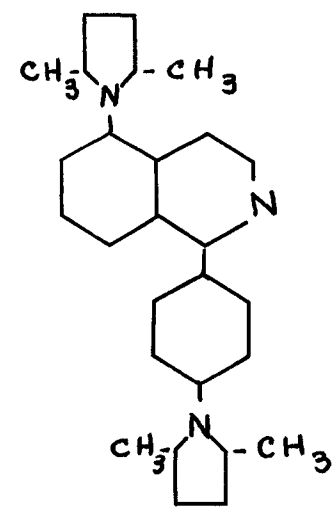
Furthermore, the products so obtained represent a continuation of recent studies from these laboratories on antimalarials containing the 2,5-dimethyl-1-pyrryl group as the basic side-chain.[100] In our investigation, the isoquinoline or 5-(2,5-dimethyl-1-pyrryl)-isoquinoline nucleus was removed from the 2,5-dimethylpyrryl- or dimethylamino- group by a phenyl group, thus:



(XXXIV)



(XXXV)



(XXXVI)

100. (a) Gilman, Stuckwisch, and Nobis, J. Am. Chem. Soc., 68, 326 (1946); (b) for the preparation of some isomeric (methoxy)-(2,5-dimethyl-1-pyrryl)-quinolines, see, Gilman and Fullhart, ibid., 68, 978 (1946).

It seemed desirable to utilize the five-membered pyrrole ring in compounds of therapeutic interest as antimalarials, since pyrrole derivatives occur naturally in chlorophyll and hemoglobin, and may be less toxic to the human system than other basic groups.

In previous communications from these laboratories there has been reported the preparation of various 2,5-dimethylpyrryl derivatives of pyridine,[100a,101] quinoline,[100] and acridine,[100a] as well as certain other 2,5-dimethylpyrryl compounds[68,102] of pharmacological interest. Walsh[103] prepared 1-p-aminobenzenesulfonamido-2,5-dimethylpyrrole and 1-p-toluenesulfonamido-2,5-dimethylpyrrole for therapeutic testing. Recently, Coates and co-workers[104a] described the preparation of 3-(2,5-dimethyl-1-pyrryl)-quinoline and 6-methoxy-8-(2,5-dimethyl-1-pyrryl)-quinoline,[104b] which were tested as spasmolytic agents. They extended the studies to include a variety of quinolyl-dicarbethoxydimethylpyrroles. Lions and co-workers[58] studied the condensation of acetonylacetone with a large number of amines to form N-substituted 2,5-dimethyl-

101. Gilman and Karmas, J. Am. Chem. Soc., 67, 343 (1945).

102. (a) Gilman and Tolman, ibid., 67, 1847 (1945); (b) Gilman, Tolman, Yeoman, Woods, Shirley, and Avakian, ibid., 68, 427 (1946).

103. Walsh, J. Chem. Soc., 726 (1942).

104. (a) Coates, Cook, Heilbron, and Lewis, ibid., 419 (1943); (b) See also reference (100a) for the preparation of this particular amine in 93% yield.

pyrrole derivatives, in order to ascertain whether those amines which resisted pyrrole formation had any significant property in common. Certain of the compounds described include 5- and 8-(2,5-dimethyl-1-pyrryl)-quinoline[58b] and 3-(2,5-dimethyl-1-pyrryl)-quinaldine.[58c] No antimalarial activities have been reported for these compounds.

In our investigation, the 2,5-dimethylpyrrole derivatives were prepared by the condensation of the appropriate amine with acetonylacetone.[58,105] The yields in this reaction were generally satisfactory and reached 97% in the preparation of 4-(2,5-dimethyl-1-pyrryl)-isoquinoline. However, all our attempts to prepare 2-(2,5-dimethyl-1-pyrryl)-quinoline failed.

