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Application of lithium compounds of nitrogen heterocycles to antimalarial syntheses

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NOTE TO USERS

APPLICATION OF LITHIUM COMPOUNDS OF NITROGEN HETEROCYCLES TO ANTIMALARIAL SYNTHESES

by

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TABLE OF CONTENTS

Page

A. LITHIUM COMPOUNDS OF NITROGEN HETEROCYCLES

I. INTRODUCTION

Of the large variety of organometallic compounds, the organolithium and the Grignard reagents are the most useful in synthetic chemistry. In the laboratory both are relatively easy to prepare and handle, requiring primarily a dry, inert, oxygen-free atmosphere; they are neither poisonous nor spontaneously inflammable when exposed to the air. Oftentimes they complement each other in the sense that where a certain Grignard cannot be prepared, the corresponding lithium compound can, and vice versa.

Unfortunately, not all RLi or RMgX compounds can be made by the customary reaction of a metal on an RX compound. An important synthetic tool, known for a long time but developed only in recent years, is the halogen-metal interconversion reaction[1,2]. Considerable use was made of this tool in extending the knowledge concerning nitrogen-containing organometallic chemistry. In the course of these studies previously

1. Kalle, Ann., 119, 153 (1861); Urion, Compt. rend., 198, 1244 (1934).

2. (a) Gilman and Jacoby, J. Org. Chem., 3, 108 (1938); Gilman and co-workers, J. Am. Chem. Soc., 61, 106 (1939) and subsequent papers; (b) Wittig and co-workers, Ber., 71, 1903 (1938) and subsequent papers.

inaccessible organometallics, such as the pyridyl- and quinolyllithium compounds, the di-lithiocarbazoles, and halogen-containing organometallics of pyridine and carbazole were prepared. Furthermore, previously known RM compounds of carbazole are now made available in decidedly improved yields.

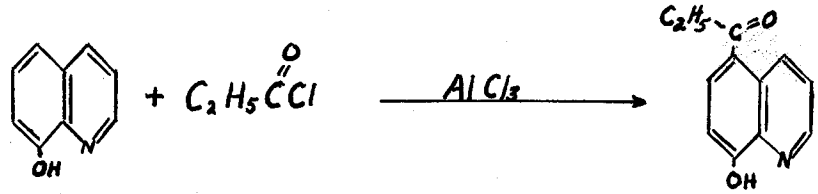
We have also attempted to throw some light on orientation in the metalation of aromatic amines, both heterocyclic and non-heterocyclic.

In the course of these studies two new syntheses of 3-quinolinecarboxylic acid were developed, both of which surpass the older methods with respect to over-all yield, availability of starting materials, and in the reduced number of intermediate steps. Because of its homologous relation to the biologically active nicotinic acid and its amides, the 3-quinolinecarboxylic acid was used as a starting material in the synthesis of new substituted amides which were examined for pharmacological activity.

II. HISTORICAL AND THEORETICAL

1. Pyridyl- and Quinolyllithium Compounds

Application of the halogen-metal interconversion reaction to the preparation of pyridyllithium and homologs provides new synthetic tools in the field of pyridine chemistry. These nuclei, widespread throughout a large variety of pharmacologically active compounds, both synthetic and natural, are important. Yet they are handicapped by inability to undergo the Friedel-Crafts reaction[3], and until very recently[4], could not be made to form a Grignard reagent. Recently, Matsumura[5] reported probably the first example of a Friedel-Crafts reaction in pyridine chemistry.



Perhaps the first evidence for the formation of Grignard reagents from 3-bromo- and 2-iodopyridine is to be found in a

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3. Sidgwick, "Organic Chemistry of Nitrogen", The Clarendon Press, Oxford, 1937, p. 523.

4. (a) Overhoff and Proost, Rec. trav. chim., 57, 179 (1938); (b) Proost and Wibaut, ibid., 59, 971 (1940).

5. Matsumura, J. Am. Chem. Soc., 57, 124 (1935).

study by Harris[6]. He observed that in the treatment of these halogenated pyridines with magnesium, Grignard formation took place as indicated by color tests, but that side reactions set in with the subsequent formation of a tarry product. No color test could be obtained from the reaction between magnesium and 2-chloropyridine, 3,5-dibromopyridine or 6-bromoquinoline. As early as 1904, Sachs and Sachs[7] stated that Grignard reagents could not be made from bromoquinolines. These findings were duplicated by Howitz and Kopke[8], although they did report the preparation of a Grignard reagent from 8-bromomethylquinoline. Since 2-bromopyridine reacts with copper powder to give a good yield of 2,2'-bipyridyl[9], various experiments were carried out by Hertog and Wibaut[10] concerned with the preparation of pyridyl Grignard reagents from activated magnesium powder, pure magnesium powder or clean magnesium turnings and 2-chloro-, 2-bromo-, or 2-iodopyridine at the reflux temperature of a solvent such as diethyl ether, dibutyl ether, benzene, and dimethylaniline. All results were negative. Carbon dioxide, acetyl chloride and acetone were employed as characterizing agents in this extensive study.

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6. S. A. Harris, Iowa State Coll. J. Sci., 6, 425 (1932) /C. A., 27, 279 (1933)/.

7. Sachs and Sachs, Ber., 37, 3088 (1904).

8. Howitz and Kopke, Ann., 396, 38 (1913).

9. Wibaut and Overhoff, Rec. trav. chim., 47, 761 (1928).

10. Hertog and Wibaut, ibid., 55, 122 (1936).

Finally, Overhoff and Proost[4a] succeeded in making 2-pyridylmagnesium bromide in 40-55% yield using ethyl bromide as an "auxiliary" agent. This procedure is suggestive of the "entrainment" method of Grignard[11], according to whom[12] best yields are obtainable when exactly one mole of auxiliary RBr is added. The double conversion (X - M interconversion) of Urion[1]

$$RMgBr + R'Br \longrightarrow R'MgBr + RBr$$

might be the real mechanism of the reaction, but Overhoff could not support either of these views since very little difference in yield was noticed when the amount of ethyl bromide was varied from one-fourth to one mole. Further theoretical aspects of the problem have been promised[4b] for a later date. Similarly, a dimagnesium compound of 2,6-dibromopyridine has been prepared[4b], and claims have been made that the method in question can be applied successfully to 2-chloro-, 4-chloro-, and 3-bromopyridine, although experimental data have not yet been reported.

The first[13] attempts to prepare organolithium compounds from 2-bromopyridine, 2-bromoquinoline, and 3-bromoquinoline by the method of X-M interconversion were carried out at the

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11. Grignard, Compt. rend., 198, 625 (1934).

12. Grignard, ibid., 198, 2217 (1934).

13. I. Banner, M. S. Thesis, Iowa State College, Ames, Iowa, 1939.

temperature of refluxing ether for 20 hours. No acid, subsequent to carbonation, was obtained in any case. This is not surprising, since there is present an azomethylene linkage which, competing with the halogen atom for the RLi compound, adds the latter as soon as it is formed. (See equation VIII, p. 10.) Furthermore, under the vigorous conditions employed above, not all, in fact, very little of the interconverting agent would be used up in the X-M reaction; most of it would be destroyed by addition to the -N=C< bond. (See equation IV, p. 9.) Inability to curb the reactivity of the azomethylene linkage in reactions of the kind described unquestionably accounts for the negative results obtained by previous investigators in this field of organometallic synthesis. It is now established that pyridyllithium[14a,14c] compounds and homologs[14a,14b] can be prepared by the method of X-M interconversion, providing mild conditions of low temperature and short reaction time, such as -35° for ten to fifteen minutes are employed. The exact optimum conditions, not yet ascertained, vary somewhat for each halogenated pyridine or quinoline compound. However, these two environmental conditions are not the only factors involved, since anil addition was not retarded in the treatment of quinoline with n-butyllithium at -35° for fifteen minutes[14b]. Consequently, in a halogenated pyridine or quinoline, which constitutes a system of two

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14. (a) Gilman and Spatz, J. Am. Chem. Soc., 62, 446 (1940); (b) ibid., 63, 1553 (1941); (c) ~~ibid., 64, 000 (1942).~~ J. org. Chem 16, 1485 (1951)

functionally active groups competing for the butyllithium, other factors are undoubtedly present which under the laboratory conditions chosen permit the selective operation of one reaction (interconversion) at the expense of the other (addition to the anil linkage). These physico-chemical factors may be any one or combination of the following:

(a) The negative halogen atom may deactivate the anil linkage toward RLi addition; or

(b) the relative reactivity of the halogen with respect to butyllithium may be greater than that of the anil linkage, and in conjunction with (a) may be exaggerated sufficiently to permit selectivity in the desired direction; and

(c) the metallic atom introduced may contribute toward the deactivation of the anil linkage.

When the environmental conditions of low temperature and short time are removed, these physico-chemical factors are altered and the activity of the anil linkage then becomes manifest in the series of reactions described elsewhere which destroy the desired organometallic product. In this respect it is interesting to observe that the m- and p-bromodimethylanilines[15], which are halogenated tertiary amines without the anil group, yield interconversion products in favorable quantity even under reflux for twenty hours.

Chlorine-metal interconversion has been observed only

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15. Gilman and Banner, ibid., 62, 344 (1940).

rarely[16]. Nevertheless, the exalted reactivity of α- and γ-halogens in quinoline suggested the possibility of preparing 2-quinolyllithium from the commercially available 2-chloroquinoline. The attempted interconversions with n-butyl- and methyllithiums were negative. Similarly, no X-M interconversions were observed between 6-methoxy-4-chloroquinoline and phenyl- or p-chlorophenyllithium, or with 4-chloroquinoline and o-anisyllithium. (See Part B of this thesis.) In Wittig's laboratory aryllithium compounds are generally employed for X-M interconversions; in this laboratory alkyllithium compounds are employed for this purpose.

Since 2- and 4-chlorcquinolines undergo hydrolysis, ammonolysis and etherification by alkoxides, whereas 3-bromoquinoline does not except under forced conditions, it could be inferred that the 2-chloro atom is more reactive than the 3-bromo atom; yet the latter is capable of X-M interconversion and the former is not. Therefore, the general inability of chloro compounds to undergo this reaction cannot be explained by a scheme of relative inertness, as one might be inclined to do from the large number of studies which indicate that the order of reactivity of halogens in the C-X linkage is I > Br > Cl.

In the reaction with methyllithium, α-chloroquinoline

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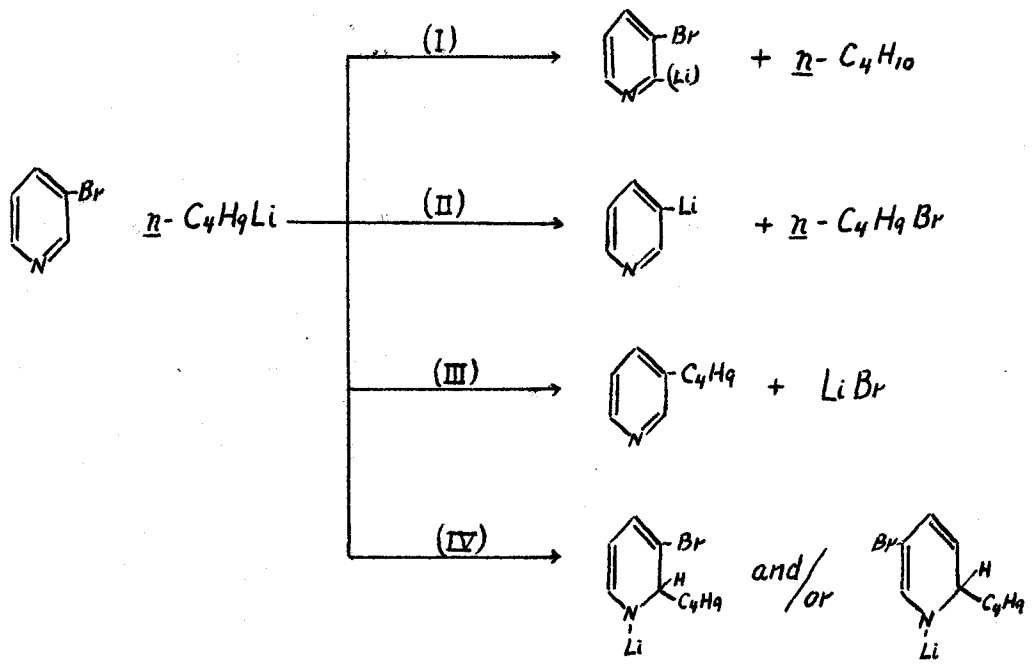
16. (a) Gilman, Langham and Moore, ibid., 62, 2327 (1940); (b) Wittig, Angew. Chem., 53, 241 (1940). Cf. the unpublished studies of Messrs. A. H. Haubein and D. S. Melstrom in ref. 16a.

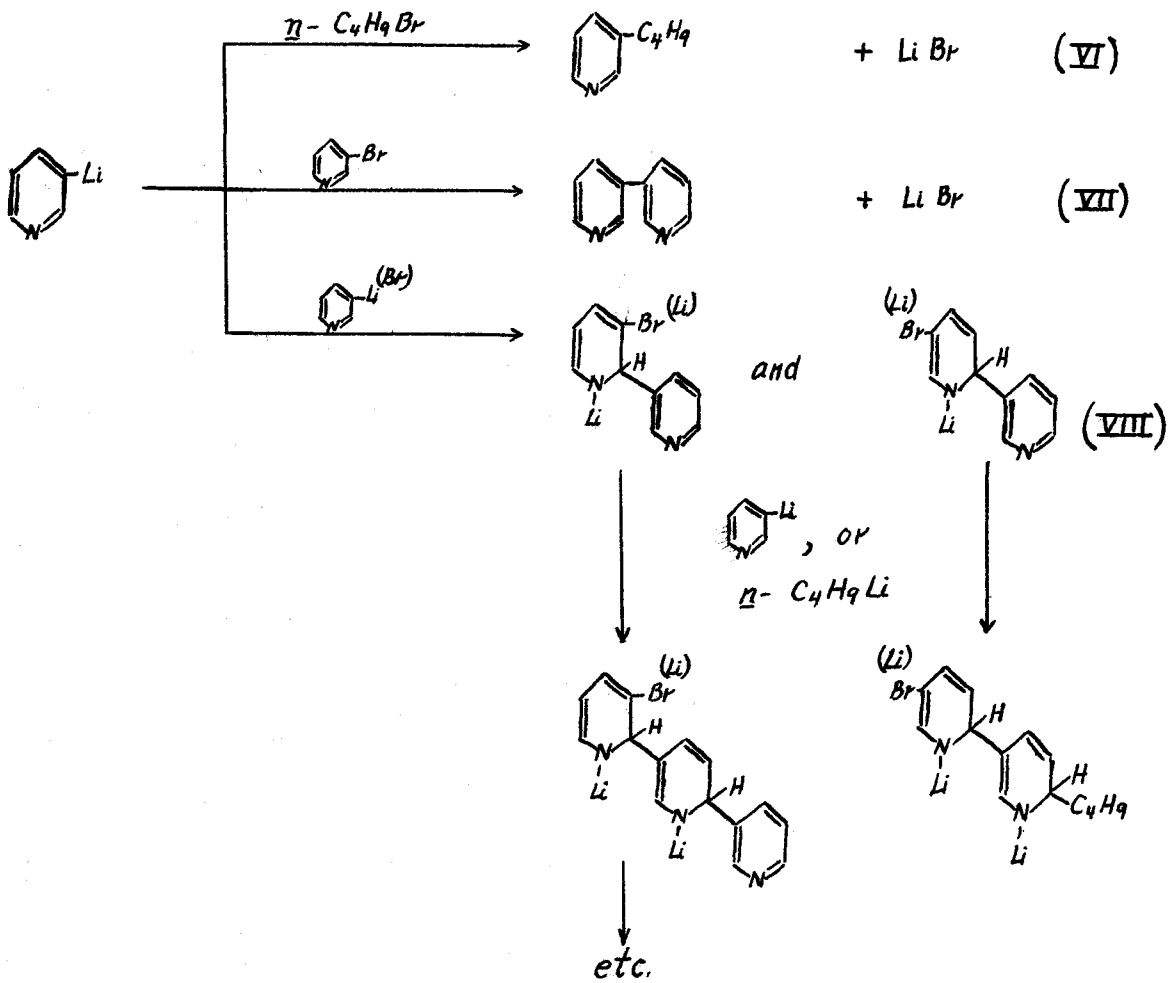
was recovered to the extent of 81.5% of the original. The significance of this is to be noted. Under the same conditions quinoline adds RLi promptly; that α-chloroquinoline does not do so, adds support to the hypothesis made earlier that the halogen atom exerts a deactivating effect upon the -N=C< linkage.

Treatment of a halogenated pyridine or homolog with alkyllithium may effect one or more of a number of possible primary reactions: (I) metalation or H-M interconversion, (II) X-M interconversion, (III) direct coupling or replacement of the halogen by the alkyl group with splitting out of LiX, and (IV) addition of RLi to the azomethylene linkage. Illustrated by means of the 3-bromopyridine-butyllithium system, these reactions are:



The system is complicated further by the possible occurrence of secondary reactions, chief of which are: (V) coupling between unused butyllithium and the alkyl halide product of reaction (II) to form octane, (VI) coupling between the pyridyllithium and alkyl halide from X-M interconversion, (VII) coupling between the pyridyllithium and unused 3-bromopyridine to form the corresponding bipyridyl compound, and finally (VIII) addition of the pyridyllithium to the anil linkage of unused 3-bromopyridine and to the anil linkage of other molecules of pyridyllithium.

$$\underline{n}\text{-}C_4H_9Li + \underline{n}\text{-}C_4H_9Br \longrightarrow \text{octane} + LiBr \qquad (V)$$



In compounds such as 2-bromo-, 3-bromo-, 3-iodo-, 2,6-dibromo- and 3,5-dibromopyridine, 3-bromoquinoline and 2-iodolepidine, metalation (reaction I) did not occur. This is so because the relatively sluggish hydrogen atom is forced to compete with two reactive functional groups—the bromine atom and the -N=C< bond—for the RLi agent. Nevertheless, the possibility of metalation exists; various alkyl-pyridines and -quinolines (p. 27) metalate, and evidence[14b] exists for a similar reaction with α-chloroquinoline. In the latter compound metalation is likely for two reasons: (1) chlorine, in general, does not give the X-M reaction and (2) the -N=C< bond is so deactivated by both the chlorine atom and the benzo group that the molecule behaves as though it contained no -N=C< bond, i.e., it behaves as a chloronaphthalene. In fact, a chloro acid has been obtained[17] from α-chloronaphthalene and n-butyllithium.

The inorganic product of coupling, lithium iodide, has been isolated from the reaction between 3-iodopyridine and n-butyllithium. At present it is impossible to ascertain which of the four coupling reactions (III, V, VI or VII) predominates; indirect evidence[14c] favors reaction VI.

Of the various bromo- and iodopyridines and quinolines studied so far the predominant reaction, under the conditions selected by us, is X-M interconversion (reaction II), except

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17. Gilman and Moore, J. Am. Chem. Soc., 62, 1843 (1940).

with 3-bromopyridine. With the latter the main reaction appears to be RLi addition. A rough estimation of the extent of X-M reaction, anil addition, and coupling between 3-iodopyridine and n-butyllithium is given in the experimental part. A more detailed discussion of reactions I-VIII inclusive is presented in reference 14c. ?

Noteworthy is the difference in behavior between 2-bromopyridine and the 3-isomer towards n-butyllithium. The former gives a 60% yield of 2-pyridyllithium without precipitate formation; the latter, a 30% yield of 3-pyridyllithium with precipitate formation[18]. The physico-chemical factors postulated previously to account for successful X-M interconversions in the pyridine and quinoline series under properly chosen conditions may be used to explain this difference in behavior. In 2-bromopyridine, the -N=C< bond is situated closer to, and may therefore be affected more markedly by, the deactivating sphere of the halogen (or lithium) atom than in the 3-isomer. Steric factors do not appear to be present in either of these pyridine molecules. Furthermore, in 3-bromoquinoline, where the distance between halogen atom and the -N=C< bond is the same as in 3-bromopyridine, the presence of the negative benzo group probably contributes to the deactivation of the anil linkage, thus permitting X-M reaction to the extent of 52% of the theoretical. Likewise, in

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18. Absence of precipitate formation does not necessarily exclude the occurrence of anil addition.

3,5-dibromopyridine two centers of deactivation are present which permit a smooth X-M reaction without precipitate formation.

On the basis of this theory it is to be predicted that the more negative groups (chlorine atom, phenyl and benzo radicals, etc.)[19] there are in the molecule, and the more closely these are situated to the -N=C< bond, the smoother will be the X-M reaction. Thus, the halogenated acridines and phenanthridines should be easily convertible to the corresponding lithium compounds. It is even to be predicted that in very heavily substituted pyridines, more vigorous conditions of time and temperature may be employed and that the quickly acting n-butyllithium may be replaced by the much slower acting lithium, without fear of interference from the azomethylene linkage. In line with this prediction is the observation by Allen and Frame[20] that lithium and 2-bromo-3,4,6-triphenylpyridine in ether react to form 2-lithio-3,4,6-triphenylpyridine, for hydrolysis yields 2,4,5-triphenylpyridine. Unfortunately, this lithium compound could not be made to react with carbon dioxide, aldehydes and ketones. However, Mr. D. S. Melstrom of this laboratory has recently prepared the same RLi compound through X-M interconversion and found it capable of reacting with carbon dioxide in 65% yield.

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19. Of course negative groups such as -C≡N, -CO-CH_3, etc., which in themselves react with RLi, are obviously excluded.

20. Allen and Frame, J. Am. Chem. Soc., 62, 1301 (1940).

The corollary follows that 4-pyridyllithium will be the most difficult of this series to prepare, unless the molecule is protected by the presence of negative groups, especially in the α and α' positions. In contrast to the difficulties attending the preparation of 3-pyridyllithium, compounds such as 2-phenyl-3-bromo- and 2,6-diphenyl-3-bromopyridine should give excellent yields of the corresponding lithium compounds.

In a study to eliminate interference from the azomethylene linkage in the preparation of 3-pyridyllithium, resort was made to a variety of alkyllithium reagents, the ideal being one which would add relatively slowly to the -N=C< bond and interconvert rapidly with the halogen atom. Information on the relative reactivities of RLi compounds toward the anil linkage is scarce[21]. However, it is known[22] that for purposes of X-M interconversion with α-bromonaphthalene certain RLi agents can be arranged in the following order of decreasing effectiveness: s-butyllithium, n-propyllithium, ethyllithium, t-butyllithium, n-butyllithium, n-amyllithium, phenyllithium and methyllithium. Yet, n-propyllithium gave only a 16.8% yield of 3-pyridyllithium, whereas n-amyllithium gave a 24.5% yield of interconversion product. To explain these contra-

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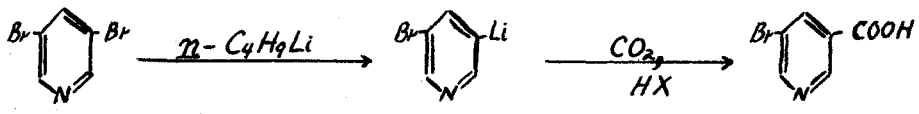
21. An unpublished study by J. A. V. Turck, Jr., showed that in general RLi agents add rapidly to the anil linkage of pyridine and quinoline.

22. Gilman and Moore, J. Am. Chem. Soc., 62, 1843 (1940); Gilman, Moore and Baine, Ibid., 63, 2479 (1941).

dictory yields, it may be inferred that n-propyllithium adds more rapidly to the -N=C< bond than does the amyl homolog. It was especially hoped that by using s- or t-butyllithium the additional factor of steric hindrance would minimize anil addition, but such was not the case, since under the same conditions of time, temperature and solvent, n-butyllithium gave the same yield of 3-pyridyllithium.

In contrast to the dihalogenated carbazoles, 2,6- and 3,5-dibromopyridine appear to undergo mono-interconversion only, even with such vigorous X-M interconverting agents as n-butyl- and n-propyllithium:



In conjunction with the carbazole studies this fact is important, because it suggests a possible mechanism of multiple X-M interconversions in polyhalogenated compounds.

2. Further Aspects of the Pyridine Family in Organometallic Chemistry.

Pyridine and homologs have been treated with the three classes[23] of metalating agents—(I) metals, (II) inorganic salts and (III) RM compounds. Metalation attempts[24] with

23. R. L. Bebb, Doctoral Dissertation, Iowa State College, Ames, Iowa, 1938.

24. Emmert, Ber., 47, 2598 (1914); 49, 1060 (1916); 50, 31 (1917); 54, 204 (1921), and Smith, J. Am. Chem. Soc., 46, 414 (1924) comprise the leading references.

alkali metals failed. In all cases, reduction, coupling and ill-defined complex formation took place. For example,

pyridine, in excess + sodium sand —shaken for 48 hrs. in inert atmosphere at room T.→ excess pyridine evaporated in vacuo

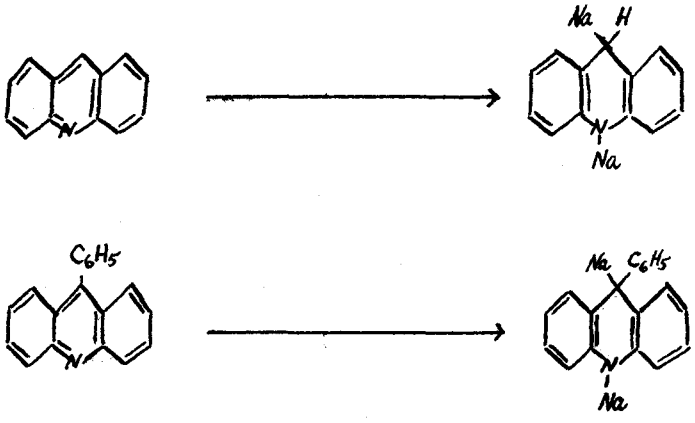
↓

$(C_5H_5N)_2.Na$ dark green body, spontaneously inflammable in air. —△ in vacuo to 130°.→ $C_5H_5N.Na$ residue, also spontaneously inflammable + pyridine in distillate

↓ water (wet ether)

tetrahydrodipyridyls —[O] (air)→ 4,4'-dipyridyl + a little of the 2,2'-isomer.

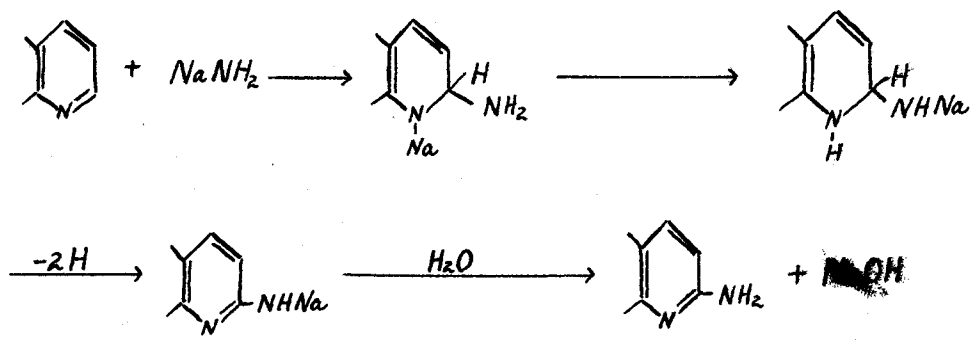
Lithium, and potassium less readily, exhibit the same behavior with pyridine, forming $(C_5H_5N)_2.Li$, $C_5H_5N.Li$, $(C_5H_5N)_2.K$ and $C_5H_5N.K$. However, with acridines 1,4-addition of the metal occurs[25]:



25. Schlenk and Bergmann, Ann., 463, 281 (1928).

The tendency toward complex formation with alkali metals suggests that applications of the Wurtz and Wurtz-Fittig reactions to pyridine compounds may be impossible.

Pyridine and quinoline compounds react with class II metalating agents. With sodium amide, the reaction is generally not metalation, but rather one of anil addition. Called Chichibabin's[26] synthesis, the reaction is believed to take the following course:

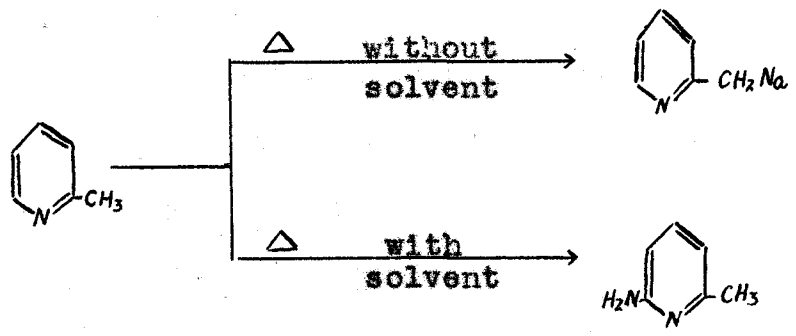


α-Picoline also adds sodium amide to form the corresponding 2-amino-6-methylpyridine[26,27]. A solvent such as toluene, xylene or dimethylaniline is generally employed in the sodamide addition. In the absence of any solvent, α-picoline undergoes lateral metalation[28] to form α-picolylsodium, several days being required for the reaction to go to completion:

26. Chichibabin and Seide, J. Russ. Phys.-Chem. Soc., 46, 1216 (1914) /C. A., 9, 1901 (1915)/.

27. (a) Seide, J. Russ. Phys.-Chem. Soc., 50, 534 (1918) /Chem. Zentr., III, 1022 (1923)/; (b) Ger. Patent 663,891 /C. A., 33, 175 (1939)/.

