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Reactions of organometallic compounds with some benzothiazole and quinoline types

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NOTE TO USERS

17

REACTIONS OF ORGANOMETALLIC COMPOUNDS WITH SOME BENZOTHIAZOLE AND QUINOLINE TYPES

by

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The author hereby expresses sincere appreciation to Dr. Henry Gilman for his encouragement, suggestions and helpful criticisms throughout the course of these investigations.

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I. INTRODUCTION

There is a considerable quantity of material to be found in the literature on the reactions of organometallic compounds with quinoline, isoquinoline, and pyridine; but there is not much information available on the reactions of organometallic compounds with the analog of quinoline, benzothiazole. Most of the work on the former heterocycles has been limited to the addition of the more active organometallic types (RLi or RMgX) to the azomethine linkage.[1] In addition, some halogen-metal interconversion reactions have been effected in the 2- and 3-positions of pyridine[2] and also in the 2- and 3- positions of quinoline.[3] Quinoline has also been mercurated in the 6- and 8- positions by mercuric acetate.[4] With the exception of the 2-arylquinolines, to which aryllithium reagents add forming 2, 2-diaryl-1, 2-dihydroquinolines, there is almost nothing in the literature about the reactions of 2-substituted quinolines with organometallic compounds. This is rather surprising in view of the interest in quinoline chemistry resulting from the wartime antimalarial programs.

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1. For a review of this material see Gainer, Doctoral Dissertation, Iowa State College, Ames, Iowa, 1946.

2. Proost and Wibaut, Rec. trav. chim., 59, 971 (1940).

3. Gilman and Spatz, J. Am. Chem. Soc., 63, 1553 (1941).

4. Ukai, J. Pharm. Soc. Japan, No. 548, 873 (1927) [C. A., 22, 785 (1928)].

Courtot and Tchelitcheff[5] have briefly mentioned the metalation of benzothiazole in the 2- position by ethylmagnesium bromide, but have neither reported a yield nor any reactions of the 2-benzothiazolylmagnesium bromide. They have also metalated 2-methylbenzothiazole laterally with ethylmagnesium bromide, sodamide, and phenyllithium. This is the extent to which organometallic compounds of benzothiazole have been investigated.

As a consequence of these factors and the physiological acitivity[6] of compounds containing the benzothiazole nucleus, it was considered of interest to prepare some organometallic compounds of benzothiazole which would be useful in the preparation of hitherto unknown derivatives. The similarity of benzothiazole to quinoline also indicated the possibility of adding organometallic compounds to the azomethine linkage in benzothiazole. In attempting to throw some light on the course of the reaction between benzothiazole and phenyllithium, certain related 2-substituted quinolines, for example, p-tolyl 2-quinolyl sulfide, were subjected to similar experimental conditions. An extensive cleavage of this compound into

5. Courtot and Tchelitcheff, Compt. rend., 217, 201 (1943); ibid., 217, 231 (1943).

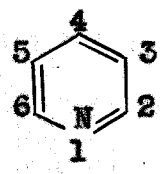
6. Bogert and Hess, Rec. trav. chim. 48, 904 (1929); Newberry and Viaud, British Patent 517, 272 (January 25, 1940) [C. A., 35, 6741 (1941)]. ; Rose, Shonle, and Chen, Pharm. Arch., 11, 81 (1940) [C. A., 35, 1522 (1941)] ; Ballowitz, Arch. exptl. Path. Pharmakol., 163, 687 (1931).

p-thiocresol and 2-phenylquinoline led to an investigation of the reactions of some organometallic types with other 2-electronegatively substituted quinolines.

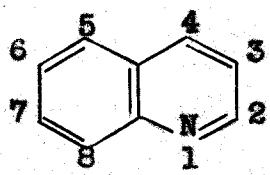
II. HISTORICAL

A. The Activating Influence of the Azomethine Grouping on the α- and γ- Positions of Some Nitrogen-containing Heterocycles.

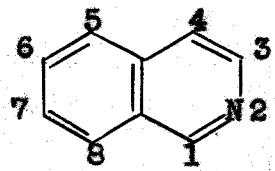
The outstanding feature of the aromatic nitrogen-containing heterocycles is the increased activity of substituents in the positions α- and γ- to the azomethine grouping. Thus the 2- and 4- positions of pyridine and quinoline, the 1- position of isoquinoline, and the 2- position of benzothiazole are much more active than the other positions toward nucleophilic reagents.



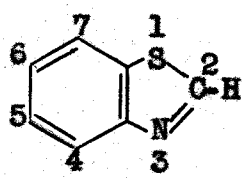
Pyridine (I)



Quinoline (II)



Isoquinoline (III)



Benzothiazole (IV)

In earlier work the chemical properties of quinoline, isoquinoline and benzothiazole were explained by accepting Erlenmeyer's static bond structures (I, II, III, and IV), while the equivalence of the 2- and 6- positions and the 3- and 5- positions of pyridine was explained by Kekule's shifting bonds.[7]

7. Marckwald, Ann., 274, 331 (1893).

Bergstrom[8] used Franklin's ammonia system[9] to explain or at least to predict the course of reactions by analogy to the carbonyl compounds of the aquo system. Table I is a brief review of compounds in the ammonia system and their aquo system analogs.

Table I

Comparison of the Ammonia System with the Aquo System

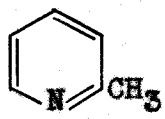
	Aquo compound	Ammonia analog
Basis of system	H_2O	NH_3
Base	KOH	KNH_2
Acid	$R-C(=O)-OH$	$R-C(=NH)-NH_2$ (amidine)
Alcohol	R-OH	$R-NH_2$ (amine)
Ether	R-OR	R_3N (tertiary amine)
Aldehyde	$R-C(=O)-H$	R-CH=NR (ammono aldehyde ether)
Ketone	$R-C(=O)-R$	$R-C(=N-R)-R$ (ammono ketone ether)
Ester	$R-C(=O)-O-R$	$R-C(=N-R)-NR_2$ (ammono ester ether)

From this table it can easily be seen that pyridine, quino-

8. Bergstrom, Chem. Rev., 35, 77 (1944).

9. Franklin, "The Nitrogen System of Compounds," A.C.S. Monograph No. 68, The Reinhold Publishing Co., New York, 1935.

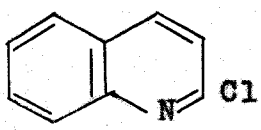
line, and isoquinoline are cyclic ammono aldehyde ethers. Benzothiazole is a cyclic ammono thio ester ether. The alkyl derivatives of pyridine, quinoline, and isoquinoline are cyclic ammono ketone ethers, while the 4-alkyl derivatives of pyridine and quinoline are vinylogs[10] as exemplified by the pyridine derivatives.



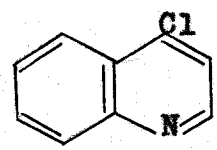
2-Methylpyridine

4-Methylpyridine

2-Chloroquinoline is an example of a cyclic ammono acid chloride ether, and 4-chloroquinoline is its vinylog.

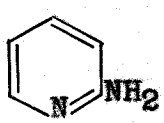


2-Chloroquinoline

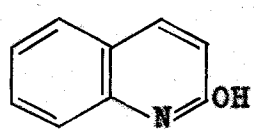


4-Chloroquinoline

The 2-amino derivatives are cyclic ammono acid ethers, and the 2-hydroxy derivatives are cyclic ammono aquo acid ethers.



2-Aminopyridine

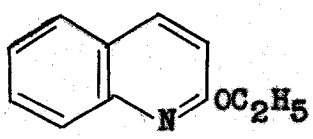


2-Hydroxyquinoline

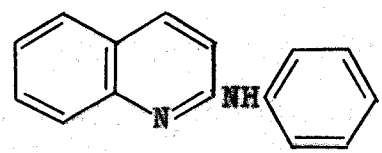
10. Angeli, Atti accad. Lincei, [6] 3, 371 (1926) [C.A., 20, 2990 (1926)]; see also Fuson, Chem. Rev., 16, 1 (1935).

The corresponding 4- derivatives are vinylogs and thus behave similarly.

2-Ethoxy quinoline is a cyclic ammono aquo ester ether and 2-phenylamino-quinoline is a cyclic ammono ester ether.



2-Ethoxyquinoline



2-Phenylaminoquinoline

These compounds should and do exhibit the properties of the corresponding aquo derivatives, with a lower reactivity due to the stabilizing effect of resonance in the various ring systems.

The parent substances have considerable resonance energy. For quinoline Pauling[11] gave a value of 69 kilocalories per mole, while Wrinch[12] gave a value of 91 kilocalories per mole. For pyridine values of 43,[11] 54,[12] and 37,[13] kilocalories per mole are to be found in the literature. This resonance energy is about the same as for the carbocyclic analogs, benzene and naphthalene, thus refuting the idea of bond fixation in the unperturbed molecule.

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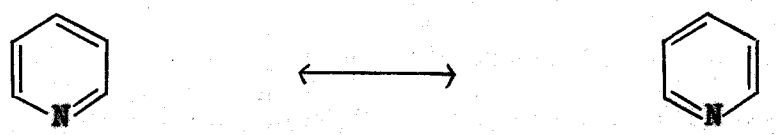
11. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1945, pp. 136-139.

12. Wrinch, Science, 92 79, (1940).

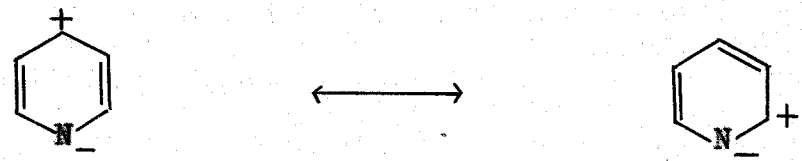
13. Maccoll, J. Chem. Soc., 670 (1946).

Electron diffraction studies[14] show that the structure of pyridine is nearly identical to benzene. In addition to stabilization by the Kekule structures (V and VI), a large electric



(V) (VI)

moment[15] (2.2 Debye units) indicates an appreciable contribution of the electromers (VII and VIII). There should, as a conse-

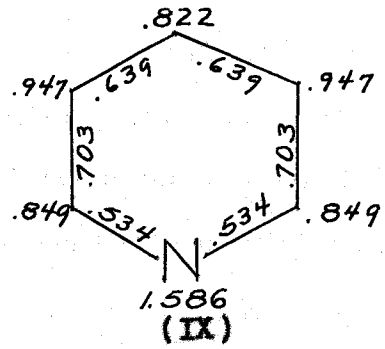


(VII) (VIII)

quence, be centers of low electron density at the 2- and 4-positions.[16] This is also evidenced by the rate and course of substitution in pyridine nucleus by the majority of cationoid reagents, which react only with difficulty and in the β-position, and anionoid reagents, which react easily in the α- and γ- positions.

14. Shomaker and Pauling, J. Am. Chem. Soc. 61, 1769 (1939).
15. Middleton and Partington, Nature, 141, 516 (1938).
16. Leis and Curran, J. Am. Chem. Soc., 67, 79 (1945).

Longuet-Higgins and Coulson[17] calculated by the method of molecular orbitals the bond orders and electron densities in pyridine and found the values indicated in figure IX.



(IX)

The values agree well with the qualitative resonance picture showing low electron densities on the 2, 4, and 6 carbon atoms. By the ozonization of pyridine at -30° Kooyman and Wibaut[18] provide the only chemical evidence of the resonance in pyridine. They found pyridine to be more stable toward ozone than three double bonds would permit and isolated products which indicated that the 2- and 6- positions and the 3- and 5- positions are identical. This shows a resonance between the Kekule forms (V and VI).

The formation of 2- and 2, 6- halogen derivatives by high-temperature halogenation of pyridine suggests the possible existence of excited forms (X and XI) in which the nitrogen has only six electrons in its outer shell.[16]

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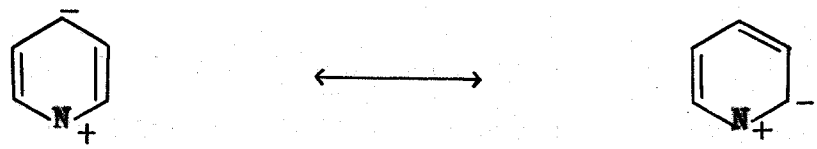
17. Longuet-Higgins and Coulson, Trans. Faraday Soc., 43, 87 (1947).

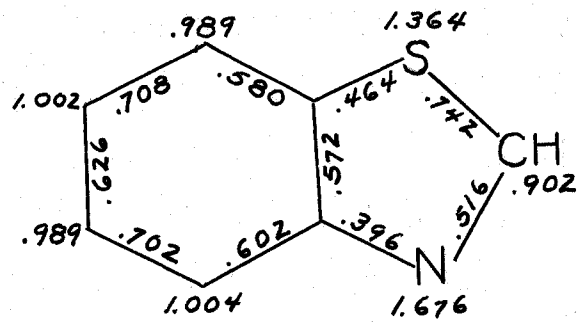
18. Kooyman and Wibaut, Rec. trav. chim., 66, 705 (1947); see also Shive, Ballweber, and Ackermann, J. Am. Chem. Soc., 68, 2144 (1946).



(X) (XI)

However, high-temperature halogenation may occur by a different mechanism, for example, by way of halogen atoms, thus eliminating the necessity of postulating the existence of such forms.

The electron densities and bond orders of benzothiazole are shown below.[19]

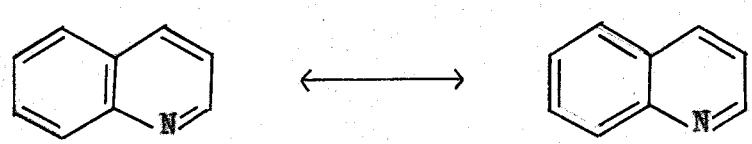


Here again a low electron density in the 2- position indicates enhanced reactivity toward nucleophilic reagents.

Bergmann, Engel, and Meyer[20] measured the dipole moments of quinoline and isoquinoline and found them to be 2.14 and 2.53 Debye units, respectively. These values are larger than

19. Pullman and Metzger, Bull. Soc. Chim., [5] 15, 1021 (1948).
20. Bergmann, Engel, and Meyer, Ber., 54B, 446 (1932).

can be attributed to the azomethine grouping alone. The higher dipole moment may be attributed to the conjugated double bonds for a similar effect is found in the case of dibenzal acetone which has a much higher dipole moment than benzophenone. Le Fèvre and Le Fèvre[21] in an investigation of dipole moments in relation to the structure of quinoline derivatives found that the forms XII and XIII exist predominantly in 6- methylquinoline, 5-nitroquinoline, 6-nitroquinoline and in 8-nitroquinoline. In all the derivatives



(XII) (XIII)

examined except the α-methyl derivatives the bond mobilities of quinoline are so diminished by ring fusion that the skeleton is best formulated by XII or XIII.

The coupling reaction has been widely used to determine the bond structure of various compounds, and Renshaw, Friedman and Gajewski[22] studied this reaction with aminoquinolines. The results of their work are tabulated in Table II.

21. Le Fèvre and Le Fèvre, J. Chem. Soc., 1470 (1935).

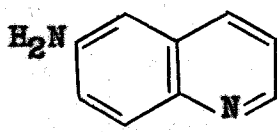
22. Renshaw, Friedman, and Gajewski, J. Am. Chem. Soc., 61, 3322 (1939).

Table II[22]

Coupling Reactions of Aminoquinolines

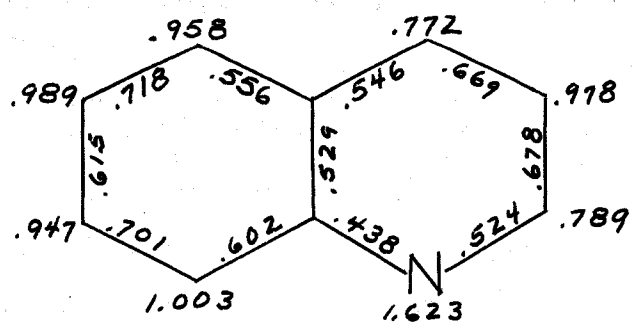
Position of $-NH_2$	Expected coupling	Observed coupling
2	2 (diazoamino)	2 (diazoamino)
3	4	4
4	3	Failed (no reaction)
2,4	3	2 (?)
5	8 or 6	8 and 6
6	5	5
7	8	8
8	5 or 7	5

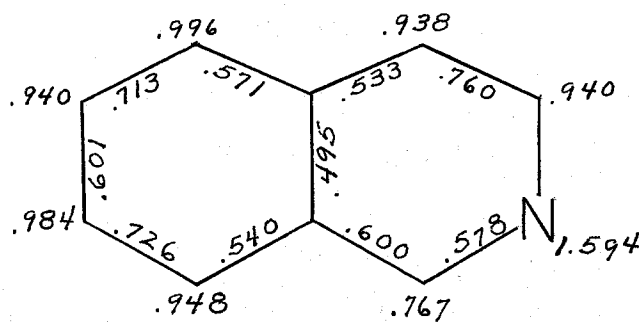
The agreement with the static Erlenmeyer structure (XIV) is good.



(XIV)

The calculated bond orders and electron densities of quinoline and isoquinoline by Longuet-Higgins and Coulson are shown below.





A high electron density at any position facilitates the rate and ease of cationoid substitution at that point while anionoid substitution is facilitated at positions of low electron density. Quinoline has positions of low electron density in the 2- and 4- positions and isoquinoline shows a low value for the 1- position.

Waters[23] in a discussion of the transition state remarked that:

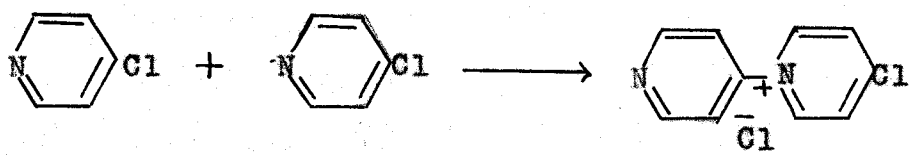
> ...Bond fixation or variations in local electron density in the normal structures of heterocyclic systems are of significance only so far as they give a clue to the ease of the initial polarization of molecules on the approach of an electric charge. This necessarily occurs before the quasi-bonded state (which involves sp^3 hybridization) is formed, and, since an easily polarized state usually indicates an ensuing transition state of relatively low energy level, these calculations when they can be made, which is, unfortunately, but seldom, are of great value.

23. Waters, J. Chem. Soc., 727 (1948).

In addition to the activity of these positions of low electron density in the free bases toward nucleophilic reagents, groups substituted in these positions are also exceptionally reactive. Thus, methyl groups are easily oxidized and are readily condensed with carbonyl groups; halogen, hydroxy, and alkoxy groups are mobile, and carboxyl groups are easily removed.

B. Reactions of Halogens α- and γ- to the Azomethine Linkage.

1. Preparation of Amines. Halogens in the 2- and 4-positions of pyridine are active while those in the 3- position are as inactive as in benzene. 4-Halogenated pyridines are unstable[24] and have to be prepared just before using. On standing they darken and become solid according to the proposed mechanism.[24]



This reaction may, of course, be repeated indefinitely to form molecules of undetermined size. Steric factors may prevent a similar reaction with 2-halogenated pyridines.

2-Chloropyridine reacts with aqueous ammonia and copper catalyst[25] at 250° or with zinc chloride and aqueous am-

24. Wibaut and Broekman, Rec. trav. chim., 58, 885 (1939).

25. Rath, German Patent 510, 432 (March 8, 1927) [C. A., 25, 974 (1931)].

monia[26] at 250° to form 2-aminopyridine while 2-chloroquinoline forms 2-aminoquinoline (in poor yield) and carbostyril by treatment with aqueous ammonia and ammonium carbonate[27] at 200-210°. 4-Aminopyridine[28] is prepared from 4-chloropyridine, ammonia, and zinc chloride at high temperature. Ammonia bubbled into a hot phenol solution of 4-chloroquinaldine forms 4-aminoquinaldine[29] almost quantitatively; under the same conditions 2-chlorolepidine yields the amine in about 10% yield, the rest being converted to 4-phenoxylepidine.

2-Aminopyridine and 2,6-diaminopyridine can be prepared by the ammonolysis at elevated temperatures of 2-bromopyridine and 2,6-dibromopyridine, respectively;[30] 4-aminopyridine[31] can be similarly prepared from 4-bromopyridine. 2-Bromoquinoline reacts with liquid ammonia in the presence of copper powder[32]

26. Fischer, Ber., 32, 1297 (1899).

27. Claus and Schaller, J. prakt. Chem., [2] 56, 204 (1897); see also Fischer, Ber., 35, 3674 (1902).

28. Emmert and Dorn, Ber., 48, 687 (1915).

29. Backeberg and Marais, J. Chem. Soc., 381 (1942).

30. den Hertog and Wibaut, Rec. trav. chim., 51, 381 (1932); ibid., 55, 122 (1936).

31. Wibaut, Overhoff, and Geldof, ibid., 54, 807 (1935).

32. Jansen and Wibaut, ibid., 56, 709 (1937).

at 70° to form 2-aminoquinoline. It is interesting that 3-aminoquinoline[33] can be prepared in the same manner from 3-bromoquinoline though the bromine atom in the 3- position is less reactive.

Hydrazine hydrate refluxed with 2-chloroquinoline forms 2-hydrazinoquinoline,[34] which is also formed if 2-chloroquinoline is heated with hydrazine hydrate in a sealed tube.[35] However, in the latter reaction some sym.-di-2-quinolylhydrazine is also produced. Marckwald and Meyer[35] reported that 4-hydrazinoquinaldine and 2-hydrazinolepidine were formed by heating hydrazine hydrate with 4-chloroquinaldine and 2-chlorolepidine, respectively, for five hours at 150°, but Koenigs and von Loesch[36] reported that 4-hydrazinoquinaldine and a diaminoquinaldine were produced by heating 4-chloroquinaldine with hydrazine hydrate. 2-Hydrazinopyridine[37] may also be prepared by heating 2-chloropyridine with hydrazine hydrate.

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33. Renshaw and Friedman, J. Am. Chem. Soc., 61, 3320 (1939).

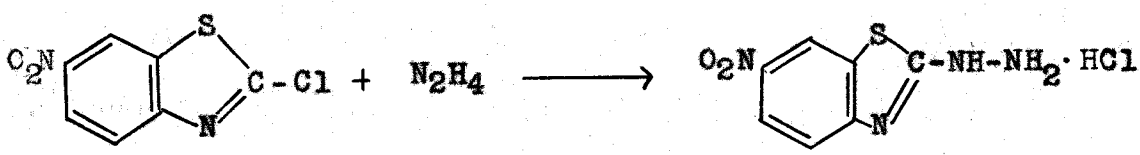
34. Perkin and Robinson, J. Chem. Soc., 103, 1973 (1913).

35. Marckwald and Meyer, Ber., 33, 1885 (1900).

36. Koenigs and von Loesch, J. prakt. Chem., [2] 143, 59 (1935).

37. Fargher and Furness, J. Chem. Soc., 107 688 (1915).

These hydrazines combine with aldehydes and ketones the same as phenylhydrazine. Colonna[38] reported that the halogen in 2-chloro-6-nitrobenzothiazole was more reactive than the extremely mobile halogen in 2-chlorobenzothiazole and that it reacted almost quantitatively with hydrazine.



Phenylhydrazine reacts with 2-chloroquinoline on heating to form 2-phenylhydrazinoquinoline[39] in 60% yield. Backeberg[40] reported that 2-chloroquinoline heated with phenylhydrazine in an inert solvent to 200° yielded 2-phenylhydrazinoquinoline, but when heated to the same temperature in a sealed tube without a solvent, it yielded the isomeric 3-anilino-4-aminoquinoline. 2-Chlorolepidine[41] and 4-chloroquinaldine also react with phenylhydrazine to form the corresponding hydrazino compounds.

2,6-Dibromopyridine reacts with piperidine to yield 2-

38. Colonna, Pubbl. ist. chim. univ. Bologna, No. 6, 3 (1943) C. A., 41, 755 (1947).

39. Ephraim, Ber., 24, 2817 (1891).

40. Backeberg, J. Chem. Soc., 1083 (1938).

41. Ephraim, Ber., 25, 2706 (1892); ibid, 26, 2227 (1893).

bromo-6-piperidinopyridine and 2,6-dipiperidinopyridine.[30] 2-Chloroquinoline reacts with diethylamine and with lithium diethylamide to give 91% and 58% yields, respectively, of 2-diethylaminoquinoline.[42] A series of pyridyl secondary and tertiary amines has been prepared by heating 2-bromopyridine with $R_2N-CH_2-CH_2-NH_2$.[43] Substituted 4-chloroquinolines react with alkyl-substituted anilines by refluxing for two hours in absolute ethanol adjusted to a pH of 3 by concentrated hydrochloric acid.[44] Innumerable alkylamino-derivatives of the 2- and 4- positions of quinoline were produced as a result of wartime antimalarial research. These were commonly prepared by heating the amine and the 2- or 4- halogenated quinoline with phenol as a solvent or without a solvent.

Aniline reacts with 2-chloropyridine with[26] or without[45] zinc chloride to form 2-anilinopyridine. This reaction was extended to other aromatic amines by Fischer.[46] Sulfanilamide and 2-chloropyridine, heated together for fifteen hours at 140°, yield 4-(2'-pyridylamino) benzenesulfonamide[47] (XV).

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42. Gilman, Crounse, Massie, Bankeser, and Spatz, J. Am. Chem. Soc., 67, 2106 (1945).

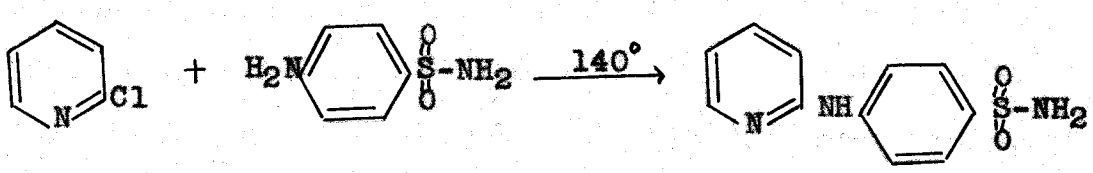
43. Huttrer, Djerassi, Beears, Mayer, and Scholz, ibid., 68, 1999 (1946).