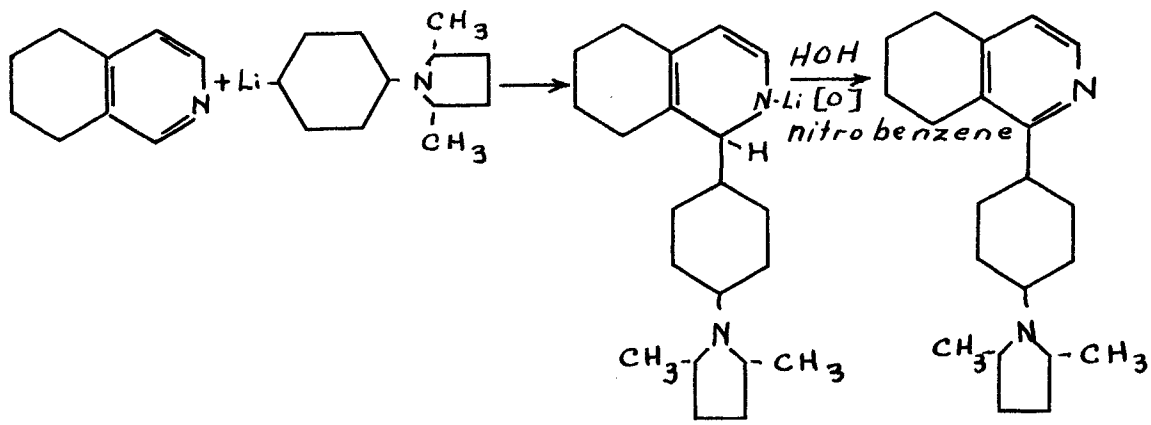
n-Butyl-, phenyl-, and p-anisyllithium have each been added to the anil linkage of isoquinoline to form the corresponding 1-substituted 1,2-dihydroisoquinoline compounds on hydrolysis.[18,31] Subsequent to oxidation, either by means of nitrobenzene[18] or through autoöxidation,[31] the corresponding 1-substituted isoquinoline compounds were obtained. Bergmann, Blum-Bergmann and v. Christiani[31] added phenyl- and p-anisyllithium to isoquinoline, and shortly thereafter Ziegler and Zeiser[18] reported the addition of phenyl- and n-butyllithium

105. (a) Bishop, J. Am. Chem. Soc., 67, 2261 (1945); (b) Barton, U. S. Patent 2,234,056; (c) Paal and Schneider, Ber., 19, 3157 (1886).

to the same compound. These results indicated that the reaction might be extended to a substituted isoquinoline.

In our work, compounds (XXXIV), and (XXXVI) were prepared through the addition of p-(2,5-dimethyl-1-pyrryl)-phenyllithium to the anil linkages of isoquinoline and 5-(2,5-dimethyl-1-pyrryl)-isoquinoline, and compound (XXXV) was formed by the addition of p-dimethylaminophenyllithium to isoquinoline.

The following reaction is an illustration of the pattern of syntheses utilized in this study. The intermediate dihydro product (formed by the addition of the RLi compound to the anil linkage) was oxidized by nitrobenzene to (XXXIV).



(XXXIV)

For the isolation of the products of reaction, the method of choice was found to include removal of the nitrobenzene and unreacted isoquinoline by vacuum distillation prior to distillation of the product.

In these reactions, the oxidation of the intermediate dihydro compounds with nitrobenzene was best carried out in a Claisen flask equipped for distillation subsequent to evaporative distillation of the ether from the reaction product. Application of vacuum by means of the water pump following the oxidation period served to remove unreacted nitrobenzene and isoquinoline. The final products were distilled, using the vacuum obtained by use of the mechanical oil pump.

Most of the products obtained in this manner were glasses. They were found to be extremely difficult to crystallize, being very soluble in the usual organic solvents such as benzene, ethanol, chloroform and acetone. Unless otherwise stated in the Experimental Section of this dissertation, the best procedure was found to comprise the complete solution of the glassy distillate in benzene, then charcoaling, filtering, and diluting of the filtrate to incipient crystallization with petroleum ether (b.p. 60-68°).

Another method of rectifying the pure compound from the glassy distillate was found in the conversion of the latter to the picrate, which was purified by crystallization prior

to its decomposition to the free base with dilute (1:1) ammonium hydroxide.

The addition of p-N,N-dilithioaminophenyllithium to isoquinoline subsequent to halogen-metal interconversion of p-bromoaniline with n-butyllithium yielded no secondary product, as was the case with quinoline. This is in keeping with the fine bond structure which has been assigned to isoquinoline.[106]

Since the product of this reaction, namely 1-(p-aminophenyl)-isoquinoline, has not been described in the literature, and since the position of substitution of isoquinoline by means of organolithium compounds heretofore was demonstrated only by comparison of melting points[18,31] and not by mixed melting point determinations, it was thought desirable to characterize the compound by its synthesis through an alternate route. Furthermore, some doubt as to the authenticity of the organolithium compound employed in this case could conceivably arise, for anomalous reactions are known to occur in the halogen-metal interconversion of p-bromoanisole.[93a]

Accordingly, the structure of 1-(p-aminophenyl)-isoquinoline was proved by its synthesis through the following alternate route. Application of the Bischler-Napieralski