28. Chichibabin, Rec. trav. chim., 57, 582 (1938).



The lateral metalation of α-picoline recalls the interesting studies[29] on the metalation of phenylacetonitrile. Both compounds are chemically very similar; they are aromatic, contain a >C=N- or -C≡N bond, and have an exalted methyl or methylene group in which the hydrogens are extremely reactive. In ether solution, the nitrile reacts with either sodium or sodium amide yielding the metalation product, $C_6H_5CH(Na)CN$, which on treatment with alkyl halides forms C_6H_5CHRCN. The resulting nitrile also metalates yielding compounds with the general formula $C_6H_5CR(Na)CN$. It is, therefore, interesting to speculate whether α-picoline can be metalated laterally by sodium also.

Quinaldine also undergoes lateral metalation with sodium amide in absence of solvent[30]; the quinaldylsodium reacts

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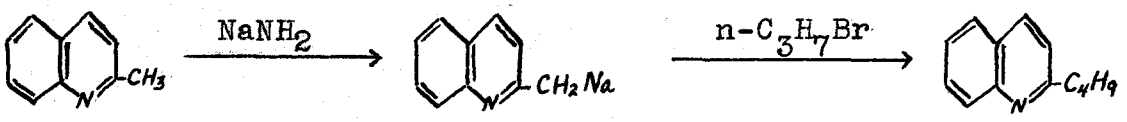
29. (a) Bodroux and Taboury, Compt. rend., 150, 531, 1241, 1274 (1910); (b) Bodroux, ibid., 151, 234, 1357 (1910); 152, 1594 (1911); 153, 350 (1911); (c) Bodroux and Taboury, Bull. soc. chim., [4], 7, 735 (1910); [4], 9, 651, 726, 758 (1911); (d) Rising and co-workers, J. Am. Chem. Soc., 49, 541 (1927); 50, 1699 (1928); 51, 262 (1929); 52, 1069, 2524 (1930); (e) Upson, Maxwell, and Parmalee, ibid., 52, 1971 (1930).

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

with n-propyl bromide to give the 2-n-butylquinoline:



Bergstrom[31] has made an extensive study of the action of various alkaline and alkaline earth amides on quinoline compounds. His results are presented in outline form:

quinoline + KNH_2 ⟶ 2- and 4-aminoquinolines; the 2-isomer predominates.

quinoline + $Ba(NH_2)_2$ ⟶ 2-aminoquinoline only.

isoquinoline + KNH_2, $LiNH_2$, $NaNH_2$ mixed amides ⟶ 1-amino-isoquinoline 60-75% yield

6-methylquinoline	+ $Ba(NH_2)_2$ ⟶ 6-Me-2-NH_2-Q	(17%)
8-methylquinoline	+ $Ba(NH_2)_2$ ⟶ 8-Me-2-NH_2-Q	(35%)
8-ethoxyquinoline	+ $Ba(NH_2)_2$ ⟶ 8-EtO-2-NH_2-Q	(76%)
6-dimethylaminoquinoline	+ $Ba(NH_2)_2$ ⟶ 6-$(CH_3)_2N$-2-NH_2-Q	(34%)
2-quinolinecarboxylic acid	$\xrightarrow[KNO_2]{KNH_2}$ 2-COOH-4-NH_2-Q	(81%)
4-quinolinecarboxylic acid	$\xrightarrow[KNO_2]{KNH_2}$ 4-COOH-2-NH_2-Q	(70%)

Q = quinoline

It should be observed that blocking of the 2-position produces 1,4-addition of the KNH_2.

Mercuric inorganic salts also belong to class II

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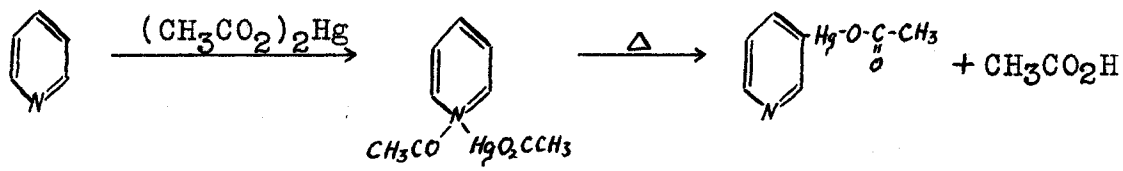
31. Bergstrom, ibid., 56, 1748 (1934); Ann., 515, 34 (1934); J. Org. Chem., 2, 411 (1937); ibid., 3, 233 (1938).

metalating agents. However, these salts effect metalation and not addition to the azomethylene linkage. The mercuration generally takes place meta to the nitrogen atom--i.e., ortho to the -N=C< bond. Heating of pyridine with mercuric acetate gives 3-pyridylmercuric acetate[32,33]. A nitrogen-addition product is formed first, which dissolves in excess pyridine; on heating, true mercuration through rearrangement takes place:



α-Aminopyridine and α-picoline were also found to mercurate easily[33]. The former gives, subsequent to decomposition of the pyridylmercuric acetate with sodium chloride, an 88% yield of 2-amino-5-pyridylmercuric chloride. The α-picoline gives a 61% yield of what is believed to be the 2-methyl-5-pyridylmercuric compound, although its structure was not definitely established. If this structure is correct, it conflicts with the observation of Ukai[34], who found that mercuric acetate mercurates quinaldine (α-methylquinoline) in the side chain. Isoquinoline[34] mercurates in the 4-position, and

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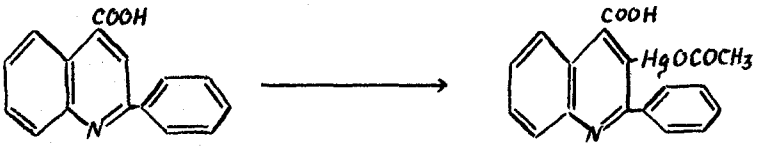
32. McClelland and Wilson, J. Chem. Soc., 1263 (1932).

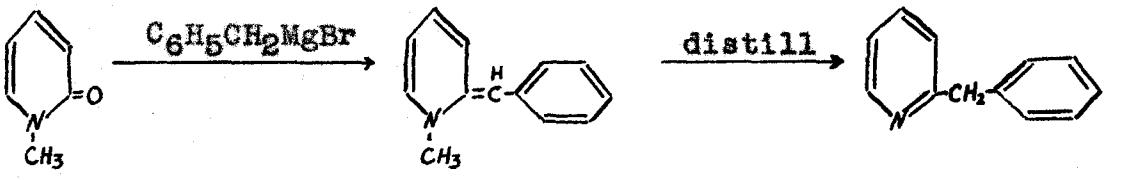
33. Swaney, Skeeters and Shreve, Ind. Eng. Chem., 32, 360 (1940).

34. Ukai, J. Pharm. Soc. Japan, 51, 542 (1931) /C. A., 25, 5427 (1931)/.

quinoline[34] in the 3-, 5- and 8- positions. An interesting quinoline compound which undergoes mercuration is cinchoninic acid[35]:



A large variety of pyridine compounds react with class III metalating agents, but generally the reaction is not one of metalation. For example, N-methyl-2-pyridone reacts with benzylmagnesium bromide to give N-methyl-2-benzylidene-1,2-dihydropyridine[36].



The first recorded observation of RMgX addition to cyclic azomethylene compounds is to be found in the work of Freund[37]. Employing the methiodides of various pyridine, quinoline, isoquinoline and acridine compounds, he observed 1,2-addition in every case except with acridine, where addition can occur only at the end of the conjugated system.

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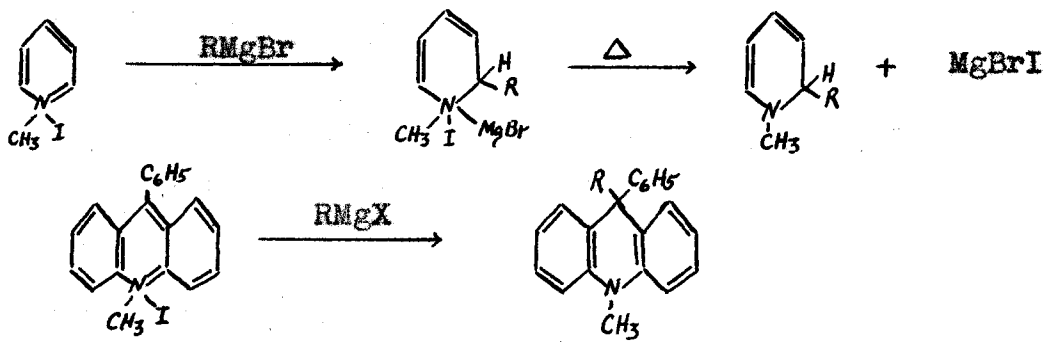
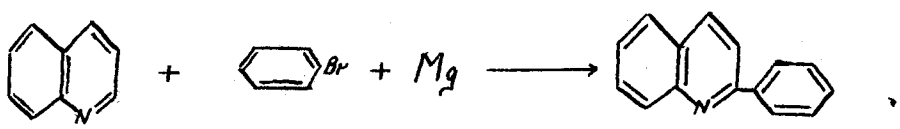
35. Dominikiewicz, Roczniki Chem., 11, 664 (1931) [C. A., 26, 3797 (1932)].

36. Decker, Ber., 38, 2493 (1905).

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



Oddo[38] also observed α-arylation of quinoline on treatment of the latter with magnesium and bromobenzene in benzene as solvent:



Similar results[38] were obtained when one mole of pyridine or quinoline was added to one mole of previously prepared phenylmagnesium bromide. Years later Bergstrom and McAllister[39], delving into the mechanism of the reaction, observed that the initially formed white precipitate yielded the original heterocycle on hydrolysis. However, if the insoluble body was heated to 180° in a sealed tube prior to hydrolysis, an α-substituted heterocycle was produced. Accordingly, they postulated the reaction to take place as follows:

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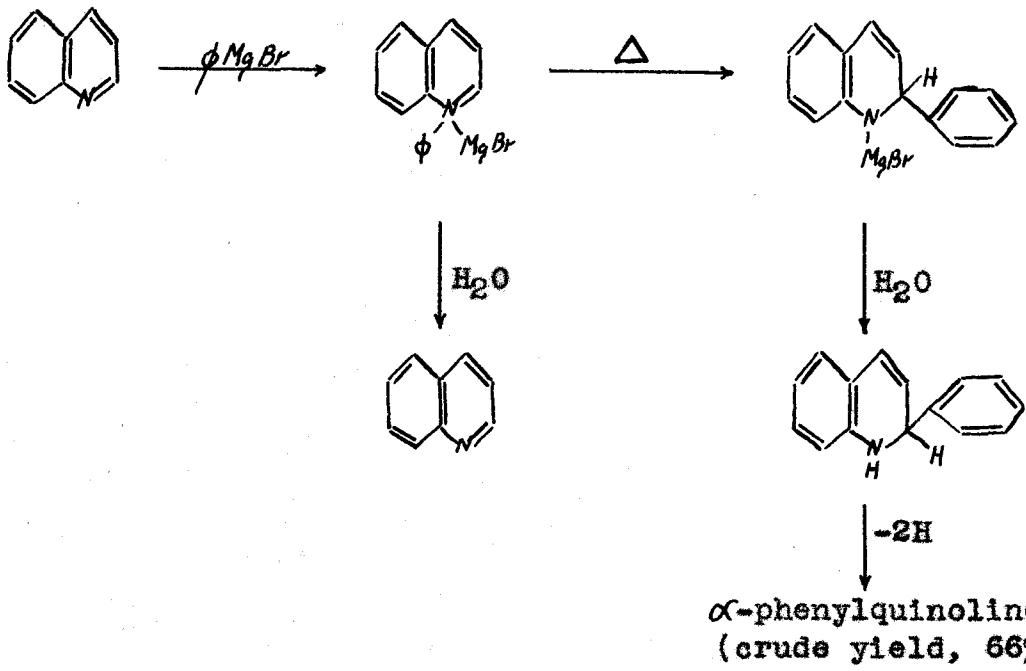
38. Oddo, Atti. accad. Lincei, (V), 16, 538 (1907); Gazz. chim. ital., 371, 574 (1907).

39. Bergstrom and McAllister, J. Am. Chem. Soc., 52, 2845 (1930).



α-phenylquinoline
(crude yield, 66%)

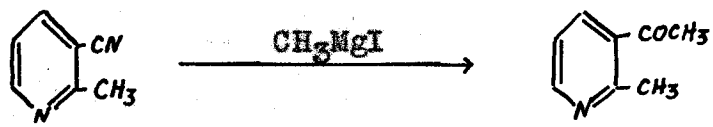
The addition compound, sparingly soluble in ether, is believed to have the structure of a substituted ammonium salt. Under the influence of heat, the aryl group migrates to the adjacent carbon atom, so that the net result is addition of RMgX to the -N=C< bond. γ- Isomers were not isolated; this is an interesting observation, since the Grignard reagent adds 1,4 to a conjugated open chain azomethylene compound[40].

A pyridyl- or quinolylnitrile is a polyfunctional molecule with two types of >C=N- bonds. The cyano group reacts preferentially with the organometallic reagent. Numerous examples occur in the literature but only a few will be cited here. LaForge[41] prepared 3-acetylpyridine from 3-cyanopyridine and methylmagnesium iodide. Likewise, 2-picolyl methyl

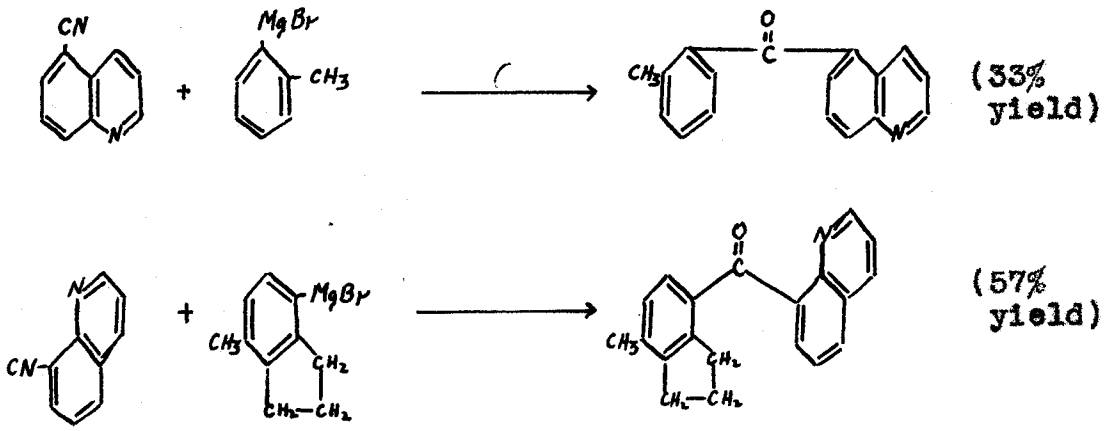
40. Gilman, Kirby and Kinney, ibid., 55, 1265 (1933); 63, 2046 (1941).

41. LaForge, ibid., 50, 2477 (1928).

ketone was prepared from the corresponding nitrile[42].



In the quinoline series, 6-methoxy-8-cyanoquinoline was treated with ethylmagnesium iodide to give 6-methoxy-8-quinolylethyl ketone[43], and more recently Fieser and Hershberg[44] found the same synthesis to be applicable with aryl Grignard reagents.



The greater reactivity of the cyano group over the azomethylene linkage is of importance, synthetically speaking, because it shows that pyridine compounds containing certain functional groups can react with RMgX compounds without fear of interference from the -N=C< bond, providing these functional groups

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42. Schmelkes and Joiner, ibid., 61, 2562 (1939).

43. Strukov, Khim. Farm. Prom., 3, 13 (1934) [C. A., 29, 1821 (1935)].

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

are above the cyano radical in the Entemann-Johnson series[45]. Established on the basis of relative reactivity toward phenylmagnesium bromide, this series is:

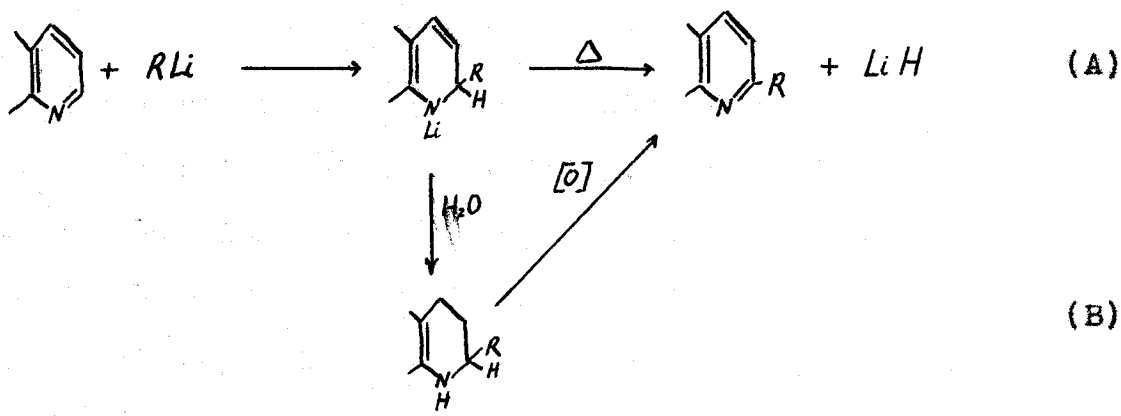
$$-CHO > -COCH_3 > -NCO > -COF > -COC_6H_5 > -COCl, -COBr > -CO_2C_2H_5 > -C\equiv N$$ [7]

In recent years considerable study has been expended on RLi compounds in pyridine chemistry. As was to be expected from studies with the Grignard reagent, the reaction is generally one of anil addition[46]. Similarly, RLi adds 1,2 to open chain conjugated azomethylene compounds, whereas RMgX adds 1,4[40]. Unlike the Grignard reagent, RLi adds to the -N=C< bond without intermediate formation of an addition complex, because hydrolysis prior to heating yields the α-substituted-1,2-dihydro compound. The yields are usually superior to those obtained with the Grignard reagent, and a very pure product in excellent yield may be obtained by running the reaction for only a few minutes in the cold[46,14b]. If the anil addition product is heated prior to hydrolysis, lithium hydride splits out, thus producing the dehydrogenated α-substituted compound. This modification of α-alkylation or

45. Entemann and Johnson, ibid., 55, 2900 (1933). See also H. D. Gooch, M. S. Thesis, Iowa State College, Ames, Iowa, 1939.

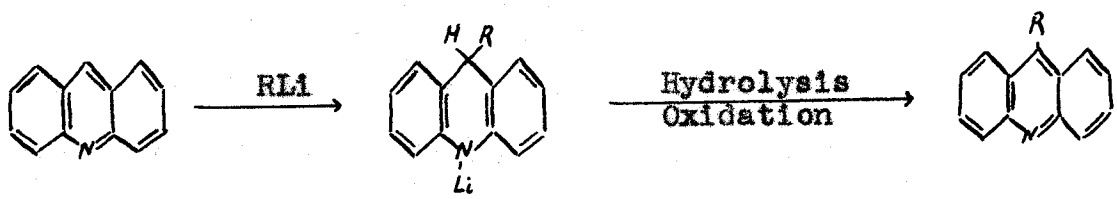
46. (a) Ziegler and Zeiser, Ber., 63, 1847 (1930); (b) Bergmann, Blum-Bergmann and v. Christiani, Ann., 483, 80 (1930); (c) Ziegler and Zeiser, Ann., 485, 174 (1931); (d) Walters and McElvain, J. Am. Chem. Soc., 55, 4625 (1933); (e) Evans and Allen, Org. Syntheses, 18, 70 (1938); (f) Oldham and Johns, J. Am. Chem. Soc., 61, 3289 (1939); (g) Part B of this thesis.

α-arylation is best employed with the pyridine compounds. With the higher homologs it is preferable to use the hydrolysis method, followed by dehydrogenation to the desired compound.

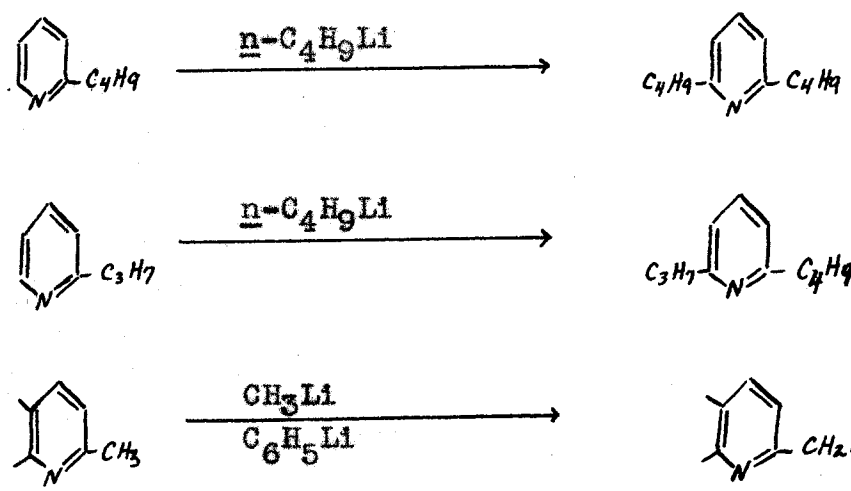


Dehydrogenation may be effected by means of nitrobenzene[46a,c], mercuric oxide[46c] or zinc dust[46f]. However, this step in the syntheses may be superfluous, since the 1,2-dihydro-compounds are generally autoöxidizable on exposure to air and it has been the experience of some investigators[46b,g] that hydrolysis of the adduct involves simultaneous auto-oxidation to the dehydrogenated product. In this respect, it should be noted that in method A, the evolution of hydrogen from the hydrolysis of the lithium hydride does not hydrogenate any of the reaction product. The adduct is surprisingly stable, and in many cases may be isolated in crystalline form[46a,g].

Acridine adds RLi with equal ease[46b,c], addition occurring at the end of the conjugated system.



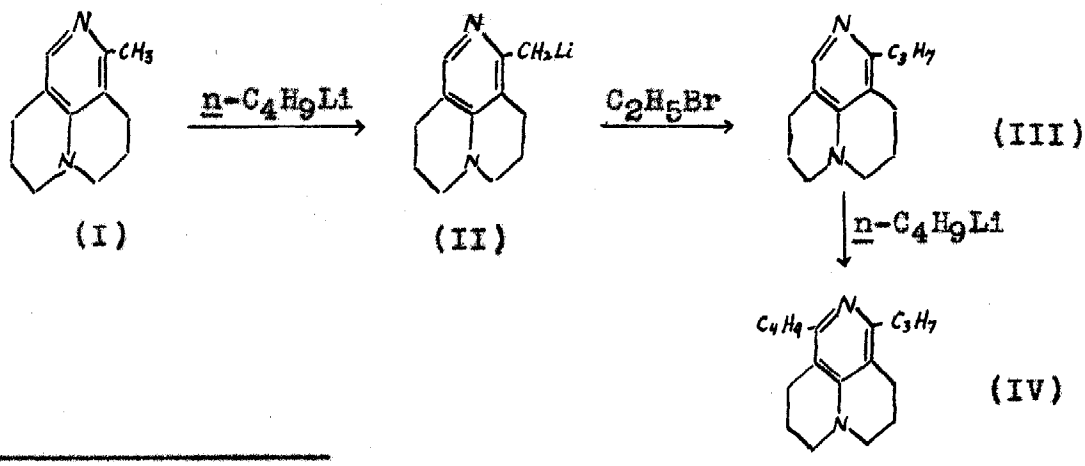
In substituted pyridines and homologs, the reaction with RLi may be other than -N=C< addition. Already discussed is the X-M interconversion of bromo and iodo compounds and the possible metalation of α-chloroquinoline. Alkyl substituted compounds may metalate in the side chain or may add to the azomethylene linkage. Prediction as to the course of reaction with such compounds is difficult. For example, α-n-butylpyridine[46c] and conyrin[47] (α-n-propylpyridine) add n-butyllithium, whereas α-picoline[46c,48] and quinaldine[46c] are metalated by methyl- and phenyllithium.



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

48. Bergmann and Rosenthal, J. prakt. Chem., 135, 267 (1932).

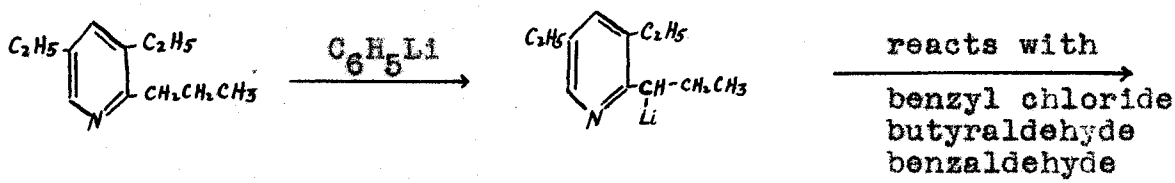
On the basis of the numerous studies from this laboratory[49], which establish unquestionably the markedly superior metalating power of n-butyllithium over methyl- and phenyllithium, one might have expected lateral metalation rather than anil addition in the cases of α-n-propyl- and butylpyridine. It may be argued that such an expectation is unwarranted since the hydrogens of an α-methyl group may be more reactive than those in the longer side chains. A gradient reactivity of alkyl hydrogens has been observed in metalation studies of alkyl-aryl thioethers. Whereas methylphenyl sulfide undergoes lateral metalation, the longer alkylphenyl sulfides undergo nuclear metalation[49a]. Also in line with this criticism is the work of Tsuda[47], who in the course of studies concerned with elucidating the structure of matrins, observed metalation of an α-methyl group with n-butyllithium.



49. See reference 22 and Gilman and Jacoby, J. Org. Chem., 3, 108 (1938).

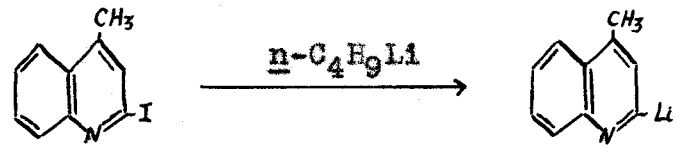
49a. Gilman and Webb, J. Am. Chem. Soc., 62, 987 (1940); F. J. Webb, Doctoral Dissertation, Iowa State College, Ames, Iowa, 1941.

But it should be noted that metalation of an α-propyl group has been effected[50] with phenyllithium, one of the weaker metalating agents.

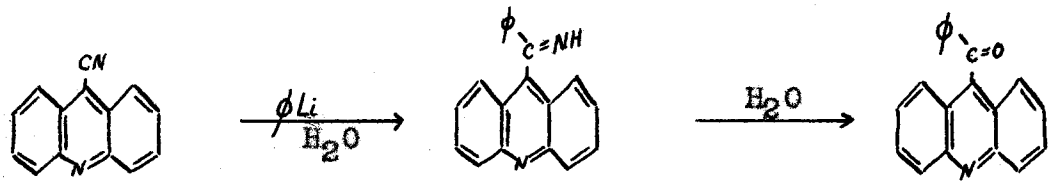


In Tsuda's work, the action of n-C_4H_9Li on (III) is no longer one of metalation.

When a halogen atom and an active methyl group are present, as in 2-iodolepidine, X-M interconversion occurs without a concomitant lateral metalation[14b].



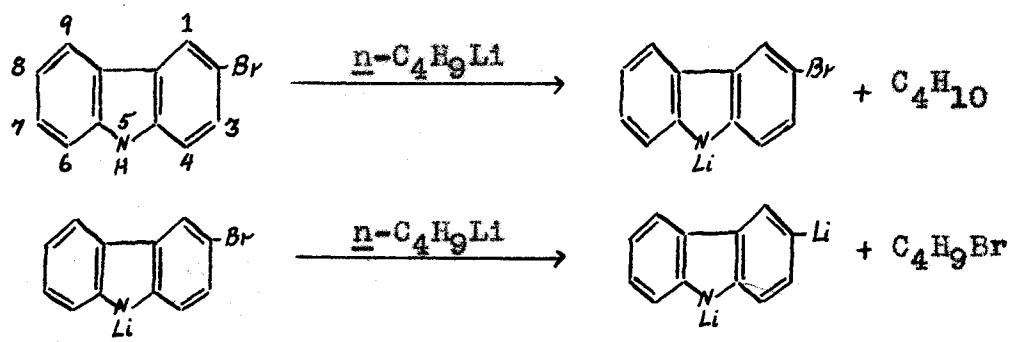
The greater reactivity of the cyano group over a cyclic >C=N- bond toward RMgX addition holds likewise with respect to RLi addition. The action of 4-lithio-7-methylhydrindene on 5-cyanoquinoline gives the proper ketone in 17% yield[44]. Treatment of 9-cyanoacridine with phenyllithium also results in ketone formation[51].