44. Burckhalter, Rawlins, Tendick, Jones, and Holcomb, U.S. Patent 2, 419, 199 (April 22, 1947) /C.A., 41, 4815 (1947)/.

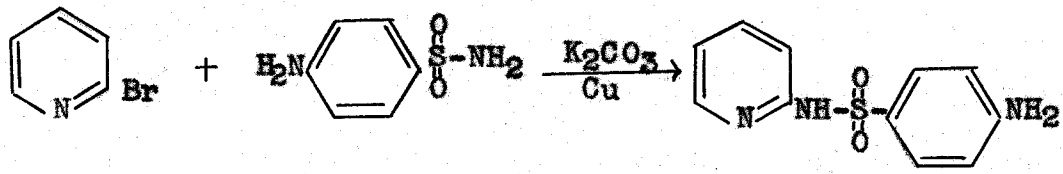
45. Wibaut and Tilman, Rec., trav. chim., 52, 987 (1933).

46. Fischer, Ber., 35, 3674 (1902).

47. Gray, J. Chem. Soc., 1202 (1939).



(XV)



(XVI)

However, 2-bromopyridine and sulfanilamide with anhydrous potassium carbonate and copper powder yield 2-(4'-aminobenzene-sulfonamido)-pyridine[48] (XVI). Analogous products are obtained from 2-chloroquinoline.

Heated to 200° with aniline, 2- or 4-chloroquinoline may be converted to 2- or 4-anilinoquinoline.[49] 4-Chloroquinoline, 2,4-dichloroquinoline, and 2-ethoxy-4-chloroquinoline yield 4-anilinoquinoline, 2,4-dianilinoquinoline and 2-ethoxy-4-anilinoquinoline, respectively, when heated with aniline at 120-130°.[41] Other arylamines give corresponding reactions.[50] 2,4-Dihalogenated quinolines treated with arylamines yield 2-arylamino-4-haloquinolines.[51]

48. Phillips, J. Chem. Soc., 9 (1941).

49. Backeberg, ibid., 1031 (1933).

50. Meyer and Drutel, Compt. rend., 205, 148 (1937).

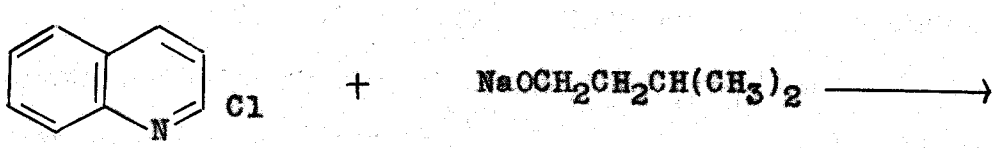
51. Curd, Raison, and Rose, British Patent 585, 362 (February 5, 1947) [C. A., 41, 4173 (1937)].

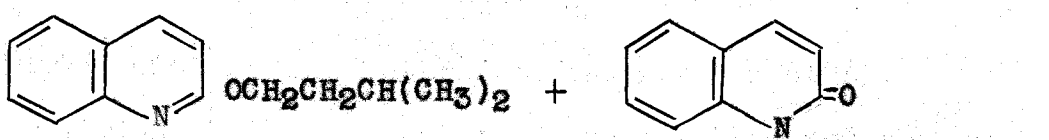
1-Chloro-3-phenylisoquinoline heated with aniline forms 1-anilino-3-phenylisoquinoline.[41] 2-Chloro-6-nitrobenzothiazole reacts quantitatively with aniline, p-aminobiphenyl, p-anisidine, and p-phenetidine.[38]

2. Preparation of Ethers. The chlorine in 2- or 4-chloropyridine is also easily replaced by the methoxyl group by refluxing with sodium methoxide in methyl alcohol.[52] Renshaw and Conn[53] reported that sodium alkoxides and sodium aryloxides reacted with 2-bromopyridine to form alkyl and aryl 2-pyridyl ethers.

By heating 2-chloroquinoline with sodium phenoxide to the boiling point of phenol (180°) 2-phenoxyquinoline is formed.[54] Sodium methoxide and 2-chloroquinoline in boiling methanol yield 2-methoxyquinoline;[55] 2-ethoxyquinoline is obtained in the same manner by employing sodium ethoxide and ethanol. However, sodium isoamylate and 2-chloroquinoline form 2-isoamyloxyquinoline (XVII) (80%) and N-isoamyloxy-2-quinolone (XVIII) (20%).

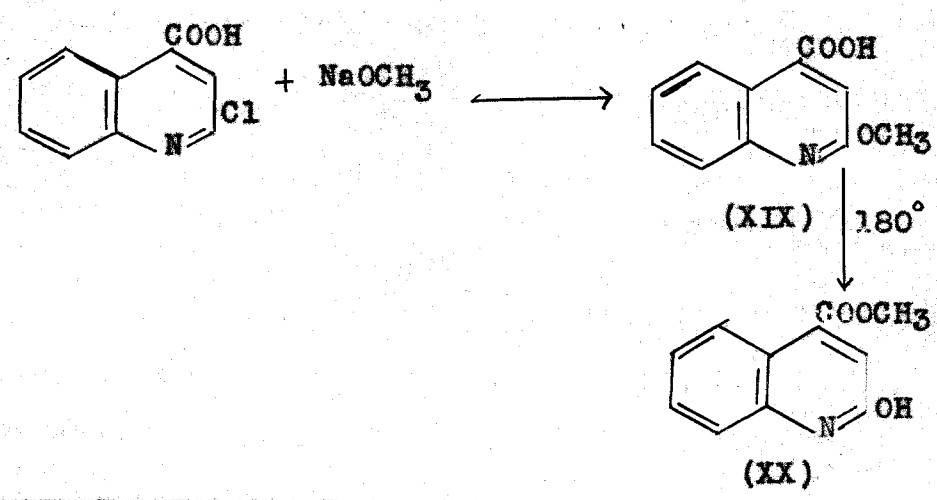
52. Haitinger and Lieben, Monatsh., 6, 279 (1885).
53. Renshaw and Conn, J. Am. Chem. Soc., 59, 297 (1937).
54. Friedländer and Ostermaier, Ber., 15, 332 (1882).
55. Bogert and May, J. Am. Chem. Soc., 31, 507 (1909).





(XVII) (XVIII)

2-Chloro-4-quinoline carboxylic acid[56] reacts with sodium methoxide in one-half hour to form 2-methoxyquinoline-4-carboxylic acid (XIX). It is interesting to note that this compound on heating to 180° rearranges to methyl 2-hydroxyquinoline-4-carboxylate (XX). The ethyl ester may be formed in the same way.

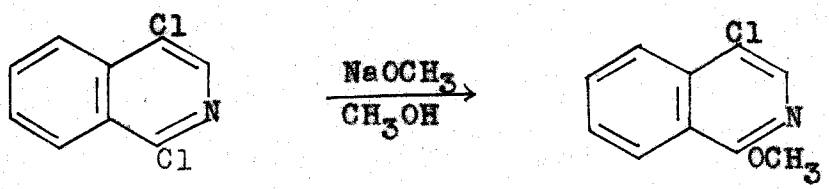


(XX)

56. Mulert, Ber., 39, 1901 (1906).

Sodium alkoxides also react with 4-chloroquinoline to form 4-alkoxyquinolines.[57] These reactions have been extended to other derivatives of quinoline. For example, 2-phenyl-4-chloroquinoline heated with potassium phenoxide to the boiling point of phenol for ten hours yields 2-phenyl-4-phenoxyquinoline.[58] 2-Chloro-4-methylquinoline dissolved in hot phenol is converted to 2-phenoxy-4-methylquinoline.[29]

1,4-Dichloroisoquinoline refluxed for three-fourths hour with sodium methoxide in methyl alcohol forms 1-methoxy-4-chloroisoquinoline.[59] (XXI).



(XXI)

1-Alkoxy-3-propyl (or isopropyl) isoquinolines can be prepared in the same manner.[60] The halogen in 2-chlorobenzothiazole is more reactive than that in 2-chloroquinoline and is easily converted to the alkoxy group; 2-chloro-6-nitrobenzothiazole is even more reactive.[61]

57. Wenzel, Monatsh., 15, 453 (1894).

58. John and Wunche, J. prakt. Chem., [2] 119, 43 (1928); see also Lockhardt and Turner, J. Chem. Soc., 424 (1937).

59. Gabriel and Colman, Ber., 33, 980 (1900).

60. Lehmkuhl, Ber., 30, 889 (1897).

61. Colonna, Pubbl. ist. chim. univ. Bologna, No. 5, 3 (1943) [C. A., 41, 754 (1947)].

3. Preparation of Hydroxy Compounds. 2-Bromo-6-hydroxypyridine[62] is obtained from 2,6-dibromopyridine by heating for three hours with 80% phosphoric acid or by heating to 90° in alkaline water-alcohol solution. In the former reaction the rate is increased by the positive charge on the nitrogen of the dibromopyridine phosphate. This charge may be distributed by resonance to the 2- and 4- carbon atoms, thereby increasing the mobility of halogens in those positions. Either acid or alkali causes replacement of the halogen in 2-chloropyridine.

The chlorine atom in 2-chloroquinoline is removed by heating with water in a sealed tube to 120°.[54] The 4-chlorine in 4-chloroquinaldine is easily removed by boiling with potassium hydroxide.[63] 2-Bromoquinoline can be hydrolyzed by prolonged boiling with water,[64] but is more easily hydrolyzed by heating with dilute acids. These reactions are in sharp contrast to the 3-halogenated quinolines which require fusion with potassium hydroxide to remove the halogen.[65] The exceptionally mobile halogens in 2-chlorobenzothiazole and 2-chloro-6-nitrobenzothiazole are removed by dilute potassium hydroxide.[61]

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62. Wibaut, Haayman, and van Dijk, Rec. trav. chim., 59, 202 (1940).

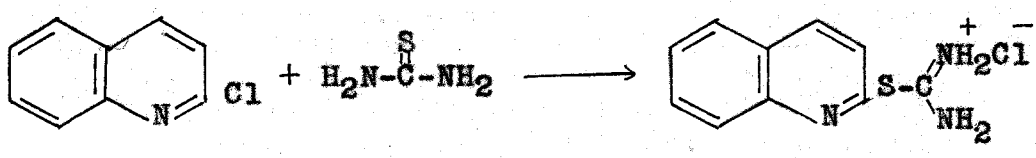
63. Knorr and Antrick, Ber., 17, 2870 (1884).

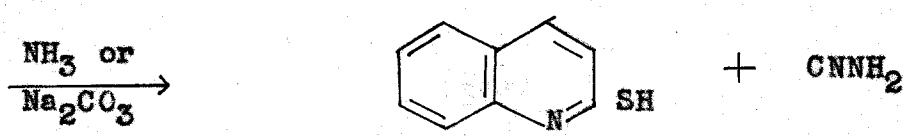
64. Claus and Pollitz, J. prakt. Chem., [2] 41, 41 (1890).

65. Friedländer and Weinberg, Ber., 15, 2679 (1882).

4. Preparation of Mercaptans. 2-Chloropyridine,[66] 2-iodopyridine,[67] and 2-bromopyridine[68] form pyridine-2-thiol by heating in an alcoholic potassium hydrosulfide solution. In like manner 4-chloropyridine forms pyridine-4-thiol.[69] 2-Chloroquinoline and 2-chloro-6-methylquinoline react with potassium hydrosulfide at 150° under pressure to form quinoline-2-thiol and 6-methylquinoline-2-thiol, respectively.[26] 2-Phenylquinoline-4-thiol is formed from 2-phenyl-4-chloroquinoline and alcoholic potassium hydrosulfide.[70]

The preparation of thiols from active halogen compounds is usually better carried out by using thiourea. Thus, quinoline-2-thiol (XXII) is prepared from 2-chloroquinoline and thiourea.[71]





(XXII)

66. Marckwald, Klemm, and Trabert, Ber., 33, 1556 (1900).
67. van Gastel and Wibaut, Rec. trav. chim., 53, 1031 (1934).
68. Thirtle, J. Am. Chem. Soc., 68, 342 (1946).
69. Koenigs and Kinne, Ber., 548, 1357 (1921).
70. John, J. prakt. Chem., /2/ 119, 49 (1928).
71. Rosenhauer, Hoffmann, and Heuser, Ber., 62B, 2730 (1929).

Under the same conditions 2-methyl-4-chloroquinoline forms 2,2'-dimethyl-4,4'-diquinolyl disulfide. Substituted quinoline-2- and -4-thiols[72] have also been prepared by this method; the quinoline-4-thiols are more deeply colored and more reactive than the quinoline-2-thiols. The reaction may be used to prepare benzothiazole-2-thiol by treating 2-chlorobenzothiazole with thiourea[73] in alcohol and decomposing the resulting thiouronium salt. Some 2,2'-dibenzothiazolyl sulfide is also obtained. Recently 4,7-dichloroquinoline was subjected to the same conditions and formed 7-chloroquinoline-4-thiol.[74]

5. Reduction. 2-Chloropyridine can be hydrogenated to form pyridine which can be further hydrogenated to piperidine.[75] 2,6-Diamino-4-bromopyridine is reduced to 2,6-diaminopyridine in alkaline solution by catalytic hydrogenation in the presence of nickel.[76] 1-Chloroisoquinoline[59] and 1,3-dichloroisoquinoline,[77] respectively, by red phosphorous and iodine at 170-180°.

72. Renfrew, J. Am. Chem. Soc., 68, 1433 (1946).

73. Watt, J. Org. Chem., 4, 436 (1939).

74. Surrey, J. Am. Chem. Soc., 70, 2190 (1948).

75. Grave, ibid., 46, 1460 (1924).

76. Wibaut, Bickel, and Brandon, Rec. trav. chim., 58, 1124 (1939).

77. Gabriel, Ber., 19, 1653 (1886).

The 3-halogen has to be heated to 200° with the same reagents before it can be removed.

Cuprous cyanide heated with 2-chloropyridine forms 2-cyanopyridine.[78] Aryl quinolyl sulfones are prepared by heating 2-chloroquinoline and sodium aryl sulfinates to 100° for several days.[79]

6. Preparation of Organometallic Compounds. By using the entrainment method of Grignard it is possible to prepare 2-pyridylmagnesium bromide as evidenced by 40-55% yields of phenyl-2-pyridylmethanol after treatment of the Grignard with benzaldehyde.[80] Pyridine-2,6-dimagnesium bromide can be prepared from 2,6-dibromopyridine, and the reaction has been extended to 2-chloro, 3-bromo- and 4-chloropyridine.[2]

Banner[81] and Harris[82] refluxed 2-bromopyridine, 2-bromo- and 3-bromoquinoline with lithium in ether for twenty hours and obtained only tars. However, 3-quinolyllithium can be prepared in 52% yield by halogen-metal interconversion from 3-

78. Craig. J. Am. Chem. Soc., 56, 231 (1934).

79. Troger and Meinecke, J. prakt. Chem., /2/ 106, 203 (1923).

80. Overhoff and Proost, Rec. trav. chim., 57, 179 (1938).

81. Banner, M. S. Thesis, Iowa State College, Ames, Iowa (1939).

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

bromoquinoline and n-butyllithium.[3, 83] Under the same conditions 3-bromopyridine gives a 70% yield of 3-pyridyllithium.

2-Chloroquinoline and n-butyllithium at -35° yield a small amount of a 2-chloro-x-quinoline carboxylic acid subsequent to carbonation, but no 2-quinolyllithium is formed. Methyllithium and 2-chloroquinoline do not react at -35°, and 81.5% of the 2-chloroquinoline can be recovered. 4-Chloro-6-methoxyquinoline adds p-chlorophenyllithium to form 2-(p-chlorophenyl)-4-chloro-6-methoxyquinoline.[84] The halogen is not affected, nor does it deactivate the azomethine linkage.

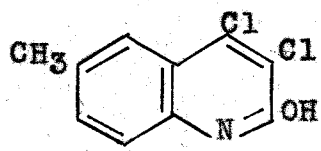
7. Relative Reactivities of Halogens. Though there is convincing evidence that the 2- and 4-halogenated pyridines are more reactive than the other isomers, there are not many studies by the same worker comparing the reactivities of the 2- and 4-halogenated pyridines. However, a study of the work of different authors might indicate a greater reactivity of the 2-halogen. 2,4,6-Tribromopyridine reacts with ammonia to form 2,6-diamino-4-bromopyridine in poor yield,[76] indicating a greater reactivity in the 2- position. The calculated electron densities of Longuet-Higgins[17] showed a slightly lower value in the 4- position than in the 2- or 6- positions, suggesting a greater activity toward nucleophilic reagents in the

83. Gilman and Spatz, J. Am. Chem. Soc., 62, 446 (1940); see also Spatz, Doctoral Dissertation, Iowa State College, Ames, Iowa (1941).

84. Gilman and Spatz, J. Am. Chem. Soc., 66, 621 (1944).

4- position. However, in a more recent work den Hertog[85] suggested that the 4- position was more active. 2,4-Dibromopyridine reacts with ammonia to give a preponderance of 2-bromo-4-aminopyridine though some 2-amino-4-bromopyridine is also formed. 2,3,4-Tribromopyridine and ammonia yield primarily 4-amino-2,3-dibromopyridine. The reactivity of the 2- or 4-halogen is considerably greater if there are other halogen atoms on the nucleus.

The electron densities are relatively the same for quinoline as for pyridine, i.e., lower on the 4-carbon than on the 2-carbon, again showing a slightly greater activity in the 4-position. Chemically 2,4-dichloroquinoline reacts with potassium hydroxide in ethanol to yield 2-chloro-4-ethoxyquinoline (31%), 4-chloro-2-ethoxyquinoline (32%), and 4-chloro-2-hydroxyquinoline (5.5%), thus inferring that the 2-chlorine atom is more reactive than the 4-chlorine atom.[86] 2,3,4-Trichloro-6-methylquinoline[87] is quantitatively converted to 3,4-dichloro-6-methylcarbostyril (XXIII) by dilute hydrochloric acid at 180°. 2-Chloroquinoline is converted to



(XXIII)

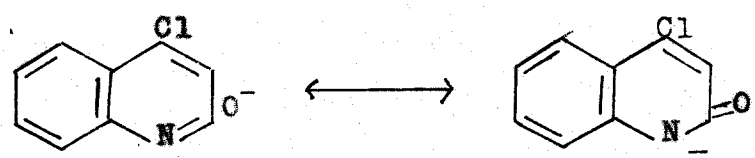
85. den Hertog, Rec. trav. chim., 65, 129 (1946).

86. Buchmann and Hamilton, J. Am. Chem. Soc., 64, 1357 (1942).

87. Rugheimer and Hoffmann, Ber., 18, 2979 (1885).

carbostyril[54] by water at 120°.

A hydroxyl grouping in the same heterocyclic ring of quinoline decreases the activity of any halogen atoms in the ring. Aniline and 4-chloroquinoline heated to 120° yield 2-anilinoquinoline, but 4-chloro-2-hydroxyquinoline and aniline do not react.[41] 2,4-Dichloroquinoline, however, yields 2,4-dianilinoquinoline. The halogen in 4-chloro-2-hydroxyquinoline is inert, but in 2-chloro-4-ethoxyquinoline and 2,4-dichloroquinoline the halogens are active. The halogen in 4-chloro-2-ethoxyquinoline is almost inert. 4-Chloro-2-hydroxyquinoline does not react with boiling alcoholic solutions of sodium alkoxides and with NaOH only if fused.[88] Thus the hydroxyl group in the 2- position deactivates the 4-halogen, but ether groups do not have much effect. Bergstrom[8] explained the deactivating effect of the hydroxyl grouping by the resonance of the unperturbed form (XXIV) which may be an intermediate in the reaction. This resonance so stabilizes the unperturbed form that further reaction is greatly hindered.



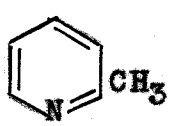
(XXIV)

88. Friedländer and Muller, Ber., 20, 2009 (1887).

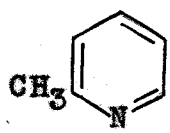
Though it does have some effect, the corresponding resonance involving an alkoxy or phenylamino group will not be as important as Bergstrom showed.[8]

C. Reactions of Methyl Groups α- and γ- to the Azomethine Linkage.

1. Tautomerism. The α-methyl groups in these heterocycles exhibit the increased activity of methyl groups attached to a carbonyl group (=C=O) or a nitro group ($-\overset{\nearrow O}{N}=O$). Because of this reactivity, it was thought for a time that two isomeric α-methylpyridines (XXV) and (XXVI) should exist, of which one (XXV) should be reactive and the other ((XXVI) inactive. However, two forms could not be isolated, and, indeed,



(XXV)

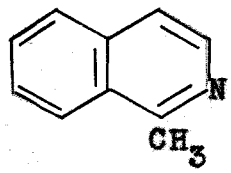


(XXVI)

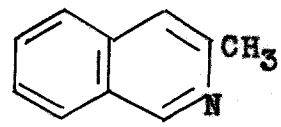
Shuster[89] gave graphic evidence of resonance in these structures

89. Shuster, Ber., 25, 2398 (1892).

when he prepared 2,6-distyrylpyridine by condensing 2,6-dimethylpyridine with benzaldehyde in the presence of zinc chloride. It was thought that the mobility of the bond could be reduced[90] by fusing with a benzene ring whereby the isomeric α-picolines (XXV) and (XXVI) should give 1-methylisoquinoline (XXVII) and 3-methylisoquinoline (XXVIII), respectively, or by replacing

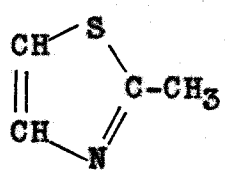


(XXVII)

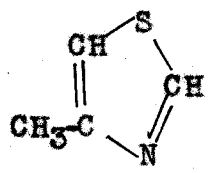


(XXVIII)

two of the carbons by a sulfur atom. As will be shown later, 1-methyl isoquinoline is much more reactive than 3-methyl isoquinoline. Replacement of two adjacent carbon atoms by sulfur gives 2-methyl- (XXIX) and 4-methylthiazole (XXX), of which



(XXIX)

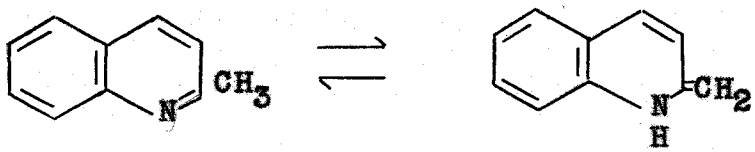


(XXX)

the former is much more reactive.[90] This was taken as evidence for static bonds.

90. Hantzsch, Ann., 250, 257 (1889).

The studies of Lapworth[91] and Dimroth[92] on the relative reactivity of keto and enol desmotropes, which related the activity of the methyl groups to the formation of the enol, were applied to these compounds. This suggested the possibility that reactivity was a result of tautomerism as illustrated by quinaldine.



Differences in reactivity of 1- and 3-methylisoquinoline were explained by the concept that 1-methylisoquinoline was capable of tautomerism, and that 3-methylquinoline was not. The same reasoning was applied to the methylthiazoles.

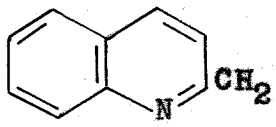
Chichibabin[93] suggested that the enol forms of 2- and 4-methylpyridine were the reactive forms in reactions with benzoylchloride, benzaldehyde, and benzyl chloride. These enolic forms have never been isolated, and in the light of modern theory, it is not necessary to postulate tautomerism, at least in base-catalyzed reactions. The base picks a proton from the methyl group, leaving the negative carbanion (XXXI)

91. Lapworth, J. Chem. Soc., 85, 30 (1904).

92. Dimroth, Ber., 40, 2404 (1907).

93. Chichibabin, Bull. soc. chim., [5] 3, 1607 (1936); Ber., 60B, 1607 (1927).

which is then free to react. This electromeric (tautomeric) effect is brought into play only on the approach of a nucleo-



(XXXI)

philic reagent.[94]

Hopkins and Hunter[95] found 2-methylbenzothiazole to be completely unassociated and therefore assumed that the hydrogens of the methyl group were incapable of tautomeric transfer because hydrogens which are capable of tautomerism will take part in -S-H-N-bonds. On the other hand, benzothiazole-2-thiol is highly associated.

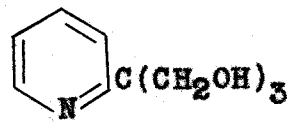
2. Aldol Condensation and Claisen Reaction. Methyl groups in the 2- and 4- positions of pyridine and quinoline, the 2-position of benzothiazole, and the 1- position of isoquinoline undergo the aldol condensation, but the reactions are not as rapid as with open-chained ketones. A high temperature and a catalyst are usually required. The aldol is formed in some cases, but in many cases the unsaturated compound results.

2-Picoline and 4-picoline react with formalin at 130-150° for fifteen hours to yield a mixture of mono, di, and

94. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, 1943, p. 136.

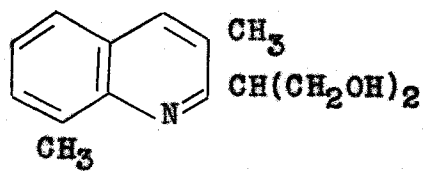
95. Hopkins and Hunter, J. Chem. Soc., 638 (1942).

trimethylolpicoline[96, 97] (XXXII).



(XXXII)

4-Methylquinoline forms only the dimethylol derivative; however, 2-methylquinoline forms α-trimethylolquinoline.[98] 2,3,8-Trimethylquinoline and formaldehyde form 3,8-dimethyl-2-dimethylolmethylquinoline (XXXIII).[99]



(XXXIII)

Acetaldehyde[96, 100] and propionaldehyde[96] react with 2-picoline to form the corresponding carbinols in rather poor yield. However, chloral condenses to form trichloromethyl-2-

96. Loenigs and Happe, Ber., 35, 1343 (1902).

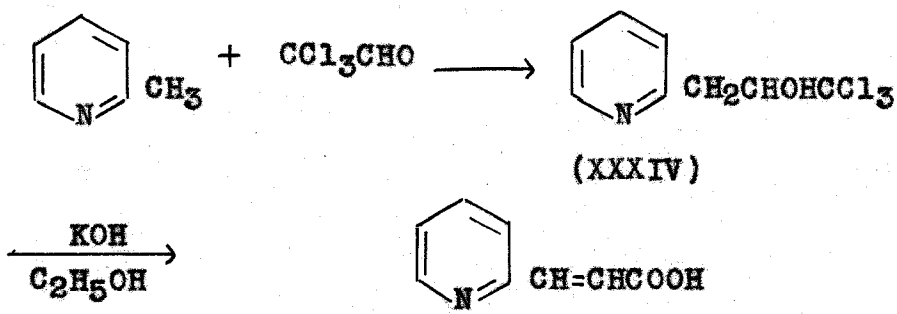
97. Ladenburg, Ann., 301, 117 (1898); Ladenburg, Ber., 22, 2583 (1889).