106. Cf. Gilman "Organic Chemistry", John Wiley and Sons, Inc., New York, N. Y., (1944), Vol. I. p. 153.

syntheses[107] of 1-substituted-3,4-dihydroisoquinolines yielded 1-(p-nitrophenyl)-3,4-dihydroisoquinoline. Thus, β-phenylethylamine was condensed with p-nitrobenzoyl chloride and the resultant substituted amide cyclicized by use of phosphorous pentoxide to yield 1-(p-nitrophenyl)-3,4-dihydroisoquinoline.[69] Attempts to prepare 1-(p-nitrophenyl)-isoquinoline from the oxidation of the latter [1-(p-nitrophenyl)-3,4-dihydroisoquinoline], using dilute nitric acid in acetic acid medium as used by Rodinov and Yavorskaya[69] in the preparation of 1-phenylisoquinoline, failed. A second attempt, using potassium permanganate in dilute sulfuric acid according to the general method described for the preparation of various 1-substituted isoquinolines,[107c] also failed. The compound was finally prepared by dehydrogenation of the 3,4-dihydro compound over palladium black by the general procedure of Späth and co-workers.[108] The 1-(p-nitrophenyl)-isoquinoline so prepared was then catalytically reduced by hydrogen in the presence of Raney nickel to obtain 1-(p-aminophenyl)-isoquinoline. By means of melting and mixed melting points this product was shown to be identical with that prepared directly from isoquinoline.

Halogen-metal interconversion of p-bromothiophenol was

107. (a) Bischler and Napieralski, Ber., 26, 1903 (1893); (b) Decker and Kropp, ibid., 42, 2075 (1909); (c) Pictet and Kay, ibid., 42, 1973 (1909).

108. (a) Späth and Polgar, Monatsh., 51, 190 (1929); (b) Späth, Berger, and Kunatra, Ber., 63B, 134 (1930).

effected by the addition of slightly less than two equivalents of n-butyllithium to one equivalent of p-bromothiophenol at the reflux temperature of ether. During the addition of the first half of the n-butyllithium, vigorous refluxing occurred and no precipitate was formed. The second half was added in a rapid stream. Refluxing occurred and immediately a fine, dense white precipitate of the insoluble aryl organometallic compound separated. Carbonation of an aliquot indicated a 75% yield of the halogen-metal interconversion product. Isoquinoline was added (in excess) to the ether suspension of the insoluble organolithium compound and the solution immediately turned dark orange in color. The reaction mixture was then refluxed twelve hours to allow complete reaction of the insoluble organometallic compound.

Subsequent to hydrolysis, the product was removed from the ether solution by extraction with 20 percent sodium hydroxide solution. Acidification of the alkaline solution with acetic acid liberated the free base which was taken up in ether and precipitated as the hydrochloride with ethereal hydrogen chloride. The compound was suitably recrystallized from a dilute hydrochloric acid solution.

Recent attempts to demonstrate 1,2-addition of phenyllithium or p-tolyllithium to an isoquinoline example of a cyclic ammono aldehyde aryl ether such as 1-p-tolylisoquinoline or 1-phenylisoquinoline have to date been unsuccessful

to the extent that crystalline products have not been isolated. However, the addition of phenyllithium to 1-(p-tolyl)-isoquinoline and of p-tolyllithium to 1-phenylisoquinoline (under the same conditions as employed with quinoline) yielded no starting material on high vacuum distillation, but rather the expected thick viscous glasses. The latter, however, could not be crystallized by any means which were employed. The picrates would not form. The hydrochlorides of the products, while being extremely insoluble in aqueous solution, appeared not to be stable since dark gums were obtained on standing. However, since no starting material was found, and since a distillable product could be obtained, it is quite possible that some product might have been formed.

C. 6-Quinolyl Sulfides and Sulfones

As a result of the high antistreptococcal activity of 4,4'-diaminodiphenyl sulfone,[109] the inhibitory effect of this compound on experimental tuberculosis in animals,[110] and the indicated antimalarial activity of certain of its derivatives,[111] a series of quinoline analogs of this compound was

109. Buttle, Stephenson, Smith, Dewing, and Foster, Lancet, 1, 1331 (1937).

110. Rist, Block, and Hamon, Ann. Inst. Pasteur, 64, 203 (1940).

111. (a) Heymann and Fieser, J. Am. Chem. Soc., 67, 1979 (1945); (b) Heymann and Heidelberger, Ibid., 67, 1986 (1945).

prepared.

It is known that the dinitro- and diaminodiphenyl sulfides and sulfones have a similar therapeutic effect to sulfanilamide,[109,112,113] but are generally more toxic.[114,115] Since the introduction of particular heterocycles in sulfanilamide adds desirable features, it was thought that certain sulfides and sulfones of quinoline might have therapeutic value.