50. Haskelberg, Chem. and Ind., 54, 261 (1935).
51. Lehmstedt and Dostal, Ber., 72B, 804 (1939).

3. The Lithiocarbazoles.

The ease of organometallic formation in the pyridine family has already been shown to depend very much on the particular halogenated compound employed. In the carbazole series, owing to the absence of an anil linkage, organometallic synthesis by the method of X-M interconversion occurs with great ease. The chief difficulties are: (1) coupling, (2) possible metalation, and (3) interference from the >N-H group. The extent of coupling cannot be very large because the yields of X-M products are in the neighborhood of 60-80%[14b]. Products of metalation have yet to be encountered although these were theoretically possible on basis of analogy to certain halogenated dibenzofurans[52]. Interference from the >N-H group consists merely of a loss of one equivalent of the interconverting agent[14b]. For example, 2-bromocarbazole reacts with two equivalents of n-butyllithium to form 2-lithiocarbazole in 57.8% yield.



The synthesis occurs in two stages, the first one being

52. Gilman, Cheney and Willis, J. Am. Chem. Soc., 61, 951 (1939); Gilman, Willis and Swislowsky, ibid., 61, 1371 (1939).

instantaneous and accompanied by the evolution of butane; the second step is slower and requires about an hour to run to completion. Apparently, the >N-Li group does not deter X-M interconversion, just as it does not deter metalation[53]. When the activity of the >N-H group is masked by alkylation an extra equivalent of X-M interconverting agent is unnecessary.

Hitherto, two methods for preparing organometallic compounds of carbazole have been used[54]. The customary one of treating an RX compound with magnesium or lithium suffers the disadvantage of furnishing the RMgX or RLi product in poor yield. Metalation is the second method. Although it also suffers from the handicap of poor yield, its chief value lies in its ability to introduce the metallic atom into a novel and otherwise inaccessible position in the molecule. The X-M interconversion method is the most versatile; it provides (1) highly satisfactory yields of mono-metallic derivatives, (2) splendid yields of di-metallic compounds, and (3) the possibility of effecting preferential X-M interconversion with dihalogen derivatives. The Grignard reagent of 5-ethyl-2-iodocarbazole is obtainable in only a 20% yield[54], and similarly the reaction between 5-ethyl-2-bromocarbazole and lithium gives a 34% yield of the corresponding RLi product[54]. The yield of the same RLi compound is more than doubled by

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53. Gilman, Brown, Webb and Spatz, ibid., 62, 977 (1940).

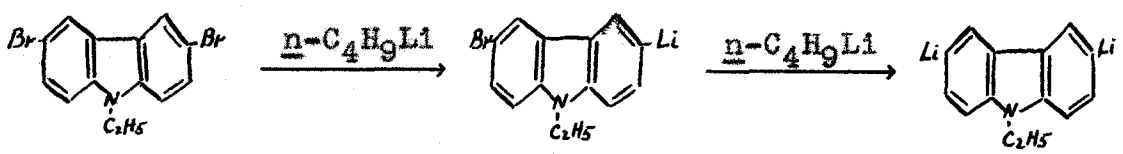
54. Gilman and Kirby, J. Org. Chem., 2, 146 (1936).

application of the X-M reaction[14b].

An illustration of di-metal formation is the reaction of 5-ethyl-2,8-dibromocarbazole with n-butyllithium to give an 84% yield of 5-ethyl-2,8-dilithiocarbazole. It is difficult to conceive of a successful synthesis of such a compound by direct action of lithium on the dibromo- or diiodo-compound.

The mono-interconversion of 5-ethyl-2,8-diiodocarbazole with n-butylmagnesium bromide is an example of preferential X-M interconversion. In this particular case, the use of methyllithium might be more effective in a selective mono-interconversion. In this connection, the mono-interconversions of 2,6- and 3,5-dibromopyridines even with vigorous interconverting agents as n-butyl- and n-propyllithium are worthy of recall.

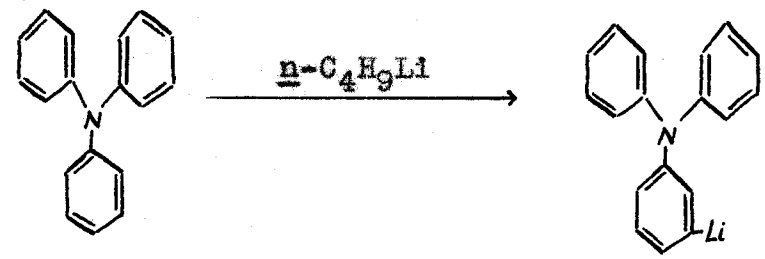
These mono-interconversions suggest that in polyhalogenated compounds the X-M reactions proceed stepwise. Thus,

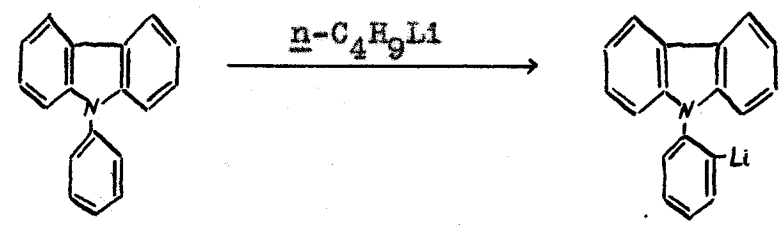


4. Orientation in the Metalation of Amines.

In nuclear metalations by organoalkali compounds, metalation occurs almost invariably ortho to the hetero element or to the group containing the hetero element. Among compounds

in which the hetero element is nitrogen, the following have been found to conform to the rule: aniline[53], N-n-butylaniline[53], diphenylamine[53], N,N-dimethylaniline[55], carbazole[54], N-ethylcarbazole[54] and N-phenylcarbazole[56]. This list comprises a variety of primary, secondary and tertiary amines. The exception to this rule is the meta metalation[56a] of triphenylamine, especially interesting because of the close chemical structure between this amine and N-phenylcarbazole.





The orienting effects of the two negative phenyl groups in triphenylamine cannot account for the anomalous metalation of the remaining phenyl group, because diphenylamine metalates according to rule. In diphenylamine the hydrogen atom and

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55. Morton and Hechenbleickner, J. Am. Chem. Soc., 58, 2599 (1936); Gilman and Bebb, ibid., 61, 109 (1939).

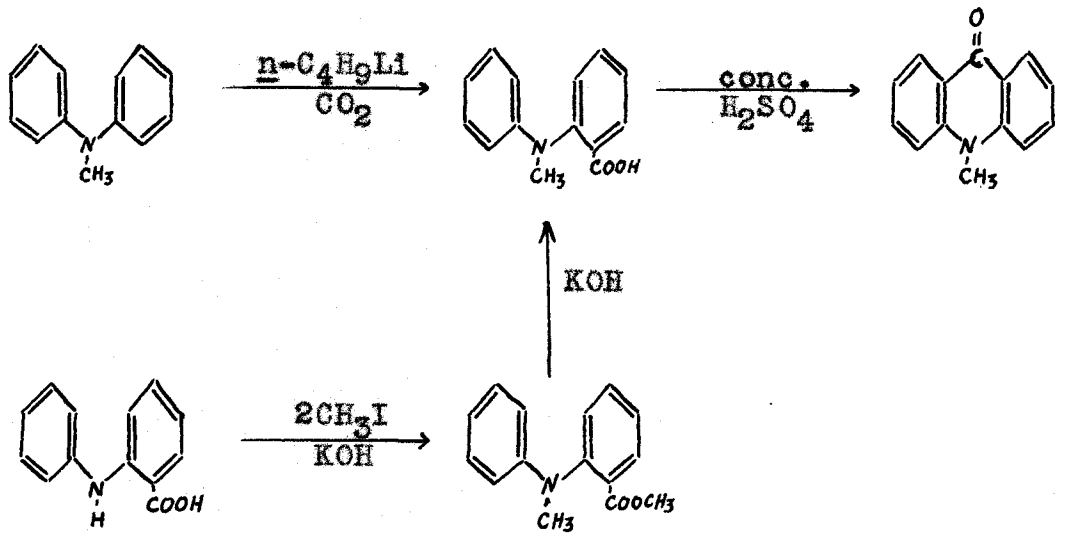
56. Gilman, Stuckwisch and Kendall, ibid., 63, 1758 (1941).

56a. Gilman and Brown, ibid., 62, 3208 (1940).

the phenyl group would constitute the orienting factors, and surely the orienting influence of the latter must outweigh that of the hydrogen.

It is proposed here that the meta metalation of triphenylamine is the result of steric hindrance from the two large phenyl groups. In triphenylamine, the three valence forces of the N atom are equidistant from each other. In N-phenylcarbazole, the equidistance is disturbed in consequence of the union of two phenyl groups to form the carbazole nucleus, so that the amount of space about one of the valence bonds is greater than any of the three in triphenylamine. It is the phenyl group attached to this one valence force which undergoes ortho metalation.

If steric hindrance accounts for the abnormal behavior of triphenylamine towards n-butyllithium, then replacement of one of the phenyl groups by a much smaller one, such as the methyl radical, should effect resumption of orthodox metalation. Such is actually the case. The position of ortho metalation was ascertained in two ways: (1) by ring closure of the N-methyl-N-phenylanthranilic acid to N-methylacridone and (2) by N-methylation of authentic N-phenylanthranilic acid.

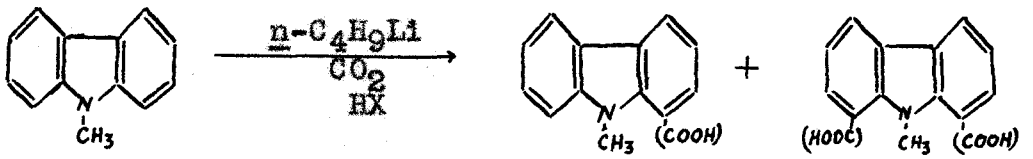


It is therefore evident that metalation of aromatic amines by organoalkali occurs always ortho to the nitrogen atom, except under conditions of steric hindrance; this orientation is determined by the nitrogen atom, cyclic or non-cyclic, and not by the groups attached to the nitrogen, whether these groups be H-H, H-alkyl, H-aryl, alkyl-alkyl, alkyl-aryl, or aryl-aryl.

Retention of meta metalation is to be expected in a compound in which the phenyl group of triphenylamine is replaced by another large group such as the cyclohexyl, t-butyl, or isobutyl. Unfortunately, the small quantity of gummy acid obtained from the metalation of cyclohexyldiphenylamine could not be purified for identification. The amine was prepared by N-phenylation of N-cyclohexylaniline; it could not be prepared by cyclohexylation of either diphenylamine or sodium diphenylamide.

Metalation of N-methylcarbazole yields, subsequent to carbonation, both a mono- and dibasic acid. Although the

structures of the acids remain to be established, the carboxyl groups are tentatively placed in the 4- and 6- positions.



The isolation of the dibasic acid is interesting, because N-ethylcarbazole does not undergo di-metalation, even with a large excess of metalating agent[54]. These facts conform with the theory of steric hindrance applied to the metalation of amines. The larger ethyl group* makes di-metalation more difficult. Possibly related is the failure of N-ethyldiphenylamine to metalate[57], in contrast to the behavior of N-methyldiphenylamine. Again, the difference in behavior between N-ethyldiphenylamine and N-ethylcarbazole is noteworthy. Unquestionably, the union of the two phenyl groups to form the carbazole nucleus destroys the steric factors present in the former molecule. The di-metalation of N-phenylcarbazole[58] is not comparable with these observations because the additional aromatic ring provides for additional metalation.

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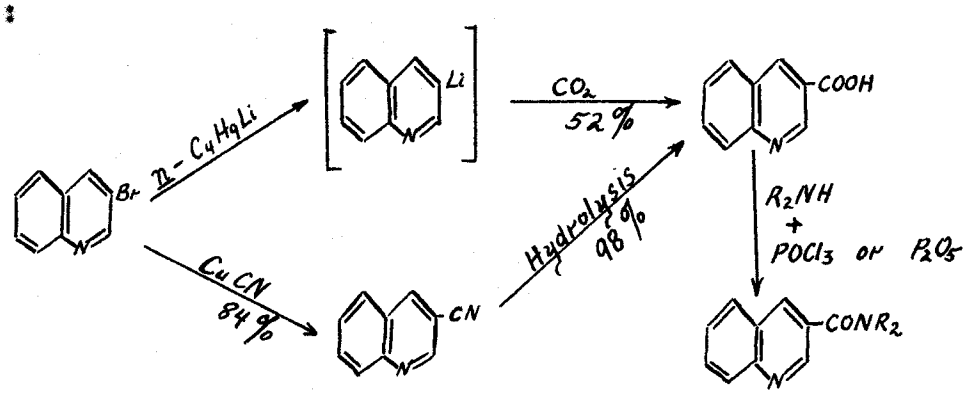
*Recently, Adams and Stewart, ibid., 63, 2859 (1941) demonstrated the markedly increased steric effect of the ethyl radical over the methyl in racemization studies of certain arylamines.

57. Unpublished studies of Drs. Wm. I. Harber and F. W. Hoyt.

58. Gilman and Stuckwisch, ibid., 64, 000 (1942).

5. Some Pharmacologically Active Derivatives.

A consideration of the various biological properties possessed by nicotinic acid and its simpler amido derivatives made desirable the syntheses of certain dialkyl amides of 3-quinolinecarboxylic acid. Hitherto[59], this acid was available with utmost difficulty, but recently[14b] by the method of halogen-metal interconversion we obtained the acid in 52% yield directly from the easily accessible 3-bromoquinoline[60]. Also recently[61], Jansen and Wibaut prepared 3-cyanoquinoline by the action of cuprous cyanide on 3-bromoquinoline. Hydrolysis of the nitrile, we found, took place almost quantitatively, and provided a second, direct route to 3-quinolinecarboxylic acid. The synthesis of the amides is summarized in the sequence of equations presented below, which includes yields of the parent acid obtained by the methods mentioned above:



59. Mills and Watson, J. Chem. Soc., 97, 71 (1910).

60. (a) Claus and Collischon, Ber., 19, 2763 (1886); (b) Edinger, Ber., 29, 2459 (1896).

61. Jansen and Wibaut, Rec. trav. chim., 56, 709 (1937).

Attempts to prepare the amides listed in Table I by the action of a secondary amine on the acyl halide hydrochloride[62] gave only poor yields of the compounds which were identified by comparison of their picrates with those of the amides obtained from heating the acid itself with the amine in the presence of phosphorus oxychloride or phosphorus pentoxide[14b].

TABLE I

Dialkylamides of 3-Quinolinecarboxylic Acid

Compound	Analgesic Action
1. N,N-Dimethyl-3-quinoline-carboxamide	Negative
2. N,N-Diethyl-3-quinoline-carboxamide	Negative
3. N,N-Di-n-propyl-3-quinolinecarboxamide	Negative
4. N,N-Di-iso-propyl-3-quinolinecarboxamide	Positive
5. N,N-Diallyl-3-quinolinecarboxamide	Positive
6. 3-Quinolinecarboxylic acid piperidide	Negative

The compounds of Table I, in the form of hydrochlorides, were examined for pharmacological activity by intraperitoneal injection in white mice. Compounds 4 and 5 showed analgesic action, particularly the latter which was about one-third as active as codeine. Unfortunately, it also exhibited certain

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62. Kolber, Ruppersberg and Strang, Monatsh., 52, 59 (1929).

undesirable secondary reactions. Strangely enough, nicotinyl diethylamide commonly known as coramine, possesses analeptic activity, whereas these compounds do not. We acknowledge our gratitude to Dr. W. G. Bywater and Mr. Rowe of Parke, Davis and Co. for the pharmacological tests.

III. EXPERIMENTAL

Metalation of N-Methyldiphenylamine.--(a) A 50 cc. ethereal solution of 18.3 g. (0.1 mole) of freshly distilled methyldiphenylamine was added to 0.126 mole of n-butyllithium in 175 cc. of ether. No color or heat change was produced. After twenty-four hours of gentle reflux the clear, colorless solution was carbonated in an ethereal slush of dry ice. Acidification of the aqueous alkaline layer yielded an oil, from which a green crystalline material precipitated, after standing in the refrigerator. Recrystallized from ethanol, the pale green acid melted at 102.5-103.5° C. Yield was 1.0 g. (4.4%).

Anal. Calcd. for $C_{14}H_{13}O_2N$: neut. equiv., 226.2; N, 6.16. Found: neut. equiv., 230.5, 231.0; N, 6.06, 6.26[63].

(b) Treatment of 0.1 mole of N-methyldiphenylamine with 0.2 mole of n-butyllithium for forty hours increased the yield of crude acid (m.p. 96-101°) to 3.2 g. (14.1%). Twice recrystallized from petroleum ether (b.p. 60-68°), the crystals melted at 103-4°, and the yield of pure product was 1.8 g. (7.9%).

Cyclization of N-Methyl-N-phenylanthranilic Acid.--One

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63. Nitrogen analysis by Mr. A. L. Dittman.

gram of the acid, isolated from the metalation and carbonation of methyldiphenylamine, was dissolved in 10 cc. of cold, conc. sulfuric acid, and warmed on a water-bath for one and one-half hours. The solution turned red-brown with a marked blue-green fluorescence. After careful dilution with water, the precipitate was filtered off, washed, digested in boiling dilute alkali, filtered once more, and crystallized from ethanol. The pale yellow crystals melted at 198-199°, and a mixed melting point with authentic N-methylacridone showed no depression. Yield was 0.7 g. (76.4%).

Preparation of Acridine Methiodide and N-Methylacridone[64].--Heating 25 g. (0.14 mole) of acridine and 40 g. (0.28 mole) of methyl iodide under reflux on the water bath for four hours yielded 33 g. (73.7%) of red, crystalline acridine methiodide.

Thirty g. (0.09 mole) of the methiodide was added at 50° C. portionwise to a 20% aqueous solution of sodium hydroxide, containing a finely powdered suspension of 92.5 g. of potassium ferricyanide. After standing overnight, the ferrocyanide redissolved, and a yellow-brown mass remained. After several recrystallizations from ethanol, the yield of N-methylacridone, melting at 198-199°, was 5 g. (25.5%).

N-Methylation of N-Phenylanthranilic Acid.--Three g. (0.014 mole mole) of N-phenylanthranilic acid, 5 g. (0.035

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64. Bergmann and Blum-Bergmann, Ber., 63, 761 (1930).

mole) of methyl iodide and 0.6 g. (0.015 mole) of sodium hydroxide in 133 cc. of water were refluxed for twenty-four hours. Twenty cc. of a 20% solution of sodium hydroxide was added and boiled for an additional hour to destroy excess methyl iodide and to hydrolyze the methyl ester. When a clear homogeneous solution was formed, the contents were diluted with 200 cc. of water and acidified with conc. hydrochloric acid. The acid was crystallized from an ether-petroleum ether (b.p. 60-68°) mixture as pale green needles. The yield was 1.6 g. (50.3%). The acid melted at 104-104.5°, and admixed with the acid obtained from the metalation of N-methyldiphenylamine, it melted at 103-4°.

Preparation of N-Cyclohexylaniline.--In accordance with the procedure of Hickenbottom[65], 120 g. (1.3 mole) of aniline and 65 g. (0.4 mole) of cyclohexyl bromide were heated in an oil bath at 115° for four hours, and at 150° for twelve hours. On cooling, the contents solidified to a crystalline mass; the oil, obtained after addition of sodium carbonate, was dried over potassium hydroxide. The cyclohexene and most of the unused aniline were removed at atmospheric pressure. The residual oil was fractionated under reduced pressure. The yield of fraction, b.p. 150-1° at 16 mm., was 32.5 g. (46.4%).

Preparation of N-Cyclohexyldiphenylamine.--(a) Seventeen

65. Hickenbottom, J. Chem. Soc., 2646 (1932).

and one-half g. (0.1 mole) of N-cyclohexylaniline, 22.4 g. (0.11 mole) of iodobenzene, 8.3 g. (0.06 mole) of potassium carbonate and 3 g. of copper powder were heated in a metal bath at 220-240° for forty-eight hours. After cooling, the crystalline mass was dissolved in ether and the copper removed by filtration. The ethereal filtrate was dried over Drierite, filtered, and the ether removed by distillation. The oily residue was distilled under vacuum. The yellow fraction, b.p. 150-160° at 3-4 mm., solidified on cooling. Twice recrystallized from ethanol-ethyl ether mixture, the large white crystals melted at 74-75.5°. The yield was 11.6 g. (46%).

In a preliminary run conducted at 180-220° for eighteen hours, the yield was 13.1%.

Anal. Calcd. for $C_{18}H_{21}N$[66]: C, 86.0; H, 8.44; N, 5.57. Found: C, 85.9; H, 8.34; N, 5.73.

(b) A mixture of 33.8 g. (0.2 mole) of diphenylamine, 46 g. (0.29 mole) of cyclohexyl bromide, 16.4 g. (0.2 mole) of powdered anhydrous sodium acetate, and 0.3 g. of iodine were heated in an oil bath at 140° for thirty hours. The contents were poured into ice-water, and the oil which separated out solidified after a short while. The recovery of crude diphenylamine was practically quantitative.

(c) Sixteen and three-tenths g. (0.1 mole) of cyclohexyl

66. The carbon and hydrogen analyses were made by Mr. R. V. Christian.

bromide and an equivalent of sodium diphenylamide, prepared from n-butylsodium and diphenylamine, failed to react after being heated and stirred for twenty hours in a nitrogen atmosphere. After working up in a customary manner, the diphenylamine was recovered.

Metalation of N-Cyclohexyldiphenylamine.--Eight and eight-tenths g. (0.35 mole) of the amine and 0.05 mole of n-butyllithium in 90 cc. of ether were kept under reflux for twenty-three hours. At the end of this time, color test I[67] was positive and color test IIa[68] negative. After carbonation in a customary manner, the aqueous alkaline layer yielded a gummy acid, which could not be purified for identification. The yield of crude acid was 0.3 g.

Preparation of N-Methylcarbazole.--This compound has already been prepared in excellent yield[69]. However, we have employed a procedure used for the N-ethylation of 2,8-dibromocarbazole[14b], because it eliminates direct, personal handling of the poisonous methyl sulfate. To a hot solution of 45 g. (0.27 mole) of carbazole in 225-250 cc. of acetone was added in one portion 60 g. (0.48 mole) of practical methyl sulfate (hood). To the hot solution was added dropwise 45 g. of

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

68. Gilman and Swiss, ibid., 62, 1847 (1940).

69. Stevens and Tucker, J. Chem. Soc., 123, 2140 (1923).

sodium hydroxide in 30 cc. of water over a twenty-minute period. Stirring and refluxing were continued for two hours and the contents then poured into ice-water. Crude N-methylcarbazole (m.p. 85-87°) precipitated out in almost quantitative yield. The compound was recrystallized from 95% ethanol in beautiful nacreous crystals, melting at 88-89° C. The yield was 44 g. (90.5%).

Metalation of N-Methylcarbazole.--A solution of 14.5 g. (0.08 mole) of the carbazole and 0.1 mole of n-butyllithium in 180 cc. of ether was refluxed and stirred for twenty-four hours, at the end of which time the dark red solution gave a positive color test I and a negative color test IIa. After carbonation and hydrolysis, the emulsion was broken up by acidification, followed by addition of dilute base. The aqueous alkaline layer was filtered, boiled with Norit and refiltered. The cooled filtrate was acidified with dilute mineral acid to yield 5.5 g. of crude mixed acids.

From the ether layer 8 g. (55%) of N-methylcarbazole was recovered.

The crude acid was digested in 100 cc. of boiling benzene for fifteen minutes, and filtered through a steam funnel. The residue was washed with 5-10 cc. of hot benzene, and the washing discarded. The residue, recrystallized in small white needles from hot ethanol, melted at 252-4° with evolution of gas. Since the neutral equivalent showed the acid to be

dibasic, the yield of 0.8 g. was 3.4% of the theoretical.

Anal. Calcd. for $C_{15}H_{11}O_4N$[70]: neut. equiv., 134.5; C, 66.94; H, 4.12. Found: neut. equiv., 138.2; C, 67.07; H, 4.09.

The benzene extract was concentrated to about one-half the original volume, cooled, and the crude monobasic acid which precipitated out melted at 176-9°. Recrystallized from ethanol, the pale tan crystals melted at 185°. Further recrystallization did not raise the melting point. The yield was 2.2 g. (12.2%).

Anal. Calcd. for $C_{14}H_{11}O_2N$: neut. equiv., 225.2; N, 6.22. Found: neut. equiv., 226.6; N, 6.07.

Estimation of X-M Interconversion, Anil Addition, and Coupling in Preparation of 3-Pyridyllithium.--Two and seven-tenths g. (0.013 mole) of 3-iodopyridine in 25 cc. of ethyl ether was added dropwise over a twenty-four minute period with vigorous stirring to 0.018 mole of n-butyllithium in 75 cc. of the same solvent. After cessation of stirring, the dark red, gummy precipitate settled at once, and a whitish material more slowly. After eight minutes standing, the clear supernatant liquid was decanted onto dry ice; the whitish body was rinsed with dry ether into a separate vessel, while the gummy residue was allowed to dry overnight in an atmosphere

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70. The carbon and hydrogen analyses were made by Mr. J. Ziffer.

of nitrogen. From the carbonation vessel, after hydrolysis, 0.65 g. (40.2%) of nicotinic acid was isolated.

The whitish substance contained lithium iodide, the inorganic product of coupling.

The gummy precipitate changed to a brick-red amorphous powder, after drying overnight in the nitrogen atmosphere. It contained lithium and iodine, and weighed 0.97 g. On the assumption that this amorphous powder consists chiefly of the addition product of butyllithium to the anil linkage of 3-iodopyridine, it is approximately the equivalent of 0.74 g. (26.4%) of 3-iodopyridine. Since 40.2% of the latter interconverted to 3-pyridyllithium, 33.4% of 3-iodopyridine remains to be accounted for, probably in coupling reactions of one type or another.

IV. DISCUSSION

The ease of organometallic synthesis of nitrogen heterocycles varies with the type of heterocycle. The carbazoles undergo nuclear metalation; the pyridines in general do not. In the pyridine family, the smoothness of X-M interconversion depends very much on the particular compound; but not so with the carbazoles. The chief difficulty with the pyridines is anil addition; with the carbazoles it is possible metalation, although such interference has never been encountered.

After years of fruitless effort, three methods now exist for organometallic synthesis in the pyridine family. These are the modified "entrainment" method, the X-M interconversion method, and finally the customary procedure of treating an RX compound with a metal. The last method is of course limited in scope, being applicable only to certain heavily substituted molecules. The "entrainment" method is also limited in scope; being slow and requiring heat, it will allow the chief secondary reaction of anil addition to become manifest in molecules the -N=C< bonds of which are not well protected by deactivating groups. Only recently, Fieser and Hershberg[44] were thwarted in an attempt to prepare 5-quinolylmagnesium bromide, using one equivalent of ethyl bromide as accessory agent. The method of X-M interconversion is unquestionably the most flexible; being very rapid and occurring even at

such low temperatures as -70° C.[71], it makes possible the suppression of -N=C< addition. The limitations of pyridine compounds with respect to the Wurtz and Wurtz-Fittig reactions, the Friedel-Crafts reaction, and Grignard formation—three important synthetic methods—make the availability of pyridyllithium compounds all the more significant.

The interesting variety of valencies exhibited by the nitrogen atom, the limitations of the molecule as a whole in the three important synthetic reactions mentioned above, the restricted positions of halogenation discussed in detail in Part B, the exalted reactivity of α- and γ- substituents, and the additive behavior of the azomethylene linkage make pyridine one of the most intriguing molecules in organic chemistry. These pronounced negative and positive properties tax the resourcefulness of the chemist in the synthesis of a given molecule.