98. Koenigs, ibid., 34, 4322 (1901).

99. Poth, Schulze, King, Thompson, Slagle, Floyd, and Bailey, J. Am. Chem. Soc., 52, 1239 (1930).

100. McElvain and Johnson, ibid., 63, 2213 (1941).

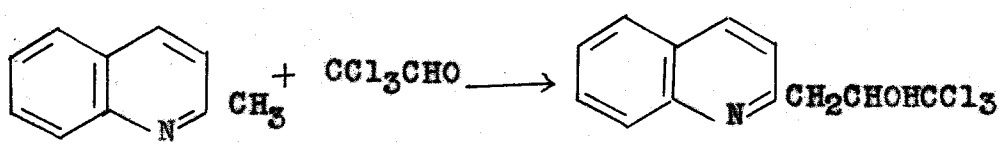
picolylmethanol (XXXIV) in 70% yield.[100] This is easily converted to β-(2-pyridyl)acrylic acid (XXXV) by refluxing with potassium hydroxide in ethanol.[101]



(XXXIV)

(XXXV)

Quinaldine can be converted to γ-trichloro-β-hydroxy-α-(2-quinolyl)propane (XXXVI) under the same conditions. This compound can be transformed by mild hydrolysis to β-(2-quinolyl)-lactic acid[102] (XXXVII) or by stronger hydrolysis to β-(2-quinolyl)acrylic acid (XXXVIII).[103]

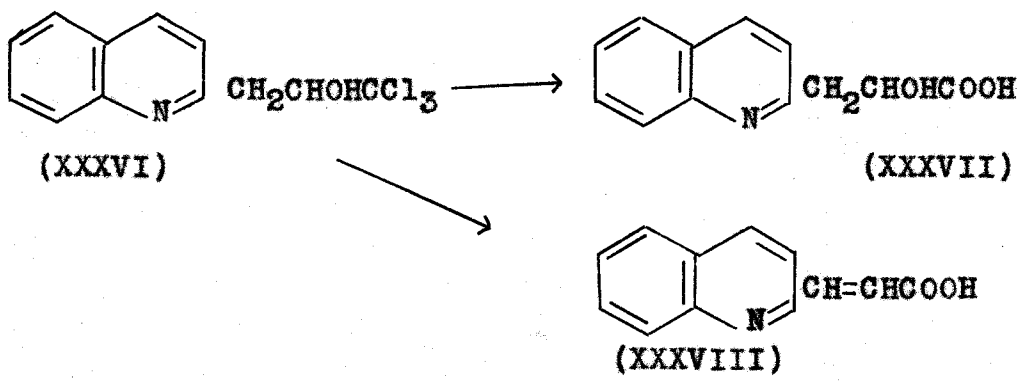


(XXXVI)

101. Tullock and McElvain, J. Am. Chem. Soc., 63, 2213 (1941).

102. Einhorn, Ber., 19, 904 (1886).

103. von Miller and Spady, ibid., 19, 130 (1886).



(XXXVI) (XXXVII) (XXXVIII)

Lepidine and chloral react to form the aldol condensation product[103] which can be hydrolyzed by alcoholic potassium hydroxide to β-(4-quinolyl)acrylic acid.[104] 2,4-Dimethylquinoline forms 4-methyl-2-(γ,γ,γ-trichloro-β-hydroxypropyl)quinoline or 4-methyl-2-(γ,γ,γ-trichloropropenyl)quinoline depending on the conditions, thus showing that the 4-methyl group is less reactive than the 2-methyl group.[105]

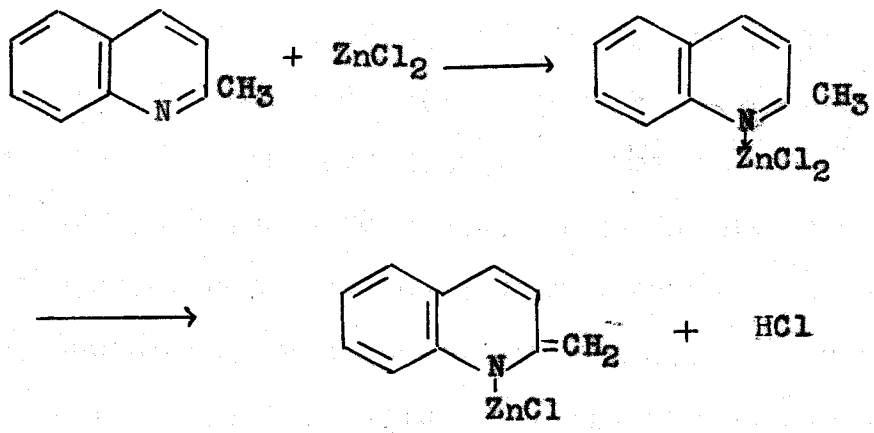
The condensation of aromatic aldehydes with methylpyridines has been carried out by refluxing in acetic anhydride, with or without zinc chloride. The preparation of pure aldol condensation products of the pyridine series can be accomplished by heating aromatic aldehydes and 2-methylpyridine in water at 140-160° for ten hours.[106] In the quinoline series potassium bisulfate, zinc chloride, sodium hydroxide, sodium alkoxides, acetic anhydride, and concentrated hydrochloric acid have been

104. Clemo and Hoggarth, J. Chem. Soc., 1241 (1939).

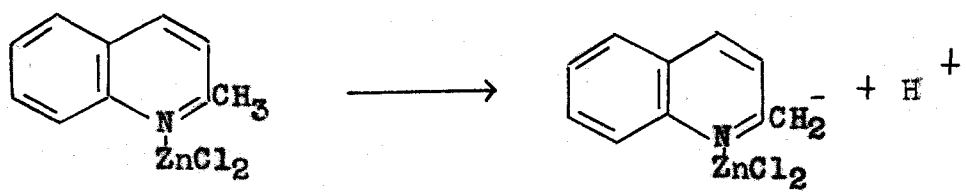
105. Spallino and Cucchiaroni, Gazz. chim. ital., 421, 517 (1912).

106. Bach, Ber., 34, 2223 (1901).

used as condensing agents in the preparation of styryl derivatives. These condensing agents plus a higher temperature and a longer time are necessary for conversion of the initially formed carbinol to be converted to the styryl derivative. However, John[107] reported that zinc chloride may be harmful to the condensation. Sidgwick,[108] on the other hand, suggested that zinc chloride could attach itself to the nitrogen by a coordinate link as in the zinc ammine compounds.



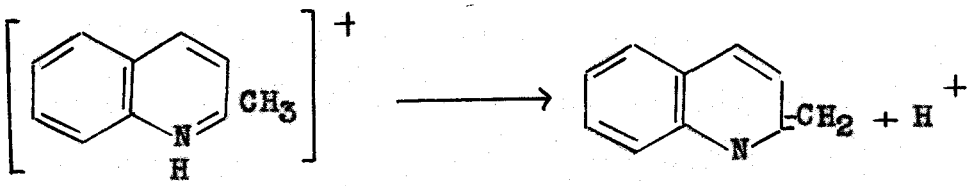
Probably the latter step would be better formulated as the following.



107. John, Ber., 59B, 722 (1926).

108. Sidgwick, Taylor, and Baker, "The Organic Chemistry of Nitrogen," The Clarendon Press, Oxford, 1937, p. 561.

Potassium bisulfate and concentrated hydrochloric acid may react similiarly to form the positive ion which then dissociates.



(XXXIX)

This indicates that the tautomeric form (XXXIX) is an intermediate in the acid-catalyzed condensation.

Benzaldehyde and other aromatic aldehydes undergo the Claisen reaction with 2- and 4-methylpyridine in acetic anhydride to give better yields than with zinc chloride. Without any condensing agent a mixture of aldol condensation product and the dehydrated product is formed,[109] though Roth[110] could not dehydrate β-(2-pyridyl)-α-(o-nitrophenyl)ethanol with zinc chloride. 2,4-Dimethylpyridine refluxed with benzaldehyde and acetic anhydride yields 2-styryl-4-methylpyridine and 2,4-distyrylpyridine in a two to one ratio,[111] while with zinc chloride as condensing agent only 2-styryl-4-methylpyridine is formed.[112] A similar reaction occurs with p-

109. Shaw and Wagstaff, J. Chem. Soc., 77 (1933).

110. Roth, Ber., 33, 3476 (1900).

111. Clemo and Gourlay, J. Chem. Soc., 478 (1938).

112. Bachér, Ber. 21, 3071 (1888).

tolualdehyde, and here again we have an indication that the 2-methyl group is more reactive than the 4-methyl group.

Many reactions of aldehydes with 2- and 4-methylquinolines are reported. Because of the higher boiling point of the quinoline compounds a catalyst is not always necessary. By condensing quinaldine with p-dimethylaminobenzaldehyde in concentrated hydrochloric acid 2-(p-dimethylaminostyryl)quinoline[113] is formed. If quinoline-2- and 4-aldehydes are refluxed in ethanol for six hours, aldols are formed with all but quinoline-4-aldehyde and 4-methylquinoline,[114] thereby providing further evidence for lower reactivity in the 4- position. m-Nitrobenzaldehyde[115] and quinaldine condense to form only the styryl derivative while o- and p-nitrobenzaldehyde heated for five hours with quinaldine at 130° yield carbinols.[116] Later work has shown that the m-nitrophenylquinaldylmethanol can be formed at 120° in three hours if mineral acid is completely excluded; refluxing in acetic anhydride yields the styryl derivative.[117] 2,4-Dinitrobenzaldehyde and quinaldine,

113. Noelting and Witte, Ber., 39, 2749 (1906).

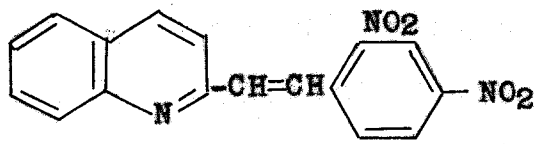
114. Kaplan and Lindwall, J. Am. Chem. Soc., 65, 927 (1943).

115. Taylor and Woodhouse, J. Chem. Soc., 2971 (1926).

116. Fischer and Merkel, J. prakt. Chem., /2/ 100, 96 (1920).

117. Walton, Tipson, and Cretcher, J. Am. Chem. Soc., 67, 1501 (1945).

refluxed in acetic anhydride, yield 2-(2',4'-dinitrostyryl)-quinoline (XXXX).[118]



(XXXX)

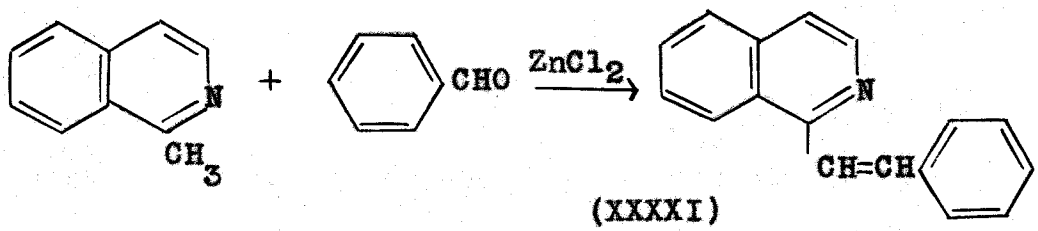
2,3,8-Trimethylquinoline and benzaldehyde react to form 2-styryl-3,8-dimethylquinoline, which can be oxidized by potassium permanganate to 3,7-dimethylquinoline-2-carboxylic acid.[99] 2,4-Dimethylquinoline reacts with benzaldehyde to form 2-styryl-4-methylquinoline.[119] If five grams of quinaldine and five grams of lepidine plus an equal weight of benzaldehyde are heated to the boiling point for three hours, about eight grams of 2-styrylquinoline and one gram of 4-styrylquinoline are formed. The methyl group in the 2- position is therefore more reactive than the one in the 4- position.[120]

Tipson has recently reviewed all previous work on the preparation of styryl derivatives. After trying all procedures, he settled on the method of heating the aldehyde and the methylquinoline to 275° for two hours and, after removing the product,

118. Bennett and Willis, J. Chem. Soc., 1960 (1928).
119. Fischer and Scheibe, J. prakt. Chem., [2] 100, 91 (1920).
120. Eibner, Ber., 37, 3605 (1904).

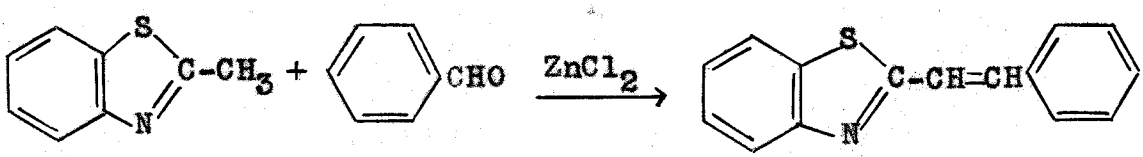
reheating the unreacted material for two hours longer.[121] He found acetic anhydride unsatisfactory as a condensing agent and zinc chloride and hydrochloric acid satisfactory but difficult to remove.

1-Methylisoquinoline reacts with benzaldehyde at 100° in the presence of zinc chloride to yield 1-styrylisoquinoline (XXXXI).[90]



(XXXXI)

The 2-methylbenzothiazoles are also easily condensed; for example, 2-methylbenzothiazole and benzaldehyde react in the presence of zinc chloride to form 2-styrylbenzothiazole (XXXXII) which has been catalytically reduced to 2-phenylethylbenzothiazole.[122]

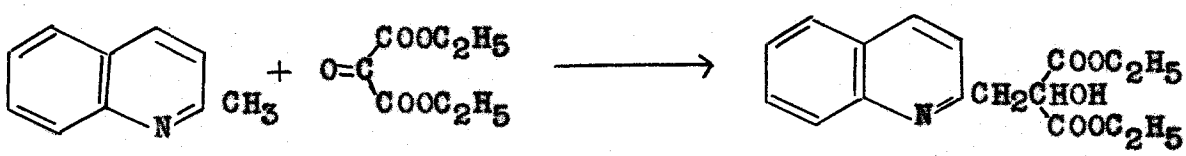


(XXXXII)

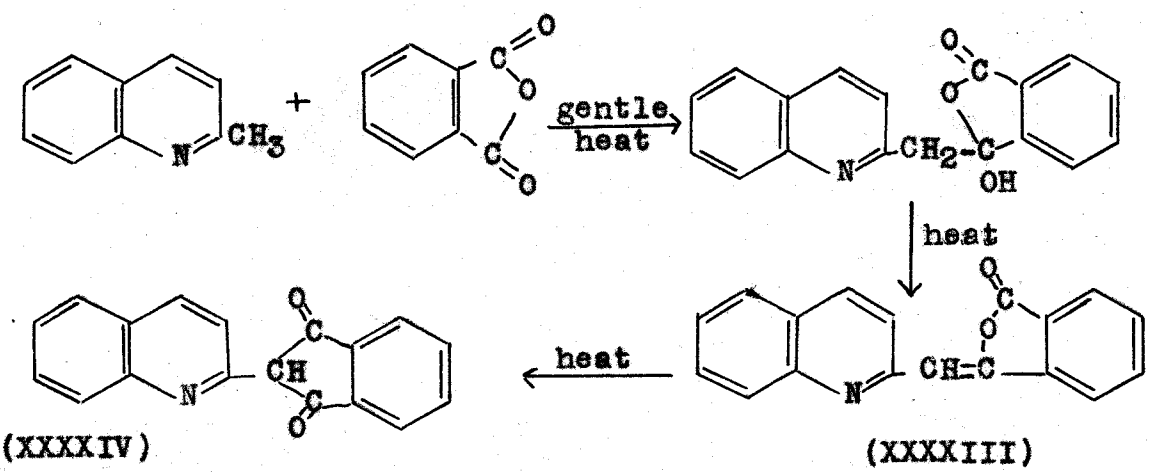
121. Tipson, J. Am. Chem. Soc., 67, 507 (1945).

122. Ochiai and Nizizawa, J. Pharm. Soc. Japan, 60, 132 (1940).

3. Miscellaneous Condensations. 2-Picoline and quinaldine have been condensed with oxomalonic ester, diphenyltriketone, ethylbenzoyloxalate, benzil, and alloxan in yields from 4% to 74%.[100] As an example, the reaction between quinaldine and oxomalonic ester is shown below.



Quinaldine reacts with phthalic anhydride[120] on gentle heating to form quinisophthalone (XXXXIII) which on further heating is converted to quinophthalone (XXXXIV) as follows.[123]



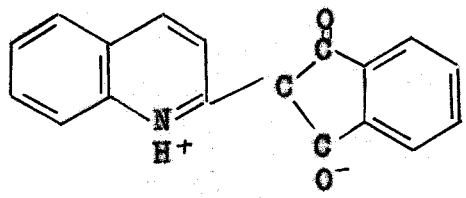
(XXXXIV) (XXXXIII)

Kuhn and Bär[124] prefer (XXXXV), or the tautomeric form

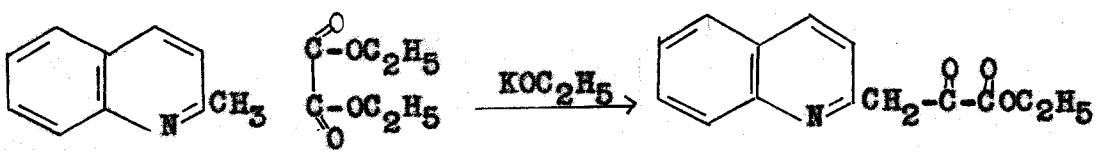
123. Manske, Chem. Rev., 30, 113 (1942).

124. Kuhn and Bär, Ann., 516, 155 (1935).

of (XXXXIV), as the structure of quinophthalone. 4-Methylquinoline, incidentally, does not give this reaction.

(XXXXV) 

Diethyloxalate[125] and quinaldine react in the presence of potassium ethoxide to form ethyl β-(2-quinolyl)pyruvate (XXXXVI).



(XXXXVI)

Lepidine forms the corresponding ethyl β-(4-quinolyl)pyruvate.

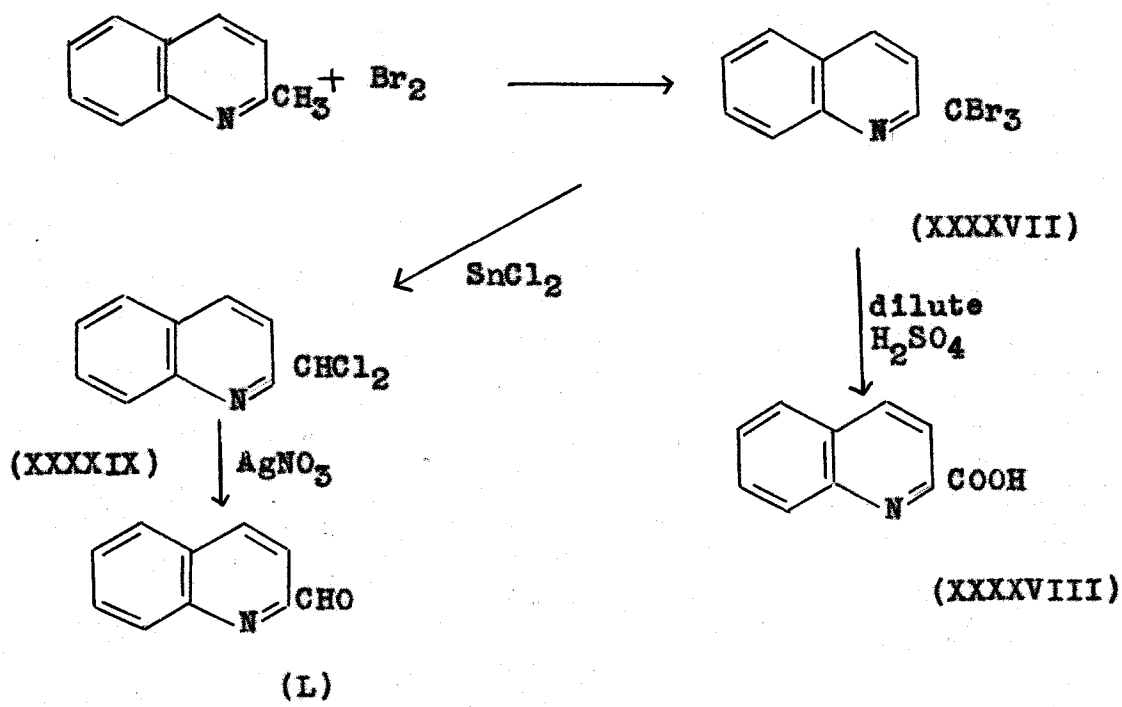
4. Bromination. Quinaldine can be brominated[126] to form 2-tribromomethylquinoline (XXXXVII) which is readily hydrolyzed by dilute sulfuric acid to quinaldinic acid (XXXXVIII).

2-Tribromomethylquinoline can be reduced[127] by stannous chloride to 2-dichloromethylquinoline (XXXXIX), which hydro-

125. Wislicenus and Kleisinger, Ber., 42, 1140 (1909).

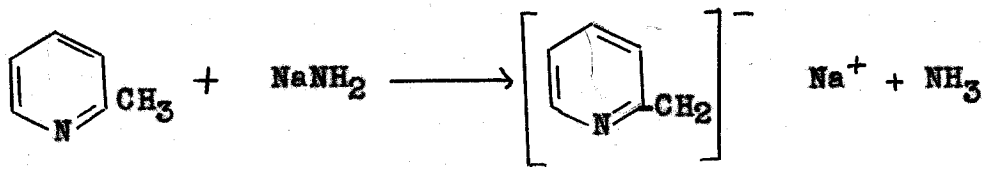
126. Hammick, J. Chem. Soc., 123, 2882 (1923).

127. Hammick, ibid., 1302 (1926).



lyzes easily to quinoline-2-aldehyde (L). By further reduction with stannous chloride 2-monochloromethylquinoline can be formed and hydrolyzed to 2-quinolinemethanol.

5. Metalation. Pyridines with a methyl group in the 2- or the 4- position react with sodamide or potassium amide to form a sodium salt.[93, 128]



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

The salt apparently is much like the salt of acetoacetic ester and without solvent reacts with alkyl halides to form alkyl derivatives of pyridine in yields of 50% to 60%. Both quinaldine and lepidine react with alkali-metal amides either in liquid ammonia[129] or without solvent;[128] these alkali-metal salts of quinoline also react with alkyl halides to yield alkyl quinolines.[129] 2-Methylbenzothiazole is readily converted to the sodium salt by the action of sodamide.[5]

Quinaldine and 2-methylpyridine[130] can be converted to what might be termed the corresponding lithiomethyl compounds by the action of phenyllithium in ether.[131] 2-Methylbenzothiazole[5] undergoes the same reaction and also reacts with ethylmagnesium bromide to form the Grignard reagent. 2-Lithiomethylbenzothiazole can also be prepared by heating 2-methylbenzothiazole with lithium to 200°.

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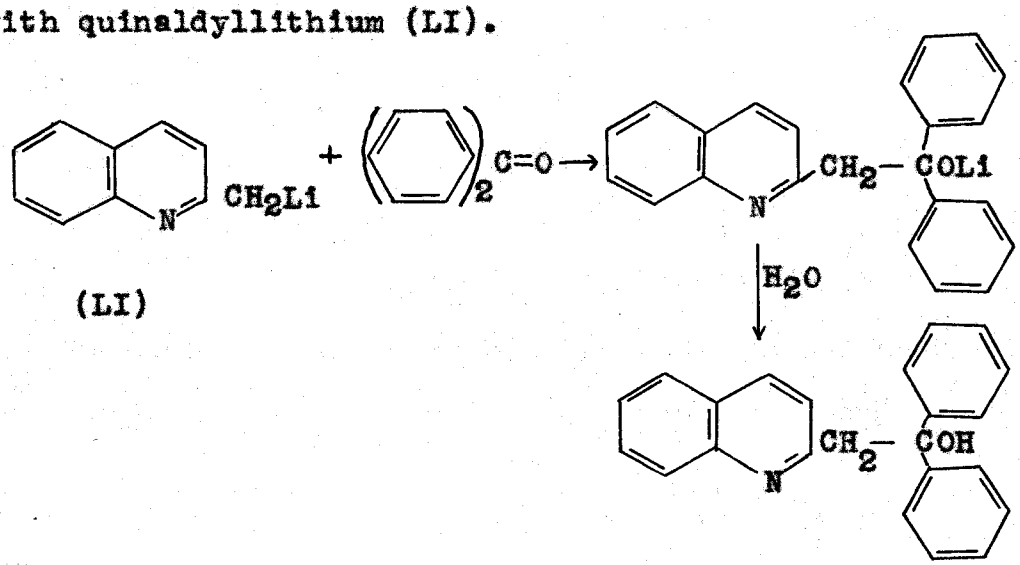
129. Bergstrom, J. Am. Chem. Soc., 53, 4065 (1931).

130. Recently Mr. J. L. Towle prepared 2-pyridylmethyllithium in good yield by the action of phenyllithium on 2-methylpyridine. Because of the similarity of 2-pyridylmethyllithium to benzyllithium and benzylmagnesium chloride, he attempted to demonstrate a rearrangement with 2-pyridylmethyllithium analogous to that of benzylmagnesium chloride, which is known to form o- and p-tolyl derivatives rather than benzyl derivatives. He was unable to show a rearrangement and found the reactions of 2-pyridylmethyllithium to be normal. However, neither 2-pyridylmethyllithium nor quinaldyllithium gave a positive Color Test I.