A number of modifications of 4,4'-diaminodiphenyl sulfone have been made in attempts to obtain drugs which are more suitable for clinical application. Bambas[116] states the toxic manifestations of 4,4'-diaminodiphenyl sulfone preclude its use as a drug in clinical tuberculosis. In the hope of reducing the toxicity and yet retaining the antistreptococcal and antituberculous activity of the compound, Bambas prepared a number of analogs of the compound in which one or both of the phenyl rings were replaced by a heterocyclic ring. The only quinoline derivatives prepared in his study were 5-amino-

112. Fourneau, J. and Mme. J. Trefouel, Nitti and Bovet, Bull. Acad. med., 118, 210 (1937); Compt. rend. 204, 1763 (1937).

113. Bauer and Rosenthal, U. S. Public Health Rpts., 53, 40 (1938).

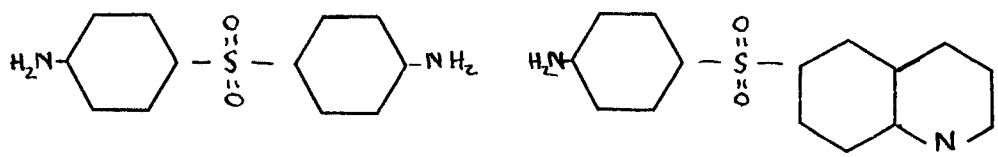
114. Welch, J. Pediatrics, II, no. 2, 159 (1937).

115. Raiziss, Clemence, Severac, and Moetsch, J. Am. Chem. Soc., 61, 2763 (1939).

116. Bambas, ibid., 67, 668 (1945).

8-quinolyl p-acetamidophenyl sulfone and the corresponding deacetylated compound. The former resulted from the interaction of the silver salt of 4-acetamidobenzenesulfinic acid and 5-amino-8-chloroquinoline or the corresponding bromo compound. Deacetylation yielded the free amine. As a result of these studies, Bambas[116] concluded that only those compounds were effective which had at least one benzene nucleus with a nitrogen atom in the para- position to the sulfur.

For these reasons, in our studies, one of the benzene nuclei of 4,4'-diaminodiphenyl sulfone was replaced by a 6-quinolyl or substituted 6-quinolyl group, which modification retained the nitrogens in the equivalent para- position to the sulfur as found in 4,4'-diaminodiphenyl sulfone, thus:



In extending the research on the type of compound represented by 6-quinolyl p-aminophenyl sulfide and sulfone, there were prepared certain 5-nitro-6-quinolyl and 5-nitro-8-amino-6-quinolyl p-aminophenyl sulfides and sulfones, and derivatives of these.

Certain other sulfides and sulfones of the benzene ring

of quinoline have been described. Surrey and Lindwall[117] prepared 8,8'-dinitro-5,5'-diquinolyl and 5,5'-dinitro-8,8'-diquinolyl sulfides (and the sulfone of the latter) for therapeutic testing. The sulfides were prepared by the action of a saturated aqueous solution of sodium sulfide on a hot ethanolic solution of the required 5-nitro-8-chloro- or 8-nitro-5-chloroquinoline. The sulfone derivative of 5,5'-dinitro-8,8'-diquinolyl sulfide was prepared by oxidation of the latter with potassium dichromate.

Winter and Reinhart[118] prepared certain 8-quinolyl phenyl sulfides and sulfones for testing as antistreptococcal agents. In their work, 5-nitro-8-chloroquinoline was reacted with thiophenol in an ethanolic sodium acetate solution to yield 5-nitro-8-quinolyl phenyl sulfide. Reduction of the nitro group with stannous chloride in concentrated hydrochloric acid yielded 5-amino-8-quinolyl phenyl sulfide. In a similar manner, 5-nitro-8-quinolyl p-nitrophenyl sulfide was prepared, using p-nitrothiophenol. Oxidation of 5-nitro-8-quinolyl phenyl sulfide with 30 percent hydrogen peroxide, under mild conditions, yielded the sulfoxide, while more vigorous conditions yielded the sulfone. The latter was reduced to the corresponding amino compound. To obtain

117. Surrey and Lindwall, J. Am. Chem. Soc., 62, 173 (1940).
118. Winter and Reinhart, ibid., 62, 3509 (1940).

the sulfone of 5-nitro-8-quinolyl p-nitrophenyl sulfide, chromium trioxide in glacial acetic acid was used as the oxidizing agent.