Pyridine has been compared with benzene and with nitrobenzene. The additive behavior of the -N=C< bond may well relegate the chemistry of pyridine to that of benzonitrile or benzalaniline. Formation of X-M interconversion products from halogenated compounds of these types will probably be encountered by the same difficulties attending the preparation of pyridyllithium. For example, X-M interconversion of an ortho-bromobenzalaniline should be attended by less RLi

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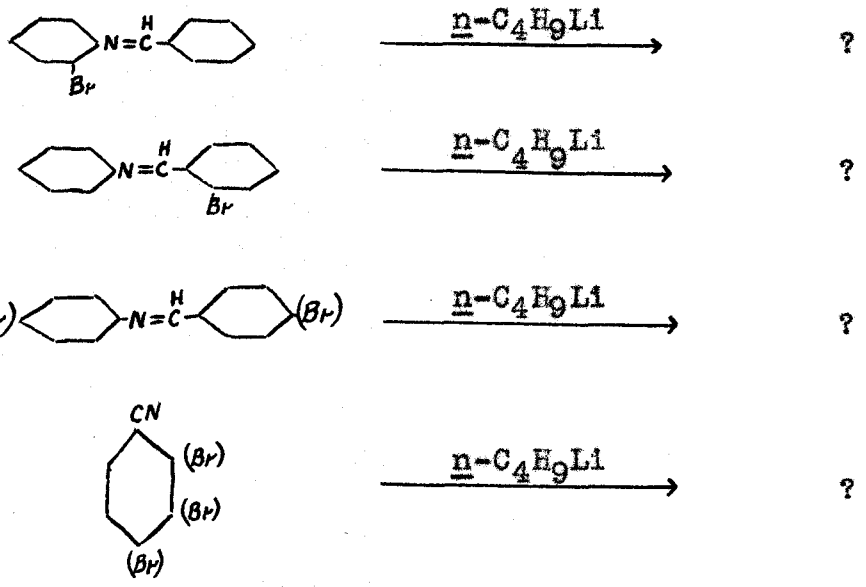
71. Unpublished studies by author.

addition to the -N=C< bond than with a para-bromobenzalaniline. The same predictions are made for benzal-o-bromoaniline and benzal-p-bromoaniline.



In a sense the halogenated carbazoles act as halogenated hydrocarbons. The amine behavior of carbazole manifests itself only under certain conditions, and absence of an azomethylene linkage facilitates organometallic synthesis. The chief contributions of X-M interconversion studies in this field have been threefold: (1) it has made available in splendid yields mono-, di-, and perhaps, poly-metallocarbazoles, (2) it has made possible by preferential X-M reaction the synthesis of halogen-containing organometallic compounds, and (3) it has improved remarkably the yields of known metallocarbazoles.

V. SUMMARY

1. New organolithium compounds of pyridine, quinoline and carbazole are now made available by the method of X-M interconversion. By the same method, previously known organometallic compounds of carbazole are made accessible in markedly improved yields.

2. Unless very mild conditions of time and temperature are employed, the presence of the -N=C< linkage in the pyridine series will prevent a smooth X-M interconversion.

3. When a halogenated pyridine (or quinoline) compound is treated with an alkyllithium reagent, the two prevailing reactions are X-M interconversion and addition of RLi to the -N=C< bond. Generally, the former predominates, but the dominance may be reversed, even with use of mild conditions. Metalation occurs to a negligible extent, if at all, and evidence exists for the occurrence of an undetermined amount of coupling.

4. Substitution of n-butyllithium with RLi compounds, combining speed of X-M interconversion and steric factors, does not reduce the extent of anil addition in the preparation of 3-pyridyllithium from bromopyridine.

5. Whereas dihalogenated carbazoles undergo di-interconversion, the dibromopyridines undergo mono-interconversion only. Mono-interconversion of a polyhalogenated carbazole can be effected by the use of a weak interconverting agent,

such as methyllithium or butylmagnesium bromide. The mono-interconversion studies suggest that the multiple X-M reactions of polyhalogenated compounds proceed stepwise.

6. Despite the sensitivity of α- and γ-halogens, α- and γ-chloroquinolines do not undergo the interconversion; only the bromo- or iodo- compounds do so.

7. X-M interconversion precedes lateral metalation, as indicated by the behavior of α-iodolepidine towards n-butyllithium.

8. An hypothesis has been proposed to explain X-M reactions in pyridine compounds. This hypothesis should be of value in predicting the smoothness (or difficulty) of X-M reaction in any compound containing the -N=C< linkage.

9. Pyridine is not metalated by alkali metals; it is metalated nuclearly by mercuric acetate, and laterally by mercuric acetate, alkali amides and RLi compounds. RLi and alkali amides also may add to the -N=C< linkage. It is difficult to predict when RLi will metalate or add to a given pyridine molecule. Sodamide metalates in absence of solvent, and adds in presence of one.

10. The >N-Li group does not interfere with metalations or with X-M interconversions.

11. The rule of orientation in the metalation of aromatic amines by organoalkali compounds is that the metal enters the ring ortho to the nitrogen atom. Steric factors may well account for exceptions to this rule. The inability of

N-ethyldiphenylamine to metalate whereas N-methyldiphenylamine does, and the ability of N-methylcarbazole to dimetalate whereas N-ethylcarbazole does not, fit in with the steric aspects of the metalation of amines.

12. 3-Quinolinecarboxylic acid is now available in quantity by two new methods. Because of its homologous relation to nicotinic acid, it may be the starting material for new pharmaceuticals.

13. A series of substituted amides of 3-quinolinecarboxylic acid have been prepared, two of which exhibit analgesic action.

B. ANTIMALARIAL SYNTHESES

I. INTRODUCTION

Malaria, widespread throughout the world, results in greater morbidity and mortality than any other infectious disease. Contrary to common belief, malaria is not confined to tropical regions, although the incidence is unusually high in such localities. In certain tropical countries the incidence reaches 100 per cent. In India alone, it attacks annually about 100,000,000 persons and causes 1,000,000 deaths. The disease was familiar to the people of antiquity by such names as chills and fever and Roman fever. Yet it was not until 1880 that the cause of the disease was discovered by Laveran, a French military surgeon then stationed in Algeria. The disease runs rampant in regions of swamps and marshes, ideal breeding places for the anopheline mosquito which serves to transmit the causative agent to the human being.

While quinine, plasmoquine and atebrine--the three most important medicaments in the treatment of malaria--are useful, the need for something better is urgent. The three drugs suffer the disadvantages of undesirable side reactions. They are also too specific, the usefulness varying with the stage and form of the disease. The price is higher than many can

afford, for the disease is especially prevalent among the lower economic levels. Furthermore, so far as quinine is concerned, the 600 tons produced annually hardly meet the needs of malarial therapy. At present this insufficient supply is precarious, since the world is practically dependent on Java in the Dutch East Indies for its quinine and this source may be cut off any day. Therefore, "the trend is toward synthetics as the direction which holds out the best promise of new and useful antimalarials."[74]

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74. Bogert, Science, 92, 176 (1940).

II. BIOLOGY OF THE INFECTION AND DRUG SPECIFICITY

Since the efficacy of malarial drugs varies with the type and stage of infecting parasite, a brief discussion of the malarial cycle is essential. Eight years after Laveran discovered the causative parasite, Ross showed that the anopheline mosquito was its vector. Malaria is a protozoan, not a bacterial, disease. At least three species of malarial parasites are known, which are associated with three distinct types of the disease:

(1) *Plasmodium vivax* ——→ benign or tertian malaria
(2) *P. malariae* ——→ quartan malaria
(3) *P. falciparum* ——→ aestivoautumnal, malignant or subtertian fever.

The life cycle of each is more or less alike. It consists of schizogony (asexual reproduction) in man, the intermediate host, and of sporogony (sexual reproduction) in the mosquito or definitive host. The infected mosquito injects the plasmodium into man by biting. The sporozoite enters the red blood cell and grows in size, becoming a so-called trophozoite or schizont, which in time undergoes schizogony or multiple fission. When the red blood cell bursts, numerous small bodies (merozoites) are liberated into the blood stream. The periodic bursting of red cells produces the characteristic

chills and fever of malaria. The fever which follows the chill is due to liberated foreign proteins. The free swimming merozoites attach themselves to new corpuscles, become schizonts and repeat once more the process of asexual multiplication. After several generations of schizonts and merozoites, and when growth conditions become unfavorable as a result of medication or developing immunity, some of the merozoites drop the asexual pattern of reproduction and differentiate into male and female gametes or gametocytes. After full growth is attained the gametes burst from the red cells into the blood stream, but do not divide again. In this stage, they do not produce symptoms in man. The mosquito cannot transmit the disease when the malarial patient is in the schizont stage. Only when the disease has reached the stage of gamete reproduction can a mosquito become infected with the Plasmodium by biting the patient.

1. Quinine

Quinine is the chief alkaloid of the cinchona bark. A bitter drug, it was used as early as 1630 for cure of malaria in Equador. For almost two centuries the bark was used as a powder, until Pelletier and Caventou (1820) isolated quinine and cinchonine. The Cinchona trees require special conditions of growth cultivation. Until the middle of the nineteenth century they were indigenous to certain regions of South

America. Indiscriminate removal of the bark increased the mortality rate of the trees, so that the rising price of quinine stimulated cinchona cultivation in other parts of the world. Today more than ninety per cent of the quinine is produced in Java. The alkaloid content of the cinchona bark is six per cent, and of this never more than seventy per cent is quinine.

Since the gametes and schizonts of the different species of plasmodia exhibit different chemotropisms, the first step in the treatment of malaria is to ascertain the species of Plasmodium infecting the patient. In general, quinine is antischizontal, and is therefore suitable in the treatment of acute malaria. The benign tertian form (P. vivax) shows an immediate response to quinine, but relapses are frequent. Quinine is even more potent against the schizonts of P. falciparum, and its efficacy against P. malariae lies intermediate between the two others. The route of administration is generally oral. The solubility of the most soluble salt, the bisulfate, is one part in nine of water. Intramuscular or subcutaneous administration is painful and may result in abscess formation or other form of tissue injury. To lessen gastric irritation, the drug is best administered after meals. The gelatin capsule, which encloses the drug, masks the bitter taste and ensures rapid intestinal absorption.

Aside from the personal idiosyncrasy (hypersensitivity) case, quinine poisoning is not infrequent. Repeated

administration of full doses may produce a train of symptoms termed cinchonism. The syndrome consists of impaired hearing and vision, nausea, and headache, and may extend to serious disturbances of the gastro-intestinal and central nervous systems.

2. Plasmoquine

The introduction of synthetic medicinals with antiplasmodial properties equal or superior to those of quinine is the result of systematic chemotherapeutic research. More than 12,000 compounds were prepared and examined by chemists throughout the world in discovering plasmoquine and atebrine.

Mühlens[75] and Roehl[77a] introduced plasmoquine into medicine in 1926, but the synthesis of the compound by Schulemann[76] was not reported until later. Plasmoquine is one of the most potent antimalarials; it is about sixty times as effective as quinine in avian malaria. It exerts a slight effect on the tertian and quartan schizonts, but manifests a powerful action

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75. Mühlens, Arch. Schiffs -u Tropen-Hyg., 30, 25 (1926).

76. Schulemann et al., Ger. Patent 486,079 (1924) [C. A., 24, 1937 (1930)]. For the preparation of the intermediates see: (a) U. S. Patent 1,747,531 (1930) [C. A., 24, 1705 (1930)]; (b) U. S. Patent 1,747,532 (1930) [C. A., 24, 1705 (1930)]; (c) Ger. Patent 492,250 (1927) [C. A., 24, 2472 (1930)]; (d) U. S. Patent 1,758,378 (1930) [C. A., 24, 3251 (1930)].

77. (a) Roehl, Arch. Schiffs -u Tropen-Hyg., 30, 311 (1926); (b) Barber, Komp and Newman, Publ. Hlth. Rep. Wash., 44, 1409 (1929); (c) Kikuth, Deut. med. Wochschr., 58, 530 (1932).

against gametocytes in general, and against the gametes of P. falciparum in particular.[77] Strangely enough, it is completely ineffective against the schizonts of P. falciparum. Whereas quinine and atebrine are generally antischizontic, plasmoquine is gametocidal. In fact, it is the most powerful gametocide known, and continued administration to malarial carriers should aid in the eventual eradication of the disease.

Plasmoquine does not produce cinchonism, but its administration is safe only under medical supervision. The most common toxic effects are cyanosis and methemoglobin formation.[78] Clinical practice today employs a combination of quinine and plasmoquine, thereby attacking both the schizonts and the gametocytes.

3. Atebrine

Atebrine was introduced to malarial therapy in 1930, but its structure and synthesis were not reported until later.[79,80] In its antiplasmodial action it resembles quinine more than

78. Fischer and Rheindorf, Arch. Schiffs -u Tropen-Hyg., 32, 594 (1928).

79. (a) Mietzsch and Mauss, Klin. Wochschr., 12, 1276 (1933); (b) Ger. Patent 553,072 (1930) [Chem. Zentr., II, 1201 (1932)]; (c) Ger. Patent 571,449 (1930) [Chem. Zentr., I, 3969 (1933)]; (d) Angew. Chem., 47, 633 (1934); (e) Ber., 69B, 641 (1936); (f) U. S. Patent 2,077,249 (1937) [C. A., 31, 4060 (1937)].

80. (a) Chelintzev, Knunyantz and Benevolenskaya, Compt. rend. acad. sci. U. S. S. R., [N. S.] I, 63 (1934) [C. A., 28, 2126 (1934)]; (b) Knunyantz et al., Bull. acad. sci. U. S. S. R., Classe sci. math. nat., 165 (1934) [C. A., 28, 4837 (1934)].

plasmoquine, since it is more schizontocidal than gametocidal.[81] In avian malaria, it is fifteen times less effective than plasmoquine, but four times more effective than quinine.

The toxicity of atebrine is relatively low.[82] Abdominal pain, headache and anorexia are occasionally noted. The skin turns yellow in about 50 per cent of the patients, but no harm results from this coloration. The color usually disappears in about fifteen days after discontinuation of the treatment. Its advantage over quinine is that it lacks the intense bitter taste of the latter, and does not cause cinchonism. Final clinical appraisal of this drug remains to be established, but it appears to be at least as effective as quinine in the three types of the disease.

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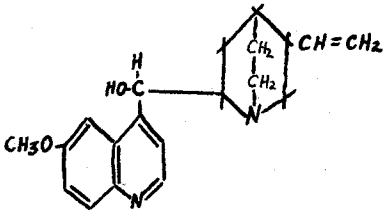
81. Kikuth and Giovannola, Riv. Malariol., 12, 657 (1933).

82. (a) Martin, Cominole and Clark, J. Pharmacol., 65, 156 (1939); (b) Clark, Cominole and Martin, ibid., 65, 166 (1939).

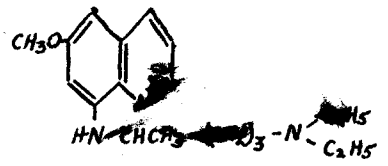
III. CHEMICAL CONSTITUTION AND ANTIMALARIAL ACTION

1. General

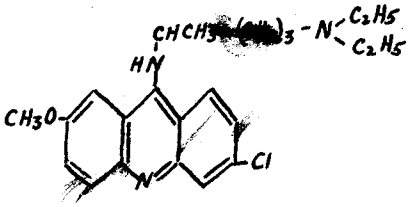
Quinine, plasmoquine and atebrine serve as points of departure in the synthesis of new antimalarial agents.



I. Quinine

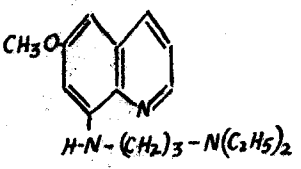


II. Plasmoquine

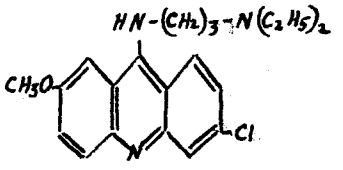


III. Atebrine (Achrichin)

Two closely related derivatives which merit attention are rhodoquinine or Fourneau 710 (France) or plasmozid (Russia) and achrichin N5.



IV. Fourneau 710 (Plasmozid)



V. Achrichin N5

Both of these compounds approach their respective quinoline and acridine homologs in effectiveness.

In this study of chemical structure and antiplasmodial action emphasis will be placed primarily on synthetic therapeutics, because independence from quinine as a starting material must be achieved, if the goal toward cheaper drugs is to be realized. The discussion of quinine[83] and closely related compounds[84] will be limited only to points which enlighten the relationship between structure and biological action.

Quinine (I) has yet to be synthesized in the laboratory. The structure assigned to it is the one generally accepted by chemists on the basis of a large variety of degradative reactions. Quinine is levorotatory. It is a quinoline molecule having a methoxy group in the 6-position and a nitrogen-containing moiety, known as the quinuclidine ring, attached to the 4-position through a secondary alcoholic group. A vinyl group is attached to the quinuclidine ring. The large number of quinine derivatives are the result of alterations, produced sometimes by nature, oftentimes by chemists, on these various groups.

The biological action is not confined to levorotatory forms. Strangely enough, quinidine, the dextrorotatory form

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83. Goodman and Gilman, "The Pharmacological Basis of Therapeutics", Macmillan and Co., New York, 1941, p. 904.

84. Cohen and King, Proc. Roy. Soc. (London), B125, 49 (1938).

of quinine, is more effective than the latter in canary malaria.[85] Similarly, Sanders found that in the treatment of 1300 human cases quinidine was superior to quinine.[83] Cinchonidine and cinchonine, which are the levo- and dextrorotatory forms, respectively, of demethoxylated quinine, approach the latter in antimalarial efficacy.[86] Apparently, the methoxy group is helpful, but not essential to antiplasmodial action. Cupreine, the phenolic or demethylated form of quinine, occurring in nature, is also effective against malaria. However, etherification of the phenolic group strongly augments the action; the same effect is observed when hydrocupreine is etherified.[85] Nor is the vinyl group essential for the biological action of the cinchona drugs, for the activity of hydroquinine, dihydrocinchonidine, dihydroquinidine, and dihydrocinchonine approximate that of the dehydrogenated parent compounds.[86]

The powerful antiplasmodial action of plasmoquine and Fourneau 710 brings out three important points: (1) that the basic side chain need not be in the heterocyclic ring, nor (2) in the same position relative to the cyclic nitrogen as it is in the cinchona drugs and (3) that the basic side chain may be of more than one type. The synthesis of plasmoquine[76,87]

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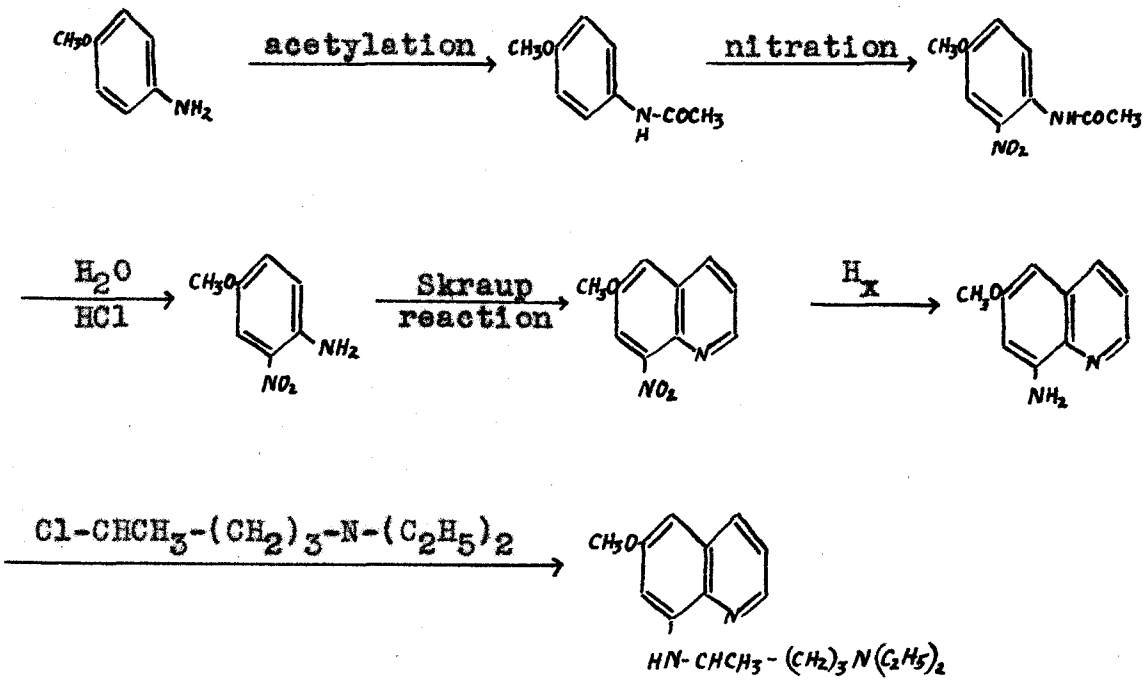
85. Giemsa, Weise and Tropp, Arch. Schiffs -u Tropen-Hyg., 30, 334 (1926).

86. Goodson, Henry and Macfie, Biochem. J., 24, 874 (1930).

87. Knunyantz et al., Bull. acad. sci. U. S. S. R., Classe sci. math. nat., 1, 153 (1934) /C. A., 28, 4837 (1934)/.

will also illustrate the synthesis of Fourneau 710.[88]



The potency of atebrine (III) and achrichin N5 (V) shows that antiplasmodial activity need not be confined to the quinoline molecule. Accordingly, Berkenheim[89] has promised the synthesis of compounds in which the quinoline ring would be replaced by carbazole, indole and isoquinoline. The replacement of quinoline by naphthalene,[88a,90] biphenyl,[88a,91]

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88. (a) Fourneau, Bovet et al., Ann. Inst. Pasteur, 44, 503 (1930); (b) ibid., 46, 514 (1931); (c) ibid., 50, 731 (1933); (d) ibid., 51, 528 (1934).

89. Berkenheim, J. Gen. Chem. (U. S. S. R.), 6, 1039 (1936) /C. A., 31, 1779 (1937)/.

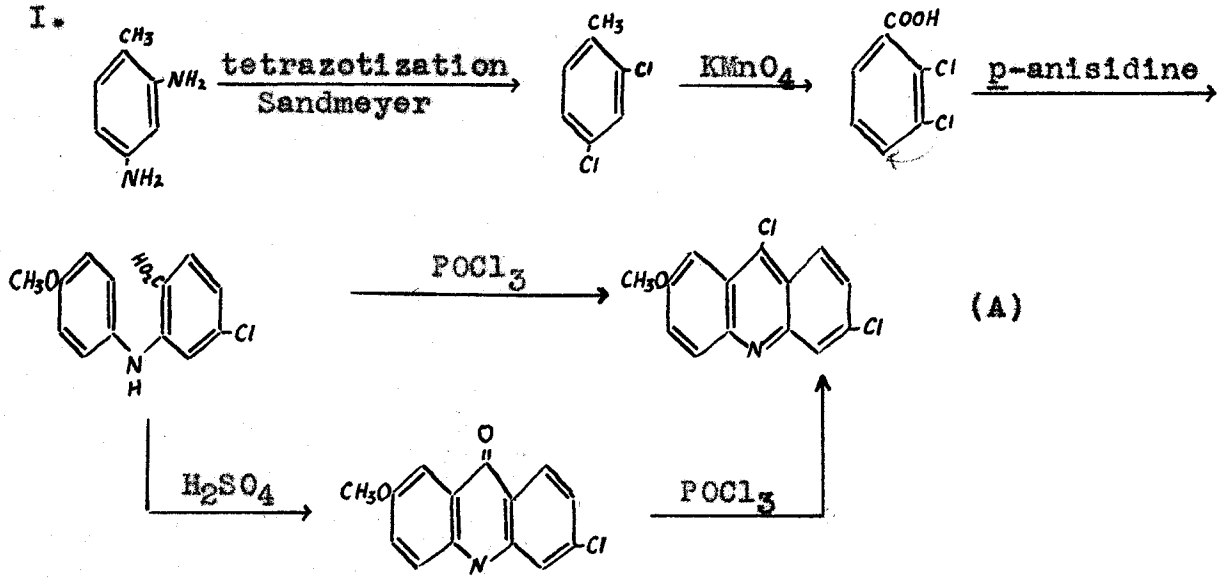
90. King and Work, J. Chem. Soc., 1307 (1940).

91. Work, ibid., 1315 (1940).

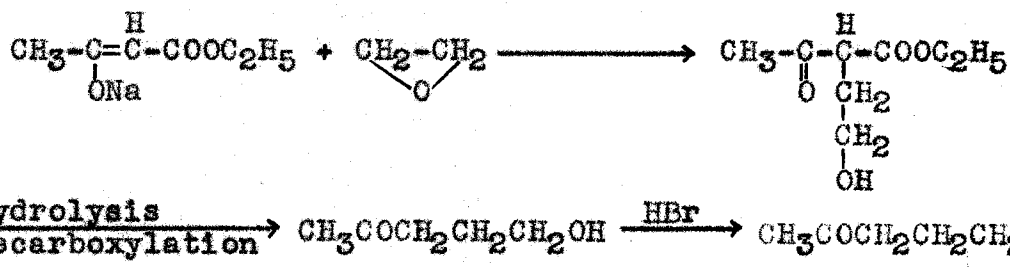
benzene,[88a] phenanthridine,[92] benzothiazole[93,94] and benzimidazole[95] has, however, proved fruitless.

The synthesis of atebrine by the Russian workers is carried out in three main steps:[80]

I.



II.



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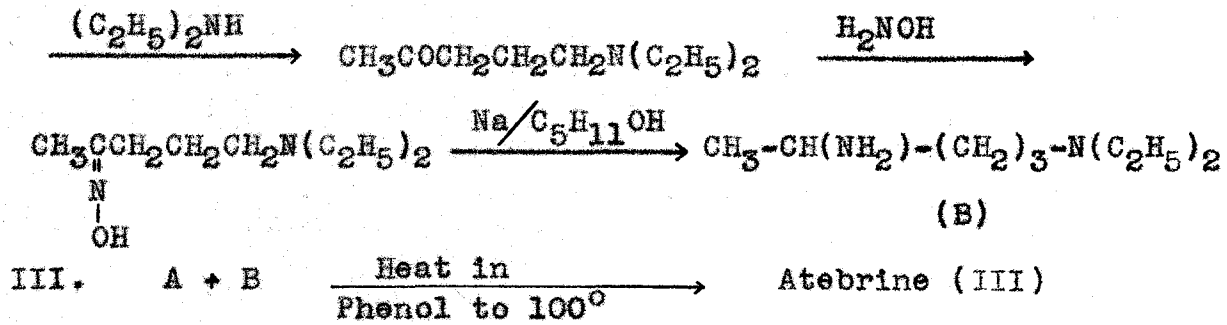
92. Walls, ibid., 104 (1934); ibid., 1405 (1935).

93. Knunyants and Benevolenskaya, J. Gen. Chem. (U. S. S. R.), 7, 2930 (1938) [C. A., 32, 5404 (1938)].

94. (a) Knunyants and Benevolenskaya, J. Gen. Chem. (U. S. S. R.), 7, 2471 (1938) [C. A., 32, 2119 (1938)]; (b) Bogert and Fox, J. Am. Chem. Soc., 61, 2013 (1939).

95. (a) Izmail'skiĭ and Siminov, J. Gen. Chem. (U. S. S. R.), 10, 1580 (1940) [C. A., 35, 2870 (1941)]; (b) Siminov, J. Gen. Chem. (U. S. S. R.), 10, 1588 (1940) [C. A., 35, 2870 (1941)].

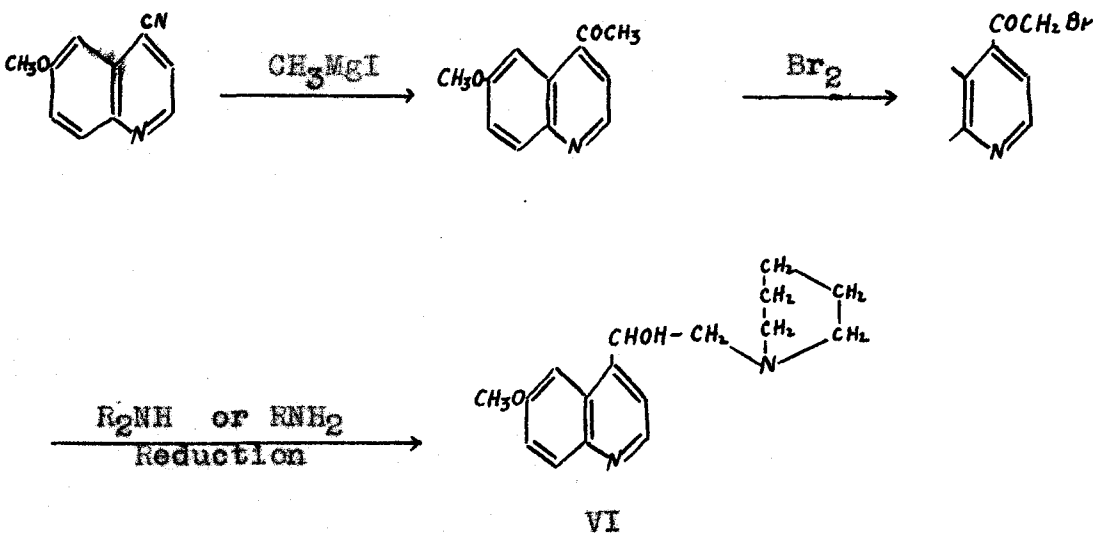
II (Continued).