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

These alkali-metal salts show many of the reactions of organometallic compounds. As mentioned previously, they react with alkyl halides. 2-Picolyllithium reacts with benzaldehyde,[132] benzoylchloride,[132] acetaldehyde,[133] acetic anhydride,[134] and ethylacetate[134] to yield the expected products. 2-Picolylsodium,[128] quinaldylsodium,[129] quinaldyllithium,[131] and 2-benzothiazolylmethylmagnesium bromide react with benzophenone to yield the corresponding carbinol as illustrated with quinaldyllithium (LI).



(LI)

The Grignard reagent of 2-methylbenzothiazole[5] can be carbonated to give 2-benzothiazolylacetic acid, and it also reacts with acetone to form 2-(2'-benzothiazolylmethyl)-2-propanol.

132. Bergmann and Rosenthal, J. prakt. Chem., [2], 135, 267 (1932).

133. Walter, Hunt, and Fosbinder, J. Am. Chem. Soc., 63, 2771 (1941).

134. Beets, Chem. Weekblad, 39, 187 (1942).

Phenyllithium and 2,6-dimethylpyridine yield the dilithio derivative.[135] An improved method for the preparation of 2-ethylpyridine from 2-picolyllithium and methyl iodide has been recently reported,[136] and several new derivatives of pyridine have been prepared by treating alkylpyridines, which must have at least one alkyl group in the 2- position and at least two hydrogen atoms on the carbon linked directly to the pyridine nucleus, with phenyllithium and then with β-ionone.[137]

6. Oxidation. Selenium dioxide is an excellent oxidizing agent for compounds which contain a methylene group activated by proximity to a negative group.[138] Thus acetone can be converted to methylglyoxal in 60% yield, and acetophenone to phenylglyoxal in 50% yield. Because of the similarity of the azomethine grouping to the carbonyl grouping it was thought that the methyl group adjacent to the azomethine might be attacked specifically by selenium dioxide to yield the aldehyde.[139] However, Henze[139] found that 2-methylpyridine in

135. Kloppenburg and Wibaut, Rec. trav. chem., 65, 393 (1946).

136. Gregg and Craig, J. Am. Chem. Soc., 70, 3138 (1948).

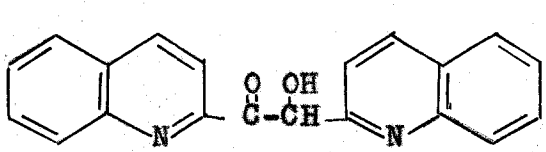
137. van Dorp and Arens, Dutch Patent 61, 159 (June 15, 1948) /C. A., 42, 7344 (1948)/.

138. Riley, Morley, and Friend, J. Chem. Soc., 1875 (1932).

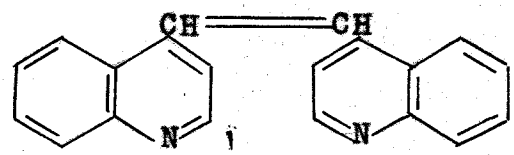
139. Henze, Ber., 67B, 750 (1934).

xylene was converted to pyridine-2-carboxylic acid with only a trace of the aldehyde. 2,6-Dimethylpyridine forms the dicarboxylic acid.

Quinaldine and selenium dioxide in boiling xylene form quinoline-2-aldehyde and quinaldinic acid, but 2-ethyl-3-methylquinoline is converted under the same conditions exclusively to 3-methylquinoline-2-carboxylic acid.[139] Kwartler and Lindwall,[140] however, were able to convert 4-methylquinoline in xylene to quinoline-4-aldehyde in 61% yield by the use of selenium dioxide. 6-Methoxy-4-methylquinoline forms the corresponding aldehyde in 52% yield. Kaplan[141] attributed the failure of other work to the selenium dioxide, which must be freshly prepared. If not freshly prepared, it converts quinaldine to quinaldoin, 2-hydroxy-1,2-di-(2'-quinolyl)ethanone (LII), and lepidine to 1,2-di-(4'-quinolyl)ethylene (LIII).



(LII)



(LIII)

140. Kwartler and Lindwall, J. Am. Chem. Soc., 59, 524 (1937).

141. Kaplan, ibid., 63, 2654 (1941).

Since the 2-methyl group is more active than the 4-methyl group, there would be more quinoline-2-aldehyde in the reaction mixture at any time and, therefore, more quinaldoin (LII) would be formed. In the reaction of 4-methylquinoline and selenium dioxide there would not be as much quinoline-4-aldehyde, and the Claisen reaction between quinoline-4-aldehyde and 4-methylquinoline would predominate.[141] A procedure for the oxidation of 4-methylquinoline by selenium dioxide in acetic acid and acetic anhydride at 85-90° has been recently published together with reduction of the aldehyde to quinoline-4-methanol by anhydrous i-propyl alcohol and aluminum i-propylate. The yields of the two reactions are 50-60%.[142]

7. Mannich Reaction.[143] The Mannich reaction is the reaction between an active methylene grouping, formaldehyde, and a primary or secondary amine (usually as the hydrochloride). The following is a representative equation.

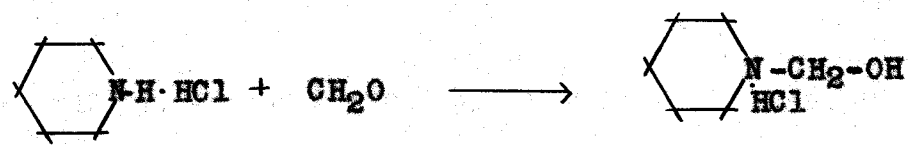
$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}R' + HCHO + HN(CH_3)_2\cdot HCl \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_2\text{-}N(CH_3)_2\cdot HCl}{\underset{|}{CH}}\text{-}R' + H_2O$$

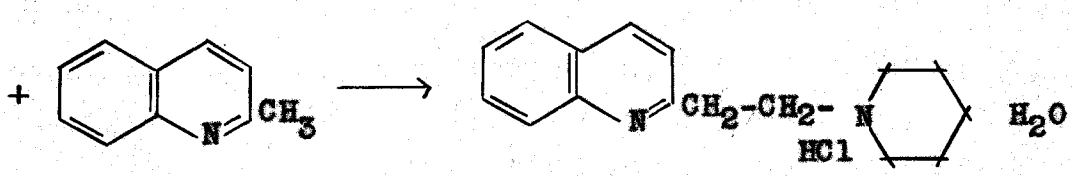
α-Picoline and 2-methylquinoline have been condensed with dimethylamine, diethylamine, methyldiethylethylene diamine, piperidine, and methylaniline, either as the free amine or as

142. MacDonald, J. Am. Chem. Soc., 69, 1219 (1947).

143. Blicke, "Organic Reactions," (Roger Adams, Editor), John Wiley and Sons, Inc., New York, 1943, Vol. I, p. 303.

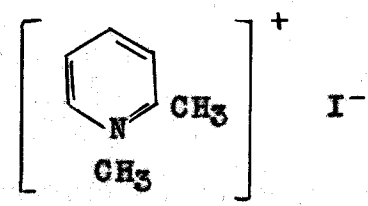
the hydrochloride.[144] 2-Methyl-4-hydroxyquinoline, 2-methyl-8-nitroquinoline, and 2-ethoxy-4-methylquinoline have been condensed with the same amines.[145] According to Tseou Héou-Féo, the most probable mechanism is the following, using piperidine and quinaldine as an example.





McDonald[142] was unable to condense quinoline-4-methanol with formaldehyde and piperidine.

8. Quaternary Ammonium Salts. The formation of quaternary ammonium salts, for example, 2-methylpyridine methiodide (LIV) increases the reactivity of the methyl groups. The posi-



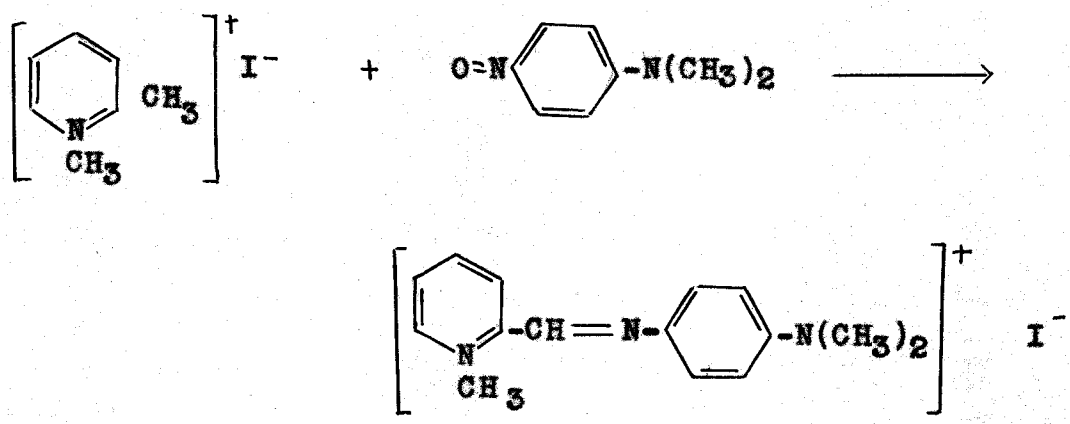
(LIV)

144. Tseou Héou-Féo, Compt. rend., 192, 1242 (1931).

145. Bartholomaus, German Patent 479,907 (May 8, 1927) [C. A., 24, 4056 (1930)].

tive charge of the ion is distributed by resonance to the 2- and 4- positions making them more active toward nucleophilic reagents.[8] The styryl derivatives of 2- and 4-methylpyridines are formed merely by refluxing the alkiodide for five hours in ethanol solution using piperidine as the catalyst.[146] The same is true of quinaldine, lepidine, and 4-methylisoquinoline methiodides. A large number of substituted styryl derivatives have been made in this way.

2-Picoline will not react with p-nitrosodimethylaniline, but the methiodide of 2-picoline reacts readily in the presence of piperidine as follows.[147]



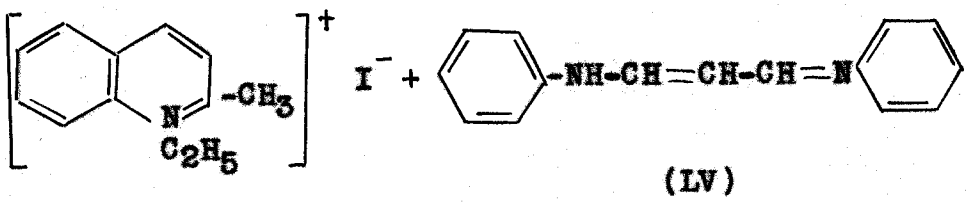
Parallel reactions are obtained with quinaldine, lepidine, and 1-methylisoquinoline methiodides. The reactivity of 2-methylquinoline methiodides is higher than that of 4-methyl-

146. Mills and Pope, J. Chem. Soc., 121, 946 (1922).

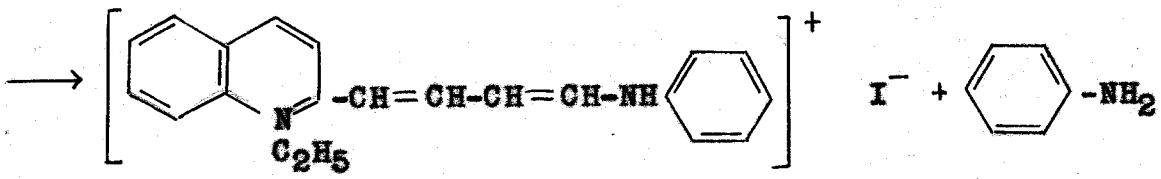
147. Kaufmann and Vallette, Ber., 45, 1736 (1912); ibid., 46, 49 (1913).

quinoline methiodides.[148]

The ethiodides of 2-methylbenzothiazole, 2-methyl-, and 4-methylquinoline are reactive enough to condense with ammono dialdehyde ethers of the general formula, R-N CH(CH=CH)n-NR_2.[8] For example, β-anilinoacrolein anil (LV) reacts with 2-methylquinoline ethiodide as follows.



(LV)



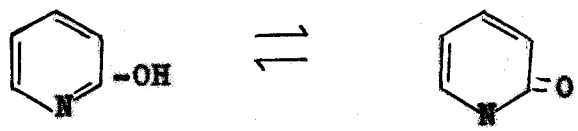
The free bases, of course, do not give this reaction.

D. Reactions of Other Substituents α- and γ- to the Azomethine Linkage.

1. Hydroxyl Groups α- and γ- to the Azomethine Linkage. As would be expected, tautomerism has been postulated in these compounds; for example, 2-hydroxypyridine tautomerizes to 2-

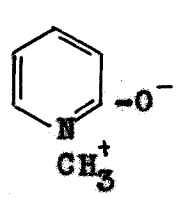
148. Brooker and Sprague, J. Am. Chem. Soc., 63, 3203 (1941).

pyridone (LVI).

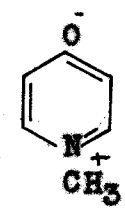


(LVI)

In the pyridine series derivatives of both structures are known, though the ultraviolet absorption spectra of the N-alkylpyridones indicate that the aromatic ring of pyridine is still present.[149] They are consequently formulated as N-alkyl derivatives of the dipolar forms (LVII) and (LVIII).[8]



(LVII)



(LVIII)

Methylation of 2-hydroxypyridine with methyl iodide at 100° forms N-methyl-2-pyridone; the same product is obtained by the reaction of methyl sulfate and methanol with 2-hydroxypyridine.[150] From the silver salt and ethereal methyl iodide, however, 2-methoxypyridine is formed in addition to N-methyl-2-pyridone. Nevertheless, it is not possible to predict which isomer will be formed as the substituents on the ring affect

149. Arndt and Kalischek, Ber., 63B, 587 (1930).

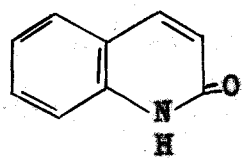
150. von Pechmann and Baltzer, ibid., 24, 3144 (1891).

the reaction. For example, the silver salt of 2-hydroxy-5-nitropyridine gives 15.6% of 2-methoxy-5-nitropyridine and 60% of N-methyl-5-nitro-2-pyridone.[151] With diazomethane 2-hydroxypyridine[152] forms 2-methoxypyridine, but 4-hydroxypyridine[153] yields a mixture of 4-methoxypyridine and N-methyl-4-pyridone (LIX).

(LIX)

Both 2- and 4-hydroxyquinoline are also tautomeric. 2-Hydroxyquinoline in alkali plus alkyl halides forms both O-alkyl and N-alkyl derivatives, thus giving no indication as to structure of the parent substance.[154] The absorption spectra of carbostyril and N-methyl-2-quinolone are similar, while that of 2-methoxyquinoline is different, suggesting a lactam structure (LX) for carbostyril.[155] Replacement of the labile hydrogen retards the tendency to change forms.[156] The carbostyril

151. Rath, Ann., 484, 52 (1930).
152. von Pechmann, Ber., 28, 1624 (1895).
153. Meyer, Monatsh., 26, 1311 (1905).
154. Goldschmidt and Meissler, Ber., 23, 253 (1890).
155. Hartley and Dobbie, J. Chem. Soc., 75, 640 (1899).
156. Bogert and Seil, J. Am. Chem. Soc., 29, 517 (1907).



(LX)

ethers, however, are converted by dilute mineral acids or by alkylhalides and alkali into N-alkylquinolones.[157]

The absorption spectra of 3-, 5-, 6-, 7-, and 8-quinolinols and 5- and 7-isoquinolinols are in general agreement with the phenolic structures, while the absorption spectra of 2- and 4-quinolinols and 1-isoquinolinol are predominantly ketonic (lactamic) in nature.[158] Chemical evidence indicates that 4-quinolinol is more phenolic than 2-quinolinol.[158, 159]

2-Quinolinol[54] and 4-quinolinol[160] react with phosphorous pentachloride or phosphoryl chloride at a higher temperature than is required for pyridinols to form the corresponding chloro derivatives. 1,4-Isoquinolinediol reacts with phosphoryl chloride at 160-170° to form both 1-chloro-4-isoquinolinol and 1,4-dichloroisoquinoline.[59] 6-Methyoxy-2-quinolinol

157. Kaufmann and de Petherd, Ber., 50, 336 (1917).
158. Ewing and Steck, J. Am. Chem. Soc., 68, 2181 (1946).
159. Reitsema, Chem. Rev., 43, 43 (1948).
160. Backeberg, J. Chem. Soc., 618 (1933).

and 2-methyl-4-quinolinol react with phosphorous pentabromide to yield 6-methoxy-2-bromoquinoline (42%) and 2-methyl-4-bromoquinoline (25%), respectively.[161] 4-Methyl-2-quinolinol heated one and one-half hours at 120° with phosphoryl bromide gives a 90% yield of 2-bromo-4-methylquinoline.

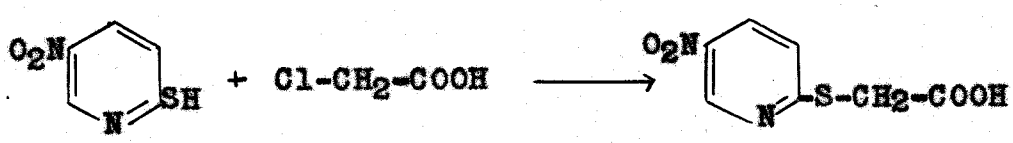
The preparation of thiols is carried out by treatment of the 2- or 4-halogen compound by potassium hydrosulfide or better by thiourea as has been discussed earlier. These compounds would be expected to exhibit the same resonance forms as the corresponding hydroxy compounds. These thiols are more difficult to oxidize to disulfides than other aryl thiols. Weak oxidizing agents like ferric chloride and iodine in sodium hydroxide had no effect, according to Roos.[162] Hydrogen peroxide is, however, effective in converting 2-quinolinethiol and 4-methylquinoline-2-thiol to corresponding disulfides. Renfrew[72] had converted 7-methylquinoline-2-thiol, 7-methylquinoline-4-thiol, 7-chloro-4-methylquinoline-2-thiol, and 6-methoxy-2-methylquinoline-4-thiol to the corresponding disulfides by means of iodine and potassium iodide, though the reaction with 7-methylquinoline-4-thiol was slow. The quinoline-4-thiols are, however, more reactive than the quinoline-

161. Kaslow and Marsh, J. Org. Chem., 12, 456 (1947).

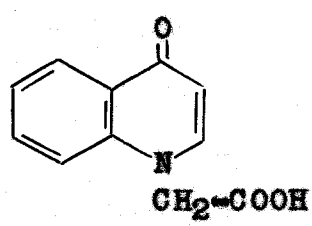
162. Roos, Ber., 21, 619 (1888).

2-thiols. The sodium salts of 2-quinolinethiol, 4-methylquinoline-2-thiol, and 2-methylquinoline-4-thiol form 2-quinolyl ethyl sulfide, 4-methyl-2-quinolyl ethyl sulfide, and 2-methyl-4-quinolyl ethyl sulfide, respectively, when treated with ethyl iodide. 6-Methylquinoline-2-thiol forms the disulfide by treating with methyl iodide[26] and sodium methylate in methanol solution at 60-70°.

5-Nitropyridine-2-thiol reacts with chloracetic acid to form 5-nitro-2-pyridylmercaptoacetic acid in 89% yield by refluxing for one hour in water.[163]



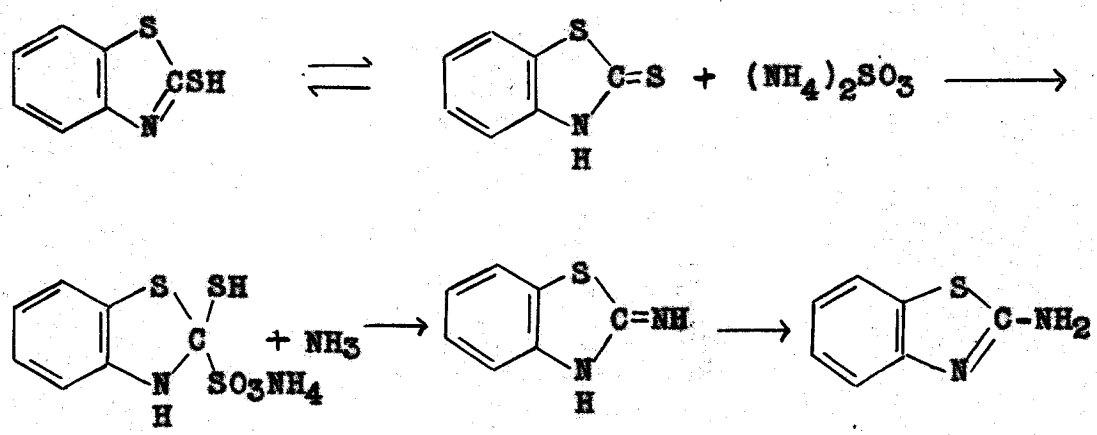
7-Chloroquinoline-2-thiol also reacts with chloracetic acid to form 7-chloro-4-quinolylmercaptoacetic acid.[74] This is at variance with 7-chloro-4-hydroxyquinoline which gives 4(1)-quinolone-1-acetic acid (LVI).



(LXI)

163. Surrey and Lindwall, J. Am. Chem. Soc., 62, 1697 (1940).

2-Mercaptobenzothiazole, heated to 150° in a sealed tube with ammonium sulfite, yields 2-aminobenzothiazole in 52% yield.



This reaction has been extended to other primary amines, but secondary amines do not react.[164]

2. Mobility of Alkoxy and Aryloxy Groups α- and γ- to the Azomethine Linkage. Both 2- and 4-alkoxypyridines should have labile alkoxy groups since these substances are cyclic ammono aquo esters,[8] but they are not as reactive as might be expected. The low reactivity may be associated with the high resonance energy of the pyridine ring. At 200° 2-methoxypyridine is partially converted to N-methyl-2-pyridone.[165] By heating to a dull red heat 2-phenoxypyridine may be converted to N-phenyl-1-pyridone.[166] By heating with hydrochloric

164. Ubaldini and Fioreza, Gazz. chim. ital., 76, 215 (1946).
165. Meyer, Monatsh., 28, 47 (1907).
166. Chichibabin and Jeletzky, Ber., 57B, 1158 (1924).

acid 2-phenoxypyridine is cleaved to phenol and 2-hydroxypyridine. 2-Methoxypyridine heated with concentrated hydriodic acid for forty-eight hours at 100° forms methyl iodide and 2-hydroxypyridine, but the reaction is slower than methyl ether cleavage in the regular Zeissel determination.[52]

In the quinoline series the 2- or 4-alkoxy group is more active than an ether group, but less active than an ester.[167] 2-Ethoxyquinoline heated to 100° with methyl iodide for forty-eight hours forms N-methyl-2-quinolone in good yield.[168] Meyer[169] reported that 2-alkoxyquinolines were converted to N-alkyl-2-quinolones by heating to 100°; the 4-alkoxyquinolines had to be heated to 280° to form the N-alkyl-4-quinolones.[170]

Chichibabin and Jeletzky[166] reported that 2-allyloxyquinoline rearranged to N-allyl-2-quinolone by distilling (b.p. 325-329°) at atmospheric pressure, but, in a more recent work, Buu-Hoi and co-workers[171] reported no rearrangement at 200° and suggested that, because of the relatively low boiling point, the product obtained previously could not have been the quinolone.

2-Ethoxyquinoline is not affected by boiling in dilute potassium hydroxide, but is converted to 2-hydroxyquinoline

167. Meyer, Monatsh., 27, 255 (1906).

168. Knorr, Ber., 30, 929 (1897).

169. Meyer and Beer, Monatsh., 34, 1173 (1913).

170. Knorr, Ann., 236, 69 (1886).

171. Buu-Hoi, Hiong-Ki-Wei, and Royer, Bull. soc. chim., 12, 886 (1945).

and ethyl chloride by heating to 120° with dilute hydrochloric acid.[157] 2-Chloro-4-ethoxyquinoline is converted to 2-chloro-4-hydroxyquinoline by heating for ten hours with 70% hydriodic acid, and 4-chloro-2-ethoxyquinoline forms 4-chloro-2-hydroxyquinoline quantitatively by refluxing for thirty minutes with 6N hydrochloric acid.[86]

Bergstrom replaced the methoxyl group in 2-methoxyquinoline with the amino group in 51% yield by treatment with potassium amide in liquid ammonia.[172] 4-Alkoxyquinolines are changed to 4-aminoquinolines or 4-alkylaminoquinolines by ammonium salts and ammonia or alkylamines.[173]

The methoxy group in 2-methoxy-6-nitrobenzothiazole is extremely mobile. Alcoholic sodium ethoxide converts the methoxy derivative to 2-ethoxy-6-nitrobenzothiazole, and sodium isopropoxide and 2-methoxy-6-nitrobenzothiazole form 2-isopropoxy-6-nitrobenzothiazole.[174]

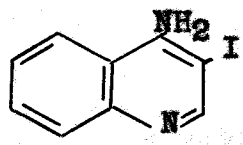
3. Amino Groupings α- and γ- to the Azomethine Linkage. Amines, in which the amino group is α- or γ- to the azomethine linkage in pyridine, quinoline, benzothiazole, or isoquinoline, have a special reactivity. Amino groups in other positions in

172. Bergstrom, J. Org. Chem., 3, 233 (1938).

173. German Patent 708,116 (June 5, 1941) [C. A., 37, 5084 (1943)].

174. Colonna, Pubbl. ist. chim. univ. Bologna, 1943 (No. 7), 3 [C. A., 41, 755 (1947)].

these heterocycles are just like any other aromatic amine. For instance, 3-aminopyridine forms a dihydrochloride[175] while 2- and 4-aminopyridines form only a monohydrochloride.[153] 3-Aminopyridine can be diazotized in the usual manner, but 2-aminopyridine diazotized in dilute sulfuric acid forms 2-hydroxypyridine.[176] Diazotization of 2-aminopyridine in hydrofluoric acid, hydrochloric acid, or hydrobromic acid leads to 2-fluoropyridine, 2-chloropyridine, and 2-bromopyridine, respectively.[176] 4-Aminoquinoline diazotized in hydrochloric acid yields 4-chloroquinoline, and diazotized in hydrobromic acid it yields 4-bromoquinoline. By diazotizing 4-aminoquinoline in hydroiodic acid some 4-iodoquinoline is formed, but also 3-iodo-4-aminoquinoline (LXII) can be isolated.[177]



(LXII)

Thiazoles are very similar to pyridine in many respects, and diazotization of 2-aminothiazoles provides no exception to this relationship. 2-Aminothiazole diazotized in hydro-

175. Crippa, Long, and Martini, Gazz. chim. ital., 64, 83 (1934).

176. Chichibabin and Rjasancev, J. Russ. Phys. Chem. Soc., 47, 1571 (1915) [J. Chem. Soc., 110 I, 224 (1915)].

177. Claus and Frobenius, J. prakt. Chem., [2], 56, 181 (1897).

chloric acid forms 2-chlorothiazole.[178] 2-Aminobenzothiazole readily forms an unstable diazo compound, but attempts to form 2-hydroxybenzothiazole from this diazo compound result only in 2-aminobenzothiazole hydrochloride.[179]

2-Aminoquinoline can be converted to 2-hydroxyquinoline by either acid or alkali.[27] 2,6-Diaminopyridine changes to 2-amino-6-hydroxypyridine if it is heated to 100° in 70% sulfuric acid for two hours.[180] 2,4-Dianilinoquinoline forms 2,4-dihydroxyquinoline by heating with alcoholic potassium hydroxide to 220°.[181]

Tautomerism has been postulated for these amino compounds as in the case of the methyl compounds. This is, of course, based on chemical reactions, which implies that the parent base need not be tautomeric, but that a tautomeric shift may be induced by the approach of certain reagents. Chichibabin[182]

178. Morgan and Morrow, J. Chem. Soc., 107, 1291 (1915).

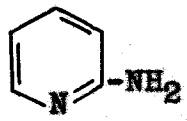
179. Hunter, J. Chem. Soc., 1385 (1926).