In connection with certain studies in these laboratories involving the syntheses of some sulfur-substituted heterocycles as possible antimalarial and antituberculous agents, the preparation of 8-amino-6-quinolyl methyl sulfone[119] and γ-(6-methoxy-8-quinolyl-amino)-propyl β-diethylamino-ethyl sulfone[89] has been reported. Recently a sulfur analog of the well known plasmochin type, 8-(γ-diethylaminopropyl-amino)-6-quinolyl methyl sulfide, was reported.[87] Certain long-chain alkyl, substituted 6-quinolyl sulfides have been prepared as well.[120] In addition, the preparation of a series of quinoline compounds with sulfur-containing side-chains has been reported from these laboratories. The effect of variation of the length of the alkyl groups and also the nature of the terminal amino group was studied.[102a,121] Similar work, carried on at the same time, has been reported from the laboratories of the Winthrop Chemical Company.[122]

119. Gilman and Lindblad, J. Am. Chem. Soc., 68, 982 (1946).

120. Massie, S. P., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1946.

121. Gilman and Woods, J. Am. Chem. Soc., 67, 1843 (1945).

122. Huber, Bair, Boehme, Laskowski, Jackman, and Clinton, ibid., 67, 1849 (1945).

The compounds reported in our investigation have been chiefly 6-quinolyl (or substituted 6-quinolyl) p-substituted phenyl sulfides and sulfones. In all of these (except 5-nitro-6-quinolyl p-chlorophenyl sulfide) a nitro, amino or acetamido group occupied the position para- to the sulfur linkage. The latter, in turn, maintained a position para- to the nitrogen contained and included in the quinoline nucleus. These requirements were fulfilled by the exclusive use of the 6-quinolyl or substituted 6-quinolyl group. This arrangement of the nitrogen and sulfur groups thus simulated the relative positions of these groups in the antistreptococcal compounds of the benzene series.

The 6-quinolyl p-substituted phenyl sulfides and sulfones were prepared either directly or indirectly by means of the Skraup reaction. For example, 6-quinolyl p-nitrophenyl sulfide and sulfone were prepared in good yield by application of the arsenic oxide modification of the Skraup synthesis to 4-nitro-4'-amino-(or preferably 4'-acetamido-)diphenyl sulfide and sulfone, respectively.

Prior to the inception of this work there was no record in the literature concerning the Skraup synthesis of a quinolyl sulfide or sulfone. Presumably the oxidizing conditions of the Skraup reaction discouraged the extension of this valuable synthetic tool to include such syntheses. The results of our orienting experiments bore out this idea.

For example, 4-nitro-4'-aminodiphenyl sulfide and sulfone, as well as the corresponding acetamido compounds, were subjected to the Skraup reaction using the general procedure given by Cohen.[79] This method utilizes nitrobenzene as the oxidizing agent, its violent action being modified somewhat by use of ferrous sulfate and boric acid. Only a 10% yield of isolable product was obtained by this means. Oils and tars were invariably formed.

In considering the arsenic oxide modification of the Skraup reaction, preliminary experiments were made in an endeavor to evaluate the oxidizing power of the Skraup mixture without the glycerol. These were performed under the same conditions as employed in the Skraup synthesis using 4-nitro-4'-aminodiphenyl sulfone (or the acetamido derivative). No isolable product was obtained in such trials, even when heating was reduced to one hour.

In view of these results it was somewhat surprising to note the high yields of 6-quinolyl p-nitrophenyl sulfide and sulfone which were invariably obtained subsequent to the use of the arsenic oxide modification. In these syntheses we found the best general procedure to include the mass relations suggested by Richter and Smith,[78a,123] that is, one mole

123. Richter and Smith, "Phenanthroline and Substituted Phenanthroline Indicators", G. F. Smith Chemical Company, Columbus, Ohio.

of the aromatic amine, four moles of glycerol (dried by passing air through the liquid for three hours at 170-180°), three-fourths mole of arsenic pentoxide, and a weight of sulfuric acid (density 1.84) equal to fifty-five percent of the weight of glycerol employed. Use of the acetamido compounds in the Skraup syntheses, as recommended by Manske and co-workers,[78b] while not materially improving the yield, gave a cleaner product which was even freer from tarry by-products, and which facilitated purification of the 6-quinolyl sulfide or sulfone.

The corresponding 6-quinolyl p-aminophenyl sulfide and the sulfone were conveniently obtained by catalytic reduction of the parent nitro compounds with hydrogen.

In contrast to the facility with which 4-nitro-4'-aminodiphenyl sulfone and sulfide (or corresponding acetamide compounds) yielded the 6-quinolyl derivatives, our attempts to prepare bis-6-quinolyl sulfone by application of the arsenic oxide modification of the Skraup synthesis to 4,4'-diaminodiphenyl sulfone yielded only intractable tars. Noteworthy, also, is the fact that p-acetamidophenyl methyl sulfide yielded in the vicinity of 5% of 6-quinolyl methyl sulfide.[124] p-Acetamidophenyl methyl sulfone yielded 27% of 6-quinolyl methyl sulfone, using the same conditions as were used in this investigation.[119]

124. Unpublished studies by F. J. Marshall of these laboratories.

The series of 5-nitro-6-quinolyl p-substituted phenyl sulfides and sulfones was prepared by interaction of the sodium salt of the desired thiophenol or sulfinic acid with the labile chlorine atom of 5-nitro-6-chloroquinoline. The 5-amino-6-quinolyl compounds were prepared by catalytic reduction of the parent sulfur-containing nitro compounds.