III. A + B $\xrightarrow[\text{Phenol to } 100^{\circ}]{\text{Heat in}}$ Atebrine (III)

2. Quinoline Compounds

6-Alkoxy-4-Amino Quinolines. On the basis of analogy to quinine, a large number of 6-methoxyquinoline derivatives have been prepared with a basic substituent of some kind or another in the 4-position. The earliest efforts[96] were closely patterned after quinine.

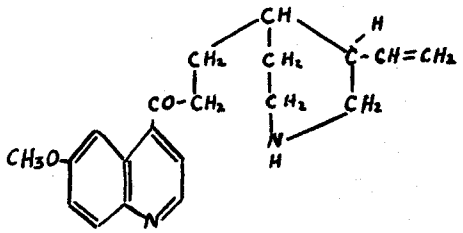


VI

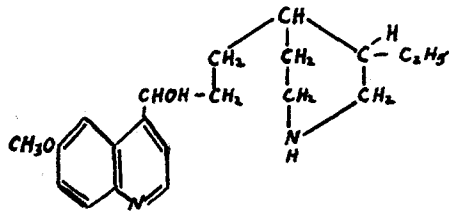
96. (a) Kaufmann, Ber., 46, 1823 (1913); (b) Rabe, Pasternack and Kindler, Ber., 50, 144 (1917).

But in the years following, considerable variation was employed in regard to the nitrogen-containing side chain. The pharmacological action of the Kaufmann type of compound (VI) is quite different from that of quinine.[97] It is toxic to paramecia, but not to the plasmodial protozoan. It should be noted that a methylene or substituted methylene group bridges the secondary carbinol to the piperidine nitrogen atom, both in quinine (I) and in compound (VI).

More recently, King and co-workers[90,98] resumed the study of synthetic analogs of quinine and cinchonine. Quinicine (VII), an isomer of quinine, is devoid of



VII. Quinicine



VIII

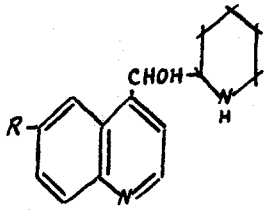
antiplasmodial activity.[99] Since retention of the >CHOH group in the cinchona molecule is essential for antimalarial action,[84] it appeared logical that reduction of (VII) to the carbinol (VIII), which occurs in two diastereoisomeric forms, might restore activity. Both carbinols were prepared and found to

97. Schönhöfer, in "Medicine in Its Chemical Aspects", Vol. III, "Bayer", Germany, 1936.

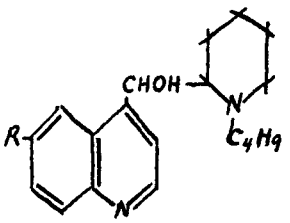
98. Ainley and King, Proc. Roy. Soc. (London), B125, 60 (1938).

99. Giemsa and Oesterlin, Arch. Schiffs -u Tropen-Hyg., 37, Beiheft No. 4, (1933).

be inactive, as was a methylation product.[98] It was therefore considered highly desirable to prepare molecules in which the piperidine ring would be as near the quinoline nucleus as possible with retention of the >CHOH group. Accordingly, compounds of types (IX) and (X) were prepared, in which R = H or CH_3O-. The N-butyl derivative (X) appeared especially attractive, since it differs in molecular weight from quinine (R=CH_3O-) and from cinchonine (R=H) by only four H atoms.

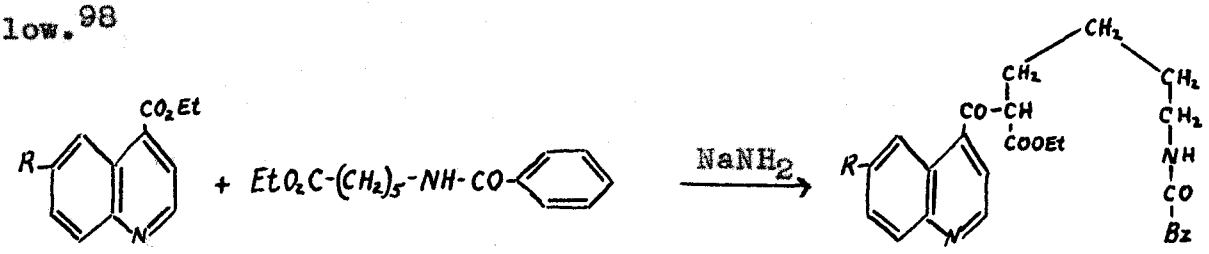


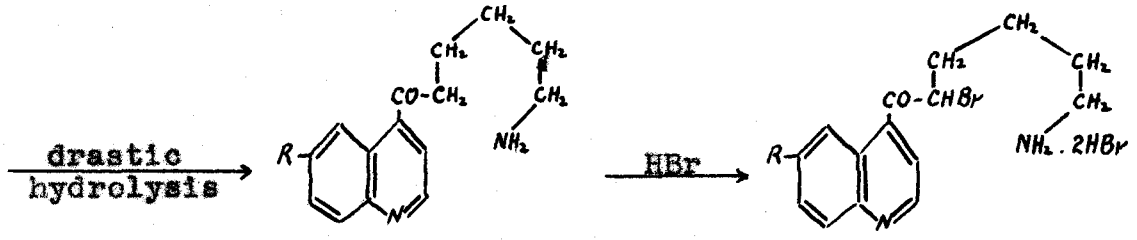
IX

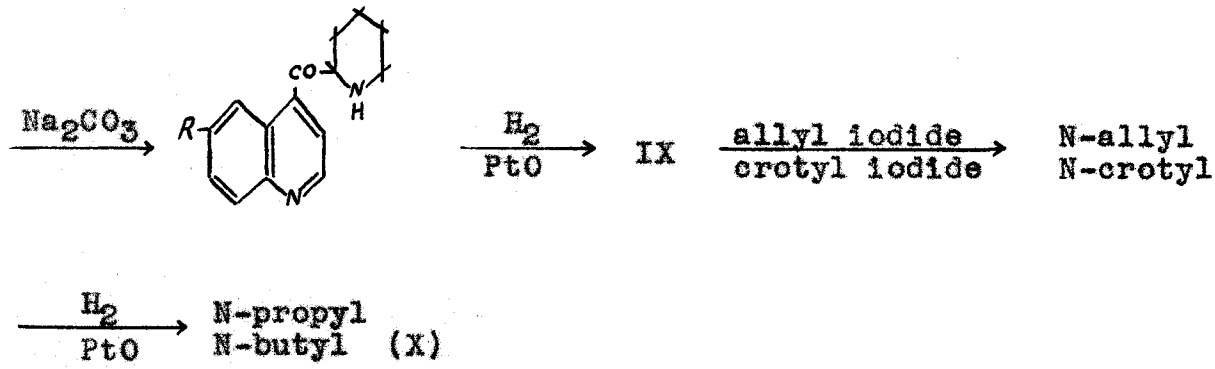


X

The syntheses were difficult, and the over-all yields very low.[98]

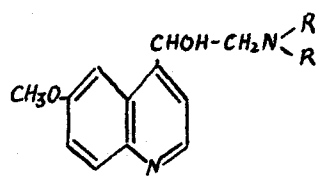






The compounds were tested on avian malaria. Compound (IX), when R = H, was inactive as were its N-methyl, allyl, crotyl, propyl and butyl derivatives (X). The two diastereoisomerides of IX, when R = CH_3O^-, were both biologically active, being about one-half as effective as quinine. Surprisingly enough, none of the N-alkyl derivatives in the methoxy series (X) showed activity. Yet, N-alkylation makes both nitrogen atoms tertiary as in the cinchona molecule (I), and increases the molecular weight towards that of (I). The two methoxy carbinols (IX) are the first synthetic molecules, closely patterned after quinine, which show antimalarial activity. The importance of the methoxy group should be noted.

Later,[90] the α-piperidyl group of IX (when R = OCH_3) was replaced by a series of homologous amines from $-CH_2N(CH_3)_2$ to $-CH_2N(C_7H_{15})_2$.

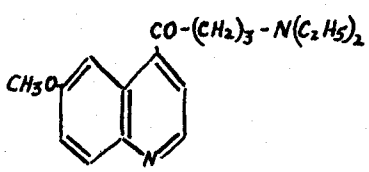


XI

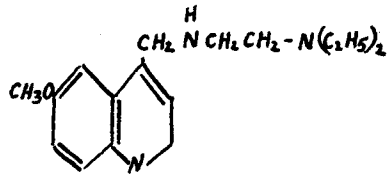
The dibutyl-, diamyl- and dihexylcarbinolamines (XI) were active. Twenty-seven years earlier Kaufmann[96] had almost made the first synthetic antimalarials.

When the 6-methoxyquinoline base of (XI) was replaced by quinoline or by 6-methoxynaphthalene the biological activity was destroyed.[90]

Since the -CHOH- group may be converted by oxidation to a carbonyl or by reduction to a methylene, it is not impossible for quinine to undergo similar changes in the body. It is also possible that the changed form, not quinine, is the active antiplasmodial agent. Although quinicine (VII), also known as quinotoxin, is devoid of activity, nevertheless relatively simple substances (XII, XIII) were prepared, containing a carbonyl or methylene group in place of the carbinol.[97,100]



XII



XIII

These were inactive. Likewise, the introduction of $-COOCH_2CH_2N(C_2H_5)_2$ in positions 4-, 5-, or 8- of 6-methoxyquinoline proved to be ineffective.[97]

In general, little or no activity is manifested when the

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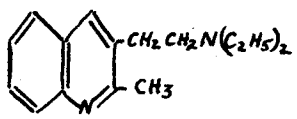
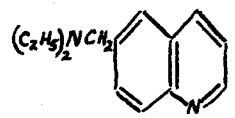
100. Wojahn, Arch. Pharm., 271, 539 (1933).

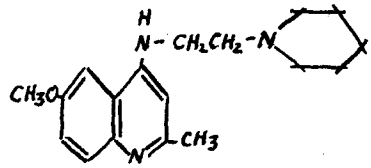
basic side chain is an amino- or an N-acetylamino group. 4-Amino-6-ethoxy-2-phenylquinoline, and 3-amino-2-phenylquinoline ethiodide were slightly active in canaries infected with P. praecox.[101] No influence was exerted by 4-amino-6-methoxy-2-phenylquinoline and 4-amino-2-phenylquinoline. Likewise, when the amino group is in the 8-position of 6-methoxyquinoline, the base for plasmoquine and Fourneau 710, no therapeutic action is observed.[88a,102] Incidentally, the activity of the 3-amino compound is the first of its kind and points to the possibility of introducing basic substituents in positions other than the 4- and 8-. However, compounds (XIV) and (XV) were found to be inactive.[97]



XIV



XV



XVI

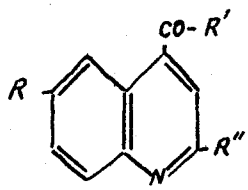
Kermack and Smith[103] prepared 4-piperidino-2-methylquinoline, 4-piperidino-6-methoxy-2-methylquinoline, 4-piperazino-2-methylquinoline and 4-β-N-piperidinoethylamino-6-methoxy-2-methylquinoline (XVI) for antimalarial studies. Biological data for only the last named compound were reported, and this was inactive.

101. John and Glowazky, Z. Immunitäts, 78, 280 (1933) [C. A., 29, 3724 (1935)].

102. Magidson and Strukov, Arch. Pharm., 271, 359 (1933).

103. Kermack and Smith, J. Chem. Soc., 1356 (1930); ibid., 3096 (1931).

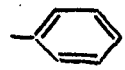
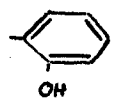
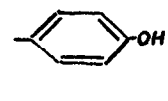
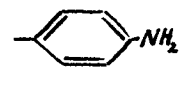
Likewise, certain compounds (XVII) related to atophan, were inactive.[88a]



XVII

R = H, CH_3-, CH_3O-

R' = $-NH_2$, -OH, $-OC_2H_5$

R" = $-CH_3$, $-CH_2CH(CH_3)_2$,  ,  ,  , 

But when the dialkylaminoalkylamino groups of the type found in plasmoquine and related compounds were introduced in the 4-position of 6-methoxyquinoline, activity was restored.[104] Also, the 4- derivatives were less toxic than the corresponding 8-isomers. The groups introduced were:

$(C_2H_5)_2N-CH_2CH_2CH_2-NH-$

$(C_2H_5)_2N-CH_2CH_2CH_2CH_2-NH-$

$(C_2H_5)_2N-CH_2CHOHCH_2-NH-$

Introduction of the -OH group in the side chain of the 4-compounds lowered the toxicity and raised the therapeutic index, which is exactly the opposite effect produced in the 8-compounds by such a change (p. 78).

6-Methoxy-4-methyl-2-hydroxyquinoline,[105] the 8-methoxy

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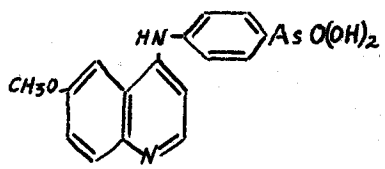
104. Magidson and Rubstov, J. Gen. Chem. (U. S. S. R.), 7, 1896 (1937) [C. A., 32, 564 (1938)].

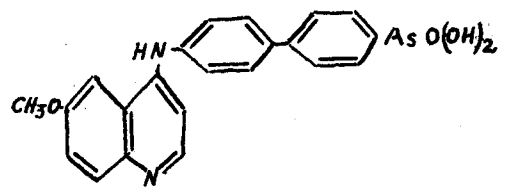
105. Monti and Verona, Gazz. chim. ital., 62, 14 (1932) [C. A., 26, 2980 (1932)].

isomer,[105] and 6-methoxy-4-acetoacetylquinoline have also been prepared as potential antimalarials.[106]

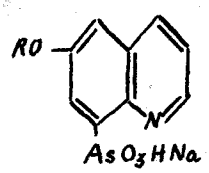
Arsenic compounds (XVIII, XIX) of 6-methoxyquinoline have also been prepared for antimalarial purposes.[107] Fourneau[88a] found that certain sodium arsonates of 6-alkoxyquinoline (XX) exhibited some activity toward bird malaria, but were without effect in human malaria.



XVIII



XIX



XX

R = CH_3-, C_2H_5-

A search of the literature failed to reveal the use of phosphorus-containing compounds in antimalarial studies.

6-Alkoxy-8-Amino Quinolines. Like the 4-amino isomers, the simple 6-alkoxy-8-aminoquinolines manifest little or no

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106. Linnel and Rigby, Quart. J. Pharm. Pharmacol., 11, 722 (1938) [C. A., 33, 3524 (1939)].

107. Slater, J. Chem. Soc., 1209 (1930).

activity. 6-Methoxy-8-aminoquinoline is completely inactive, while the 6-ethoxy homolog shows some activity toward avian malaria. However, the latter is impotent against human malaria.[88a] When the $-NH_2$ group of 6-methoxy-8-aminoquinoline is replaced by the $-NHNH_2$ group, some activity is restored as indicated by the behavior of the compound toward P. relictum.[108] Although in quinine and the other cinchona alkaloids only two basic centers are necessary for antiplasmodial action, in the synthetic compounds three basic centers appear to be more favorable for the endowment of such action.[75,76,77a,88,102,109,110] In the acridine series of synthetic drugs, three basic centers also favor the manifestation of antimalarial activity. It even appears that four basic centers might exaggerate the activity still further. The series of compounds prepared by Baldwin, Robinson and others[109] contain from two to four nitrogen atoms, according to the pattern indicated by general formula (XXI).

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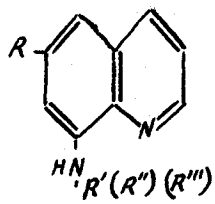
108. Nandi, J. Indian Chem. Soc., 17, 449 (1940).

109. (a) Baldwin, J. Chem. Soc., 2959 (1929); (b) Brahmachari and Bhattacharjee, J. Indian Chem. Soc., 8, 571 (1931); (c) Baldwin and Robinson, J. Chem. Soc., 1264 (1934); (d) Meisel and Robinson, ibid., 1267 (1934); (e) Robinson and Tomlinson, ibid., 1524 (1934).

110. (a) Magidson and Strukow, Arch. Pharm., 271, 569 (1933); (b) Magidson, Madajewa and Rubzow, ibid., 273, 320 (1935); (c) Krichevskiĭ, Shternberg and Halperin, J. Microbiol., Epidemiol., Immuniol., (U. S. S. R.), 14, 642 (1935) [C. A., 30, 4218 (1936)]. See also ref. 104.



XXI

R = H, CH_3-, CH_3O-, C_2H_5O-, C_4H_9O-

R' = C_4H_9-, C_5H_{11}-

R" = $-(CH_2)_nNH_2$, $-CHCH_3-CH_2NH_2$, $-CH_2CH_2-O-CH_2CH_2NH_2$

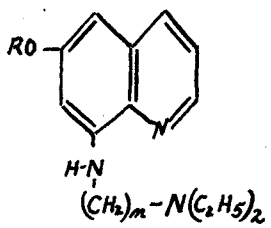
n = 2, 3, 4, 5

R"' = $-(CH_2)_3-NH-(CH_2)_3NH_2$, $-(CH_2)_3-NH-(CH_2)_4-NH_2$,

$-(CH_2)_4-NH-(CH_2)_3NH_2$, $-(CH_2)_4-NH-(CH_2)_4-NH_2$

The methoxyquinolines were more active than the ethoxyquinolines. The R" derivatives were described as good curative agents,[109d] and the R"' as powerful antimalarial agents.[109e] The R' compounds when R = $-OCH_3$ were all inactive. Likewise, the N,N-di-isoamyl derivative of 6-methoxy-8-aminoquinoline was found to be inactive.[102]

The effect of length of the basic side chain has been studied by Fourneau,[90b,c,d] Magidson[112] and their co-workers. The type of compound studied is given in formula (XXII).



XXII

When R = CH_3, and when	n =	c.i./6
	2	
	3	26.5
	4	10.6
	5	25.0
	6	13.3
	7	33.3
	9	40.0
	11	5.0

The figures in the above table are those of Magidson and Krichevskiĭ.[110c] The chemotherapeutic index (c.i.) is defined as the ratio of the minimum curative to the minimum lethal dose. In Fourneau's series, n = 2, 3, 4, 5, 6 and 11. The last five were very effective. It should be noted that the effectiveness of the undecylamino compound as reported by Fourneau and Bovet[88c,d] does not agree with that of the Russian investigators. It is also claimed that the salt of this base with m-acetylamino-p-hydroxyphenylarsonic acid acts on the asexual and sexual forms of the malarial parasite and in addition is only slightly toxic.[111] Altman[112] has practically

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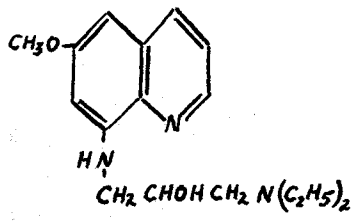
111. Fr. Patent 769,263 (1934) [C. A., 29, 556 (1935)]. In addition to this reference and references 112 and 114, see also Brit. Patent 504,024 (1939) [C. A., 33, 7494 (1939)], for further methods of making the long chain dialkylaminoalkyl halides, employed in the condensation with the 8-aminoquinoline compounds.

112. Altman, Rec. trav. chim., 57, 941 (1938).

completed the series by preparing the compound where n = 8, as well as the n = 7 and 9 homologs. The three compounds are reported as being very effective against bird malaria, attacking the gametes. In the Magidson series, the compounds from n = 3 to n = 9 are very effective. The periodicity of biological properties with alternating odd and even numbers is to be noted, the odd numbers being strikingly more effective than the even. The chemotherapeutic index when n = 3 (Fourneau 710 or the Russian plasmozid) is somewhat less than that of plasmoquine, but the toxicity was so little that the compound was tried in the clinics of the Moscow Tropical Institute and other malarial stations. It was reported to have cured completely 90 per cent of the cases of tertian and quartan malaria and 50 per cent of the tropical malaria cases. Like plasmoquine it is effective chiefly against the gametes. Earlier, Fourneau[88b] claimed this very compound was more active than plasmoquine, producing a quick effect in avian malaria in doses as small as 0.000003 g., and he predicted the compound would eventually replace plasmoquine because it is less toxic, offers a greater safety of margin and is less expensive to make than plasmoquine.

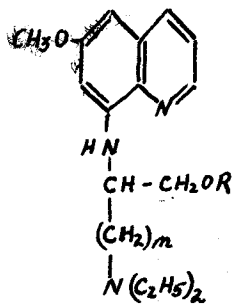
The introduction of an -OH group in the side chain on basis of analogy to quinine lowers the c.i. of the resulting molecule (XXIII)



XXIII

to 14, chiefly as a result of increased toxicity.[110a] It will be recalled (p. 73) that the same basic side chain in the 4-position produces the opposite effect. In quinine and in King's compounds the carbinolamine is also in the 4-position.

When an alkoxymethyl group is introduced into the basic side chain (XXIV), a marked inhibition of activity is observed.[88b]

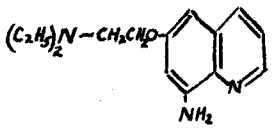


XXIV

Since on the principle of isosterism an -O- atom is the equivalent of a $-CH_2-$ group, the diminution of biological activity may be due rather to branching of the side chain. In compounds of type (XXII), where n = 3, 4 and 5, the normal or straight chain dialkylaminoalkyl groups were shown to be more effective than the branched chains.[88c] A similar effect of

increased branching on therapeutic activity was demonstrated by Magidson.[113]

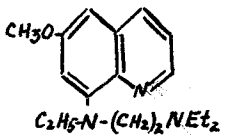
Replacement of the methoxy by an ethoxy group in plasmozid or Fourneau 710 (n=3) lowers the c.i. from 26.5 to 13.3.[110] A shift of part of the basic side chain to the alkoxy group (XXV) destroys the activity completely.[88b,110,114] A further discussion of the effect



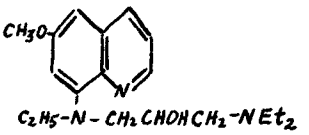
XXV

of variation of the alkoxy group on biological activity is given elsewhere (p. 84).

Especially striking was the complete disappearance of therapeutic activity when the amino group in position 8- was converted to á tertiary amine (XXVI, XXVII).[110]



XXVI



XXVII

In the plasmoquine type of antimalarial, the basic side chain is attached to the 8-position of the quinoline nucleus through a nitrogen atom. Interposition of a methylene group between the nitrogen of various side chains and the quinoline ring produced a series of compounds, none of which were

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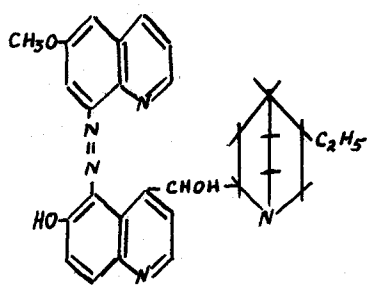
113. Magidson, Delektorskaya and Lipowitsch, Arch. Pharm., 272, 74 (1934).

114. Matejka and Robinson, J. Chem. Soc., 1322 (1934).

effective in avian malaria.[115] Unfortunately, none of Kermack's compounds contained a methoxy group, so that comparison with plasmoquine is not strictly valid.

When the 8-dialkylaminoalkylamino group is replaced by an 8-azohydrocupreine group, compounds are obtained which have a pronounced efficacy against the malarial parasite.[116,117,118] These products are prepared by coupling the diazo compounds from 8-aminoquinoline or its substitution products with hydrocupreine or a substitution product thereof. Some examples are quinoline-8-azohydrocupreine, 6-methoxyquinoline-8-azohydrocupreine sulfonic acid -(?) and 6-methoxyquinoline-8-azohydrocupreine. Although the position of coupling in the cupreine molecule is not given, it appears to be ortho to the hydroxy group in the 5-position, so that the drugs probably have the constitution indicated in formula XXVIII.



XXVIII

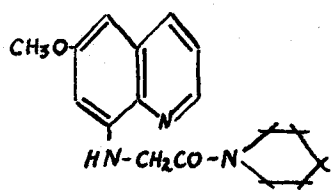
115. Kermack et al., ibid., 1143, 1421 (1925).

116. Ger. Patent 551,094 (1931) [C. A., 26, 4417 (1932)].

117. Brit. Patent 399,818 (1933) [C. A., 28, 1816 (1934)].

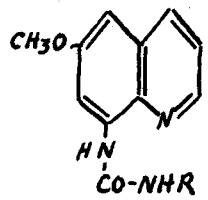
118. U. S. Patent 1,972,988 (1934) [C. A., 28, 6947 (1934)].

A series of piperidines, including piperidinoacetyl-8-amino-6-methoxyquinoline (XXIX), failed to show antimalarial action.[119]



XXIX

The series of interesting α-(6-methoxyquinolyl-8)-β-alkylureas of type (XXX), prepared by Boehmer,[120] also shows that not all basic side chains are suitably equipped for antimalarial endowment.



R = H, Me, Et, n-Pr, n-Bu, iso-Bu

XXX

Only when R = Me does the substituted urea appear to have any action against P. relictum.

2- Basically Substituted Quinolines. Very little work has been done on compounds containing a basic substituent in the 2-position of quinoline. Therefore, the statement that this position (insofar as basic substituents are concerned) is not favorable towards antimalarial endowment is made with

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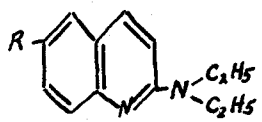
119. Brahmachari, Calcutta Med. J., 34, 327 (1938) /C. A., 33, 9448 (1939)/.

120. Boehmer, Rec. trav. chim., 56, 901 (1937).

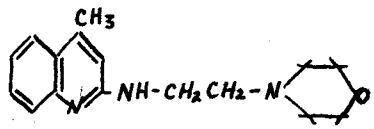
reservations. The introduction of $-NHCH_2CHOHCH_2N(C_2H_5)_2$ in the 2-position of 6-methoxyquinoline does not produce a biologically active compound, whereas the same substituent in either the 4- or 8- position does.[104,110a] The 2-dialkylaminoquinolines (XXXI) of Fourneau were all inactive. Recently, N-β-(2-lepidylamino)ethylmorpholine (XXXII),



R = H, Cl, CH_3O-

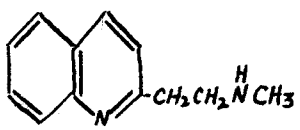
XXXI

synthesized for antimalarial purposes, was found wanting.[121]

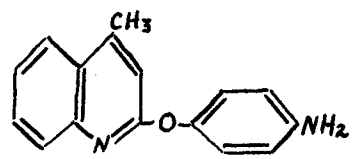


XXXII

Although the biological reports are lacking, the compounds (XXXIII-XXXV) of certain English investigators are cited here.[122]



XXXIII



XXXIV

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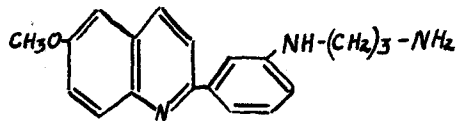
121. Krahler and Burger, J. Am. Chem. Soc., 63, 2367 (1941).

122. (a) Kermack and Muir, J. Chem. Soc., 3089 (1931); (b) Murray and Turner, ibid., 856 (1934); (c) Mathur and Robinson, ibid., 1520 (1934).



XXXV

Effect of Variation of the Methoxy Group. Krichevskiĭ and Sternberg state that the chemotherapeutic action of quinoline derivatives depends on a 6-OH (or a 6- OCH_3) group.[123] The quinolylcarbinolamines of King constitute an excellent example of this point of view. However, a more accurate statement is that the methoxy group, although not essential, is decidedly helpful toward antimalarial endowment. This principle has been established in the cinchona drugs as well as in the synthetic compounds. In human malaria the superiority of quinine and quinidine to cinchonidine and cinchonine, respectively, has been known for a long time.[124,125] Likewise, the action of quinine and cinchonidine, of hydroquinine and dihydrocinchonidine, and of dihydroquinidine and dihydrocinchonine in avian malaria demonstrated the superiority of the methoxy compounds over the demethoxylated forms.[86] In the synthetic series Fourneau observed[88c] retention of biological action, although with diminished

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123. Krichevskiĭ and Sternberg, Z. Immunitäts, 80, 438 (1933) /C. A., 28, 5532 (1934)/.