180. Seide and Titow, Ber., 69B, 1884 (1936).

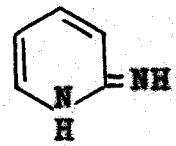
181. Dzievonski and Dymek, Bull. intern. acad. polon. sci., Classe sci. math. nat., 1936A, 413 /C. A., 31 1812 (1937)/.

182. Chichibabin, Bull. soc., chim. /5/ 3, 762 (1936).

showed the tautomerism of 2-aminopyridine as an equilibrium between the amino (LXIII) and the imino form (LXIV).



(LXIII)



(LXIV)

Acetic anhydride and 4-aminoquinoline react to form 4-acetaminoquinoline.[177] If 2-aminopyridine is treated with methyl iodide, the main product is N-methylpyridonimine, but if the sodium salt is treated with methyl iodide, 2-methylaminopyridine is formed.[183] Methylation and ethylation of 2-aminobenzothiazole result in N-methylpyridonimine and N-ethylpyridonimine, respectively, but acetylation leads almost exclusively to 2-acetaminopyridine.[179]

According to Steinhauser and Diepolder,[184] aliphatic aldehydes react with two moles of 2-aminopyridine to form 2, 2'-dipyridylaminoalkanes while aromatic aldehydes react with one mole of 2-aminopyridine to form monopyridyl derivatives. Kirpal and Reiter,[185] however, have formed the dipyridyl

183. Chichibabin, Konowalowa, and Konowalowa, Ber., 54B, 814 (1921).

184. Steinhauser and Diepolder, J. prakt. Chem., [2] 93, 387 (1916).

185. Kirpal and Reiter, Ber., 60B, 664 (1927).

derivative of benzaldehyde, which they converted to the monopyridyl derivative and aniline by heating. 2-Aminobenzothiazole reacts with both aliphatic and aromatic aldehydes, but Hunter[179] was not able to isolate any pure products from these reactions.

4. Carboxyl Groups α- and γ- to the Azomethine Linkage. The activating effect of the azomethine influences α and γ-carboxyl groups in much the same way that the carboxyl group in an α-keto acid is influenced. These heterocyclic acids are, however, more stable than keto acids because of resonance in the ring structures.[8] Carboxyl groups in the 3- position in pyridine and quinoline are not affected; for example, pyridine 2,3- or 3,4-dicarboxylic acids are easily decomposed by heating into the corresponding nicotinic acid,[186] and quinoline-2,3-dicarboxylic acid[187] forms quinoline-3-carboxylic acid by heating to 120-130°. The ease of loss of carbon dioxide by pyridine carboxylic acids decreases as follows.

$$\text{2-COOH} \rangle \text{ 4-COOH} \rangle \text{ 3-COOH}$$

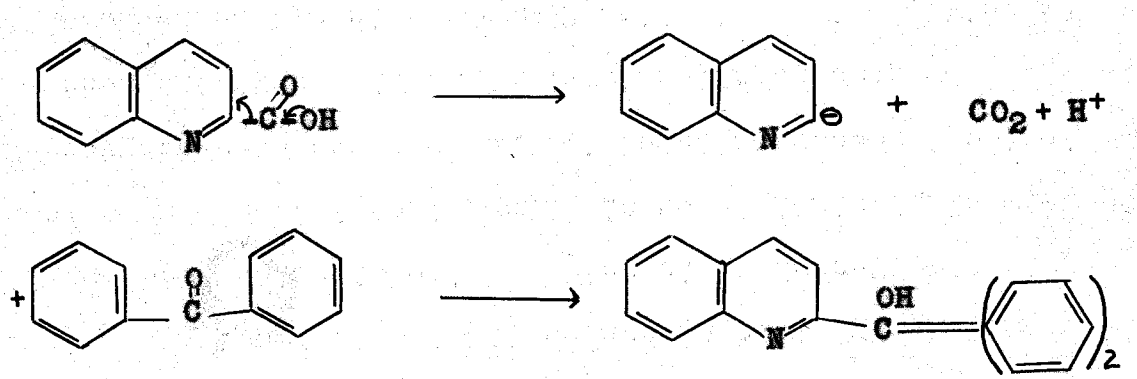
Quinoline-2,4-dicarboxylic acid heated for ten minutes

186. Camps, Arch. Pharm., 240, 345 (1902).

187. Graebe and Caro, Ber., 13, 99 (1880).

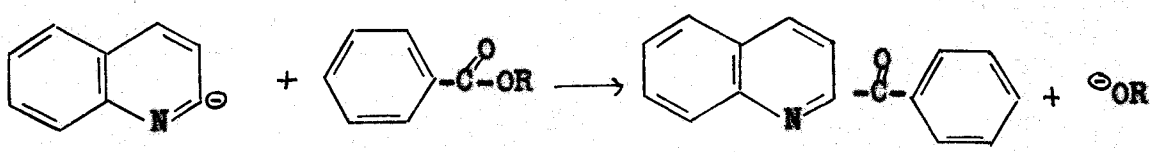
in boiling nitrobenzene forms quinoline-4-carboxylic acid in 90% yield.[33] The same effect can be accomplished by heat alone (240°)[188] or by heating in boiling phenol.[189] Quinoline-2-acetic acid,[190] which decarboxylates at 274-275°, is much more stable than pyridine-2-acetic acid, which loses carbon dioxide in water at 50-60°. Benzothiazole-2-carboxylic acid[191] melts with loss of carbon dioxide at 106°.

Quinoline-2-carboxylic acid and isoquinoline-1-carboxylic acid form alkylquinolyl- or alkylisoquinolylmethanols and carbon dioxide if decarboxylated in the presence of aldehydes or ketones. The same reaction is obtained with pyridine-2-carboxylic acid. Using quinoline 2-carboxylic acid and benzophenone as an example, the probable reaction mechanism[192] is shown below.



188. Pfitzinger, J. prakt. Chem., [2] 56, 283 (1897).
189. Koenigs and Mengel, Ber., 37, 1322 (1904).
190. Kenner and Nandi, Ber., 69B, 635 (1936).
191. Bogert and Stull, J. Am. Chem. Soc., 48, 248 (1926).
192. Ashworth, Daffern, and Hammick, J. Chem. Soc., 809 (1939).

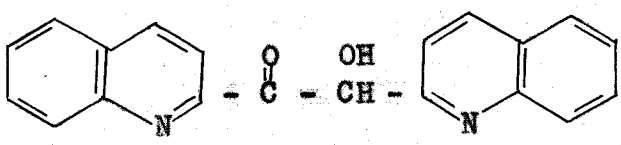
The carboxyl group must be alpha to an azomethine grouping as acids containing ethylenic, acetylenic, and nitrile groups do not react. If the azomethine linkage is destroyed by hydrogenation, as in tetrahydroquinaldinic acid, no reaction occurs. In the presence of decarboxylating quinoline-4-carboxylic acid and pyridine-2-carboxylic acid the alkoxy groups of esters can be exchanged for quinolyl and pyridyl groups.[193] These groups may also be substituted at cationoid centers in aromatic molecules.



The course of this reaction confirms the view that quinolyl and pyridyl anions are produced during the decarboxylation.

5. Aldehyde Groups α- and γ- to the Azomethine Linkage. Though 2- and 4-quinoline and 2- and 4-pyridine aldehydes exhibit many of the reactions of aromatic aldehydes, the 3-aldehydes are more characteristically aromatic. Quinoline-2-aldehyde forms a p-nitrophenylhydrazone,[134] and is converted to the benzoin analog, quinaldoin (LXV), by potassium cyanide and water. Quinoline-4-aldehyde reduces Tollen's reagent slowly, forms a bisulfite addition product slowly, forms an oxime and a p-nitrophenylhydrazone. Most of these reactions

193. Brown, Hammick, and Thewlis, Nature, 162, 73 (1948); Brown and Hammick, J. Chem. Soc., 173 (1939).



(LXV)

are also given by 6-methoxyquinoline-4-aldehyde.[140] Benzothiazole-2-aldehyde[194] and isoquinoline-1-aldehyde[195] also form phenylhydrazones. The 2,4-dinitrophenylhydrazone of pyridine-2-aldehyde[196] is easily prepared, and the semicarbazone of isoquinoline-1-aldehyde is readily formed.

Condensation reactions are usually fairly smooth though side reactions are sometimes extensive. Pyridine-2-aldehyde, for example, forms only tars with hippuric acid and with diketopiperazine.[197] Quinoline-4-aldehyde and 6-methoxyquinoline-4-aldehyde condense with nitromethane in the presence of diethylamine[140] to form carbinols. These aldehydes generally form aldols in aqueous alcohol with diethylamine as catalyst and ethenes in glacial acetic acid with zinc chloride as condensing agent.

Both 6- and 7-chloroquinoline-4-aldehyde undergo the

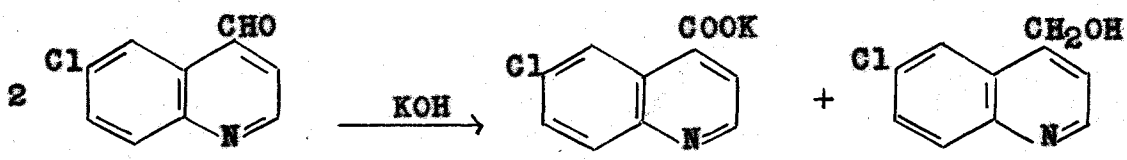
194. Borsche and Doeller, Ann., 537, 39 (1938).

195. Barrows and Lindwall, J. Am. Chem. Soc., 64, 2430 (1942).

196. Dyson and Hammick, J. Chem. Soc., 781 (1939).

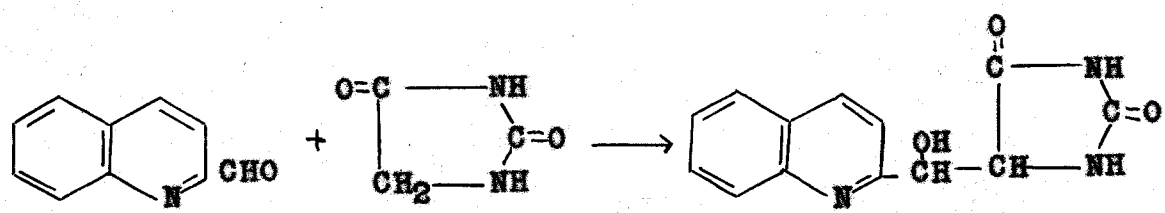
197. Neimann, Lewis, and Hays, J. Am. Chem. Soc., 64, 1678 (1942).

Cannizzaro reaction when treated with concentrated potassium hydroxide.



These aldehydes form anils with amines like ethanolamine and 6-ethylaminohexylamine.[198]

Quinoline-2- and-4-aldehydes condense with hydantoin and related compounds in the presence of diethylamine.[199]



The 2-aldehyde appears to be somewhat more reactive than the 4-aldehyde because the yields of condensation products are higher. Quinoline-4-aldehyde is reduced to the methanol in 50-60% yield by aluminum i-propylate in excess i-propyl alcohol.[142] 3,8-Dimethyl-5-nitroquinoline-2-aldehyde condenses with diazoalkanes to give good yields of ketones.[200] Quino-

198. Campbell, Kerwin, Sommers, and Campbell, J. Am. Chem. Soc., 68, 1559 (1946).

199. Phillips, ibid., 67, 744 (1945).

200. Burger and Modlin, Jr., ibid., 62, 1079 (1940).

line-4-aldehyde reacts with methylmagnesium iodide to form α-methyl-4-quinolinemethanol in 55% yield.[201]

6. Generalized Comparison of Reactivities of Substituents in the 2- and 4- Positions of Quinoline. Physiologically it has been found that the 4-aminoquinolines and 4-quinolinemethanols are more effective as antimalarials than 2-aminoquinolines[159, 202] or 2-quinolinemethanols. In the series of 8-aminoquinolines with 3-diethylaminopropyl side chains the toxicity of compounds decreases in the order:

$$6\text{-MeO} > 2\text{-CH}_3\text{O} > 4\text{-CH}_3\text{O}$$

If a 2-methoxyl group is added to the compound containing a 6-methoxyl group, a decrease in toxicity is observed. However, 8-aminoquinolines containing 6-diethylaminohexyl side chains show toxicities decreasing in the order:

$$4\text{-CH}_3\text{-} > 2\text{-CH}_3\text{-} > 6\text{-CH}_3\text{-}$$

The information on toxicity is conflicting and, therefore, not conclusive.

Wojahn and Kramer[203] prepared a series of substituted 2-

201. Johnson and Hamilton, J. Am. Chem. Soc., 63, 2864 (1941).
202. Wiselogle, "Survey of Antimalarial Drugs, 1941-1945," J. W. Edwards, Ann Arbor, Mich., 1946, Vol. I, p. 94.
203. Wojahn and Kramer, Arch. Pharm., 276, 291 (1938).

alkoxyquinoline compounds. They attributed the local anesthetic action of these compounds to the 2-alkoxy group. The 2-butoxy compounds were the most effective as local anesthetics.

According to Bergstrom[8] the 2-position of quinoline is active because of its proximity to the azomethine linkage, and by the principle of vinylogy this effect is transmitted to the 4- position. One would expect from this that the 2-position would be the more reactive; however, the electron densities of Longuet-Higgins and Coulson[17] show a lower value for the 4- position of quinoline, indicating a greater reactivity for that position.

In the halogenated quinolines the 2- position seems to be the most reactive chemically. Thus, 2,4-dichloroquinoline reacts with potassium hydroxide in ethanol to yield 2-chloro-4-ethoxyquinoline (31%), 4-chloro-2-ethoxyquinoline (32%), and 4-chloro-2-hydroxyquinoline (5.5%).[86] 2,3,4-Trichloro-6-methylquinoline[87] is converted quantitatively to 3,4-dichloro-6-methyl-2-hydroxyquinoline by dilute hydrochloric acid at 180°.

2-Methylquinoline is more reactive than 4-methylquinoline. By mixing 2-methylquinoline and 4-methylquinoline with benzaldehyde[120] and heating, the ratio of 2-styrylquinoline to 4-styrylquinoline is 8 : 1. 2-Methylquinoline forms phthalones while 4-methylquinoline does not react[120] with phthalic anhydride. 2-Methylquinoline forms a trimethylol derivative with formaldehyde and 4-methylquinoline forms only a dimethylol

derivative.[98] Here the evidence is all in favor of greater reactivity in the 2- position.

Neither the 2- nor the 4-hydroxy group is as phenolic in character as the 3-hydroxy group though the 4-hydroxy group is more phenolic than the 2-hydroxy group.[158, 159] This may be contrasted with the thiols in which the 4-thiols are more reactive and more highly colored than the 2-thiols.[72] The 4-alkoxyquinolines have to be heated to a much higher temperature to convert them to the N-alkyl-4-quinolones than do the 2-alkoxyquinolines.[170]

4-Aminoquinoline is more basic than 2-aminoquinoline, which would indicate a lesser effect of the azomethine on the amine.[204]

Of the 2- and 4-substituted carboxylic acids the 2-carboxyl is most easily eliminated.[186] The 2-carboxylic acids on decarboxylation react with aldehydes, ketones,[192] and esters[193] while the 4-carboxylic acids do not give this reaction.[199]

Thus from the chemical evidence the 2- position of quinoline appears to be more reactive than the 4- position. This comparison may also be applied to pyridine for which there is not so much chemical evidence available. Of the other two heterocycles mentioned in this discussion, only one position is active, the 2-position of benzothiazole and the 1- position of isoquinoline.

204. Albert, Goldacre, and Phillips, J. Chem. Soc., 2240 (1948).

III. EXPERIMENTAL

All of the following reactions involving organometallic compounds were carried out in essentially the same equipment set-up. This consisted of a three-necked flask with ground glass joints, equipped with a stirrer, dropping funnel, and a Friedrich condenser. The apparatus was carefully dried and flushed out with dry nitrogen before starting a reaction.

Analyses for sulfur were made by the macro Parr bomb method, and analyses for nitrogen were made by the micro Dumas method. The melting points were uncorrected.

Attempt to Prepare 2-Benzothiazolylmagnesium Chloride from Magnesium and 2-Chlorobenzothiazole.- Fifty milliliters of dry ether, 2.5 g. (0.10 g.-atom) of magnesium turnings, a small crystal of iodine, and 1 g. of 2-chlorobenzothiazole were placed in a 250 ml. flask, and the solution was heated to boiling. There was no evidence of reaction so the remaining 16 g. (0.10 mole total) of 2-chlorobenzothiazole was added, and the mixture was refluxed for three hours. At this point a Color Test I[205] was negative. Most of the 2-chlorobenzothiazole (92%) was recovered.

The preceding attempt was repeated using Cu-Mg alloy as a catalyst, but, again, there was no evidence at all of reac-

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

tion. Some activated Cu-Mg-I[206] was employed as catalyst as well as methyl iodide, but no reaction was induced.

Attempt to Prepare 2-Benzothiazolyllithium from Lithium and 2-Chlorobenzothiazole.- A solution of 16.9 g. (0.10 mole) of 2-chlorobenzothiazole in 50 ml. of dry ether was added to 1.8 g. (0.24 g.-atom) of lithium in 50 ml. of ether using the same equipment set-up as in the previous experiment. Color Tests I[205] were negative at the end of two and four hours. Eighteen hours later the solution had colored brown, but a Color Test I[205] was still negative. Most of the 2-chlorobenzothiazole (89%) was recovered. A small amount of tarry residue was left in the distillation flask.

Metalation of Benzothiazole by Phenyllithium.- Phenyllithium (0.065 mole in 132 ml. of ether) was made in the usual way[207] and cooled to -75° (bath temperature). A solution of 8.8 g. (0.065 mole) of freshly-distilled benzothiazole in 30 ml. of ether was added during a period of twenty minutes. The mixture was stirred for ten minutes longer before it was poured into a slush of ether and Dry Ice and allowed to stand overnight. After hydrolyzing with 100 ml. of water, the layers were separated and the ether layer was extracted with two 100 ml. portions of water. Acidification with hydrochloric acid produced a heavy white precipitate which was

206. Gilman, Peterson, and Schulze, Rec. trav. chim., 47, 20 (1928).

207. Gilman, Zoellner, and Selby, J. Am. Chem. Soc., 52, 1252 (1933).

filtered, dried, and redissolved in 10% potassium hydroxide. This solution was filtered and acidified with hydrochloric acid, and the white precipitate was filtered and washed repeatedly with water. It was dried at room temperature for twenty-four hours in a vacuum desiccator. The compound melted at 105°, decomposing into benzothiazole and carbon dioxide. The melting points in the literature for benzothiazole-2-carboxylic acid vary from 105° to 108°.[191]

Anal. Calcd. for $C_8H_5O_2NS$: neut. equiv., 179.2. Found: neut. equiv., 182.0.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the ether-layer residue yielded 3.4 g. (38.6% recovery) of benzothiazole (b.p. 123-127° at 18 mm.) and about 1 ml. of tar. The benzothiazole was identified by means of its picrate (m.p. 167°)[122] and mixed melting point of this picrate with an authentic specimen.

Table III lists the experiments carried out to determine the optimal conditions for the preparation of 2-benzothiazolyllithium.

Optimal Conditions for Metalation of Benzothiazole.- A solution of 0.078 mole of n-butyllithium was prepared in the usual manner[208] in 235 ml. of ether (0.33M.) and was

208. This preparation utilized the older method of preparing n-butyllithium which gave yields of 40-55%; see Gilman and Stuckwisch, J. Am. Chem. Soc., 65, 1461 (1943). See also reference 215 for a better preparation of n-butyllithium developed subsequent to this work.

Table III

Metalation of Benzothiazole

Metalating Agent	Temp. (bath), °C.	Addition time (minutes)	Time after addition (minutes)	Yield,[a] %	Recovery of benzothiazole,[b] %
Phenyllithium	-75	20	60	68	17
Phenyllithium	-50	20	60	68.5	23.3
Phenyllithium[c]	0	20	—	40	26.5
Phenyllithium	0	15	5	5.9	24.1
Methyllithium	-50	5	30	74	13.1
Methyllithium	-50	20	60	70	9.6
Methyllithium[d]	-78 to -50	20	80	c. 80.5	11.8
n-Butyllithium	-50	20	10	73.5	—
n-Butyllithium[e]	-72	20	—	83.8	—
n-Butyllithium[f]	-75	20	—	76.5	—
n-Butyllithium[g]	-75	10	—	89.7	—

a. The yield was determined by the amount of benzothiazole-2-carboxylic acid obtained after carbonation. b. Identified by picrate and mixed melting point of the picrate with an authentic specimen.[122] c. Also 10 g. (5.3%) of 2-phenylbenzothiazole and a large amount of tarry residue were obtained. d. Acid from this run was not pure, and darkened on standing. e. Molarity of n-butyllithium was 0.435. f. Molarity of n-butyllithium was 0.96. g. Molarity of n-butyllithium was 0.33.

cooled to -78° by an acetone-Dry Ice bath. To this was added a solution of 10.5 g. (0.078 mole) of benzothiazole in 30 ml. of ether. The addition required ten minutes. Immediately after the addition, the solution was poured into a slush of ether and Dry Ice. Hydrolysis and neutralization of the water layer produced 12.5 g. (89.7%) of benzothiazole-2-carboxylic acid (m.p. 105°).[191] A small amount (1.3 g.) of yellow oil was found in the ether layer.

Decomposition of 2-Benzothiazolyllithium.- A solution of 0.11 mole of 2-benzothiazolyllithium in 195 ml. of ether was prepared by the method outlined above. This solution was stirred eighteen hours while it slowly warmed up to room temperature. The light yellow solution began to turn red at about -35° and continued to darken to a reddish black color. The mixture was hydrolyzed at this point with 100 ml. of 20% ammonium chloride solution. A yellow precipitate which occurred was filtered and dried. It melted at 189° with softening at 150° and weighed 16.7 g. This was dissolved except for a small amount, which an ignition test proved to be inorganic, in 75 ml. of nitrobenzene and boiled for one hour. On cooling 6.6 g. of material (m.p. 310°) was obtained. This is a 44.5% yield of 2,2'-bibenzothiazole, identified by melting point with an authentic specimen prepared by heating acetanilide with sulfur.[209]

209. Hunter, J. Chem. Soc., 127, 1318 (1925).

The resulting nitrobenzene-mother liquor was boiled twice with decolorizing carbon and filtered, but the black color could not be removed. Concentration to one-half volume produced no further 2,2'-bibenzothiazole and only a black tar was obtained by adding petroleum ether (b.p. 77-115°) to the solution.

Attempt to Metalate Quinoline.- A solution of 0.114 mole of n-butyllithium in 155 ml. of ether was cooled to -75°. Over a period of fifteen minutes, 14.9 g. (0.114 mole) of quinoline in 30 ml. of ether was added. At the end of the addition and at five and ten minutes later Color Tests[205] were positive. A Color Test II[210] was negative. An excess of powdered Dry Ice was added to the mixture, turning the red color to gray. The mixture was hydrolyzed with 100 ml. of water. No acid was found in the water layer on careful neutralization.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 10.9 g. (73.1%) of 2-n-butylquinoline, identified by melting point of the picrate (163°) and a mixed melting point with an authentic specimen.[3]

A repeat run of the same reaction for thirty minutes at -75° gave a 84.2% yield of 2-n-butylquinoline.

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

Preparation of 2-Benzothiazolyl Phenyl Ketone.- A solution of 0.16 mole of 2-benzothiazolyllithium in 304 ml. of ether was prepared in the usual manner. As soon as the addition of the benzothiazole was completed at a bath temperature of -75°, 20 g. (0.19 mole) of freshly-distilled benzonitrile was added slowly and washed through the addition funnel with 10 ml. of dry ether. The mixture turned a cherry red in color, and gave a positive Color Test I^{205} at the conclusion of the addition. Twenty minutes later a Color Test I^{205} was weak, and at the end of forty minutes was negative. The reaction mixture was hydrolyzed with 100 ml. of water, and enough hydrochloric acid was added to make the mixture distinctly acid. Some material precipitated from the solution. This was filtered and combined with the residue obtained by evaporation of the ether layer. A total of 31.5 g. (84.4% crude yield) of 2-benzothiazolyl phenyl ketone (m.p. 95-101°) was obtained. (If a 90% conversion of benzothiazole to 2-benzothiazolyllithium is assumed, the yield is 93.8%). Two recrystallizations from ethanol raised the melting point to 102.5° and resulted in 26.8 g. (71.1% yield).