In the preparation of the p-aminophenyl sulfide types, p-aminothiophenol was required. Since previous procedures seemed somewhat unwieldly, a more convenient method was sought. This was found in the preparation of the compound by refinement of the method indicated by Lantz.[80] This consisted in the dual reaction of p-nitrochlorobenzene with aqueous sodium sulfide, firstly by reaction of the latter with the labile chlorine atom of the former to form p-nitrothiophenol, and secondly by reduction of the nitro group of the p-nitrothiophenol to form p-aminothiophenol. Lantz carried out the isolation of the product by formation of the insoluble zinc salt, prior to the liberation of the amphoteric product, to yield an impure product which melted at 30° (literature, 46°[125]). No yields were given. In our procedure, the p-aminothiophenol was liberated by the addition of an amount of glacial acetic acid equivalent to the amount of sodium sulfide which had been added. The partially soluble product

125. (a) Hinsberg, Ber., 39, 2428 (1906); (b) Zincke and Jörg, ibid., 42, 3366 (1909).

was then salted out by adding excess powdered sodium chloride. Ether extraction of the liberated p-aminothiophenol and subsequent vacuum distillation gave a 69% yield of the pure compound.

In the preparation of the 5-nitro-8-amino-(or acetamido-)6-quinolyl p-substituted-phenyl sulfones, the labile chlorine atom of 5-nitro-6-chloro-8-amino-(or acetamido-) quinoline was reacted with the sodium salt of p-acetamidobenzenesulfinic acid.

The required 5-nitro-6-chloro-8-amino-(or acetamido-) quinoline was prepared by the nitration of 6-chloro-8-acetamidoquinoline. The position of nitration was shown by the ethanolic deamination of the diazotate of the 5-nitro-6-chloro-8-aminoquinoline (formed by deacetylation of the corresponding acetamido compound) to yield 5-nitro-6-chloroquinoline. The latter was found to be identical with an authentic sample prepared by the direct nitration of 6-chloroquinoline. The experimental procedures used in these reactions are given in a recent publication.[87]

All our attempts to prepare 2-hydroxy-4-methyl-6-quinolyl p-nitrophenyl sulfide and sulfone (preliminary to the projected preparation of 2-hydroxy-4-methyl-6-quinolyl p-aminophenyl sulfide and sulfone by reduction of these compounds) failed. The primary condensations of ethyl acetoacetate with both 4-nitro-4'-diaminodiphenyl sulfide or the

sulfone, with vigorous evolution of ethanol, seemed to take place, since compounds whose analyses agreed fairly well with the theoretical, were obtained. However, all attempts at cyclization of these primary condensation products failed, since 4-nitro-4'-aminodiphenyl sulfide[126] (or the sulfone) was regenerated in every case.

The pharmacological tests on the above types of compounds are not yet complete. However, the results of the tests on these compounds for antimalarial activity are available and will be published in a forthcoming survey. They failed to show any activity against avian malaria. The sulfides were toxic, whereas the sulfones, while not exhibiting any appreciable antimalarial activity, were non-toxic. This is of interest. Generally great changes in activity may be brought about by slight changes in chemical structure, while the toxicity of compounds is usually inherent in the type of compound. It is possible that slight modifications in the structure of the 6-quinolyl sulfones might result in increased activity without increasing toxicity.

126. An alternate name for this compound which would conform to the usage adopted by Chemical Abstracts is p-(p-nitrophenylsulfonyl)-aniline. However, since the majority of authors in the past have named the compound as a derivative of diphenyl sulfide, the latter nomenclature is used in this dissertation.

D. Miscellaneous Compounds

In connection with the preparation of some quinoline-sulfur compounds recently reported from these laboratories,[87,102a,119,120,121] it seemed desirable to prepare a series of compounds which incorporated the p-aminophenyl group with an aliphatic side-chain containing the sulfone group. Intense interest has recently centered about 4,4'-diaminodiphenyl sulfone (see pp. 160-162) as an antituberculous agent. Relatively few compounds in which one of the p-aminophenyl- groups of the latter has been replaced by an alkyl group have been prepared as possible antituberculous agents. For these reasons it seemed desirable to synthesize a representative of this modification. One of the compounds prepared, namely γ-(p-aminophenoxy)-propyl β-chloroethyl sulfone hydrochloride, had marked vesicant action. This is similar to the vesicant action of γ-(p-nitrophenoxy)-propyl β-chloroethyl sulfide,[89] which has recently been reported. From a physiological standpoint, the former compound has the advantage of being extremely water soluble.

The γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide required in the syntheses of the compounds was prepared by a series of reactions recently described by Gilman and Fullhart.[89]

The preparation of the corresponding sulfone presented an interesting problem. Framm and Jörg[127] prepared β-hydroxyethyl benzyl sulfone from the corresponding sulfide by conversion of the compound to the benzoic acid ester, prior to oxidation to the sulfone with cold 5 percent aqueous potassium permanganate. The ester was then saponified to yield the desired β-hydroxyethyl benzyl sulfone. Attempts to apply this procedure to our compound failed. Recently, Morgan and Hamilton[128] prepared p-β-hydroxyethylsulfonylphenylarsenic acid and the corresponding γ-hydroxy- homolog by oxidation of the corresponding water soluble sulfides, utilizing 30 percent hydrogen peroxide. However, our attempts to prepare γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone by this method failed since the sulfide was extremely insoluble in water. The compound was best prepared by modification of the method of Pomerantz and Conner[129] who successfully oxidized a series of α-(alkylthio)-amides to the corresponding sulfones, using 30 percent hydrogen peroxide in a glacial acetic acid-acetic anhydride medium.

In its final form the oxidation of γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide to the corresponding sulfone was

127. Framm and Jörg, Ber., 304 (1925).

128. Morgan and Hamilton, J. Am. Chem. Soc., 66, 874 (1944).

129. Pomerantz and Conner, ibid., 61, 3386 (1939).

accomplished by use of 30 percent hydrogen peroxide in glacial acetic acid. Despite the elimination of acetic anhydride (used in conjunction with glacial acetic acid by Pomerantz and Conner),[129] the acetic acid ester of the β-hydroxy ethyl sulfone compound was formed at least to some extent. The presence of the ester was shown by its separation from the β-hydroxyethyl sulfone compound by a tedious process of fractional crystallization. Its structure was established by two separate syntheses. In one, γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone was acetylated with acetic anhydride to yield the β-acetoxy compound. In the other, γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide was acetylated to the β-acetoxy compound, previous to hydrogen peroxide oxidation (in glacial acetic acid) to the corresponding sulfone. The compounds were all shown to be identical by the method of melting and mixed melting points.

In rectifying the crude product of oxidation of β-hydroxyethyl sulfide containing the corresponding sulfone and a varying amount of the β-acetoxy compound, it was found that acid hydrolysis of the latter (contained in the crude mixture) using 2N sulfuric acid yielded crude γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone which could be very satisfactorily purified by crystallization. When the latter procedure was omitted a eutectic mixture was obtained which could be purified only through fractional crystallization

with attendant low yields.

The reduction of γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfone to the corresponding amino compound, using hydrogen in the presence of Raney nickel, was carried out with some apprehension in view of the evidence which, in the past, has regarded such a procedure as impracticable because of the poisoning of the catalyst that may take place. The poisoning of Raney nickel by sulfur compounds in various degrees of oxidation during hydrogenation of several organic compounds is the topic of a paper by Deem and Kaveckis.[130]

Moreover, diaryl sulfides are cleaved through hydrogenolysis to form hydrogen sulfide and aryl hydrocarbons, when heated with rather large quantities of Raney nickel.[131] The use of Raney nickel in the hydrogenation of sulfur-containing compounds was therefore disparaged. Only a single instance could be found in which a nickel catalyzed reduction of a nitro group had been effected in a sulfur-containing compound. For instance, Morgan and Hamilton[128] reduced p-nitrophenyl β-hydroxyethyl sulfide to the corresponding amino compound, in excellent yield, using hydrogen in the presence of Raney nickel.

130. Deem and Kaveckis, Ind. Eng. Chem., 33, 1373 (1941).

131. (a) Mozingo, Wolf, Harris, and Folkers, J. Am. Chem. Soc., 65, 1013 (1943); (b) Mozingo, Harris, Wolf, Hoffhine, Easton, and Folkers, ibid., 67, 2092 (1945).

In our work, the γ-(p-aminophenoxy)-propyl β-hydroxyethyl sulfone was prepared from the corresponding nitro compound in good yield by catalytic reduction using Raney nickel, hydrogen at three atmospheres, and a temperature of 95-100°. Subsequently essentially these same conditions were used in the reduction of the nitro group contained in certain of the 6-quinolyl sulfides and sulfones previously discussed. Recently, Broadbent[132] has described the catalytic reduction of several nitro diaryl sulfones.