124. McGilchrist, Ind. J. Med. Res., 3, 1 (1915).

125. Fletcher, Studies from the Inst. Med. Res. Kuala Lumpur F. M. S., no. 18 (1923). Reference taken from ref. 88c.

effectiveness, when the CH_3O- group of compound XXII was replaced by H-, HO-, or C_2H_5O-. In this particular series n was 3. Noteworthy is the high degree of effectiveness retained when the CH_3O- group was replaced by H. But replacement with methyl destroyed the activity completely. To clear up the effect of the alkyl radical in the 6-alkoxy group, Magidson[102] examined a series of compounds of type XXII, where n = 2, and R = H, CH_3-, C_2H_5-, n-C_3H_7-, iso-C_3H_7-, n-C_4H_9, iso-C_5H_{11}, n-C_8H_{17} and allyl. The phenol and methyl ether were the most potent. Effectiveness diminished with increasing number of carbon atoms, and disappeared when the isoamyl group was reached. The iso-propyl and allyl derivatives were inactive. The phenolic form is twice as active as the methyl ether, which is surprising because cupreine is much less effective than quinine.

Little is known concerning the effect produced by a shift of the methoxy group to other positions of the molecule.

When the 6-methoxy group of plasmozid is replaced by a chlorine atom, the c.i. drops from 16.5 to 2.5.[126] Recently, a series of biologically active quinoline compounds containing chlorine has been reported in the patent literature.[127] These compounds which contain a basically substituted amino

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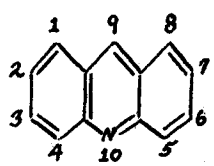
126. Magidson and Bobyshev, J. Gen. Chem. (U. S. S. R.), 8, 899 (1938) [C. A., 33, 1327 (1939)].

127. Andersag, Breitner and Jung, U. S. Patent 2,233,970 (1941) [C. A., 35, 3771 (1941)].

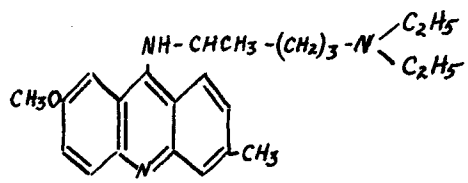
group in the 4-position and a methyl group or preferably a chlorine atom in the 7-position, are claimed to be especially effective against the schizont form of the parasite. The absence of a methoxy group should be noted.

3. Acridine Compounds

The acridines comprise the next largest group of compounds studied for antimalarial purposes. Atebrine (III), also known as achrichin to the Russians, is the most commonly employed by clinicians. The numbering of substituents in this discussion is indicated in formula XXXVI.



XXXVI



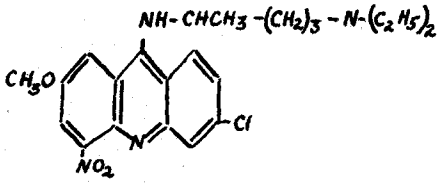
XXXVII

The studies of Mietzsch and Mauss demonstrate the importance of a chlorine atom or a methyl group in the 6-position of 2-methoxy-9-basically substituted acridines.[79] For example, atebrine and compound XXXVII are strongly active against the schizonts of malaria, but removal of the Cl- atom or the CH_3- group destroys this activity. These findings, first demonstrated on canaries,[128] were confirmed by Russian observers on the sparrow.[129] Replacement of the Cl- by a $-NO_2$ group

128. Mietzsch, in "Medicine in Its Chemical Aspects", Vol. III, "Bayer", Germany, (1936).

129. Feldman and Kopeliovich, Arch. Pharm., 273, 488 (1935).

practically destroys all activity,[110c,128,130] but a shift of the $-NO_2$ group from position 6- to 7- raises the c.i. to about 2-4 units.[110c,130,131] The introduction of a nitro group into the 4-position of atebrine (XXXVIII) decreases the antimalarial effect,



XXXVIII

and replacement of the $-NO_2$ group by an $-NH_2$ or dialkylamino group destroys the effect entirely.[132] In contrast to the effect of the nitro group, replacement of the 6-chloro atom with the -CN radical yields compounds which retain the biological activity to a high degree.[133] The c.i.'s of the cyano compounds corresponding to achrichin N5 and atebrine are 10 and 23.3, respectively. The therapeutic index reported for achrichin N5 is 15, which is equal to that of atebrine.[133,134] A shift of the Cl- atom from position 6- to 7- lowers the c.i. considerably,[110c,130,135] an effect exactly opposite to that observed in the quinoline series. The introduction of a

130. Magidson and Grigorovskiĭ, Ber., 69B, 396 (1936).
131. Magidson and Grigorovskiĭ, Khim. Farm. Prom., 187 (1933) [C. A., 28, 1138 (1934)].
132. Knunyants and Benevolenskaya, J. Gen. Chem. (U. S. S. R.), 10, 1415 (1940) [C. A., 35, 3642 (1941)].
133. Magidson and Travin, Ber., 69B., 537 (1936).
134. Krichevskiĭ, Magidson, Halperin and Grigorovskiĭ, Giorn. batter., 13, 685 (1934) [C. A., 31, 3208 (1937)]. However, Tareev, Therap. Arch. (U. S. S. R.), 12, 102 [C. A., 31, 6736 (1937)] states that achrichin N5 has a somewhat feebler effect than atebrine.
135. Feldman and Kopeliovich, Org. Chem. Ind. (U. S. S. R.), 1, 31 (1936) [C. A., 30, 3821 (1936)].

second chlorine atom in the 7-position also lowers the therapeutic efficacy.[135]

Replacement of the CH_3O- group by a C_2H_5O- or CH_3- radical in the atebrine type of compound (III) lowers the therapeutic effectiveness.[110c,130] The same effect was observed in the quinoline series. The introduction of a second methoxy group brings the c.i. down to zero.[110c,130] Substitution of the methoxy group by the methylmercapto (CH_3S-) radical lowers the antimalarial effect considerably. Chemiochine is chemically like atebrine except for the hydroxymethyl group which replaces the methoxy. It is claimed[136] to act promptly on P. vivax and P. malariae, and less effectively against P. falciparum.

Some of the dialkylaminoalkylamino groups used by the Russian investigators with considerable success are listed in order of decreasing effectiveness:

$(C_2H_5)_2N-(CH_2)_4-NH-$

$(C_2H_5)_2N-(CH_2)_3-NH-$

$(C_2H_5)_2N-(CH_2)_2-NH-$

$(C_2H_5)_2N-CH_2CHOHCH_2-NH-$

Achrichin NS, or 2-methoxy-6-chloro-9-diethylaminobutylaminoacridine is reputed to have a therapeutic index greater than that of atebrine or achrichin N5.[134]

136. Di Mauro, Gazz. ospedali clin., 60, 544 (1939) /C. A., 33, 8810 (1939)/.

Hydrogenation of the acridine ring destroys the antimalarial activity. For example, all nitro and chloro derivatives of 1, 2, 3, 4- tetrahydroacridine containing a dialkylaminoalkylamino group were inactive, and were more toxic than the corresponding dehydrogenated compounds.[137]

Other acridines as possible antimalarials have been prepared, but since the pharmacological assays have not been reported these studies[138,139] will not be discussed. Basu and Das-Gupta[140] expected their acridine compounds to be therapeutically active because the molecular weights of 400-450 were within or near the limits suggested for an antimalarial drug.[141]

4. Phenanthridines and Benzoquinolines

None of the phenanthridines (XXXIX, XL) reported by Walls[92] possess antimalarial activity. In XXXIX neither a chlorine atom nor a methoxy group is present, and in XL the methoxy group is *meta* to the N atom, and not *para* as it is

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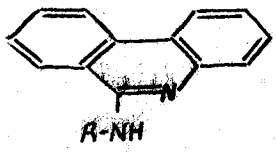
137. Magidson and Travin, J. Gen. Chem. (U. S. S. R.), 7, 842 (1937) /C. A., 31, 5800 (1937)/. See also Das-Gupta and Basu, Science and Culture, 2, 654 (1937) /C. A., 31, 7060 (1937)/.

138. Clemo and Hook, J. Chem. Soc., 608 (1936).

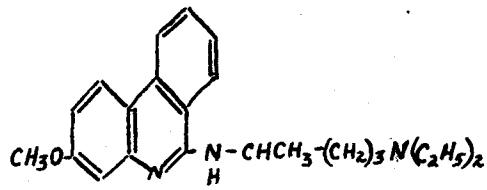
139. Goodall and Kermack, ibid., 1546 (1936).

140. Basu and Das-Gupta, J. Indian Chem. Soc., 15, 160 (1938).

141. Slotta and Behnisch, Ber., 68, 754 (1935).



XXXIX



XL

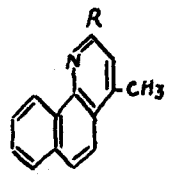
R= $-CH_2CH_2N(C_2H_5)_2$

$-CH_2CH_2N$

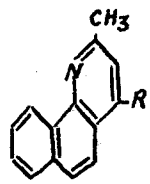
$-CH_2CH_2N-(\underline{iso}\text{-}C_4H_9)_2$

in plasmoquine and atebrine.

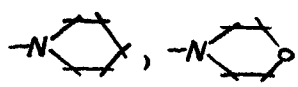
The biological activity of the benzoquinolines (XLI, XLII) prepared by Untermohlen and Hamilton have not been reported,[142] but similar compounds (XLIII) are claimed to be suitable for combating malaria.[143]



XLI



XLII

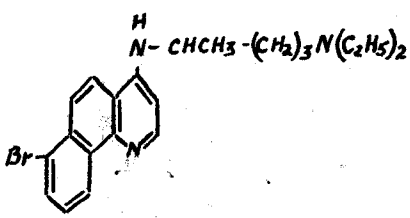
R = 

$-NHCH_2CH_2OH$,

$-NH(CH_2)_4N$

$-NH(CH_2)_4N(C_2H_5)_2$,

$-NH(CH_2)_3N$ 



XLIII

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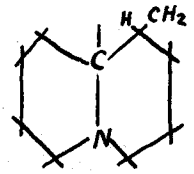
142. Untermohlen and Hamilton, J. Am. Chem. Soc., 63, 160 (1941).

143. U. S. Patent 2,231,844 (1941) [C. A., 35, 3394 (1941)].

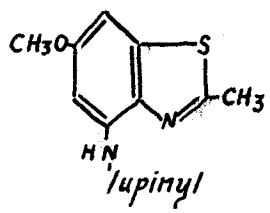
5. Benzothiazoles

The introduction of the lupinyl group (XLIV) into the 8-position of 6-methoxy-8-aminoquinoline produces a molecule possessing strong antimalarial action.[93] However, replacement of the



XLIV

6-methoxy-8-aminoquinoline nucleus by the isosteric 7-amino-5-methoxy-2-methylbenzothiazole yields a compound (XLV) which is completely inactive.

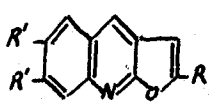


XLV

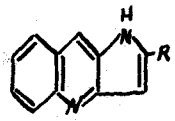
Likewise, the introduction of the very active -diethylamino-propylamino group into the 7-position of 5-methoxy-2-methyl-benzothiazole is without effect.[94] These experiments indicate that the benzothiazole nucleus does not impart antimalarial activity even in the presence of active substituents.

6. Other Ring Systems

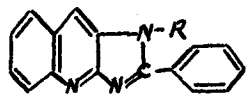
A large variety of ring systems have been examined as potential sources of antimalarial action. Generally, where the results have been negative, the compounds under question contained a few or no active substituents. Hence further study is necessary before one can conclude with some degree of certainty, as in the benzothiazoles and the naphthalenes, that a given ring system is unsuitable for antimalarial synthesis. It is therefore likely that the conclusions of Walls[92] in regard to phenanthridine may be unjustifiable. For example, the introduction of the active substituents of plasmoquine and atebrine into triphenylmethane, thiazine and xanthine have produced active compounds.[79a] The furanoquinolines[144] (XLVI), the pyrroloquinolines[145] (XLVII), and the glyoxalinoquinolines[146] (XLVIII) prepared so far leave much to be desired before any definite conclusions can be drawn concerning their antimalarial possibilities. The α-picolyl-1-isoquinolines are mentioned here merely as a matter of interest.[147]



XLVI



XLVII



XLVIII

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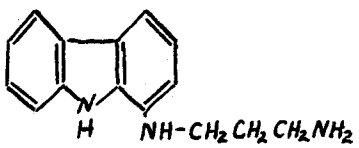
144. Haq, Kapur and Ray, J. Chem. Soc., 1087 (1933).

145. Barger and Robinson, ibid., 2947 (1929).

146. Narang and Ray, ibid., 976 (1931).

147. Clemo, McIlwain and Morgan, ibid., 610 (1936).

Certain α-pyrrylindoles[150] were prepared as likely antimalarials because of their analogy to harmine, a non-cinchona alkaloid reported to have antimalarial properties. Berkenheim[89] has already declared intention to investigate the field of carbazoles, indoles and isoquinolines. Preliminary steps in the carbazole field have already been taken by Robinson[149] and Mottier.[150] The latter demonstrated that the 4-amino- and 4-γ-aminopropylaminocarbazoles (XLIX) were ineffective against the malarial organism, but this study does not establish



XLIX

the ineffectiveness of the carbazole ring as a base for antimalarial synthesis.

Siminov[95] is of the opinion that the structure of therapeutic reagents may be greatly simplified, and accordingly embarked upon the synthesis of antimalarials (L, LI, LII, LIII) containing neither quinoline nor acridine.

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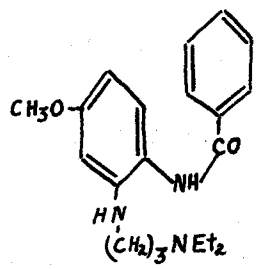
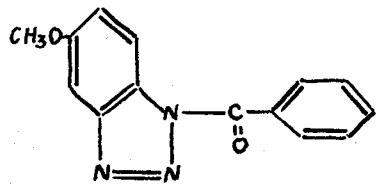
148. Aggarwal, Qureshi and Ray, J. Am. Chem. Soc., 54, 3988 (1932).

149. Robinson and Tomlinson, J. Chem. Soc., 1524 (1934).

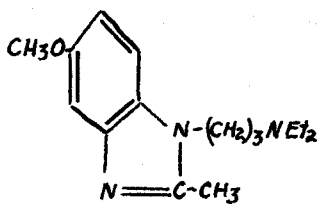
150. Mottier, Helv. Chim. Acta, 17, 1130 (1934).



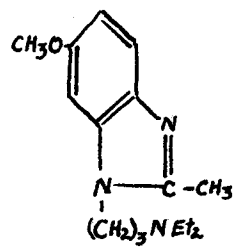
L



LI. 5-Methoxy-1-benzoylbenzotriazole



LII. 2-Methyl-5-methoxy-1-(3-diethylamino-propyl-)benzimidazole



LIII. 2-Methyl-6-methoxy-1-(3-diethyl-aminopropyl-) benzimidazole

Compounds (LII) and (LIII) when tried on birds showed no activity to P. relictum.

The ineffectiveness of naphthalene as an antimalarial nucleus has already been demonstrated.[90] Likewise large molecular weight derivatives of biphenyl, bipiperidyl, and open-chain compounds were ineffective.[91] Most of Fourneau's amino-alcohols of naphthalene, biphenyl, and benzene displayed little or no activity against bird malaria, and all were inactive in human malaria.[88a]

Paget's[151] claim that sulfanilamide and "prontosil" possess no therapeutic value in malaria is not supported by other workers.[152] Coggeshall[153] found sulfanilamide therapy to be successful in monkeys infected with P. knowlesi. A residual immunity lasted for three months after eradication of the infection. Sulfapyridine, when administered in massive doses has a definite lethal action against P. knowlesi in rhesus monkeys.[154] Sulfathiazole was also found effective in simian malaria.[155]

The status of 1, 11-undecanediamidine as an antimalarial remains to be established.[156,157] The very simple molecule, d-alanine, is without action against bird malaria.[158]

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151. Paget, Palmer and Sherwood, U. S. Pub. Health Repts., 53, 1364 (1938).

152. Das-Gupta and Chopra, Indian Med. Gaz., 73, 665 (1938) [C. A., 33, 1818 (1939)].

153. Coggeshall, Am. J. Trop. Med., 18, 715 (1938).

154. Singh and Singh, J. Malaria Inst. India, 2, 181 (1939) [C. A., 33, 7897 (1939)].

155. Dikshit and Ganapathi, J. Malaria Inst. India, 3, 525 (1940) [C. A., 35, 5567 (1940)].

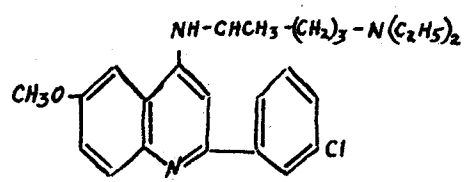
156. Glyn-Hughes, Lourie and Yorke, Ann. Trop. Med., 32, 103 (1938) [C. A., 33, 3457 (1939)].

157. Christopher and Fulton, Ann. Trop. Med., 32, 257 (1938) [C. A., 33, 3458 (1939)].

158. Sternberg, Z. ges. exptl. Med., 79, 517 (1932) [C. A., 26, 4879 (1932)].

IV. PURPOSE OF INVESTIGATION

The purpose of this study was to synthesize an antiplasmodial agent which would be schizontocidal and gametocidal. Plasmoquine and the related compounds of Magidson and Fourneau are of the latter type, whereas atebrine is of the former. Atebrine (III) may be looked upon as a chlorobenzo derivative of 6-methoxy-4-dialkylaminoalkylaminoquinoline. It was therefore hoped that through replacement of the chlorobenzo group by a chlorophenyl group the resulting quinoline molecule (LIV) would incorporate the biological properties of both the quinoline and acridine medicaments, and behave, therefore, as a gametocidal as well as a schizontocidal agent.

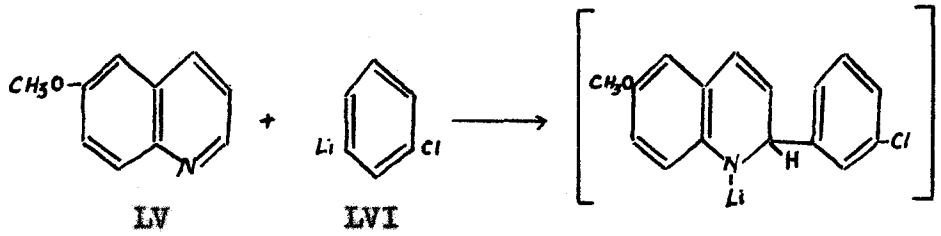


LIV

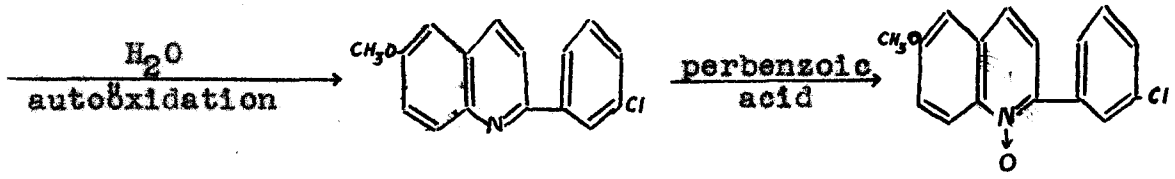
The molecular weight of (LIV) approaches that of acridine and is within the limits considered desirable for an antimalarial compound.[141] The methoxy group is in the same position relative to the heterocyclic N atom as in quinine, plasmoquine and atebrine. Although not essential, the usefulness of the methoxy group has already been established. The basic side chain is <u>para</u> to the py-nitrogen atom as in

quinine and atebrine, and the same type of side chain is employed as in plasmoquine and atebrine. It has also been shown that retention of antimalarial activity with diminished toxicity may be effected by a shift of the dialkylaminoalkylamino group from position 8- to 4- of 6-methoxyquinoline. Furthermore, 4-basically substituted derivatives of 6-methoxyquinoline, closely patterned after quinine, were found to possess antimalarial action. Hence, it appears that the presence of a N- containing residue in the 4-position of quinoline is favorable toward antimalarial endowment.

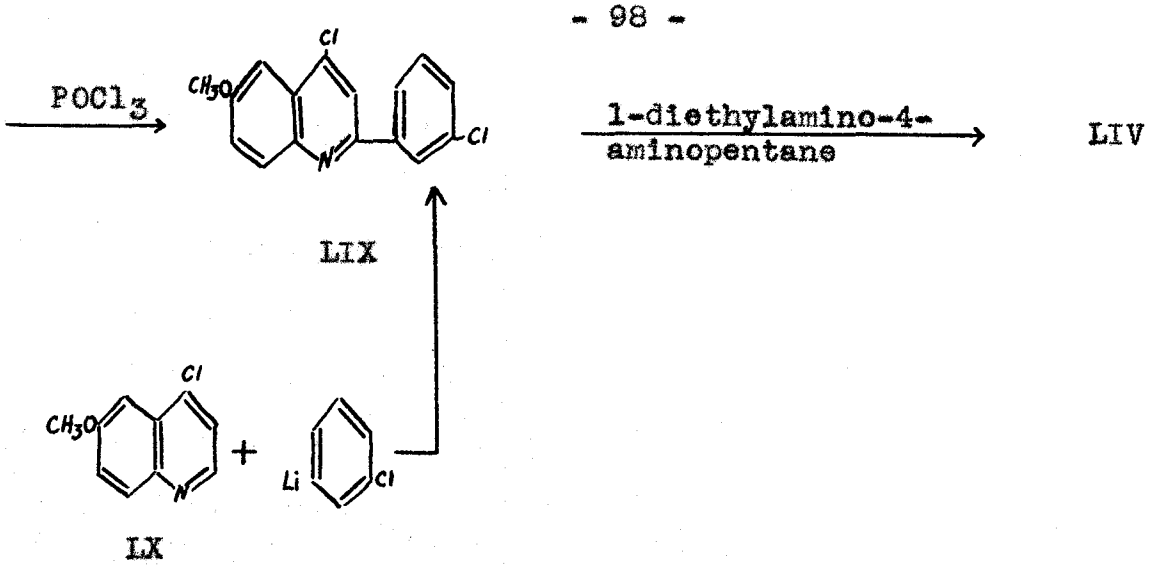
To effect the proposed change in chemical structure from atebrine (III) to (LIV) the following synthesis was carried out:



LV LVI



LVII LVIII

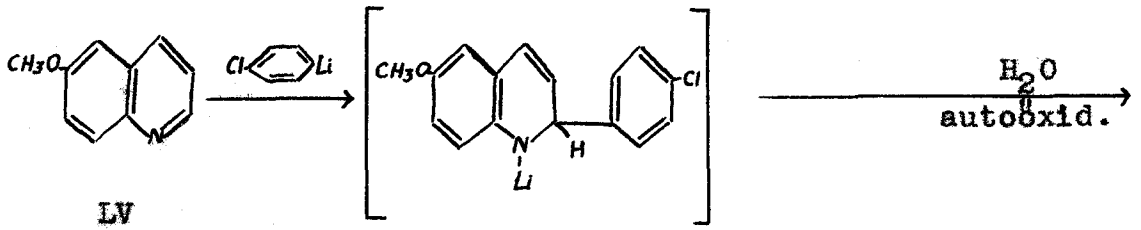


The m-chlorophenyllithium (LVI), employed for the α-m-chlorophenylations of (LV) and (LX), was available in 70% yield from m-chlorobromobenzene and n-butyllithium at -35° C. for ten minutes. Oxidation of the 2-(3'-chlorophenyl)-6-methoxyquinoline to its N-oxide (LVIII) was effected with perbenzoic acid by the method of Meisenheimer.[159,161,104] Phosphorus oxychloride converted the N-oxide to 2-(3'-chlorophenyl)-4-chloro-6-methoxyquinoline (LIX); the position of halogenation was established by an alternate synthesis (LX ⟶ LIX) which left no doubt as to the position of each substituent. The otherwise active chlorine atom in 4-chloro-6-methoxyquinoline was not expected to interfere with the addition of the RLi compound to the -N=C< linkage because (1) the chlorine atom is generally ineffective in X-M reactions; (2) aryllithium compounds are weak X-M interconverting agents; and (3) the chlorine atom is at a relatively great distance from the

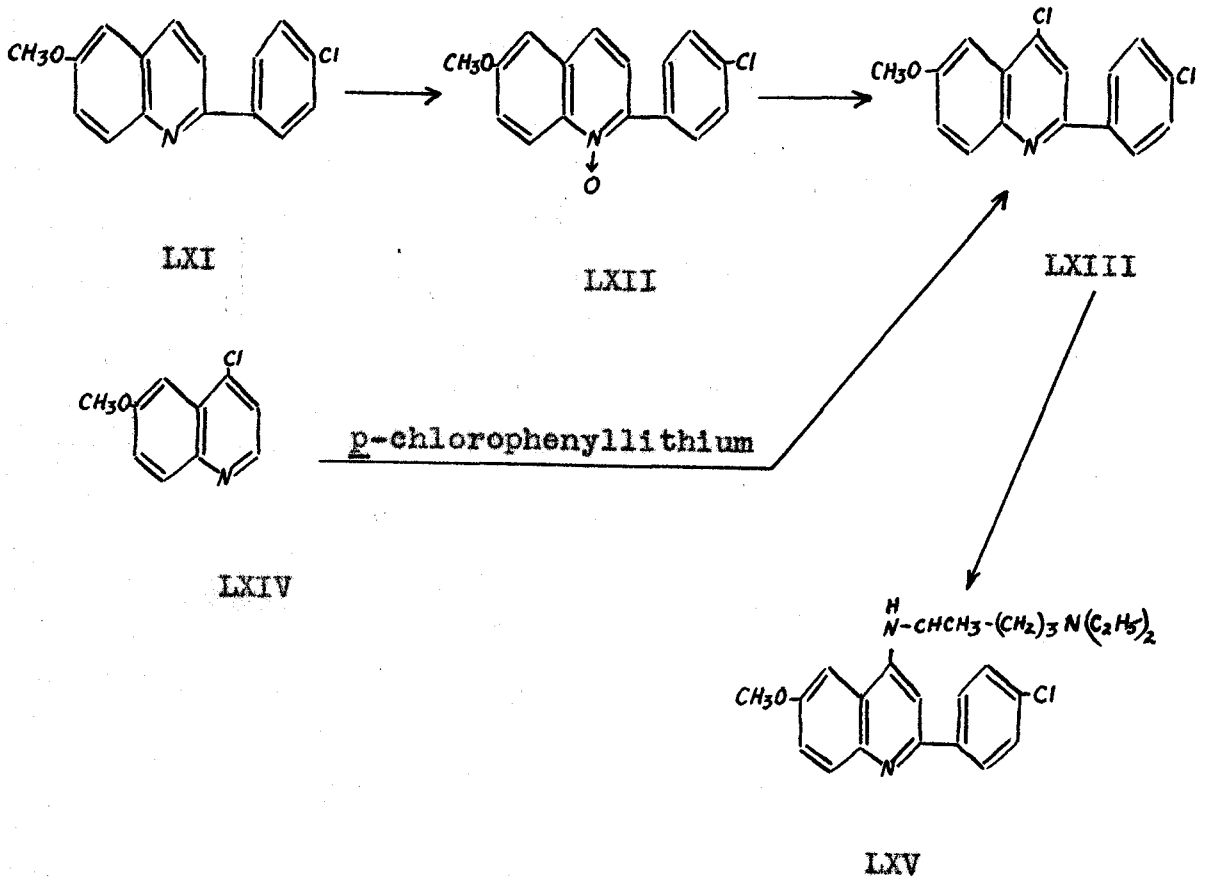
159. (a) Meisenheimer and Stotz, Ber., 58, 2335 (1925); (b) Meisenheimer, Ber., 59, 1848 (1926).

-N=C< group, so that the deactivating influence of the halogen is reduced to a minimum and the predominant reaction becomes anil addition. Compare, for example, the difference in behavior between 2-bromo- and 3-bromopyridine towards alkyllithium compounds.[14c] However, the exalted reactivity of the chlorine atom in the 4-position permitted condensation with the diethylamino-4-aminopentane.