Anal. Calcd. for $C_{14}H_9NOS$: N,5.86; S, 13.39. Found: N, 5.96; S, 12.92.

The phenylhydrazone of 2-benzothiazolyl phenyl ketone was prepared by adding phenylhydrazine to a 95% ethanol solution of the ketone. The crystals obtained melted at 93-135° and were recrystallized from 95% ethanol to a con-

stant melting point of 149°.

Anal. Calcd. for $C_{20}H_{15}N_3S$: N, 12.76; S, 9.73. Found: N, 12.92; S, 9.53.

Preparation of Di-(2-benzothiazolyl)phenylmethanol.- A solution of 0.054 mole of 2-benzothiazolyllithium was prepared in 170 ml. of ether. At -75° a solution of 13.5 g. (0.054 mole) of 2-benzothiazolyl phenyl ketone in 200 ml. of ether was added. A Color Test I^{205} was negative at the end of the end of the addition. The stirring was continued for twenty minutes before hydrolyzing with 100 ml. of water. A precipitate was filtered and combined with more solid obtained by evaporating the ether from the ether layer and replacing it with absolute ethanol. This material melted at 95-110° and weighed 18.3 g. Repeated alternate crystallization from benzene and anhydrous alcohol yielded 12.8 g. (61.5%) of di-(2-benzothiazolyl)phenylmethanol (m.p. 158°).

Anal. Calcd. for $C_{21}H_{14}ON_2S_2$: N, 7.51; S, 17.12. Found: N, 7.47; S, 16.89.

Preparation of α,α-Diphenyl-2-benzothiazolemethanol.- A solution of 0.065 mole of 2-benzothiazolyllithium in 195 ml. of ether was treated with 11.7 g. (0.065 mole) of benzophenone in 50 ml. of ether. The reaction mixture became cloudy and was stirred for four hours, during which time the temperature changed from -75° to -20°. The mixture was hydrolyzed with 100 ml. of water; the resulting layers were separated, and the ether layer was dried over sodium sulfate. Some crystals,

however, began to crystallize from the ether so the solution was filtered from the sodium sulfate and cooled in the refrigerator. This yielded 19.6 g. of material (m.p. 150°) (95.1% crude yield). The α,α-diphenyl-2-benzothiazolemethanol was recrystallized from anhydrous ethanol yielding 16.7 g. (80.0%) of product (m.p. 150°).

Anal. Calcd. for $C_{20}H_{15}ONS$: N, 4.42; S, 10.12. Found: N, 4.33; S, 10.22.

Preparation of α-Methyl-α-phenyl-2-benzothiazolemethanol.- A solution of 0.078 mole of 2-benzothiazolyllithium in 223 ml. of ether was prepared in the usual way at -75°. To this was added dropwise 9.5 g. (0.078 mole) of acetophenone in 30 ml. of ether. After stirring for one hour a Color Test I[205] was negative and the bath temperature was -35°. The stirring was allowed to continue for six hours until the bath reached room temperature. Hydrolysis was effected by the addition of 100 ml. of water, and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was partially removed by distillation and was diluted with petroleum ether (b.p. 28-38°). This yielded 13.4 g. (67% crude yield) of α-methyl-α-phenyl-2-benzothiazolemethanol (m.p. 87-88°). Recrystallization from an ether-petroleum ether (b.p. 28-38°) mixture yielded 11.2 g. (56.0%) of product (m.p. 88-89°). Recrystallization from benzene and from petroleum ether (b.p. 77-115°) did not raise the melting point.

Anal. Calcd. for $C_{15}H_{13}ONS$: N, 5.49; S, 12.54. Found:

N, 5.52; S, 12.19.

Preparation of α-(p-Chlorophenyl)-α-methyl-2-benzothiazolemethanol.- 2-Benzothiazolyllithium (0.102 mole) was prepared in 250 ml. of ether at -75°. A solution of 15.5 g. (0.102 mole) of p-chloroacetophenone in 30 ml. of ether was added slowly. The mixture was stirred for one and one-half hours at -75° and for one-half hour longer with the cooling bath removed. At this point a Color Test I^{205} was negative, so 100 ml. of water was added to hydrolyze the mixture. The layers were separated, and the ether layer was dried over sodium sulfate. All but about 50 ml. of the ether was removed by distillation, and 50 ml. of petroleum ether (b.p. 28-38°) was added. This yielded 21.1 g. (72.0%) of product (m.p. 131). Recrystallization from 95% ethanol yielded 15.75 g. (53.7%) of α-(p-chlorophenyl)-α-methyl-2-benzothiazolemethanol (m.p. 134-136°).

Anal. Calcd. for $C_{15}H_{12}C_1ONS$: N, 4.84; S, 11.08. Found: N, 4.88; S, 10.95.

Preparation of α-Phenyl-2-benzothiazolemethanol.- A solution of 0.073 mole of 2-benzothiazolyllithium in 180 ml. of ether at -75° was treated with 7.7 g. (0.073 mole) of benzaldehyde in 30 ml. of ether. After the addition, the cooling bath was removed, and the reaction mixture was allowed to warm up to room temperature. This required about one hour, and a Color Test I^{205} at this point was negative. Hydrolysis was effected by pouring onto crushed ice. The

The layers were separated; the ether layer was dried over sodium sulfate, and the ether was distilled away and all volatile material was removed by means of a steam bath and water pump. The resulting oil was dissolved in benzene from which 13.9 g. (79.3% crude yield) of product (m.p. 121.5°) crystallized. Recrystallization from 95% ethanol yielded 11.55 g. (66.2%) of α-phenyl-2-benzothiazolemethanol (m.p. 123.5°).

Anal. Calcd. for $C_{14}H_{11}ONS$: N, 5.80; S, 13.28. Found: N, 5.63; S, 12.79.

Preparation of α-Methyl-α-(p-tolyl)-2-benzothiazolemethanol.- 2-Benzothiazolyllithium (0.073 mole) was prepared in 180 ml. of ether at -75°. To this was added dropwise 9.8 g. (0.073 mole) of methyl p-tolyl ketone in 30 ml. of ether. After the addition the cooling bath was removed, and the reaction mixture was allowed to warm up to room temperature. This required about one hour after which the mixture was hydrolyzed by pouring onto crushed ice. The layers were separated, and the ether layer was dried over sodium sulfate before the ether was removed by distillation. Petroleum ether (b.p. 28-38°) was added to dissolve the residue, and this solution yielded 12.4 g. (63.1% crude yield) of crystalline product (m.p. 98°). By recrystallizing from petroleum ether (b.p. 77-115°) 12.2 g. (62.9%) of α-methyl-α-(p-tolyl)-2-benzothiazolemethanol (m.p. 100.5°) was obtained.

Anal. Calcd. for $C_{16}H_{15}ONS$: N, 5.19; S, 11.87. Found:

N, 5.02; S, 11.27.

Preparation of α,α-Di-(p-dimethylaminophenyl)-2-benzothiazolemethanol.- A solution of 0.084 mole of 2-benzothiazolyllithium in 215 ml. of ether at -75° was treated with 19 g. (0.069 mole) of p,p'-dimethylaminodiphenyl ketone. The cooling bath was removed and the reaction mixture was allowed to warm up to room temperature during one hour. Hydrolysis was effected by pouring onto crushed ice. Some insoluble material was filtered off and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was removed by distillation. This residue and the solid material obtained previously were dissolved in benzene, and the solution was filtered and cooled. This yielded 21.8 g. (64.3%) of α,α-di-(p-dimethylaminophenyl)-2-benzothiazolemethanol (m.p. 195°). The compound gives an intense green color in acetic acid.

Anal. Calcd. for $C_{24}H_{25}ON_3S$: N, 10.40; S, 7.94. Found: N, 10.28; S, 7.50.

Preparation of α-(n-Propyl)-2-benzothiazolemethanol.- 2-Benzothiazolyllithium (0.089 mole) in 180 ml. of ether at -75° was treated with 6.5 g. (0.089 mole) of n-butyraldehyde in 30 ml. of ether. The cooling bath was removed, and the mixture was stirred for three hours. At this point the entire reaction mixture was poured into 300 ml. of water, and the resulting layers were separated. The ether layer was dried over sodium sulfate before the ether was removed by

distillation. Twenty-five ml. of petroleum ether (b.p. 77-115°) was added to the residue. This yielded 10.3 g. (55.7%) of crystalline material (m.p. 82°). Recrystallization from petroleum ether (b.p. 77-115°) did not serve to raise the melting point of the α-(n-propyl)-2-benzothiazolemethanol.

Anal. Calcd. for $C_{11}H_{12}ONS$: N, 6.78; S, 15.57. Found: N, 6.68; S, 15.36.

Preparation of α-(p-Dimethylaminophenyl)-2-benzothiazolemethanol.- A solution of 0.081 mole of 2-benzothiazolyllithium in 180 ml. of ether at -75° was treated with 12.5 g. (0.081 mole) of solid p-dimethylaminobenzaldehyde. The cooling bath was removed and the mixture was stirred for three hours before it was hydrolyzed by pouring into 300 ml. of water. A precipitate was filtered away, and the layers were separated. The ether layer was dried over sodium sulfate before the ether was removed by distillation. The residue was combined with the initial residue, and the combined material was dissolved in benzene. This yielded 14.3 g. (59.6%) of α-(p-dimethylaminophenyl)-2-benzothiazolemethanol (m.p. 157°). Recrystallization from benzene did not raise the melting point.

Anal. Calcd. for $C_{16}H_{16}ON_2S$: N, 9.84; S, 11.28. Found: N, 9.68; S, 11.24.

2-Benzothiazolyllithium and Quinoline.- To a solution of 0.08 mole of 2-benzothiazolyllithium in 200 ml. of ether at -70° was added slowly 10.5 g. (0.08 mole) of quinoline. The mixture turned red-brown and a precipitate began to form. The

mixture was stirred while the temperature increased and Color Tests I^{205} were taken at frequent intervals. At the end of three hours a Color Test I^{205} was negative, and the temperature was 20°.

The reaction mixture was hydrolyzed with 100 ml. of 10% ammonium chloride. A yellow precipitate (4.3 g.) was filtered from the mixture. This melted at 164-183° (sintered at 150°). Part of this solid was dissolved in petroleum ether (b.p. 77-115°) to yield 1.05 g. of red crystals (m.p. 189-196°). The rest was dissolved in toluene to yield 0.75 g. of yellow crystals (m.p. 186-196°). By condensing mother liquors another 0.85 g. of material was obtained. Of the total of 2.6 g., 1.8 g. was dissolved in toluene and cooled to yield 1.2 g. of a light yellow solid (m.p. 199-200°). Recrystallization from toluene did not raise the melting point. At first this was thought to be the desired 2-benzothiazolyl-2'-quinoline or the 1,2-dihydro compound, but analysis indicated 2-benzothiazolyl-2'-benzothiazoline.

Anal. Calcd. for $C_{14}H_{10}N_2S_2$; N, 10.36; S, 23.70 Found: N, 10.56; S, 23.46.

The compound is not stable and turns yellow in light with an attendant decrease in melting point. A solution of 0.4 g. of the compound in 5 ml. of nitrobenzene was boiled for one hour. The solution turned very dark. On the addition of 3 ml. of anhydrous ethanol, 0.1 g. (25%) of shiny platelets (m.p. 310°) was obtained. A mixed melting point

with an authentic specimen of 2,2'-bibenzothiazole[209] showed no depression.

The original ether layer was separated and dried over sodium sulfate. The ether was evaporated, and the residue was distilled to yield 13.1 g. of oil (b.p. 122-132° at 26 mm.). This may be a mixture of benzothiazole and quinoline which have similar boiling points, though the picrate melted at 202° and showed no depression of melting point when mixed with an authentic sample of quinoline picrate.

2-Benzothiazolyllithium and Benzoyl Chloride.- A solution of 0.11 mole of 2-benzothiazolyllithium in 250 ml. of ether was prepared in the usual way. To this solution at -75° was slowly added 16 g. (0.12 mole) of freshly-distilled benzoyl chloride. The mixture turned red and finally cream-colored and at the end of forty minutes gave a negative Color Test I.[205] The mixture was hydrolyzed by pouring into a beaker of cracked ice. The ether layer yielded 3.4 g. of an unidentified material which melted at 210°. Treatment of the alcoholic mother liquor with phenylhydrazine produced a small quantity of needle-shaped crystals which melted at 149°. This gave no depression of melting point when mixed with a pure sample of the phenylhydrazone of 2-benzothiazolyl phenyl ketone prepared by adding 2-benzothiazolyllithium to benzonitrile.

2-Benzothiazolyllithium and Benzyl Chloride.- To 0.072 mole of 2-benzothiazolyllithium in 217 ml. of ether at -75°

was added 9.0 g. (0.072 mole) of benzyl chloride in 30 ml. of ether. There was no apparent reaction, so the mixture was allowed to warm up to room temperature and stirred for six hours. There was a heavy tan precipitate in the mixture which stood twelve hours before being hydrolyzed with 125 ml. of water. The layers were separated, and the ether layer was dried over sodium sulfate. The ether was distilled away, and the residue was distilled to yield 1.8 g. of foul-smelling material (b.p. 60-170° at 0.1 mm.). This partially solidified on standing, but no pure product could be obtained by crystallization from 95% ethanol. There was apparently no 2-benzylbenzothiazole present. A large amount of residue after the distillation did not yield any pure compound possibly because there was some decomposition during the distillation.

Phenyllithium and Benzothiazole.- Preliminary attempts to add phenyllithium to the azomethine linkage of benzothiazole showed the reaction to be not so smooth as with quinoline. Table IV lists some of the attempts made to improve the yield of 2-phenylbenzothiazole. The best yield was obtained by the following procedures: To 0.235 mole of phenyllithium[207] in 200 ml. of ether was added 14.3 g. (0.155 mole) of benzothiazole. The reaction mixture was kept at 0°during the addition (fifteen minutes) and for two hours after the addition. Hydrolysis was effected by the addition of 100 ml. of 10% ammonium chloride. The layers were separated, and the ether layer was

dried over sodium sulfate before removing the ether. The resulting residue was distilled to yield 3.7 g. of benzothiazole (b.p. 85-90° at 0.5 mm.) identified by the melting point of its picrate (m.p. 167°) and mixed melting point with an authentic specimen.[122] This is a 26.9% recovery of benzothiazole. The second fraction (b.p. 165-170° at 0.5 mm.) weighed 10.2 g. and was mostly 2-phenylbenzothiazole (41.9% crude yield). This was recrystallized from 95% ethanol to yield 7.7 g. (31.7%) of pure 2-phenylbenzothiazole (m.p. 114°) which showed no depression in a mixed melting point determination with an authentic specimen.[211]

In other experiments it was found that if water were used to hydrolyze the mixture rather than ammonium chloride solution, the greater part of the organic matter was dissolved in the water layer. No 2-phenylbenzothiazole was found by hydrolyzing with water and neutralizing the aqueous layer with dilute hydrochloric acid. Several attempts were made to isolate products from this layer, but none succeeded. Air, hydrogen peroxide, and iodine were added to the aqueous layer to effect oxidation of the suspected thiophenol to the disulfide, and the material was also shaken with benzoyl chloride. In the latter case a small amount of pure material (m.p. 181°) was obtained, but this was not identified.

Anal. Found: N, 2.93 and 2.98, S, 6.09 and 6.03.

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211. Bogert and Abrahamson, J. Am. Chem. Soc., 44, 826 (1922).

Table IV

Reaction of Phenyllithium and Benzothiazole

Reactants					
Phenyllithium (moles)	Benzothiazole (moles)	Temp. °C.	Time (hours)	Benzothiazole recovered, %	Other Products
0.065	0.065	-75	.16	36.6	Benzothiazole-2-carboxylic acid[a] (54%)
0.16	0.08	-75	1.0	65.7	
0.16	0.08	-75 to 28	3.0	8.0	2-Phenylbenzothiazole[b] (9.7%)
0.17	0.086	-80 to -50	3.2	81.7	Trace of material (m.p. 190°)[b, c]
0.17	0.086	-35	1.0	72.2	2-Phenylbenzothiazole[b] (12.2%)
0.087	0.087	-50	1.0	23.3	Benzothiazole-2-carboxylic acid[a] (68.5%)
0.16	0.08	-10	1.0	37.9	2-Phenylbenzothiazole[b, d] (41.1%)
0.088	0.088	0	.25	26.5	Benzothiazole-2-

a. Carbonated by pouring into a slush of ether and Dry Ice. b. Reaction hydrolyzed with dilute ammonium chloride solution. c. May be 2-benzothiazolyl-2'-benzothiazoline as the compound is converted to bibenzothiazole (m.p. 310°) by boiling with nitrobenzene. d. Purified yield is 26.2%.

Table IV (continued)

Reaction of Phenyllithium and Benzothiazole

Reactants: Phenyllithium (moles)	Reactants: Benzothiazole (moles)	Temp. °C.	Time (hours)	Benzothiazole recovered, %	Other Products
					carboxylic acid[a] (40%) 2-Phenylbenzothiazole (5.3%)
0.08	0.08	0	.5	24.1	Benzothiazole-2-carboxylic acid[a] (10%) 2-Phenylbenzothiazole (2.8%)
0.16	0.08	0	1.0	18.	2-Phenylbenzothiazole[b] (44.2%)
0.115	0.225	0	2.2	26.8	2-Phenylbenzothiazole[b,e] (41.9%)
0.18	0.09	28	1.6	17.0	2-Phenylbenzothiazole[b] (42%)
0.18	0.09	28	1.0	____	2-Phenylbenzothiazole[b] (40%)
0.18	0.09	28	0.6	____	2-Phenylbenzothiazole[b] (41%)
0.09	0.09	28	0.5	40	2-Phenylbenzothiazole (29%)

e. Purified yield is 31.7%.

Phenyllithium and 2-Benzothiazolyllithium.- A solution of 0.044 mole of 2-benzothiazolyllithium in 167 ml. of ether was prepared as previously described. At -75° a solution of 0.052 mole of phenyllithium[207] in 45 ml. of ether was added rapidly. The temperature was allowed to warm up, and after stirring for two hours the temperature was -10°. After hydrolysis with water the ether layer was dried over sodium sulfate, and the ether was removed by distillation. The residue yielded 4.3 g. (b.p. 61° at 0.03 mm.) of benzothiazole (71.6% recovery). There was a considerable residue, but no 2-phenylbenzothiazole was obtained from it.

Phenyllithium and 2-Phenylbenzothiazole.- To a solution of 24.2 g. (0.115 mole) of 2-phenylbenzothiazole in 100 ml. of ether was added 0.118 mole of phenyllithium[207] in 123 ml. of ether. On addition of the phenyllithium solution the color deepened and a gentle reflux occurred. After stirring for one hour at room temperature, a Color Test I[205] was positive, and the reaction mixture was carbonated by pouring into a slush of ether and Dry Ice. The mixture was hydrolyzed by the addition of 100 ml. of water, and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Toluene was added, and this solution was extracted with concentrated hydrochloric acid. These extracts were poured into water to yield 13.9 g. of impure 2-phenylbenzothiazole (m.p. 80-95°). This was dissolved as far as possible in 95% ethanol and cooled to yield 5.6 g.

of amorphous material (m.p. 108-111°). This is a 23.3% recovery of 2-phenylbenzothiazole, identified by mixed melting point with an authentic specimen.[211]

The acid filtrate from which the 2-phenylbenzothiazole was obtained was neutralized with potassium hydroxide to yield 3.2 g. of a greenish precipitate. On recrystallizing from 95% ethanol this yielded 1.1 g. (7.7%) of bis-(o-aminophenyl) disulfide (m.p. 93-94°).[212]

Anal. Calcd. for $C_{12}H_{12}N_2S_2$; N, 11.23; Found: N, 11.17.

From the toluene layer 3.6 g. of a crude product (m.p. 157° with softening at 144°) was obtained. Recrystallization from toluene and petroleum ether (b.p. 77-115°) yielded 2.5 g. (8.4%) of material (m.p. 162°) which showed no depression of melting point when mixed with an authentic specimen of triphenylmethanol.

Benzothiazole and Phenylmagnesium Bromide.- To 0.18 mole of phenylmagnesium bromide in 165 ml. of ether at -10° (bath temperature) was added 12.2 g. (0.09 mole) of benzothiazole in 30 ml. of ether. Stirring for one hour at -10° produced a yellow precipitate. Because of the slushy character of the material, an attempt was made to carbonate by adding powdered Dry Ice to the rapidly stirred mixture. The material soon gummed up the stirrer, however, so the stirring had to be discontinued. Hydrolysis by water was slow and resulted

212. Hofmann, Ber., 12, 2346 (1879).

in an emulsion which was broken up by acidifying with hydrochloric acid. The layers were separated, and the ether layer was extracted with two 200 ml. portions of 5% potassium hydroxide. Acidification of these extracts yielded 15.3 g. (68.6%) of benzoic acid (m.p. 122°; mixed m.p. with pure benzoic acid, 122°).

Distillation of the ether layer yielded 6.4 g. (52.4% recovery) of benzothiazole, identified by melting point of picrate (167°)[122] and mixed melting point with an authentic specimen of the picrate. The oily residue was extracted with concentrated hydrochloric acid; neutralization of these extracts with potassium hydroxide yielded a small amount of greenish precipitate. This precipitate (0.4 g.) was dissolved in 95% ethanol and decolorized with carbon. Needle-shaped crystals (0.15 g.) formed which melted at 114° and showed no depression of melting point when mixed with pure 2-phenylbenzothiazole.[211] This is a 0.8% yield.

2-Phenylbenzothiazole and Phenylmagnesium Bromide.- A solution of 13.5 g. (0.1 mole) of 2-phenylbenzothiazole in ether was treated with 0.12 mole of phenylmagnesium bromide in 120 ml. of ether. At the end of twenty-four hours' stirring at the reflux point of ether a Color Test I[205] was positive. After hydrolysis the ether layer yielded 12.5 g. (92.8% recovery) of pure 2-phenylbenzothiazole (m.p. 114°), identified by melting point, and mixed melting point with an authentic specimen.[211]

Attempt to Metalate Benzoxazole.- A solution of 0.09 mole of methyllithium in 100 ml. of ether was cooled to -75°. To this was added 11.2 g. (0.09 mole) of benzoxazole. On addition of the benzoxazole a strong evolution of gas (possibly methane) was observed. Immediately after the addition the mixture was carbonated by pouring into a slush of ether and Dry Ice. After hydrolyzing with water the layers were separated, and the water layer was neutralized with concentrated hydrochloric acid. No acid was obtained.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 7.4 g. of benzoxazole (b.p. 82° at 21 mm.). This is a 66.1% recovery.

Several other attempts were made to metalate benzoxazole using n-butyllithium, phenyllithium, and butylmagnesium bromide. In most cases a negative Color Test I[205] was obtained, and no acid was found after carbonation. The recovery of benzoxazole varied from 20% to 80%. One attempt employed benzophenone, but no α,α-diphenyl-2-benzoxazolemethanol could be isolated.

Preparation of p-Tolyl 2-Quinolyl Sulfide.[213] An excess of p-thiocresol was dissolved in absolute ethanol and treated with lead acetate. The canary-yellow precipitate was filtered and washed several times with water and finally with alcohol. It was then dried for twenty-four hours in a vacuum desiccator.

213. See Brooker and Van Dyke, British Patent 483,071 (May 12, 1938) [Chem. Zentr., 38II, 1863 (1938)].

A mixture of 11.1 g. (0.025 mole) of lead p-thiocresoxide and 12.3 g. (0.075 mole) of 2-chloroquinoline was heated to 150° for five hours during which time the mixture turned from yellow to white. The mixture was cooled and extracted with ether. The white precipitate remaining was lead chloride as proved by its solubility in hot water and by positive lead and chloride ion tests. The ether layer was dried over sodium sulfate, and the ether was distilled away and replaced by petroleum ether (b.p. 60-70°). This yielded 9.4 g. (75%) of p-tolyl 2-quinolyl sulfide (m.p. 68°).

Anal. Calcd. for $C_{16}H_{13}NS$: S, 12.76. Found: S, 12.87.

In another preparation 31 g. (0.25 mole) of p-thiocresol in 100 ml. of ether was treated with 0.25 mole of phenyllithium in 208 ml. of ether. After the addition 41 g. (0.25 mole) of 2-chloroquinoline was added, and the ether was removed by distillation. The residue was heated to 140° for eighteen hours. After cooling water was added to hydrolyze the mixture, and ether was added to extract the organic material. The ether layer was dried over sodium sulfate and was replaced by petroleum ether (b.p. 77-115°). This yielded 50.5 g. (80.3%) of p-tolyl 2-quinolyl sulfide (m.p. 68°).

Phenyllithium and p-Tolyl 2-Quinolyl Sulfide.- To a solution of 6.5 g. (0.03 mole) of p-tolyl 2-quinolyl sulfide in 50 ml. of ether was added 33 ml. (0.03 mole) of 0.92 M phenyllithium.[207] The reaction mixture became pink and then

turned brown, and a gentle reflux of the ether occurred. At the end of three and one-half hours' stirring, a Color Test I[205] was positive though a considerable amount of 2% iodine in glacial acetic acid was required to develop the color. The mixture was refluxed for fifteen minutes before hydrolyzing with 100 ml. of water. The layers were separated and the water layer was acidified to yield 2.12 g. (57%) of p-thiocresol (m.p. 43.5°). A mixed melting point with an authentic specimen showed no depression.

The ether was distilled from the ether layer and was replaced by petroleum ether (b.p. 60-70°). This yielded 2.92 g. (47.4%) of 2-phenylquinoline (m.p. 81-83°). A mixed melting point with an authentic specimen of 2-phenylquinoline[214] showed no depression. The picrate[215] melted at 191° and showed no depression of a mixed melting point with an authentic specimen.