Previous to attempts to convert γ-(p-aminophenoxy)-propyl β-hydroxyethyl sulfone to the corresponding β-chloroethyl compound, a thorough search of the literature revealed no instance of the replacement of an alcoholic hydroxyl by a halogen in the presence of an aromatic primary amino group within the same molecule. Since no precedent existed, the closest analogies to be found in the literature were studied. Thus, Burrows and Reid[133] described the preparation of bis-β-bromoethyl sulfide in 95% yield from the reaction of thiodiglycol and aqueous hydrogen bromide. The starting materials were soluble in water, while the product was insoluble, which made for completeness of reaction. For unknown reasons, no isolable material could be obtained when the procedure was applied to our compound.

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132. Broadbent, H. S., Doctoral Dissertation, Iowa State College, Ames, Iowa, 1946.

133. Burrows and Reid, J. Am. Chem. Soc., 56, 1720 (1934).

Accordingly, the use of thionyl chloride was investigated.[134] Recently, Gerrard completed an investigation and detailed evaluation of the mechanism of reaction in the interaction of thionyl chloride with hydroxylic compounds, using pyridine as the solvent. Excellent procedures are given. However, when such were applied to our compound, no product could be isolated. When thionyl chloride was added to a chloroform solution of the compound, the result was the same. Only intractable oils and gums were obtained.

The compound, γ-(p-aminophenoxy)-propyl β-chloroethyl sulfone hydrochloride, was finally obtained by dusting the amine into an ice-cold solution of thionyl chloride with continuous shaking. Subsequent to warming gently a vigorous reaction ensued and complete solution was effected. For rectification, most of the excess thionyl chloride was removed *in vacuo*, and the remainder of the latter effectively removed by decomposition with cold absolute ethanol, accompanied by external cooling. The latter procedure converted the ethanol to gaseous ethyl chloride with attendant formation of sulfur dioxide and hydrogen chloride, until all the excess thionyl chloride was removed, at which point the amine remained as the hydrochloride. Additional ethanol was added and the hydrochloride crystallized directly in a very satis-

134. Gerrard, *J. Chem. Soc.*, 99 (1939).

factory manner. The compound is water soluble and, as mentioned previously, has a powerful vesicant action.

In continuation of studies initiated in these laboratories on the preparation of antimalarials with sulfur-containing side-chains, γ-(6-methoxy-8-quinolylamino)-propyl mercaptan was prepared by the condensation of 6-methoxy-8-aminoquinoline with γ-chloropropyl mercaptan. Separation of the crude product from unreacted 6-methoxy-8-aminoquinoline was effected by extraction of an ethereal solution of the crude reaction mixture with 20 percent sodium hydroxide, acidification of the alkaline extract with hydrochloric acid, and final liberation of the soluble hydrochloride with ammonium hydroxide, prior to solution in ether. Subsequent to vacuum distillation, the product was obtained as an oil which was converted to the solid hydrochloride for crystallization. The compound, however, was found to be inactive toward avian malaria.

V. SUMMARY

1. A general review has been made on the addition of organometallic compounds to pyridine, and the analogous hexacyclic nitrogen compounds, quinoline and isoquinoline.
2. The relationship of these compounds to the ammonia system has been indicated and the mechanisms of addition of organolithium compounds to such cyclic ammono aldehyde ethers has been discussed.
3. A new reaction, namely the addition of organolithium compounds to examples of a cyclic ammono ketone ether, has been indicated. The mechanism of addition in this reaction has been discussed in the light of the experimental findings.
4. Several substituted organolithium compounds have been added to the anil linkage of isoquinoline and a basically substituted isoquinoline.
5. The addition to quinoline and isoquinoline of organolithium compounds containing otherwise reactive functional groups has been described. Thus the applicability of such organolithium compounds to addition reactions has been demonstrated by their addition to the azomethine linkage of quinoline and isoquinoline. The proof of structure of one of the compounds, 1-(p-aminophenyl)-isoquinoline, is described.

6. The Skraup synthesis of an aryl 6-quinolyl sulfide and sulfone has been accomplished.
7. A series of substituted 6-quinolyl nitro-, amino- and acetamidophenyl sulfides and sulfones has been synthesized and submitted for testing for antimalarial and tuberculocidal activity. An improved method for the preparation of p-aminothiophenol was worked out.
8. A few p-aminophenyl-derivatives containing the sulfone group in an alkyl "side-chain" have been prepared and were tested for antimalarial and antituberculous activity. None of the compounds was found to be active. One of the compounds, γ-(p-aminophenoxy)-propyl β-chloroethyl sulfone hydrochloride showed pronounced vesicant action.
9. Complete pharmacological results are not yet available. Many of the compounds for which reports have been received have shown no activity. However, the lack of toxicity exhibited by some of the 6-quinolyl sulfone compounds is of interest.