Although a shift of the chlorine atom from position 6- to 7- in atebrine nullifies the antimalarial action, the same effect could not be predicted for compound (LIV) if the m-chlorophenyl group were replaced by the p-chlorophenyl group. It will be recalled that 6-chloro-8-dialkylaminoalkylaminoquinoline is weakly active, but a shift of the chlorine atom to the 7-position confers increased activity upon the molecule. To effect the shift of the Cl atom in compound (LIV), parallel to that of the atebrine analog, the following syntheses were carried out:



LV



LXI LXII LXIII

LXIV

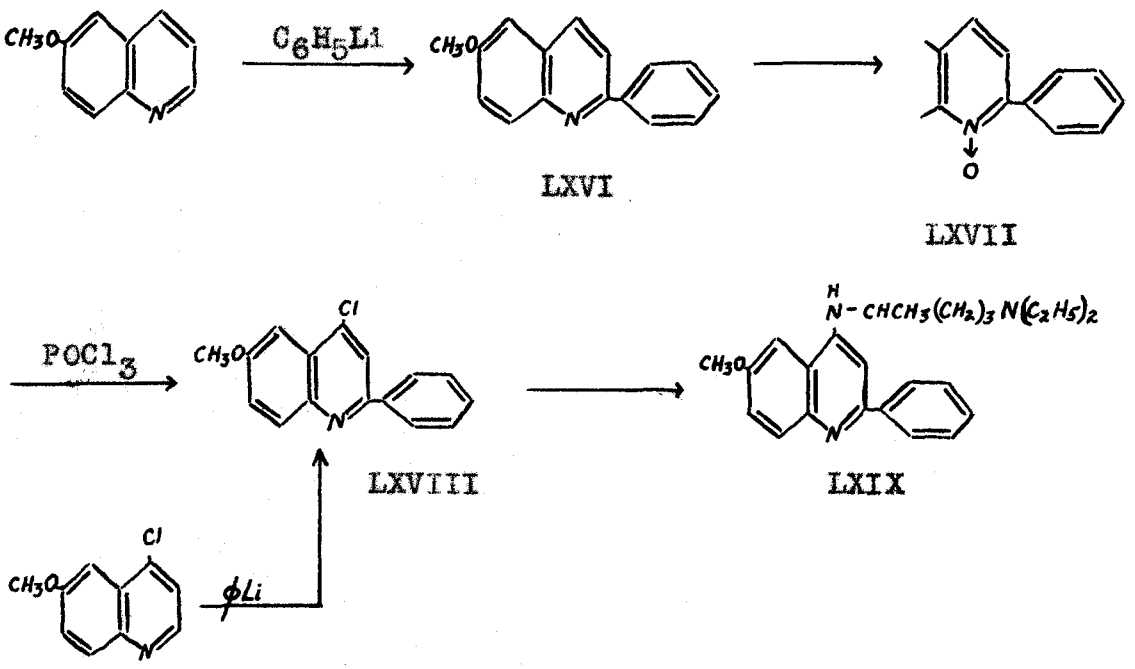
LXV

The p-chlorophenyllithium was prepared by X-M interconversion from p-chlorobromobenzene.[160] The position of halogenation (LXII ⟶ LXIII) was established by the α-p-chlorophenylation of 6-methoxy-4-chloroquinoline (LXIV ⟶ LXIII). In the amination of (LIX) and (LXIII) to (LIV) and (LXV), respectively, the quinoline chlorine is assumed to be replaced, because it is generally well known that the α- and -γ-chlorine atoms of pyridine, quinoline, acridine and homologs show exalted reactivity towards amine condensation. In a large

160. Gilman, Langham and Moore, J. Am. Chem. Soc., 62, 2327 (1940).

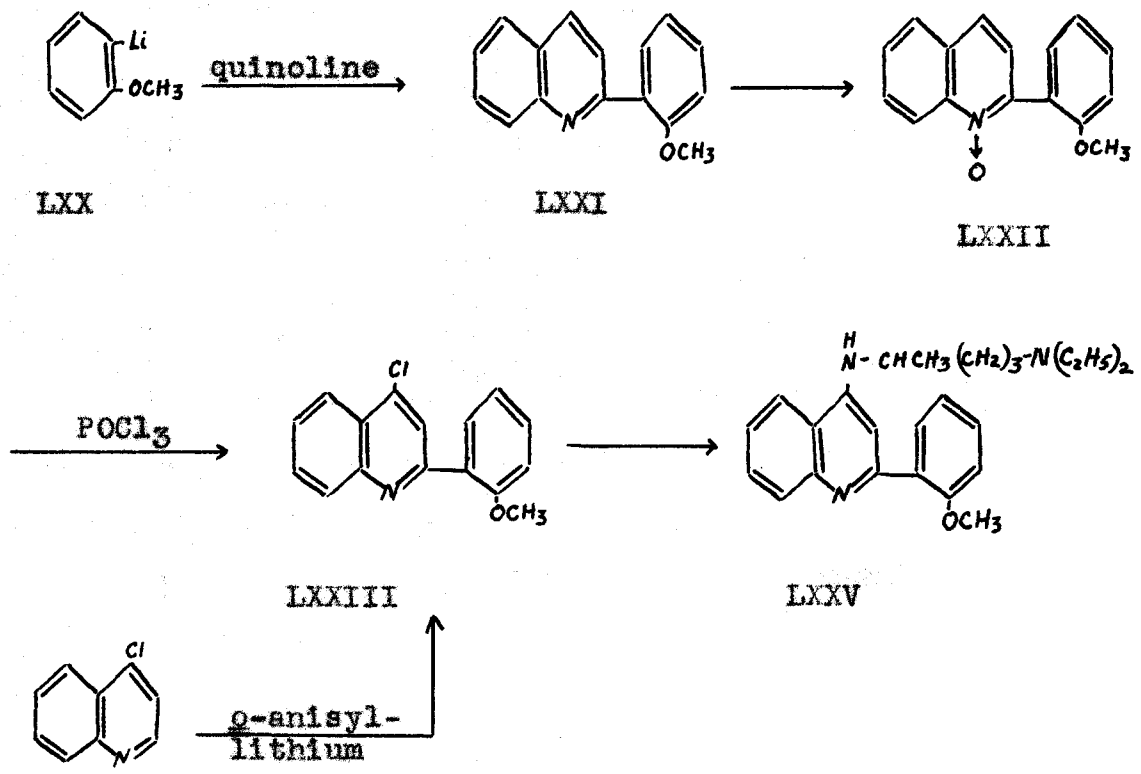
variety of amination reactions with 4,x-dichloroquinolines and 9,x-dichloroacridines, the 4- and 9- chloro atoms are the ones always involved.

Although it was considered possible that the schizontocidal or gametocidal effect or both might be destroyed by removal of the chlorine atom from (LIV) and (LXV), nevertheless such a change (LXVI ——→ LXIX) was undertaken because quinoline antimalarials are known to maintain their biologic effect without the presence of a chlorine atom. The change was effected through the following sequence of reactions:



It was also considered desirable to study the effect of transposing the methoxy group from the quinoline ring to the phenyl nucleus. Accordingly, 2-(2'-methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)amino]quinoline (LXXV) was prepared

by the method developed above.



LXX LXXI LXXII

LXXIII LXXV

LXXIV

Halogenation of pyridine and quinoline compounds by the action of inorganic acid halides such as phosphorus pentachloride, phosphorus oxychloride and sulfuryl chloride on the corresponding N-oxides occurs always ortho or para to the nitrogen atom (i. e., in the α- and γ-positions); generally a mixture of the two isomers is obtained.[159,161,104] By blocking the α-position in every one of the four N-oxides described above (LVIII, LXII, LXVII and LXXII), we have been

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161. Bobrański, Kochańska and Kowaleska, Ber., 71B, 2385 (1938).

able to direct halogenation exclusively to the γ-position. The corollary therefore follows that blocking of the γ-position with a suitable substituent will direct halogenation exclusively to the α-position. Since meta halogenation of quinoline, isoquinoline and homologs is effected by molecular rearrangement of the per- or hydrohalide dihalides at high temperatures,[162] general methods now exist for the specific orientation of halogen to any of the three positions in the py- ring. The halogenation reaction is discussed in further detail elsewhere (p. 132).

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162. (a) Claus and co-workers, Ber., 19, 2763 (1886); J. prakt. Chem., [2], 50, 232 (1894); ibid., [2], 39, 314 (1889); ibid., [2], 40, 389 (1889); ibid., [2], 42, 233, 328 (1890); ibid., [2], 50, 31 (1894); ibid., [2], 51, 477 (1895); ibid., [2], 53, 109, 198, 390 (1896); ibid., [2], 57, 49 (1898); (b) Edinger, ibid., [2], 43, 192 (1891).

V. EXPERIMENTAL

6-Methoxy-2-phenylquinoline.--To a filtered solution of 0.1 mole of phenyllithium in 100 cc. of ether was added at 0° over a thirty-minute period with rapid stirring 12.7 g. (0.08 mole) of 6-methoxyquinoline in 50 cc. of ether. The 1-lithio-2-phenyl-1,2-dihydro-6-methoxyquinoline precipitated as a yellow-orange, finely crystalline meal. The entire contents were hydrolyzed in ice-water. The ether layer was dried over Drierite, and the ether removed by distillation. The oily residue was kept on a sand-bath (110-120°) overnight to remove traces of benzene, and to ensure dehydrogenation of traces of the 1,2-dihydro compound. On cooling, the oil solidified to a crystalline mass, which, recrystallized from ethanol, melted at 130-2°. The yield was 13.5 g. (72%), and the picrate melted at 205°. A second recrystallization raised the melting point to 132-133°, but that of the picrate remained at 205°. The yield of pure 6-methoxy-2-phenylquinoline was 12.4 g. (66%).

In a check run, a sample of the oily residue gave a picrate of m.p. 205°. After treatment with mercuric oxide the product still gave the same picrate, and a mixed melting point of the two showed no depression. Evidently, the dihydro compound undergoes autoöxidation shortly after its formation from the 1-lithio-1,2-dihydro compound. In all our α-arylations

by means of RLi we have never been able to isolate the dihydro compound, and these findings concur with those of Bergmann.[46b]

The melting points of our product and its picrate agree with those of Döbner[163] who prepared 6-methoxy-2-phenylquinoline by decarboxylation of p-methoxycinchoninic acid, which in turn was prepared in 18% yield from p-anisidine, pyruvic acid and benzaldehyde.

6-Methoxy-2-phenylquinoline-N-Oxide.--To a solution of 22.9 g. (0.17 mole) of perbenzoic acid in 400 cc. of chloroform was added 26.5 g. (0.11 mole) of 6-methoxy-2-phenylquinoline. The solution, which colored to red shortly afterwards, was kept in a refrigerator for one to three days. The solution was concentrated to one-half the original volume and poured into a hot solution of 30 g. of picric acid in 250 cc. of 95% ethanol. On cooling, 44 g. (80%) of a yellow crystalline picrate came down, which melted at 107-108°. Decomposition of the picrate was effected by boiling with 10% sodium hydroxide solution. The N-oxide, recrystallized from hot ethanol as hard, thick, lustrous crystals, melted at 170-171°. The overall yield was 55-65%. The compound is difficultly soluble in cold ethanol.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.66.

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163. Döbner, Ann., 249, 106 (1888).

4-Chloro-6-methoxy-2-phenylquinoline.--(a) Fifteen and seven-tenths g. (0.063 mole) of the crystalline 6-methoxy-2-phenylquinoline-N-oxide was placed in a 200 cc. three-necked flask with ground glass connections, to which was attached a dropping funnel and a long condenser protected by a calcium chloride tube. After chilling the contents with an ice bath, 76.5 g. (0.5 mole) of phosphorous oxychloride was added with caution through the dropping funnel. The reaction was vigorous and immediate. After the initial reaction subsided, the contents were warmed on a water bath for thirty minutes, and then refluxed gently over a direct flame for ten minutes. During the warming, a crystalline body may settle out, which redissolves on heating. The contents were poured onto 1200 g. of chopped ice; the oily material, after gradual solidification, was filtered off and washed with water. The filtrate and washings were made alkaline to give an additional crop of 4-chloro-6-methoxy-2-phenylquinoline. Recrystallized from ethanol as long, hard needles, the compound melted at 110-111°, and a mixed melting point with an authentic specimen prepared by the α-phenylation of 4-chloro-6-methoxyquinoline showed no depression. The yield was 13.7 g. (81%).

In smaller runs, employing one to five grams of the N-oxide, the yield of chlorination product was 88-91%.

The over-all yield by our three-step procedure, beginning with 6-methoxyquinoline, is superior to that obtained by the longer method of John.[164]

164. John and Lukas, J. prakt. Chem., [2], 130, 328 (1931).

(b) One g. of the N-oxide was treated with 10 g. of sulfuryl chloride (Eastman's practical) at 0°; then boiled on the water bath for ten minutes. The contents were poured upon chopped ice, but the red oil which was obtained could not be transformed into a crystalline body.

6-Methoxyquinoline-N-Oxide Hydrochloride.--In accordance with the procedure of Magidson,[104] 28.6 g. (0.18 mole) of 6-methoxyquinoline was added to 0.216 mole of perbenzoic acid[165] in 750 cc. of chloroform. The solution colored to red shortly afterwards. After standing in the ice-box for two days, the solution was concentrated to a volume of about 300 cc. and extracted with 20% hydrochloric acid. The extract was washed with a little chloroform and evaporated to dryness under vacuum. The residue was recrystallized by dissolving in ethanol and precipitating with ether. The yield of N-oxide hydrochloride, melting at 192-4°, was 33.2 g. (87.5%).

The yellow, finely crystalline picrate melted at 173-4°.

4-Chloro- and 2-Chloro-6-methoxyquinolines.--Following the procedure of Magidson,[104] 10 g. (0.057 mole) of 6-methoxyquinoline-N-oxide hydrochloride was warmed with 50 g. (0.33 mole) of phosphorus oxychloride in an oil bath. At 55°, a vigorous reaction set in; the contents were heated under

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165. Braun, Org. Syntheses, 13, 86 (1933).

gentle reflux on a wire gauze for thirty minutes, and then poured upon 250 g. of chopped ice. On neutralizing the solution barely to the acid side of congo red, colorless crystals separated out and were filtered off. The yield of 2-chloro-6-methoxyquinoline, melting at 106-7°, was 5.6 g. (58.4%).

The filtrate was made alkaline; the pale yellow precipitate, after cooling in the ice-box, was filtered off and recrystallized from Skelly B. The yield of the 4-chloro isomer, melting at 77-8°, was 3.4 g. (35.5%).

4-Chloro-6-methoxyquinoline and Phenyllithium.--In an atmosphere of nitrogen 2.8 g. (0.015 mole) of the quinoline compound in 20 cc. of ethyl ether was added to 0.022 mole of phenyllithium in 30 cc. of ether at 0°. Addition was complete in two minutes, the solution coloring from yellow through orange to orange red. At the end of about two minutes, 1-lithio-2-phenyl-1,2-dihydro-4-chloro-6-methoxyquinoline settled out as orange-colored crystals. After hydrolysis, the ether layer was dried over Drierite, filtered, and the ether removed by distillation. The dark gummy residue was twice recrystallized from ethanol to give pale yellow crystals of 4-chloro-6-methoxy-2-phenylquinoline, which melted at 110-111°. The yield was 2.4 g. (61.5%).

6-Methoxy-2-phenyl-4-/(α-methyl-δ-diethylaminobutyl) amino/quinoline.--Four g. of 4-chloro-6-methoxy-2-phenylquinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane[166] were heated in a metal bath at 135° for twenty-four hours, at 175-180° for another twenty-four hours and at 210° for forty-eight hours. On cooling a glassy melt was obtained, which was dissolved in warm ethanol. The alcoholic solution was added dropwise with stirring to a slight excess of 2% sodium hydroxide solution. After evaporation of the water and alcohol, the dark gummy oil was dried in a vacuum desiccator over calcium chloride, redissolved in absolute ethanol, boiled with Norit and filtered. The alcohol was removed by distillation, the last traces under vacuum. The glassy, dark brown melt obtained thereby is very hygroscopic. Dissolved in water, it forms a colloidal solution, from which the compound settles out as a voluminous, tan precipitate on gentle warming; the precipitation is hastened by the addition of 2-5 cc. of 6% sodium bicarbonate solution. The compound was filtered on a Büchner funnel, and after drying in vacuo over calcium chloride, it was obtained as a pale tan amorphous powder. In this form, it is insoluble in water; soluble in ethanol, acetone and benzene. In the latter two, it exhibits a weak bluish fluorescence. The yield was 4.0 g. (69%).

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.60.

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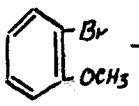
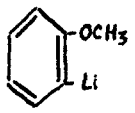
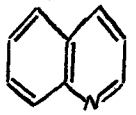
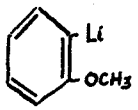
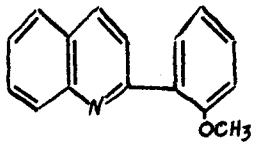
166. Kindly furnished by Dr. L. A. Sweet of Parke, Davis and Co.

2-(2'-Methoxyphenyl)quinoline.--This synthesis makes use of the X-M interconversion reaction. The sequence of steps follows:

(1) $\underline{n}\text{-}C_4H_9Br + 2Li \longrightarrow \underline{n}\text{-}C_4H_9Li + LiBr$

(2) $\underline{n}\text{-}C_4H_9Li +$  $\longrightarrow$  $+ \underline{n}\text{-}C_4H_9Br$

(3)  +  $\longrightarrow$ 

Aside from the preparation of n-butyllithium, which requires about two to four hours, the synthesis is completed within thirty minutes. All steps were executed in an atmosphere of nitrogen, and steps (2) and (3) at -14° C.

To a filtered solution of 0.246 mole of n-butyllithium in 250 cc. of ether was added 49.5 g. (0.26 mole) of o-bromoanisole in 50 cc. of ether over a three-minute period with vigorous stirring. No color change was observed, but vigorous reflux may set in if the addition is too rapid. Stirring was continued for one more minute before 28.5 g. (0.22 mole) of freshly distilled quinoline in 30 cc. of ether was added over a four- to five-minute period to the solution of o-anisyllithium. After eight additional minutes of stirring, the contents were hydrolyzed in ice-water. The ether layer was dried over Drierite; after removal of the ether, the oily residue was diluted with a little ethanol, and added to a hot

solution of 55 g. of picric acid in 500 cc. of ethanol. A yellow crystalline picrate came down at once. The crude picrate was decomposed by boiling with 5% sodium hydroxide solution. The oil was extracted with benzene from the hot mixture, and the extract dried over Drierite. After distilling off the benzene, the residual oil was fractionated under vacuum. The largest fraction, a heavy yellow oil, distilled at 201-4° at 2mm., chiefly at 203.5°. The yield was 24 g. (41.2%).

Anal. Calcd. for $C_{16}H_{13}ON$: N, 5.96. Found: N, 6.11.

In two subsequent runs approximately the same yields of 2-o-anisylquinoline were obtained, an 18% recovery of quinoline was effected, and no butylquinoline was isolated. It appears therefore that the preparation of o-anisyllithium is complete, but that addition of the latter to the -N=C< bond of quinoline is incomplete. Hence, to improve the yield of o-anisylquinoline it is suggested that the time allotted to step (3) be prolonged beyond that employed above.

2-(2'-Methoxyphenyl)quinoline Hydrochloride.--Four g. of the base, dissolved in sodium-dried ether, was treated with dry HCl gas. The white product was dissolved in ethanol; addition of dry ether precipitated the hydrochloride as cream-colored, fine crystals, which melted at 184.5-185° with decomposition. The yield was quantitative. The salt is easily hydrolyzed to the free base.

Anal. Calcd. for $C_{16}H_{14}ONCl$: N, 5.16; Cl, 13.06. Found: N, 5.17; Cl, 12.74.

2-(2'-Methoxyphenyl)quinoline Picrate.--A sample of the base, dissolved in hot glacial acetic acid and ethanol, was treated with a hot alcoholic solution of picric acid. On cooling, a yellow crystalline picrate came down, which melted at 177-8°. The picrate may also be prepared from the hydrochloride.

Anal. Calcd. for $C_{22}H_{16}O_8N_4$: N, 12.07. Found: N, 12.01.

2-(2'-Methoxyphenyl)quinoline-N-Oxide.--(a) A one-liter chloroform solution of 46.4 g. (0.2 mole) of 2-(2'-methoxyphenyl)quinoline and two equivalents of perbenzoic acid were kept in a refrigerator for two days. The solution was concentrated to a volume of about 300 cc., and to it was added a hot solution of 52 g. of picric acid in 300 cc. of ethanol. The crude picrate, decomposed with dilute alkali, gave a dark tan product. Crystallized from ethanol-water as large, glassy tan-colored crystals, the compound melted at 178-178.5°. The yield was 34 g. (68.6%).

(b) An alternate procedure for isolating the N-oxide is as follows: the chloroform solution was concentrated to one-third its volume, and extracted with dilute alkali to remove the benzoic acid. The chloroform layer was dried over sodium

sulfate. The chloroform was removed by distillation, the last traces under vacuum. The brown crystalline residue weighed 16.2 g. (90.5%). After several recrystallizations from ethanol, the N-oxide was obtained as tan, hard glassy crystals, which melted at 178-178.5° with softening from 177-178°. The yield was 11.7 g. (64%).

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.76.

2-(2'-Methoxyphenyl)quinoline-N-Oxide Picrate.--A hot alcoholic solution of picric acid, added to a hot solution of the N-oxide, gave a pale yellow picrate which melted at 133.5-134.5°.

Anal. Calcd. for $C_{22}H_{16}O_9N_4$: N, 11.67. Found: N, 11.66.

4-Chloro-2-(2'-methoxyphenyl)quinoline.--The reaction between 5.8 g. (0.023 mole) of 2-o-anisylquinoline-N-oxide and 21.5 g. (0.14 mole) of phosphorus oxychloride was immediate. After the vigorous reaction subsided, the contents were heated to gentle reflux for ten minutes and then carefully poured upon 300 g. of chopped ice. Agitation of the gummy mixture with a thick glass rod yielded a solid product. Crystallized from hot petroleum ether (b.p. 60-68°), the pale yellow, hard needles melted at 96-98°. The yield was 3.5 g. (56.5%). The chloro compound is very soluble in ethyl ether, hot methanol, ethanol and petroleum ether. It is difficultly

soluble in cold methanol, ethanol and petroleum ether.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.37; Cl, 12.91.

A mixed melting point with an authentic specimen prepared by the α-arylation of 4-chloroquinoline with o-anisyllithium showed no depression.

4-Chloro-2-(2'-methoxyphenyl)quinoline Picrate.--The picrate was prepared in the customary manner. The dull yellow, fine crystals melted at 200-201°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.19.

Quinoline-N-Oxide Hydrochloride.--Meisenheimer's procedure[159] was employed with certain variations. Chloroform was employed as the solvent instead of benzene, because the former is an exceedingly convenient solvent in the preparation of perbenzoic acid. A 600 cc. chloroform solution of 25.2 g. (0.2 mole) of quinoline and 32.2 g. (0.23 mole) of perbenzoic acid was kept in the refrigerator for thirty-six hours. Concentrated to a volume of about 400 cc., the solution was extracted with 10% hydrochloric acid, and the extract washed with chloroform. The extract was evaporated to dryness under reduced pressure. The residue was recrystallized by dissolving in hot

absolute ethanol followed by addition of dry ether. After thorough cooling, the product was quickly filtered off and dried *in vacuo* over calcium chloride. The melting points of the hydrochloride and the picrate were 130-2° and 142-3°, respectively, in close conformity with the values reported by Meisenheimer.[167] The yield of the N-oxide hydrochloride approached the theoretical.

4-Chloroquinoline.--In accordance with the procedure of Meisenheimer,[159] 35 g. (0.19 mole) of quinoline-N-oxide hydrochloride was treated with 350 g. (0.38 mole) of sulfuryl chloride. The yield of 4-chloroquinoline was 23 g. (73%) as reported by Meisenheimer. The melting point (212°) of the picrate also checks with the reported value.

4-Chloroquinoline and o-Anisyllithium.--The sequence of steps in this synthesis follows: $n\text{-}C_4H_9Br \xrightarrow{2Li} n\text{-}C_4H_9Li \xrightarrow{o\text{-bromoanisole}}$ o-anisyllithium $\xrightarrow{4\text{-Cl-Q}}$ 4-chloro-2-(2'-methoxyphenyl)quinoline. To a filtered solution of 0.17 mole of n-butyllithium in 50 cc. of ether at 0° was added 35.6 g. (0.19 mole) of o-bromoanisole in 30 cc. of ether over a four-minute period. Stirring was continued for two minutes. To the solution of o-anisyllithium was added 23 g. (0.14 mole)

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167. The melting points reported by Meisenheimer, ref. 159, are 131-2° for the quinoline-N-oxide hydrochloride and 143° for the picrate.

of 4-chloroquinoline in 30 cc. of ether over a three-minute period; stirring was continued for three more minutes. After hydrolysis, the ether layer was dried over Drierite for three hours, and filtered. From the ethereal filtrate an amorphous yellow body settled out slowly for two days. The unknown substance was crystallized from ethanol as pale yellow needles, which melted at 227-228° with decomposition. It was soluble in dilute base, insoluble in dilute acid and gave a green color with ferric chloride. It could not be acted on by diazomethane.

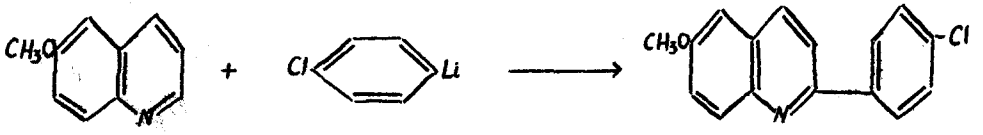
The ethereal filtrate was evaporated by distillation and the residual oil converted to the picrate, melting at 199-201°. A mixed melting with the picrate of 4-chloro-2-(2'-methoxyphenyl)quinoline showed no depression. Decomposition of the picrate yielded 2.4 g. (6.3%) of 4-chloro-2-(2'-methoxyphenyl)quinoline melting at 97-98°. Admixed with the chlorination product of 2-(2'-methoxyphenyl)quinoline-N-oxide, the compound melted at 96-98°.

2-(2'-Methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]quinoline.--Four g. of 4-chloro-2-(2'-methoxyphenyl)-quinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 190-200° for seventy-five hours. The glassy melt, obtained on cooling, was dissolved in the minimum amount of hot absolute ethanol and poured into 300 cc. of 5% alkali solution. The pale yellow gum dissolved in

ether and the solution dried over Drierite. Removal of the ether left an orange-colored transparent jell. The product was purified by distillation under high vacuum (b.p., 248-255° at 0.025 mm.). The yellow oil cooled at room temperature to a glass-like substance, transparent to light. The yield was 4.0 g. (69%).

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.56.

6-Methoxy-2-(4'-chlorophenyl)quinoline.--The sequence of steps is:



Both steps were carried out at 0°.

To 0.19 mole of n-butyllithium was added 38.2 g. (0.2 mole) of p-chlorobromobenzene in 50 cc. of ether with vigorous stirring. The addition was completed in two minutes, and stirring continued for five minutes. To the solution of p-chlorophenyllithium was added 27 g. (0.18 mole) of 6-methoxyquinoline in 30 cc. of ether over a four-minute period, and stirring continued for an additional four minutes. An orange-colored crystalline precipitate, the 1-lithio-2-(4'-chloro-

phenyl)-1,2-dihydro-6-methoxyquinoline, settled out immediately. After hydrolysis, the ether layer was dried over Drierite. Removal of the ether left an oily residue which solidified on cooling to a crystalline mass. Collected on a Büchner funnel, and washed with cold ethanol the white, long needles melted at 194-5°. Recrystallization of a sample from ethanol-pyridine mixture did not raise the melting point. The yield was 23 g. (50.2%).

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.35, Cl, 12.99.

6-Methoxy-2-(4'-Chlorophenyl)quinoline Picrate.--A sample of the quinoline compound, dissolved in hot glacial acetic acid, was treated with a hot alcoholic solution of picric acid. On cooling, bright yellow glistening crystals of the picrate came down which melted at 205°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.30.

6-Methoxy-2-(4'-chlorophenyl)quinoline-N-Oxide.--A tetrachloroethane solution of 19 g. (0.07 mole) of 6-methoxy-2-(4'-chlorophenyl)quinoline was added very slowly and with shaking to an ice-cold solution of 18.4 g. (0.13 mole) of perbenzoic acid in 500 cc. of chloroform. The solution was kept in the refrigerator, and shortly afterwards most of the

parent quinoline compound reprecipitated. Oxidation was slow, as indicated by the gradual conversion of the difficultly soluble parent compound to the more soluble N-oxide. At the end of one week, the red solution was concentrated to a volume of about 400 cc., and extracted with dilute base. The neutral layer was dried over sodium sulfate, and concentrated by vacuum distillation to a volume of about 100 cc. The oil was diluted with 100 cc. of ethanol, brought to a boil, and treated with a hot concentrated alcoholic solution of a slight excess of picric acid. The yield of the yellow, finely crystalline picrate (m.p. 171-2°) was 27 g. (73%).

The unrecrystallized picrate was decomposed by boiling with dilute base. Twice recrystallized from ethanol, the N-oxide melted at 166-168° with softening from 164° on. The yield was 11 g. (55%).