The reaction between phenyllithium and p-tolyl 2-quinolyl sulfide was repeated at -75° (bath temperature) for twenty-five minutes. On working up this reaction as before an odor of p-thiocresol, but no precipitate, was detected. A recovery of 93.8% of starting material was obtained.

p-Tolyl-2-quinolyl Sulfide and n-Butyllithium (-75°).-

214. Doebner and Miller, Ber., 16, 1665 (1883).

215. Doebner and Miller, ibid., 19, 1197 (1886).

A solution of 0.10 mole of n-butyllithium[216] in 165 ml. of ether was cooled to -75°. To this was added slowly 12.5 g. (0.05 mole) of p-tolyl 2-quinolyl sulfide in 80 ml. of ether. At the end of the ten minute addition period no reaction was noted. The stirring was continued for fifteen minutes before 100 ml. of water was added to hydrolyze the mixture. Neutralization of the water layer after separation yielded 0.85 g. (13.3%) of p-thiocresol, identified by melting point (41-43°) and mixed melting point with an authentic specimen.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. The residue was distilled to yield 1.03 g. (11.2%) of 2-n-butylquinoline (b.p. 95° at 0.2 mm.), identified by the melting point of the picrate (163°) and a mixed melting point with an authentic specimen of the picrate.[3] The residue from the distillation was dissolved in petroleum ether (b.p. 60-70°) and yielded 11.3 g. (82.2% recovery) of p-tolyl 2-quinolyl sulfide (m.p. 68°). There was no depression of melting point with an authentic specimen of the sulfide. This recovery increases the yields of 2-n-butylquinoline and p-thiocresol to 62% and 68%, respectively.

n-Butyllithium and p-Tolyl 2-Quinolyl Sulfide.- A solution of 26.4 g. (0.10 mole) of p-tolyl 2-quinolyl sulfide in

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216. This and subsequent preparations of n-butyllithium utilized the improved procedure which gives yields of 75% to 90%; see Gilman, Beel, Brannen, Bullock, Dunn, and Miller, J. Am. Chem. Soc., 71, 1499 (1949).

150 ml. of ether was treated at room temperature with 0.11 mole of n-butyllithium[216] in 120 ml. of ether. Eight minutes after the addition a Color Test I[205] was negative, so the permanganate-colored solution was poured into a slush of ether and dry ice. The mixture was hydrolyzed with water, made acid with hydrochloric acid, and realkalinized with 10% sodium hydroxide. After separation the ether layer was dried over sodium sulfate, and the ether was distilled away. Distillation of the residue yielded 13 g. (63.8%) of 2-n-butylquinoline (b.p. 95° at 0.2 mm.; n_D^{20} 1.5754). Identification was completed by preparation of the picrate which melted at 163° and showed no depression of melting point when mixed with an authentic specimen of the picrate.[3] There was also about 1.5 g. of a red oil, which was dissolved in dilute ethanol to yield 1.2 g. of bis-(p-tolyl) disulfide (m.p. 44-45°). A mixed melting point with an authentic specimen of the disulfide showed no depression.

The basic water layer was acidified and cooled. The resulting precipitate was dissolved as far as possible in dilute sodium hydroxide. The insoluble material was recrystallized from dilute ethanol to yield 0.5 g. of bis(p-tolyl) disulfide, identified as above. Acidification of the base-soluble portion yielded 3.4 g. of p-thiocresol (m.p. 41°), identified by mixed melting point with pure p-thiocresol. The total yield of p-thiocresol and disulfide was 41%.

p-Tolyl 2-Quinolyl Sulfide and Phenylmagnesium Bromide.-

A solution of 0.046 mole of phenylmagnesium bromide in 40 ml. of ether was added to 11.6 g. (0.046 mole) of p-tolyl 2-quinolyl sulfide in 50 ml. of ether. Shortly after the addition a red color appeared. This color darkened to a deep permanganate color after stirring for eighteen hours. The reaction mixture was hydrolyzed with 100 ml. of 5% hydrochloric acid. A crystalline precipitate appeared which weighed 5.9 g. and melted at 199-204°. It dissolved in water difficultly and gave a precipitate with silver nitrate. Addition of base yielded p-tolyl 2-quinolyl sulfide (m.p. 68°), so the compound is apparently the hydrochloride of p-tolyl 2-quinolyl sulfide (44.5%).

A small amount (0.24 g.) of p-thiocresol (4.2%), identified by melting point (41-43°) and mixed melting point with an authentic specimen was obtained. From the ether layer 3.5 g. (30.1% recovery) of p-tolyl 2-quinolyl sulfide (m.p. 68°) was obtained. In the hydrochloric acid extracts 0.3 g. (3.2%) of 2-phenylquinoline,[214] identified by melting point (83°) and mixed melting point with an authentic specimen, was found. The total recovery of p-tolyl 2-quinolyl sulfide was 74.5%. This increased the yields of 2-phenylquinoline and p-thiocresol to 12% and 17%, respectively.

2-Phenoxyquinoline and Phenyllithium. The 2-phenoxyquinoline was prepared in 77% yield from sodium phenoxide and 2-chloroquinoline in boiling phenol (181°) according to the directions of Friedlander and Ostermaier.[54] After drying in

a vacuum desiccator for eighteen hours, 11.1 g. (0.05 mole) of 2-phenoxyquinoline was dissolved in 50 ml. of ether and treated with 55 ml. of 0.10 N phenyllithium (0.055 mole).[207] The mixture began to reflux and turned red in color. The stirring was continued for eighteen hours at room temperature before hydrolyzing with 100 ml. of water. The layers were separated, and the basic water layer was acidified with hydrochloric acid and extracted with three 50 ml. portions of ether. The ether was distilled away and the residue was distilled yielding 3.2 g. of a colorless liquid (b.p. 78° at 18 mm.) which formed beautiful crystals on standing and had the odor of phenol (m.p. 41-42°). A mixed melting point with pure phenol melted at 41-42°. The yield of phenol was 72.3%.

The ether was removed from the original ether layer by distillation, and the residue was dissolved in petroleum ether (b.p. 60-70°). An oily red precipitate was extracted with dilute hydrochloric acid (1:1) to extract any 2-phenylquinoline. Neutralization with sodium hydroxide yielded 7.2 g. (m.p. 84°) of 2-phenylquinoline (70.2%). A mixed melting point with an authentic specimen showed no depression.[214]

2-Phenoxyquinoline and n-Butyllithium.- A solution of 20 g. (0.09 mole) of 2-phenoxyquinoline[54] in 100 ml. of ether was treated at room temperature with 120 ml. of a solution of n-butyllithium[216] (0.09 mole) in ether. A gentle reflux occurred, and the solution became red and then permanganate in color. After stirring for four hours a Color Test I[205]

was negative, so the reaction mixture was carbonated by pouring into a slush of ether and Dry Ice. After warming up to room temperature, the mixture was hydrolyzed with water and acidified with hydrochloric acid to break up the emulsion. The mixture was realkalinized with potassium hydroxide, and the layers were separated. The water layer was made strongly acid, and the phenol was extracted with ether. After drying over sodium sulfate and removing the ether by distillation, the residue was distilled to yield 5.3 g. (62.6%) of phenol (b.p. 78° at 18 mm.). This material melted at 41-42°, and a mixed melting point with phenol showed no depression.

The original ether layer was dried over sodium sulfate and the ether was removed. Distillation yielded 1.6 g. (b.p. 70° at 0.05 mm.) of 2-n-butylquinoline (9.6%) which was identified by the melting point of the picrate (161°) and a mixed melting point of the picrate with an authentic specimen.[3] Also there was obtained 3.0 g. (b.p. 140-150° at 0.05 mm.) of 2-phenoxyquinoline (14.9% recovery) which was identified by melting point (66°) and mixed melting point with pure 2-phenoxyquinoline.[54] A higher boiling red oil was obtained which after solution in petroleum ether (b.p. 60-70°) formed a small amount of unidentified crystals (m.p. 94°).

2-Phenoxyquinoline and Phenylmagnesium Bromide.- To 8.5 g. (0.038 mole) of 2-phenoxyquinoline[54] in 60 ml. of ether was added 40 ml. (0.04 mole) of phenylmagnesium bromide in ether. The addition was rapid, and there was no evidence

of reaction. At the end of eighteen hours at room temperature a considerable amount of white precipitate was present and the supernatant liquid was pink. Some of the white precipitate was removed and washed with dry ether. A Color Test I[205] on this material was negative. A halogen test with silver nitrate was positive. The pink supernatant liquid gave a strongly positive Color Test I.[205] After stirring for twenty-two hours longer, the white precipitate was removed by filtration.

From this white precipitate (3.9 g.) on hydrolysis was obtained 1.7 g. (20% recovery) of 2-phenoxyquinoline (m.p. 64-65°). The water layer, which was slightly basic to litmus, showed a strong test for halogen with silver nitrate, and had a slight odor of phenol. Of the total amount of precipitate 46.3% was found to be 2-phenoxyquinoline.

The original ether layer was hydrolyzed, and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was distilled. The residue was dissolved in petroleum ether (b.p. 60-70°), but only an oil precipitated out. The petroleum ether solution was extracted with 10% sodium hydroxide. Neutralization of the extracts with hydrochloric acid yielded a precipitate of 0.15 g. of phenol (4.6%), identified by melting point (41-42°) and mixed melting point with an authentic specimen. From the petroleum ether layer was obtained 3.5 g. (43.5%) of 2-phenoxyquinoline (m.p. 58-61°), identified by mixed melting point. This is a total recovery of 84.7% of the 2-phenoxyquinoline.[54]

Condensation of the mother liquors yielded some impure 2-phenoxyquinoline and finally 0.2 g. (2.6%) of 2-phenylquinoline (m.p. 78-81°). A mixed melting point with pure 2-phenylquinoline[214] melted at 80-83°.

2-Ethoxyquinoline and Phenyllithium.- A solution of 0.048 mole of phenyllithium[207] in 70 ml. of ether was added to 8.2 g. (0.048 mole) of 2-ethoxyquinoline, prepared from 2-chloroquinoline and sodium ethoxide,[55] in 50 ml. of ether, and the mixture was stirred for eighteen hours at room temperature. At this point the solution was dark brown, contained a white precipitate, and a Color Test I[205] was negative. Water was added for hydrolysis, and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 4.5 g. (54.8% recovery) of 2-ethoxyquinoline (b.p.74° at 0.4 mm.; n_D^{20} 1.5892) and 4.1 g. (41.5%) of 2-phenylquinoline (b.p. 170° at 0.4 mm.). This solidified on cooling and melted at 83-84° and showed no depression of a mixed melting point with an authentic specimen.[214]

2-Ethoxyquinoline and n-Butyllithium.- A solution of 0.19 mole of n-butyllithium[216] in 253 ml. of ether was added slowly at room temperature to 32.2 g. (0.19 mole) of 2-ethoxyquinoline.[55] Twenty minutes after the addition the refluxing stopped and a Color Test I[205] was negative. The mixture was carbonated by pouring into a slush of ether and Dry Ice. Hydrolysis was effected by adding water and a precipitate of

lithium bicarbonate was removed by filtration. Acidification of the aqueous layer yielded 2.42 g. of an acid which melted at 120-130°. Solution in sodium hydroxide and reprecipitation by hydrochloric acid yielded a compound which melted at 132-133°. This is the melting point of 2-ethoxyquinoline-3-carboxylic acid.[217]

Anal. Calcd for $C_{12}H_{11}NO_3$: N, 6.45; neut. equiv., 217.2. Found: N, 6.38; neut. equiv., 218.0.

A small amount of the acid was treated with thionyl chloride and then with concentrated ammonium hydroxide to form the carboxamide (m.p. 155-157°). A mixed melting point with this material and a sample of 2-ethoxyquinoline-3-carboxamide[203, 218] melted at 156-157°.

The ether layer was dried over sodium sulfate; the ether was removed by distillation, and the residue was distilled in a still of sixteen theoretical plates at a vacuum of 0.1 mm. This resulted in 4.8 g. (14.9% recovery) of 2-ethoxyquinoline (n_D^{20} 1.5882) and 17.0 g. (49.4%) of 2-n-butylquinoline, identified by melting point of its picrate (163°) and mixed melting point of the picrate with an authentic specimen.[3] The last fraction (n_D^{20} 1.5462) formed a crystalline precipitate on standing. This was filtered and washed with petroleum ether

217. Friedländer and Göhring, Ber., 17, 456 (1884).

218. The authentic specimen of 2-ethoxyquinoline-3-carboxamide was kindly supplied by Prof. Hans Wojahn.

(b.p. 60-70°). The melting point of this unidentified material was 95°.

2-Ethoxyquinoline and Phenylmagnesium Bromide.- A solution of 0.10 mole of phenylmagnesium bromide in 100 ml. of ether was added to 17.3 g. (0.10 mole) of 2-ethoxyquinoline[55] in 50 ml. of ether, and the mixture was stirred at room temperature for eighteen hours. A purple color developed and a heavy white precipitate was obtained. Hydrolysis was effected by the addition of 100 ml. of ammonium chloride, and the layers were separated. After drying over sodium sulfate the ether was removed by distillation, and the residue was distilled to yield 15.7 g. (90.8% recovery) of 2-ethoxyquinoline (b.p. 106° at 0.3 mm.; n_D^{20} 1.5876).

2-Ethoxyquinoline and Phenylcadmium Chloride.[219] To a solution of 0.10 mole of phenylmagnesium bromide in 120 ml. of ether was added 18.3 g. (0.10 mole) of anhydrous cadmium chloride. A black precipitate appeared immediately and a Color Test I[205] was negative after ninety minutes. A solution of 17.3 g. (0.10 mole) of 2-ethoxyquinoline in ether was added. A white precipitate formed, and the mixture was stirred for forty-eight hours at room temperature before hydrolyzing with a strong solution of ammonium chloride and ammonium hydroxide. The ether layer was dried over sodium sulfate; the ether was removed by distillation, and the residue was distilled to yield

219. Gilman and Nelson, Rec. trav. chim., 55, 518 (1936).

16.1 g. (93.2% recovery) of 2-ethoxyquinoline (b.p. 81-83° at 0.05 mm.; N_D^{20} 1.5914). There was a slight residue after distillation.

2-Chloroquinoline and Phenyllithium.- To 15 g. (0.093 mole) of 2-chloroquinoline was added 0.093 mole of phenyllithium[207] in 82 ml. of ether. A vigorous reaction took place, resulting in a white precipitate and a dark red solution. A Color Test I[205] was negative within thirty minutes after the addition. The mixture was carbonated by pouring into a slush of ether and Dry Ice. After hydrolysis with water the ether layer was separated and dried over sodium sulfate. After removing the ether the residue was distilled to yield 1.2 g. (8.0% recovery) of 2-chloroquinoline (b.p. 115° at 0.03 mm.), and 12.5 g. (65.7%) of 2-phenylquinoline (b.p. 160° at 0.05 mm.). This was recrystallized from petroleum ether (b.p. 60-70°) to yield 11.8 g. of pure 2-phenylquinoline (m.p. 83-84°). A mixed melting point with an authentic specimen[214] of 2-phenylquinoline showed no depression. This is a 62.0% purified yield. Considering the recovery of 2-chloroquinoline the net yield is 67.3%.

No acid was obtained from the water layer on neutralization with hydrochloric acid.

2-Chlorobenzothiazole and Phenyllithium.- To 10.6 g. (0.06 mole) of 2-chlorobenzothiazole in 50 ml. of ether was added 120 ml. of 0.96 M phenyllithium[207] in ether. Rapid refluxing took place during the addition. The mixture was

stirred for eighteen hours before hydrolyzing with 100 ml. of water. The ether was removed from the ether layer and replaced with 95% ethanol to yield 4.6 g. (36.6%) of 2-phenylbenzothiazole (m.p. 106-110°), identified my mixed melting point with an authentic specimen.[211]

The rest of the organic material was in the water layer but no pure product could be isolated.

2-Chloroquinoline and n-Butyllithium.- To 0.12 mole of n-butyllithium[216] in 120 ml. of ether at -50° (bath temperature) was added 19.6 g. (0.12 mole) of 2-chloroquinoline in 60 ml. of ether. After the addition (twenty minutes) the mixture was stirred for twenty minutes before a negative (questionable) Color Test I[205] was obtained. The mixture was carbonated by pouring into a slush of ether and Dry Ice. Hydrolysis was effected by the addition of 100 ml. of 10% hydrochloric acid. The layers were separated, and the acid layer was neutralized with potassium hydroxide and extracted with ether. Distillation of the residue yielded 11.6 g. (52.2%) of 2-n-butylquinoline (b.p. 90-100° at 0.08 mm.). This was identified by the melting point of this picrate with an authentic specimen.[3] No 2-chloroquinoline was recovered.

Distillation of the residue from the original ether layer yielded 3.9 g. (31.6%) of valeric acid (b.p. 61-63° at 0.15 mm.).

2-Chloroquinoline and Phenylmagnesium Bromide.- A mixture of 0.10 mole of phenylmagnesium bromide and 16.4 g. (0.10 mole) of 2-chloroquinoline was stirred for forty-eight hours at room

temperature, but a negative Color Test I^{205} could not be obtained. The mixture was carbonated by pouring into a slush of ether and Dry Ice. After hydrolysis a small amount of benzoic acid was obtained from the water layer. Distillation of the residue from the ether layer yielded 8.3 g. (50.6% recovery) of 2-chloroquinoline (b.p. 115°at 0.03 mm.) and 6.49 g. (31.2%) of 2-phenylquinoline (b.p. 165° at 0.03 mm.). This melted at 83-84 after recrystallization from petroleum ether (b.p. 60-70°) and showed no depression of melting point when mixed with 2-phenylquinoline.[214] The net yield was 61.6%.

2-Chlorobenzothiazole and Phenylmagnesium Bromide.- A solution of 0.10 mole of phenylmagnesium bromide in 50 ml. of ether was added to 16.9 g. (0.10 mole) of 2-chlrorbenzothiazole in 50 ml. of ether at 0° (bath temperature). No reaction took place so the ice bath was removed, and the mixture was stirred at room temperature for twelve hours at which time a Color Test I^{205} was still positive. The solution was refluxed for two hours, and a Color Test I^{205} was negative at the end of this time. Hydrolysis was effected by the addition of 100 ml. of ammonium chloride solution, and the layers were separated. After drying the ether layer over sodium sulfate the ether was removed by distillation. Distillation of the residue yielded 6.6 g. (39.1% recovery) of 2-chlorobenzothiazole (b.p. 80-85° at 0.05 mm.; n_D^{20} 1.6308) and 9.8 g. (47.8%) of 2-phenylbenzothiazole (b.p. 160° at 0.05 mm.). This was recrystallized from 95% ethanol to yield 9.6 g. (41.9%) of pure

2-phenylbenzothiazole (m.p. 114°), identified by mixed melting point with an authentic specimen.[211] The net yield was 67.7%.

2-Chloroquinoline and Phenylcadmium Chloride.-[219] A suspension of 0.10 mole of phenylcadmium chloride in 70 ml. of ether was prepared by adding 18.3 g. (0.10 mole) of anhydrous cadmium chloride to 0.10 mole of phenylmagnesium bromide. A solution of 16.3 g. (0.10 mole) of 2-chloroquinoline was added, and the mixture was stirred at room temperature for eighteen hours. The mixture was hydrolyzed with a strong solution of ammonium chloride and ammonium hydroxide, and the layers were separated. The ether layer was dried over sodium sulfate; the ether was removed by distillation, and the residue was distilled to yield 15.9 g. (97.5% recovery) of 2-chloroquinoline (b.p. 124° at 0.5 mm.), identified by means of its picrate (m.p. 126-127°) and mixed melting point with an authentic specimen.

Preparation of 2-(N-Piperidyl)quinoline.- A mixture of 17.0 g. (0.20 mole) of piperidine and 33.3 g. (0.20 mole) of 2-chloroquinoline was heated to 130° for eighteen hours. The completely solidified reaction mixture was cooled and dissolved in dilute hydrochloric acid and then precipitated with 10% sodium hydroxide. The material was extracted with ether, and the ether extracts were dried over sodium sulfate. After removal of the ether the residue was dissolved in petroleum ether (b.p. 60-70°) and cooled to yield 32.9 g. (81.6%) of 2-(N-piperidyl)quinoline (m.p. 41-48°). This product was redissolved in petroleum ether (b.p. 60-70°) and decolorized with

carbon. On cooling 24.4 g. (57.6%) of pure 2-(N-piperidyl)-quinoline (m.p. 51°) was found.

Anal. Calcd. for $C_{14}H_{16}N_2$: N, 13.18. Found: N, 13.10.

The same compound was obtained by stirring 0.10 mole of lithiumpiperidide, prepared from phenyllithium and piperidine, and 16.3 g. (0.10 mole) of 2-chloroquinoline in ether for eighteen hours while the temperature rose from 0° to that of the room. On distillation and recrystallization of the product from petroleum ether (b.p. 60-70°) 7.3 g. (36.2%) of 2-(N-piperidyl)quinoline was obtained. The recovery of 3.3 g. (21.1%) of 2-chloroquinoline raised the net yield to 45.9%.

Phenyllithium and 2-(N-Piperidyl)quinoline.- A solution of 10.1 g. (0.05 mole) of 2-(N-piperidyl)quinoline in 50 ml. of ether was treated at room temperature with 0.05 mole of phenyllithium.[207] After stirring for eighteen hours at room temperature a Color Test I[205] was still positive. Hydrolysis was effected by the addition of 50 ml. of water; the layers were separated, and the ether layer was dried over sodium sulfate. Distillation of the residue from the ether layer yielded 1.9 g. of biphenyl (m.p. 70°) which was identified by the method of mixed melting point. Also 4.4 g. (44% recovery) of 2-(N-piperidyl)quinoline (b.p. 165-170° at 0.2 mm.) was obtained. This was identified, after recrystallization from petroleum ether (b.p. 60-70°), by melting point (50°) and mixed melting point with an authentic specimen.

No product could be isolated from the large amount of

residue left after the distillation.

n-Butyllithium and 2-(N-Piperidyl)quinoline.- To a solution of 21.1 g. (0.10 mole) of 2-(N-piperidyl)quinoline in 50 ml. of ether at room temperature was added 0.10 mole of n-butyllithium[216] in 120 ml. of ether. The solution turned dark red. At the end of four hours a Color Test I[205] was positive so the stirring was continued for twelve hours longer before carbonating by pouring into a slush of ether and Dry Ice. After hydrolysis with water, the mixture was acidified with hydrochloric acid and then realkalinized with dilute potassium hydroxide. The basic layer was carefully neutralized to litmus with hydrochloric acid which produced heavy fumes of piperidine hydrochloride. The oil which precipitated out was extracted with ether. Distillation of the residue from the ether layer yielded 1.9 g. (22%) of piperidine, identified by conversion to benzensulfonylpiperidide (m.p. 93°) and mixed melting point with an authentic specimen.

Distillation of the original ether layer yielded 3.3 g. (17.8%) of 2-n-butylquinoline, identified by melting point of the picrate (161°) and mixed melting point with an authentic specimen of the picrate.[3] Further distillation yielded 11.9 g. of a viscous oil which was not identified.

Phenylmagnesium Bromide and 2-(N-Piperidyl)quinoline.- To 8.5 g. (0.04 mole) of 2-(N-piperidyl)quinoline in 50 ml. of ether was added rapidly at room temperature 0.04 mole of phenylmagnesium bromide in 40 ml. of ether. After stirring

for sixty hours a Color Test I[205] was strongly positive. There was no precipitate, and the reaction mixture had darkened slightly. An ammonium chloride solution was added to hydrolyze the mixture, and the layers were separated. The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 6.7 g. (78.8% recovery) of 2-(N-piperidyl)quinoline (b.p. 140-145° at 0.05 mm.). This was recrystallized once from petroleum ether (b.p. 60-70°) and melted at 51°. A residue from the distillation resisted all attempts at crystallization.

Preparation of 2-Allyloxyquinoline.[166]- Into 150 ml. of allyl alcohol was dropped 4.6 g. (0.2 g.-atom) of sodium. After the sodium had reacted 32.7 g. (0.2 mole) of 2-chloroquinoline was added, and the mixture was refluxed for eighteen hours. The excess allyl alcohol was removed by distillation under vacuum, and ether and water were added to the residue. Distillation of the oil from the ether layer yielded 32.6 g. (87%) of 2-allyloxyquinoline (n_D^{20} 1.5942; d_4^{20} 1.0912. Calcd. for $C_{12}H_{11}NO$: M_R, 57.00. Found: 57.61).

Phenyllithium and 2-Allyloxyquinoline.- A solution of 0.10 mole of phenyllithium[207] in 90 ml. of ether was added slowly at -35° to 18.5 g. (0.10 mole) of 2-allyloxyquinoline[166] in 50 ml. of ether. The solution turned slightly red in color, but a Color Test I[205] was strongly positive after stirring for one hour, so the acetone-Dry Ice bath was replaced by an ice-bath. The mixture was stirred at this temperature for ten hours

and then for one hour longer while it warmed up to room temperature. At this point a Color Test I[205] was negative, so the mixture was hydrolyzed with water, and after separation the water layer was acidified giving an odor of phenol.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 2 g. (10.8% recovery) of 2-allyloxyquinoline (b.p. 145° at 0.1 mm.; n_D^{20} 1.5948). Also 3.8 g. (18.5%) of 2-phenylquinoline (b.p. 170° at 0.1 mm.), which after recrystallization from petroleum ether (b.p. 60-70°) melted at 83-84° and showed no depression of melting point when mixed with an authentic specimen of 2-phenylquinoline,[214] was obtained.

Attempts to crystallize the large amount of residue from the distillation failed.

In a similar reaction carried out at room temperature for one and one-half hours a 15.6% recovery of 2-allyloxyquinoline and a 10.6% yield of 2-phenylquinoline were obtained.

Phenyllithium and 2-Benzyloxyquinoline.-[220] A solution of 0.10 mole of phenyllithium[207] in 80 ml. of ether was added to 23.5 g. (0.10 mole) of 2-benzyloxyquinoline in 30 ml. of ether cooled to 0°. The color darkened immediately, and at the end of eighteen hours was a reddish-black. A Color Test I[205] was negative. The mixture was hydrolyzed by pouring onto

220. Kindly supplied by Mr. I. Zaremberg of these Laboratories.

ice. The layers were separated, and the water layer was acidified. White radiating crystals (m.p. 187°) which weighed 0.5 g. were obtained. Recrystallization from ethanol yielded 3.42% of 2-hydroxyquinoline (m.p. 188-192°), identified by melting point and mixed melting point with an authentic specimen (192-194°).