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91; Cl, 12.42. Found: N, 4.74; Cl, 12.22.

4-Chloro-6-methoxy-2-(4'-chlorophenyl)quinoline.--Seven g. (0.025 mole) of 6-methoxy-2-(4'-chlorophenyl)quinoline-N-oxide was treated with 40 g. (0.26 mole) of phosphorus oxychloride in the manner described for the other chlorinations. After hydrolysis, the gummy material solidified into an amorphous body, which crystallized from hot ethanol. The yield of pure product, melting at 163.5-164°, was 5.7 g. (76.5%).

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61; Cl, 23.33. Found: N, 4.72; Cl, 23.06.

A mixed melting point with an authentic specimen prepared from the α-p-chlorophenylation of 6-methoxy-4-chloroquinoline showed no depression.

A mixed melting point with the parent N-oxide was 138-145°.

4-Chloro-6-methoxyquinoline and p-Chlorophenyllithium.--A solution of 5.5 g. (0.029 mole) of p-chlorobromobenzene in 20 cc. of ether was added at 0° to 0.027 mole of n-butyllithium in 35 cc. of ether. The reactants were stirred for three minutes, and then 3.86 g. (0.02 mole) of 6-methoxy-4-chloroquinoline in 25 cc. of ether was added during a four-minute interval. Stirring was continued for four minutes, before the contents were hydrolyzed in ice-water. The ether was evaporated, and the gummy residue crystallized from ethanol. The white crystals melted at 163-4°. The yield of 4-chloro-6-methoxy-2-(4'-chlorophenyl)quinoline was 2.9 g. (48%).

6-Methoxy-2-(4'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)amino]quinoline.--Two and one-half g. of 4-chloro-6-methoxy-2-(4'-chlorophenyl)quinoline and 2.85 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 200° for 72 hours. The melt was dissolved in warm ethanol,

and added to a slight excess of dilute base. The gummy product was dissolved in warm ethanol and precipitated as a yellow amorphous product by careful dilution with water. The powder was dried in a current of warm air (about 40°) for several hours, and then overnight in a vacuum desiccator over calcium chloride. The yield of 6-methoxy-2-(4'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)amino]quinoline was 2.4 g. (69%).

Anal. Calcd. for $C_{25}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.72.

The compound is soluble in cold ethanol, forming a brown solution which possesses a blue-green fluorescence.

m-Chlorophenyllithium.--(a) To a clear filtered solution of 0.2 mole of n-butyllithium in 250 cc. of ether, cooled to -35°, was added 38.3 g. (0.2 mole) of m-chlorobromobenzene in 50 cc. of ether under vigorous stirring. No reflux set in. Theoretically, 0.2 mole of m-chlorophenyllithium was present in 300 cc. of solution. Fifty cc. aliquots were withdrawn at intervals of three minutes and carbonated with finely powdered dry ice. Since the addition of m-chlorobromobenzene required one minute, the first aliquot was withdrawn two minutes later. Each carbonation mixture was worked up in a customary manner. Acidification of the aqueous alkaline layer with dilute mineral acid yielded in each case a white crystalline acid of relatively high purity, as indicated by the melting

point.[168] Therefore, the yields of m-chlorophenyllithium given in the table below are based on the unrecrystallized m-chlorobenzoic acid. The data of Table II show that at -35° the optimum yield of m-chlorophenyllithium is obtained over a range of 6 to 12 minutes.

TABLE II

Yield of m-Chlorophenyllithium at -35°

Time in minutes	Crude yield (grams)	% Yield	M.p. of Unrecrystallized acid
3	2.6	50.3	149.5-151°
6	3.4	66.0	148 -150°
9	3.6	69.7	149 -150°
12	3.5	67.7	148 -150°
16	2.5	48.4	152 -153°

(b) During a three-minute interval, 11.5 g. (0.06 mole) of m-chlorobromobenzene in 50 cc. of ether was added at room temperature to a rapidly stirred solution of n-butyllithium (0.05 mole) in 150 cc. of ether; vigorous reflux occurred. Toward the end of about twelve minutes a white crystalline material began to settle out. Carbonation was effected in a customary manner at the end of fifteen minutes to yield 2.3 g. (29.4%) of crude m-chlorobenzoic acid, melting at 137-141°.

168. The melting points reported in "Beilstein", 4th Ed., Vol. IX, p. 337, vary from 152 to 158°.

Mr. Wright Langham[169] obtained a 41% yield of acid, melting at 138-145°, in a twenty-minute reaction between equimolecular quantities of the two reagents. The occurrence of reflux was noted. When 0.03 mole of n-butyllithium was added all at once to 0.02 mole of m-chlorobromobenzene, carbonation at the end of two minutes gave a 50% yield of crude acid, melting at 145-149°. Recrystallized from water, the acid, melting at 149-151°, was obtained in 42% yield.

Although the temperature of -35° appears to be admirably suited for the preparation of m-chlorophenyllithium, this temperature may be unsuitable for the reaction of the RLi with a given reagent. With powdered dry-ice, which is inherently a low temperature reagent, this effect is not noticed. But in the reaction between m-chlorophenyllithium and the -N=C< group of 6-methoxyquinoline, the yield of anil addition product is definitely a function of the temperature. See Table III.

TABLE III

Effect of Temperature on Addition of m-Chlorophenyllithium to 6-Methoxyquinoline

Temperature (° C.)	% Yield
-35	11.1
-7 to -5	29.6
0	49 to 54
36	16.7

169. Private communication to author.

6-Methoxy-2-(3'-chlorophenyl)quinoline.--This preparation constitutes another example of the application of the X-M interconversion reaction to synthesis. In an atmosphere of nitrogen, 38.3 g. (0.2 mole) of m-chlorobromobenzene in 90 cc. of ethyl ether was added over a three-minute period to a vigorously stirred solution of 0.2 mole of n-butyllithium in 200 cc. of ether, cooled to 0°. After five additional minutes of stirring, 15.9 g. (0.1 mole) of 6-methoxyquinoline in 100 cc. of ether was added to the solution of m-chlorophenyllithium over a four-minute interval. The ice-bath was removed, and stirring continued for ten minutes. The entire contents of supernatant liquid and yellow crystalline precipitate were poured into ice-water. When hydrolysis was completed, the ether layer was separated and concentrated to about one-half the volume. To the hot ether solution was added a hot alcoholic solution of 27 g. of picric acid. The picrate was chilled in the refrigerator overnight, filtered off, dried and decomposed by boiling with dilute base. The crude red-brown product was dissolved in hot Skelly B-benzene mixture, and filtered off from an insoluble dark-colored gum. On cooling, the 6-methoxy-2-(3'-chlorophenyl)quinoline settled out in almost colorless crystals, melting at 110-111°. The yield was 11.9 g., and an additional crop of 1.4 g. obtained by concentration of the filtrate increased the total yield to 13.3 g. (49.3%).

In a duplicate run under the same conditions, the yield

was approximately the same (53%). When the synthesis was carried out at -35°, a temperature well suited for the preparation of m-chlorophenyllithium, the yield of anil addition product was only 11.1%. Raising the temperature of both reactions (X-M interconversion in the preparation of m-chlorophenyllithium, and addition of the latter to the -N=C< bond) to -7° increased the yield to 29.6%. However, when the entire synthesis was run at room temperature, the yield dropped to 16.7%. In the last case the poor yield of end product was probably due to the poor conditions employed in the preparation of m-chlorophenyllithium.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20. Found: N, 5.28.

6-Methoxy-2-(3'-chlorophenyl)quinoline Picrate.--Prepared in the customary manner, the glistening yellow crystals melted at 196-197°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.35.

6-Methoxy-2-(3'-chlorophenyl)quinoline-N-Oxide.--A 700 cc. chloroform solution of 32.5 g. (0.12 mole) of 6-methoxy-2-(3'-chlorophenyl)quinoline and 32 g. (0.23 mole) of perbenzoic acid was kept in the ice box for three days. The ruby red solution was concentrated to a volume of about 250 cc., diluted with 100 cc. of ethanol, brought to a boil, and then

added with stirring to a hot concentrated alcoholic solution of 32 g. of hydrated picric acid. On cooling, a yellow crystalline picrate (m.p. 155-158°) precipitated. The unrecrystallized picrate, was dried and then decomposed by boiling with dilute base to yield 25 g. (73%) of crude N-oxide, melting at 147-149°. Recrystallized from an alcohol benzene mixture (1:1), the N-oxide melted at 153-154°. The yield of pure product was 23 g. (67%).

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91. Found: N, 4.99.

6-Methoxy-2-(3'-chlorophenyl)quinoline-N-Oxide Picrate.--A hot solution of picric acid was added to a hot alcoholic solution of the N-oxide. On cooling, rosettes of the pale yellow picrate crystallized out. The picrate melted at 158.5-159°.

Anal. Calcd. for $C_{22}H_{15}O_9N_4Cl$: N, 10.89. Found: N, 10.96.

4-Chloro-6-methoxy-2-(3'-chlorophenyl)quinoline.--Ten g. (0.035 mole) of 6-methoxy-2-(3'-chlorophenyl)quinoline was treated with 43 g. (0.28 mole) of phosphorus oxychloride. The reaction was instantaneous. After the reaction subsided, the contents were heated, first on a water bath for ten minutes, then gently over asbestos for twenty minutes. The contents were poured upon 300 g. of chopped ice, and after

hydrolysis was complete, the crude chlorination product was filtered off. The filtrate was made alkaline to yield an additional crop of 4-chloro-6-methoxy-2-(3'-chlorophenyl)-quinoline. The compound is difficultly soluble in cold or hot ethanol. It is soluble in hot acetone, and in hot pyridine. Crystallized from an ethanol-pyridine (3:1) mixture, the compound melted at 153-4°. A mixed m.p. with the parent N-oxide was 129-133°. The yield was 6.7 g. (63.2%).

In a second run between 8.4 g. (0.029 mole) of the N-oxide and 37 g. (0.24 mole) of phosphorus oxychloride, the yield of chlorination product was 5.7 g. (63.8%).

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61. Found: N, 4.77.

4-Chloro-6-methoxyquinoline and m-Chlorophenyllithium.--To 0.01 mole of n-butyllithium, cooled to 0°, was added 1.9 g. (0.01 mole) of m-chlorobromobenzene in 20 cc. of ether. After the reactants had been stirred for three minutes, 1.1 g. (0.0057 mole) of 4-chloro-6-methoxyquinoline in 20 cc. of ether was added over a three-minute period. The reactants were stirred for five minutes more, and then hydrolyzed in ice-water. The hydrolysis mixture was boiled to remove the ether. The oily residue solidified to a gum on cooling. Crystallized from absolute ethanol, the compound melted at 153-4°; a mixed melting point with a sample of the chlorination product of 6-methoxy-2-(3'-chlorophenyl)quinoline-N-oxide

showed no depression.

The yield of anil addition product was 0.6 g. (34.7%).

6-Methoxy-2-(3'-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)amino]quinoline.--Four g. of 4-chloro-6-methoxy-2-(3'-chlorophenyl)quinoline and 5.0 g. (2.4 equivalents) of 1-diethylamino-4-aminopentane were heated together at 200-205° for 100 hours. The melt was worked up in the manner described for the preparation of the 4'-chlorophenyl isomer. The 6-methoxy-2-(3'-chlorophenyl)-4-[(-methyl- -diethylaminobutyl)amino]quinoline was obtained as a yellow, amorphous powder. The yield was 3.4 g. (60.7%).

Anal. Calcd. for $C_{25}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.63.

The compound is soluble in cold ethanol, forming a brown solution with a marked greenish fluorescence. The compound is also soluble in cold acetone and in cold benzene with red-blue fluorescence. It is difficultly soluble in ether.

VI. DISCUSSION

Very little is known concerning the mode of action of antimalarial drugs on the plasmodium organism. Provision of such information should be of inestimable aid to the organic chemist. Hegner, Shaw and Manwell[170] observed that the methoxylated cinchona drugs were more soluble in the red blood cells than the demethoxylated forms, and they therefore attributed the greater curative effect of the former to this difference in solubility. If the only requirement for a potential antimalarial is that it be able to penetrate the red blood cell, the problem must narrow down to the question: what enables a molecule to penetrate the cellular membrane? Is the presence of fat-solubilizing (or water-solubilizing) groups the determining factor? Perhaps, the cellular absorption of the drug is governed by the selective permeability of the outer cell membrane to certain chemical groups and arrangements of groups. The answers to these questions may some day provide the clue to new and better antimalarials.

For quinine it is definitely established that the drug does not exert its effect by direct plasmocidal action. *In vitro* treatment of malarial blood with high concentrations of

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170. (a) Hegner, Shaw and Manwell, *Amer. J. Hyg.*, **8**, 564 (1928); (b) Shaw, *ibid.*, **8**, 583 (1928).

quinine does not destroy the infectiveness of the blood,[171] whereas the *in vivo* concentration in blood is never high and is maintained for only a short time after either oral or intravenous administration.[172] Furthermore, these facts suggest that in the body not quinine but a derivative thereof, produced by enzymic degradation, exerts the antiplasmodial effect. Magidson has suggested that a phenolic derivative of atebrine may be the active therapeutic agent.[130]

The limitations of quinine, atebrine and plasmoquine with respect to cost, specificity towards stage and type of invading organism, toxic side reactions, personal idiosyncrasies and special condition of the patient (*i.e.*, pregnancy) justifies the continuation of research efforts toward improved chemotherapeutics. However, an additional point of view, that of chemoprophylaxis,[173] must be stressed, since prophylaxis must be the goal of all malarial control. Quinine, plasmoquine and atebrine, although therapeutically effective, are prophylactically ineffective. Pretreatment with any of these drugs does not prevent infection. Molitor[173] urges that future efforts should be also directed toward the synthesis of prophylactic antimalarials.

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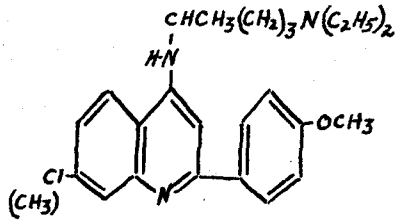
171. Kirschbaum, *Klin. Wochschr.*, *2*, 1404 (1923).

172. Chopra, Roy and Das-Gupta, *Indian med. Gaz.*, *69*, 561 (1934).

173. Molitor in "Human Malaria", American Association for the Advancement of Science, 1941.

Our potential antimalarials designed for gametocidal as well as schizontocidal purposes were based on the viewpoint that atebrine is a chlorobenzo derivative of 6-methoxy-4-substituted aminoquinoline. Atebrine may also be considered as a methoxybenzo derivative of 7-chloro-4-substituted aminoquinoline, so that compounds of type (LXXVI) may be worthy of investigation.



LXXVI

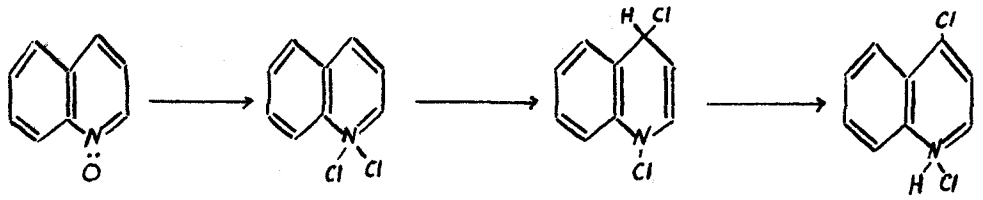
Because 7-chloroquinoline is difficultly accessible whereas 6-methoxyquinoline is commercially available, we have approached the problem from the viewpoint described earlier. Since replacement of the chlorine by a methyl group in atebrine retains the therapeutic properties, analogous compounds of type (LXXVI) may also be worthy of synthesis, especially since Andersag[127] claims that 4-basically substituted 7-methylquinolines can be used for combating malaria. 7-Methylquinoline is commercially available.

In making the compounds described earlier for antimalarial possibilities, we have introduced substituted aryl groups into relatively complex quinoline molecules through

RLi addition to the -N=C< bond. The preparation of 2-(4'-chlorophenyl)-4-chloro-6-methoxyquinoline by the action of p-chlorophenyllithium on 4-chloro-6-methoxyquinoline constitutes an interesting example. It is difficult to conceive of a similarly successful preparation by means of the Oddo-Bergstrom method with the corresponding Grignard reagent, because the drastic conditions of high temperature and pressure necessary for decomposing the initially formed complex salt would surely introduce certain side reactions such as ether cleavage and coupling, especially when an active chlorine is present.

The introduction of substituents into the quinoline molecule is limited to definite positions, depending on the substituent introduced and the method of introduction. Nitration and sulfonation occur in the 5- and 8- positions, generally producing a mixture of the two isomers. Amination with sodamide and alkylation (or arylation) with RLi involve the 2-position. Halogenation through the perhalide occurs in the 3-position, but in the 2- and 4-positions through the N-oxide. By the method of blocked halogenation, the substituent may be introduced exclusively to the 4- (or 2-) position.

A mechanism for N-oxide halogenation has already been advanced by Meisenheimer.[159b] He explains the formation of 4-chloroquinoline from the N-oxide as follows: first, the oxygen atom is replaced by two chlorine atoms (II). A chlorine atom then wanders to the γ-position (III), a change

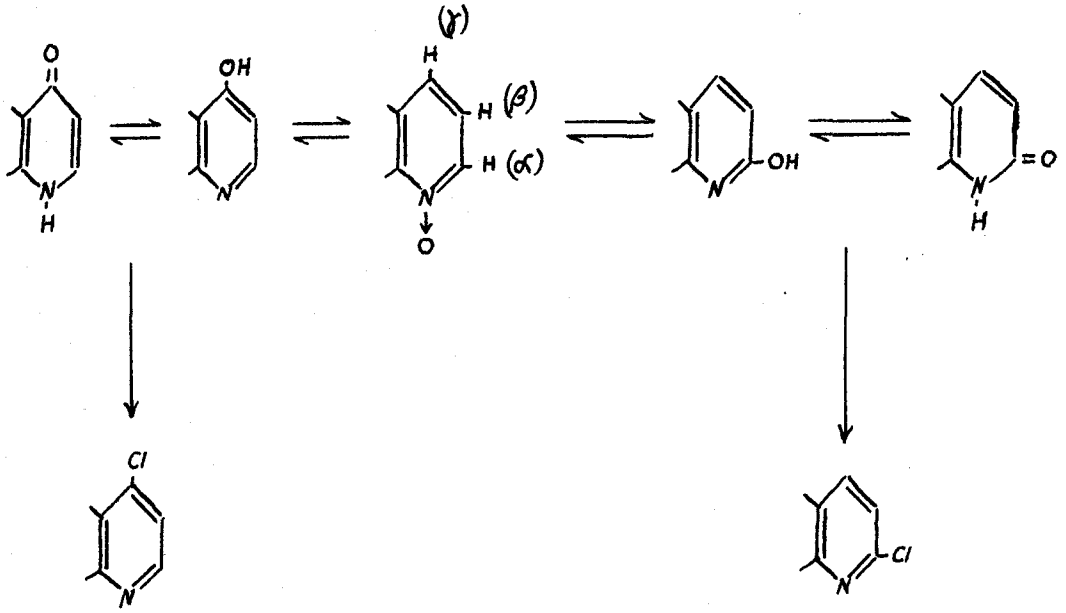


which corresponds to the Decker rearrangement of quaternary pyridinium bases. Finally, the hydrogen wanders to the nitrogen atom (IV), a change which denotes the re-establishment of the stable aromatic ring system.

Whatever the true mechanism of N-oxide halogenation may be, it is our contention that the one offered by Meisenheimer is incorrect. In the first place, the perhalides of quinoline, isoquinoline, and benzoquinoline have been isolated in crystalline form with definite melting point. In general, these addition-complexes are somewhat unstable, continuously emitting vapors of bromine at room temperature, so that the halogen analysis, is usually a little below the theoretical. This physical phenomenon of instability suggests that the chemical structure of these halide salts is of a type akin to Meisenheimer's compound II. It is impossible to conceive of a way in which this loose halogen is attached to the py-ring except by way of the nitrogen atom through residual valence forces. It is the halogen attached to the nitrogen which must act as the brominating agent when heat is applied. The looseness of the nitrogen-halogen bond, already manifest at room temperature, is completely disrupted at 180-200°, resulting in rearrangement and nuclear halogenation (i.e., C-X formation).

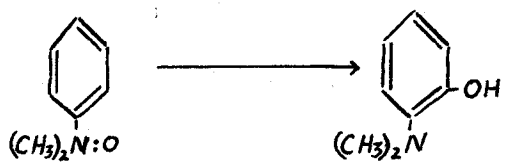
The position of halogenation always occurs <u>meta</u> to the nitrogen atom. Hence, the intermediate formation of (II) in Meisenheimer's scheme cannot be correct, because <u>meta</u> substitution has never been found to occur by the method of N-oxide halogenation.

Therefore, any theory which proposes to explain the mechanism of the reaction between cyclic N-oxides and inorganic acid halides must disregard the formation of an intermediate halogen addition complex. It is the author's opinion that the oxygen atom displays a special affinity for the α- and γ-hydrogens of the py-ring, an affinity which may perhaps be catalysed by the presence of the inorganic acid halide, so that the N-oxide appears to behave as an α- or γ-hydroxypyridine or an α- or γ-pyridone. The mechanism proposed here follows:



The facts in support of the above mechanism are four-fold:

(1) Bamberger and Tschirner[174] found that the action of sulfuric acid on dimethylaniline-N-oxide, a very rapid reaction even at 0°, gave in addition to the main products of o- and p-dimethylaminobenzene sulfonic acids, a 22% yield of dimethylaniline and 0.6% yield of o-dimethylaminophenol. The isolation of the latter two products, especially the phenol indicates the lability of the ≡N⟶O oxygen atom in the presence of certain reagents. The formation of o-dimethylaminophenol was explained as due to an intramolecular shift of the oxygen atom.



(2) α- and γ-Hydroxypyridines and quinolines and the corresponding pyridones and quinolones react with the halides of phosphorus to give the corresponding halogenated pyridines and quinolines.

(3) The action of phosphorus oxychloride on pyridine[161] and 6-methoxyquinoline[104] yields mixtures of the corresponding 2- and 4-chloro substituted derivatives.

(4) If the above mechanism is correct, replacement of

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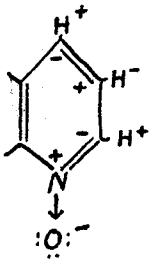
174. Bamberger and Tschirner, Ber., 32, 1882 (1899).

the α- or γ- hydrogen atoms by another group should direct halogenation to the γ- or α- position, exclusively to that position, and to no other position. This was actually the case when the α-H atom of 6-methoxyquinoline or of quinoline was replaced with a phenyl-, o-anisyl-, m-chlorophenyl- or a p-chlorophenyl radical; halogenation occurred in the 4-position and no meta isomer (or any other isomer) was ever isolated.

Why the oxygen atom should display a particular affinity for the α- and γ-hydrogens is difficult to say. An electronic consideration of the N-oxide structure points to a clue. Since the nitrogen must donate its two unused outer electrons to the oxygen atom in the formation of the $\equiv N \longrightarrow O$ link, it (the nitrogen atom) becomes positively charged and the oxygen negatively charged. The charge on these two atoms automatically determines the polarity of the remaining atoms in the ring, since the poles of an electrical force are

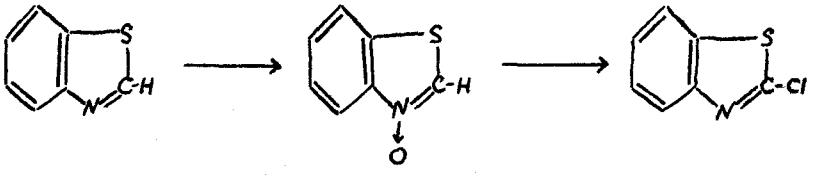


oppositely charged.

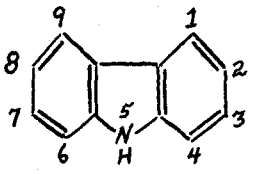
It is interesting to speculate whether blocking of the α-position with a methyl group would effect halogenation of the N-oxide in the active side chain or in the γ-position of the nucleus. Nitration and sulfonation studies of

pyridine and quinoline are also worthy of study. Pyridine is not easily nitrated by the customary methods, and quinoline nitrates and sulfonates in the 5- and 8-positions. Perhaps through means of the N-oxide, pyridine may be nitrated with great ease, and quinoline in positions other than the 5- and 8-.

Bromination of benzothiazole through the perbromide occurs in the bz-ring. In benzothiazole the same type of nitrogen is present as in pyridine or quinoline. Direct halogenation of the heterocyclic ring of benzothiazole is yet to be achieved. This may be accomplished by the method of N-oxide halogenation.



Carbazole and N-alkylcarbazoles undergo nitration, sulfonation, halogenation, mercuration and the Friedel-Crafts reaction in the 2- and 8-positions. N-Acetylcarbazole



Carbazole

acylates in the 3-position with aluminum chloride, and carbazole and N-alkylcarbazoles metalate in the 4- and 6- (?)

positions. If carbazole or its N-alkyl derivatives can be oxidized to the N-oxide, it may be possible to introduce substituents in the 4- and 6-positions other than by metalation, a procedure which leaves much to be desired in regard to yields in the carbazole series. Bamberger[174] has already shown that sulfonation of dimethylaniline N-oxide gives about 60% of the o-sulfonic acid and 20% of the p-sulfonic acid.

VII. SUMMARY

Malaria results in greater mortality than any other infectious disease. It is not confined to regions of the tropics, contrary to common belief. Although quinine, plasmoquine and atebrine are therapeutically effective, each suffers certain disadvantages with respect to cost, undesirable side reactions and personal idiosyncrasies. Further, each is effective only in certain stages and types of the disease. In general, quinine and atebrine are schizontocidal, whereas plasmoquine is gametocidal. None of these medicaments, however, possesses prophylactic properties against the malarial organism.

More than 12,000 compounds have been studied for antimalarial action. Of these, the quinoline and acridine molecules have been the most favorable. Other ring systems investigated as possible sources for antimalarial therapeutics are phenanthridine, benzoquinoline, benzothiazole, carbazole, isoquinoline, benzimidazole and naphthalene. But the antimalarial inefficacy of a given ring has been established in only a few cases, such as naphthalene, benzothiazole and benzimidazole.

The quinoline nucleus has been studied the most thoroughly. In this nucleus only two functional groups are necessary: the basic side chain and the alkoxy (or hydroxy)

radical. The basic side chain may be introduced with advantage into the 4- and 8-positions, but not in the 2-position. Little is known concerning the effectiveness of the basic side-chain in other positions. Some of the more potent basic residues are the naturally occurring quinuclidine and lupinyl radicals, and the synthetic dialkylaminoalkylamino chains of Mietzsch and Mauss, Fourneau, and Magidson. The methoxy group, although not essential, is decidedly helpful. Its effectiveness in positions other than the 6- is not known. But effectiveness is retained when it is replaced with a Cl atom or a CH_3- group in the 7-position.

Analyses of the various publications show that in the acridine medicaments three functional groups play important rôles contributing to the biological efficacy of the compound. These are the basic side chain in the 9-position, the methoxy group in the 2-position, and the chlorine atom or methyl group in the 6-position. Removal of any one of these groups destroys the potency of the compound.

The importance of molecular size and weight has been stressed by Slotta and Behnisch[141] and intimated by Fourneau[88] and King,[98] but the broad limits of 270-450 cover a multitude of sins. A more accurate view is that for compounds of molecular weight 270-370 two functional groups are desirable, whereas three functional groups appear to be more desirable in compounds of molecular weight 370-450. Overlapping is to be expected at the borderline, and this is illustrated by

some of the longer-chain dialkylaminoalkylaminoquinoline compounds of Magidson. According to this view, phenanthridine compounds possessing the three active functional groups in the proper positions should exhibit antiplasmodial activity.

In this investigation, a series of quinoline compounds were prepared, designed for schizontocidal and gametocidal action. For the preparation of certain intermediates two infrequently used reactions were combined in what may be looked upon as a one-step synthesis. The two reactions were X-M interconversion and anil addition of RLi compounds. A series of new quinoline-N-oxides was prepared, containing an aryl or a substituted aryl group in the 2-position. No difficulty was encountered in the preparation of these N-oxides, although Meisenheimer[159b] observed that 2,4,6-triphenylpyridine was more difficult to oxidize to the N-oxide than pyridine, quinoline or isoquinoline. By introducing the method of blocked halogenation we have extended the usefulness of cyclic N-oxides to synthetic chemistry. This method makes possible the exclusive orientation of halogen to either the α- or γ-positions of quinoline. Since β-halogenation is effected through thermal rearrangement of the di- (or per-) halide, methods now exist for the orientation of halogen to any one of the three positions in the py-ring of quinoline.