The ether layer was extracted with 100 ml. and then 50 ml. of 10% hydrochloric acid. On cooling 3.8 g. of a rather unstable hydrochloride (m.p. 183°) was obtained. This yielded 2-benzyloxyquinoline on neutralization with sodium hydroxide, extraction with ether, and recrystallization from 95% ethanol. This product melted at 50-51° and showed no depression of melting point when mixed with an authentic specimen of 2-benzyloxyquinoline.

After filtration of the crystalline hydrochloride the acid extracts were neutralized with sodium hydroxide and extracted with ether. Distillation of the residue from the ether layer yielded 1.2 g. of benzyl alcohol (b.p. 60° at 0.03 mm.; n_D^{20} 1.5424), identified by melting point of the 3,5-dinitrobenzoate and mixed melting point with an authentic specimen. Also 9.1 g. of an oil (b.p. 160-170° at 0.05 mm.) was obtained. From this by fractional crystallization from petroleum ether (b.p. 60-70°) was obtained 4 g. (17% recovery) of 2-benzyloxyquinoline, identified by melting point and mixed melting point with an authentic specimen. Also 2.5 g. (12.2%) of 2-phenylquinoline, identified by melting point (79-81°).

and mixed melting point with an authentic specimen[214] (80-82°), was found.

There was also obtained 0.5 g. of a higher melting material. More of this product, which melted at 108-110°, was obtained on distillation of the original ether layer. The melting point of this unidentified compound was raised to 110-112° by recrystallizing from petroleum ether (b.p. 60-70°).

Anal. Found: N, 6.38; N, 6.47.

This analysis does not check for any of the expected products. Distillation of the original ether layer increased the amount of benzyl alcohol to 2.8 g. (24.8%).

Benzylmagnesium Chloride and 2-Chloroquinoline.- A solution of 0.10 mole of benzylmagnesium chloride in 80 ml. of solution was cooled to -8°, and 16.3 g. (0.10 mole) of 2-chloroquinoline in 50 ml. of ether was added dropwise during twenty-five minutes. After stirring for six hours a Color Test I[205] was faintly positive. The entire reaction mixture was poured into a slush of ether and Dry Ice, and hydrolysis was effected by an ammonium chloride solution.

Acidification of the water layer yielded 5.0 g. (36%) of phenylacetic acid. This indicated that something had interfered with the Color Test I[205] which had been only faintly positive.

In the ether layer a small amount of an impure solid (m.p. 155-160°) was found. Also 8.5 g. (52.1% recovery) of 2-chloroquinoline was obtained. No 2-benzylquinoline was isolated.

Preparation of 2-Benzylquinoline.- Approximately 0.18 mole of benzylsodium was prepared according to the directions of Gilman, Pacevitz, and Baine[221] by the metalation of toluene with phenylsodium. This was cooled to -40° (bath temperature) and 30 ml. of quinoline was added. After stirring for one hour a Color Test I[205] was weak, so the reaction mixture was carbonated by pouring into a slush of ether and Dry Ice. After hydrolyzing with water, the layers were separated, and the water layer was acidified with hydrochloric acid, but no acid was obtained.

The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Distillation of the residue yielded 15 g. of quinoline (b.p. 75-80° at 0.04 mm.) and 15.4 g. of a yellow oil (b.p. 145-50° at 0.04 mm.). This gave a reddish-orange picrate which melted at 153.5-154.5°. Recrystallization from 90% ethanol did not change the melting point.

The yellow oil was dissolved in anhydrous alcohol, and 15 g. of mercuric oxide was added. After heating on the steam-plate for eighteen hours, the mercury and mercuric oxide were removed by filtration. The alcohol was removed by distillation, and the residue was distilled to yield 13.4 g. (34%) of 2-benzylquinoline (b.p. 145-50° at 0.04 mm.), identified by

221. Gilman, Pacevitz, and Baine, J. Am. Chem. Soc., 62, 1518 (1940).

melting point of the picrate (154-155°) and mixed melting point (154-155°) with an authentic specimen prepared by fractional crystallization of the picrates of 2- and 4-benzylquinoline from n-propyl alcohol. The mixture of 2- and 4-benzylquinoline was obtained by treatment of quinoline with benzylmagnesium chloride in dioxane according to the directions of Bergmann and Rosenthal.[132]

Phenyllithium and 2-Benzylquinoline.- A solution of 0.035 mole of phenyllithium[207] in 40 ml. of ether was added at room temperature to a solution of 8.77 g. (0.04 mole) of 2-benzylquinoline in 50 ml. of ether. The solution turned a deep red, and after stirring for eighteen hours a Color Test I[205] was negative. The material was carbonated by pouring into a slush of ether and Dry Ice. The layers were separated after acidification and realkalinization to break up an emulsion. No acid was obtained on acidification of the water layer. Distillation of the ether layer residue yielded 7.2 g. (82.6% recovery) of 2-benzylquinoline (b.p. 170-176° at 0.1 mm.; n_D^{20} 1.6339-1.6370), identified by melting point of picrate (152-154°) and mixed melting point with an authentic specimen.

Phenyllithium and 4,7-Dichloroquinoline.- A solution of 0.10 mole of phenyllithium[207] in 100 ml. of ether was added dropwise at 0° to 19.8 g. (0.10 mole) of 4,7-dichloroquinoline in 300 ml. of ether. After stirring for one hour a yellow precipitate had appeared and a Color Test I[205] was

negative. After hydrolysis with water the layers were separated and the ether layer was dried over sodium sulfate. The ether was removed by distillation, and the residue was replaced with 400 ml. of anhydrous ethanol. To this solution was added 30 g. of mercuric oxide, and the mixture was kept just below the boiling point for eighteen hours. After filtration of mercury and mercuric oxide the solution was cooled to yield 19.6 g. of material (m.p. 100.5-101.5°). Concentration of mother liquors yielded 4.3 g. bringing the total to 23.2 g. (84.9%) of 2-phenyl-4,7-dichloroquinoline.[222] Recrystallized from ethanol the product melted at 101-102°.

Anal. Calcd. for $C_{15}H_9Cl_2$; N, 5.12. Found: N, 5.22

2-Phenyl-4,7-dichloroquinoline and Phenyllithium.- A solution of 0.05 mole of phenyllithium was added to a suspension of 13.7 g. (0.05 mole) of 2-phenyl-4,7-dichloroquinoline in 200 ml. of ether at 0° (bath temperature). The reaction mixture turned black and gave no Color Test I[205] at the end of one hour. The material was poured into a slush of ether and Dry Ice and then hydrolyzed with 100 ml. of water. A precipitate which weighed 11.6 g. was removed by filtration. This was a mixture of substances which resisted all attempts at separation by fractional crystallization.

The reaction was repeated between -50° and room temperature for twleve hours, and an attempt was made to sep-

222. Gilman and Benkeser, J. Am. Chem. Soc., 69, 123 (1947).

arate the mixture by chromatographic adsorption. Some separation was achieved, but the compounds were not pure enough to analyze. The proper choice of solvents might effect a separation by this method.

Phenylcadmium Chloride[219] and Quinoline.- To 0.10 mole of phenylmagnesium bromide in 100 ml. of ether was added 18.4 g. (0.10 mole) of anhydrous cadmium chloride. After stirring for two hours a Color Test I[205] was negative. A solution of 12.9 g. (0.10 mole) of quinoline in 30 ml. of ether was added. The black suspension gradually turned white during a reaction time of eighteen hours. The mixture was hydrolyzed with water, made strongly basic with sodium hydroxide, and filtered. The ether-layer residue was distilled to yield 8.1 g. (b.p. 70-72° at 0.01 mm.; n_D^{20} 1.6218) of quinoline. There was almost no residue left in the distillation flask.

The insoluble hydroxides were dried and extracted with ether in a Soxhlet extractor. These extracts were combined with extracts from the water layer and were distilled to yield 2.6 g. (b.p. 72-74° at 0.15 mm.). This is a total of 10.7 g. of quinoline (83% recovery). The change of color from black to white during the addition may indicate complex formation as in the case of the Grignard reagent.

Phenylcadmium Chloride and Quinoline Methiodide.- The quinoline methiodide was prepared according to the directions of Meisenheimer and Dodonow.[223] To a suspension of 0.10 mole

223. Meisenheimer and Dodonow, Ann., 385, 137 (1911).

of phenylcadmium chloride[219] in 60 ml. of ether was added 17 g. (0.06 mole) of the carefully-dried quinoline methiodide. The mixture was refluxed for eighteen hours before it was poured into a solution of ammonium chloride and concentrated ammonium hydroxide. The ether layer was dried over sodium sulfate, and the ether was removed by distillation. Petroleum ether (b.p. 60-70°) was added to crystallize 7.8 g. (58%) of N-methyl-2-phenyl-1,2-dihydroquinoline (m.p. 87-88°). This is the same melting point for the compound as that reported by Meisenheimer, Stotz, and Bauer.[224]

Quinoline Methiodide and Diphenylmercury.- To a suspension of 8.1 g. (0.03 mole) of quinoline methiodide[223] in 50 ml. of ether was added 10.7 g. (0.03 mole) of diphenylmercury. This suspension was stirred vigorously and refluxed for eighteen hours. The mixture was hydrolyzed with water, and the layers were separated. The ether layer was dried over sodium sulfate. The solid remaining after removal of the ether weighed 10.2 g. (95.3% recovery) and melted at 123°. A mixed melting point with diphenylmercury showed no depression. There was no decolorization of the ether layer product, indicating that not a trace of the unstable N-methyl-2-phenyl-1,2-dihydroquinoline[224] had been formed.

Quinoline Methiodide and Phenylmercuric Bromide.- A suspension of 18. g. (0.05 mole) of phenylmercuric bromide and

224. Meisenheimer, Stotz, and Bauer, Ber., 58B, 2370 (1925).

14 g. (0.05 mole) of quinoline methiodide in 100 ml. of dry ether was refluxed for twenty-four hours. There was no evidence of reaction. Water was added to hydrolyze the mixture, and both layers were filtered from the resulting white precipitate. The layers were separated, and the ether layer was dried over sodium sulfate. Removal of the ether yielded 3.3 g. (36.6%) of diphenylmercury, identified by melting point (124°) and mixed melting point with an authentic specimen. The white precipitate is probably a mixture of mercuric bromide and phenylmercuric bromide. There was no decolorization of any material indicating that the unstable N-methyl-2-phenyl-1,2-dihydroquinoline[224] was not formed.

Quinaldine Methiodide and Phenylmagnesium Bromide.- A suspension of 19.8 g. (0.07 mole) of quinaldine methiodide was treated with 0.07 mole of phenylmagnesium bromide in 100 ml. of ether. The ether began to reflux and a Color Test I[205] was negative one hour after the addition. On hydrolysis with ammonium chloride solution a red solid precipitated out. The methylene base could not be isolated. Rosenhauer[225] reported that the methylene base polymerized to a red solid.

225. Rosenhauer, Ber., 59, 946 (1926).

IV. DISCUSSION

A. Organometallic Derivatives of Benzothiazole.

The preparation of organometallic derivatives of benzothiazole could conceivably be accomplished in three ways: (1) by direct reaction of a halobenzothiazole with a metal, (2) by halogen-metal interconversion, and (3) by metalation. Initial experiments attempted to utilize the first reaction by refluxing 2-chlorobenzothiazole in ether with magnesium. This, however, resulted in a 90% recovery of 2-chlorobenzothiazole, and similar results were obtained with CuMg alloy, activated Cu-Mg-I,[206] and methyl iodide as catalysts. A positive Color Test I[205] was not obtained in any reaction. 2-Pyridylmagnesium bromide,[80] on the other hand, has been prepared in 40-55% yield by using the "entrainment" method of Grignard, a method which has also been employed with 2,6-dibromopyridine, 2-chloropyridine, 3-bromopyridine, and 4-chloropyridine.[2] Using methyl iodide as catalyst would be expected to give similar results with 2-chlorobenzothiazole, but no reaction was induced, possibly because of a coating which formed on the magnesium. In addition, subsequent experiments with 2-benzothiazolyllithium indicated that the 2-benzothiazolylmagnesium chloride would probably not be stable at the temperatures of the experiments. Hofmann[226] has prepared 2,2'-bibenzothiazole by

226. Hofmann, Ber., 13, 1226 (1880).

heating 2-chlorobenzothiazole with zinc.

An 89% recovery of 2-chlorobenzothiazole was obtained in the reaction between 2-chlorobenzothiazole and lithium. Again the metal apparently became coated, which may have inhibited the reaction. A positive Color Test I[205] was not obtained which is not surprising in the light of subsequent experiments which showed 2-benzothiazolyllithium to be unstable above -35° (bath temperature). Hunter[227] obtained only resinous products by refluxing 2-chlorobenzothiazole in ether or xylene in the presence of sodium. Refluxing 2-bromopyridine and 2-bromoquinoline in ether with lithium also produced only tarry products.[82]

No attempt was made to use the halogen-metal interconversion reaction to prepare organometallic derivatives of benzothiazole because 2-bromobenzothiazole is not easily available, and there are not many instances in the literature of chlorine atoms taking part in X-M interconversions.[228] However, the fact that 3-bromopyridine, 3-bromoquinoline, and 2-bromoquinoline have been shown to undergo the halogen-metal interconversion reaction with n-butyllithium in satisfactory yield at low temperature[3] indicates that the reaction might be possible if 2-bromobenzothiazole were available.

In a paper describing the metalation of 2-methylbenzo-

227. Hunter, J. Chem. Soc., 127, 1488 (1925).

228. Gilman, Langham, and Moore, J. Am. Chem. Soc., 62, 2327 (1940); Wittig, Angew Chem., 53, 241 (1940); Gilman and Melstrom, J. Am. Chem. Soc., 68, 103 (1946).

thiazole by ethylmagnesium bromide Courtot and Tchelitcheff[5] mentioned that benzothiazole could be metalated in the 2-position with the Grignard reagent. No yield, conditions, or experimental information was given, and a careful literature survey indicated that no subsequent work was published on the subject. It was accordingly of interest to attempt the metalation with organolithium compounds which are better metalating reagents than Grignard reagents. Phenyllithium reacted vigorously with benzothiazole at room temperature and gave a negative Color Test I[205] almost immediately. Repeating the reaction at a lower temperature (-75°) resulted in a positive Color Test I[205] after thirty minutes, and carbonation gave a 54% yield of benzothiazole-2-carboxylic acid, which was identified by melting point[191] (105° with carbon dioxide evolution) and neutralization equivalent. In addition a 38% recovery of benzothiazole was obtained which showed that side reactions had been almost completely eliminated. This suggested the possibility that the yield of the 2-benzothiazolyllithium might be improved by using a more active metalating agent.[229] Table III (page 75) shows the variations attempted to improve the yield. Phenyllithium gave yields as high as 68.5% below -50°, but above that temperature the yield decreased rapidly to 5.9% at 0°. Methyllithium at temperatures between -78° and -50° resulted in 70% to 80% yields of 2-benzothiazolyllithium. However, the acid obtained by carbonation of the

229. Gilman, Moore, and Baine, J. Am. Chem. Soc., 63, 2479 (1941).

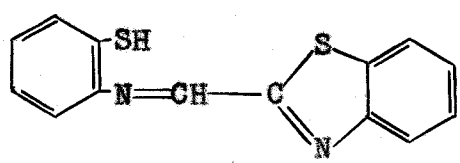
metalations with methyllithium was impure and darkened rapidly on standing. The best yields were obtained with n-butyllithium which at -75° gave 89.7% of 2-benzothiazolyllithium determined by carbonation. It was found that the concentration of the n-butyllithium affected the yield, and the above yield of 89.7% was obtained with 0.33 molar n-butyllithium. Dilution of the RLi favored the metalation reaction. In addition to improving the yield of 2-benzothiazolyllithium, these reactions qualitatively corroborated the relative metalating ability of these three organolithium derivatives as increasing in the order: PhLi, MeLi, and n-BuLi.[229]

The fact that addition to the azomethine linkage of benzothiazole could be eliminated by reacting at a temperature of -75 suggested that quinoline might be affected the same way. However, a repetition of the optimum conditions for producing 2-benzothiazolyllithium with quinoline in place of benzothiazole resulted in a 73% yield of 2-n-butylquinoline[3] and no quinoline-2-carboxylic acid. This may be explained either by a deactivation of the azomethine linkage in benzothiazole by the negative sulfur atom or by an enhanced activity of the 2-hydrogen atom.

The optimal conditions for metalation of benzothiazole were used also with benzoxazole, but apparently no metalation was effected. Solid carbon dioxide and benzophenone were employed to detect any metalation. However, during the addition of the methyllithium a gas was evolved. This might be an in-

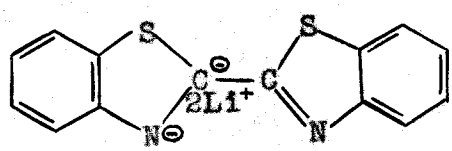
dication of metalation as the gas was probably methane. The resulting organometallic compound may not have reacted with carbon dioxide or benzophenone. If it did react with carbon dioxide the resulting acid may have been decarboxylated in subsequent procedures.

2-Benzothiazolyllithium was not stable above -35° (bath temperature). The light yellow solution darkened rapidly above -35° on warming to room temperature, and a solid was obtained in good yield after hydrolysis with ammonium chloride solution. This melted after recrystallization from toluene at 199-200°. The analyses for this compound checked for a bibenzothiazole or possibly a dihydro compound, and by boiling in nitrobenzene the material was converted in 44.5% yield to 2,2'-bibenzothiazole (m.p. 310°).[209] A compound giving a similar analysis and melting at 194° was isolated by Ochiai and Nisizawa[122] as a by-product from the reaction between benzothiazole and sodamide. As sodamide is a metalating agent the similarity of these compounds seems likely. It is not necessary, however, that the compound be 2-benzothiazolyl-2'-benzothiazoline as it could be a thiophenol (LXVI) from which the 2,2'-bibenzothiazole could be obtained by an oxidative ring closure.



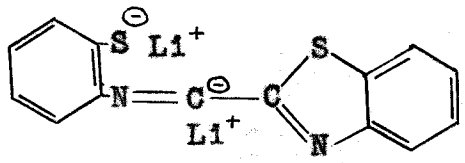
(LXVI)

No mechanism for the formation of a dihydro compound or a compound of the type shown (LXVI) has been proved. The fact that anions do not generally react with anions makes an addition of one molecule of 2-benzothiazolyllithium to the azomethine linkage of another like molecule seem rather unlikely especially in view of the fact that under the same reaction conditions in the presence of quinoline no addition to the azomethine linkage of quinoline was obtained. Instead there was found some of the intermediate compound (m.p. 199-200°) which was converted by nitrobenzene to 2,2'-bibenzothiazole.[209] The preferential reaction of the 2-benzothiazolyllithium with itself rather than with the azomethine linkage of quinoline indicates that anil-addition might not be the mechanism. If one assumes that the 2,2'-bibenzothiazole is a result of the interaction of molecules of 2-benzothiazolyllithium, then the intermediate of addition to the azomethine linkage must be the following:



The proximity of the negative centers which could probably not be screened by the positive lithium atoms makes this a poor possibility. An intermediate formed by opening a sulfur-carbon bond in one of the molecules seems a little more

attractive; however, it still involves the interaction of anions.



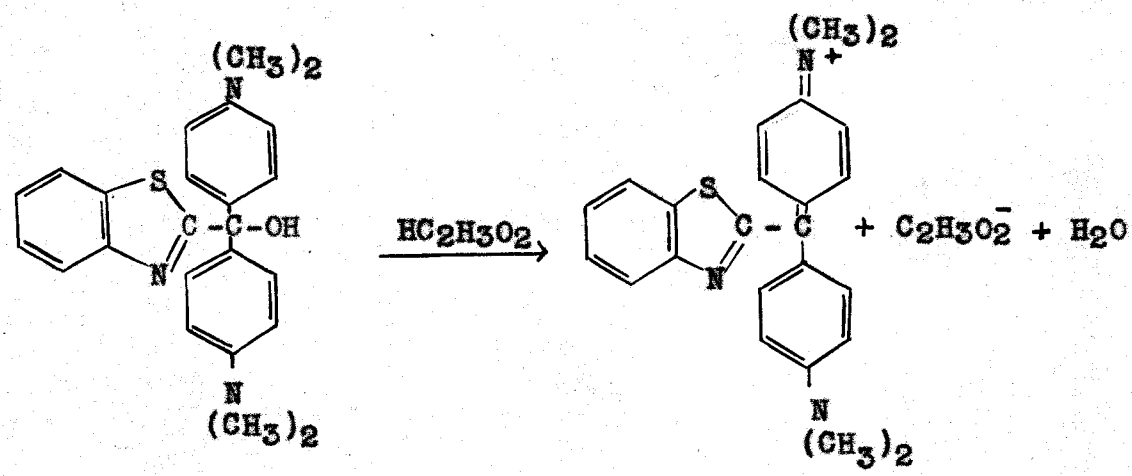
The separation of charges is greater and the possibility of stabilization by distribution of charges seems to be better in this type of intermediate. This mechanism, which involves cleavage of the sulfur-carbon bond, is, of course, essentially conjecture as the experimental evidence is not sufficiently complete to warrant postulation of a reaction mechanism.

The reactions of 2-benzothiazolyllithium appeared to be normal if the reaction took place below -35°. Benzonitrile reacted to give a 71.1% purified yield of 2-benzothiazolyl phenyl ketone which was derivatized with phenylhydrazine. The reaction of 2-benzothiazolyllithium with benzoyl chloride, which might be expected to yield the same ketone, yielded only a trace of the ketone isolated as the phenylhydrazone. There was no depression of melting point of a mixture of this substance with the phenylhydrazone prepared above.

It is interesting to note that no di-(2-benzothiazolyl)-phenylmethanol was isolated in this reaction. The only other product was a small amount of unidentified material which melted at 210°. The melting point of di-(2-benzothiazolyl)-

phenylmethanol, which was prepared from 2-benzothiazolyl phenyl ketone and 2-benzothiazolyllithium, was 158 .

Other ketones which reacted with 2-benzothiazolyllithium were benzophenone, acetophenone, p-chloroacetophenone, p-methylacetophenone, and Michler's ketone. These gave yields of 2-benzothiazolemethanols of 95%, 67%, 72%, 63%, and 72%, respectively. The α,α-di-(p-dimethylaminophenyl)-2-benzothiazolemethanol[230] turned green in air and gave a deep green color if dissolved in acetic acid. This was to be expected as the methanol would be the color base of a triarylmethane dye.



Aldehydes also gave satisfactory yields of secondary 2-benzothiazolemethanols when reacted with 2-benzothiazolyllithium. Aldehydes used in this study were benzaldehyde, n-butyraldehyde, and p-dimethylaminobenzaldehyde, which gave the cor-

230. A letter from E. J. Crane, editor of Chemical Abstracts, concerning the naming of this and other compounds is to be found in the Appendix.

responding methanols in yields of 66.2%, 55.7%, and 59.6%, respectively.

An attempt to couple 2-benzothiazolyllithium with benzyl chloride did not yield any 2-benzylbenzothiazole. The reaction, which was run at -75°, allowed to warm up to room temperature, and then stirred for six hours, yielded no isolable product. Possibly the coupling reaction was extremely slow at temperatures below which 2-benzothiazolyllithium decomposes. The fact that no benzyl chloride was recovered seems to indicate that the benzyl chloride did react with the product or products formed from the decomposition of the 2-benzothiazolyllithium.

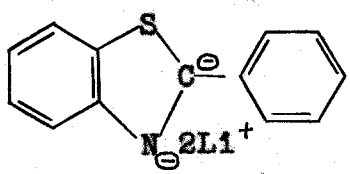
B. Reactions, other than Metalation, of Organometallic Compounds with Benzothiazole.

The similarity of benzothiazole to quinoline suggested that 2-substituted benzothiazole derivatives might be formed by addition of organometallic compounds to the azomethine linkage. Because of the ease of metalation of benzothiazole by organolithium compounds most of the attempts to add phenyllithium to benzothiazole employed two moles of the RLi compound to one mole of benzothiazole. In Table IV (page 89) the experimental results were tabulated. In all reactions below -35° the yield of 2-phenylbenzothiazole was below 12.2%. Above that temperature the yield improved, but never got above a 44% crude yield, which was obtained at 0°. Reactions

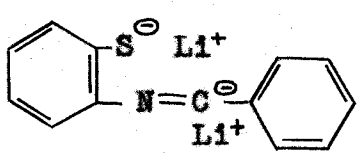
at temperatures higher than 0° did not improve the yield of 2-phenylbenzothiazole though the recovery of benzothiazole was lower. It is noteworthy that in the experiments in which the molar ratio of phenyllithium to benzothiazole was 1:1, the yield of 2-phenylbenzothiazole was always lower though some 2-phenylbenzothiazole was obtained, which may mean that the rate of anil addition at these temperatures increased to the point that it competed successfully with the metalation reaction.

In all of the reactions listed in Table IV (page 89) hydrolysis was effected by means of ammonium chloride solution. In other reactions it was found that if water were used for hydrolysis almost all of the reaction mixture was soluble in the water layer. This base-soluble material could be precipitated by acid, but, after precipitation, would not redissolve completely in base. This indicated the possibility of an unstable thiophenol which could have been formed by breaking the sulfur-carbon bond in benzothiazole. Several attempts were made to oxidize the supposed thiophenol to the disulfide with air, iodine, and hydrogen peroxide, but no disulfide was isolated. Benzoylation with benzoyl chloride was also tried, but only a small amount of an unidentified crystalline product was obtained. No 2-phenylbenzothiazole could be isolated from the residue after acidification of the base-soluble layer. Attempts to obtain solid products by crystallization from various solvents resulted only in resins.

Any attempt to discuss the mechanism of this reaction between benzothiazole and phenyllithium necessarily has to consider addition of the organometallic compound to the azomethine linkage of benzothiazole as a possibility because of the relationship of benzothiazole to quinoline which adds organolithium compounds in good yield.[1, 3, 131] However, unsubstituted quinoline is metalated by organolithium compounds and, if the benzothiazole is metalated at the higher temperatures, and there is good reason to suppose that it is because of the rapidity of the metalation reaction at low temperature, then we are concerned here, not with the addition of phenyllithium to benzothiazole, but with the addition of phenyllithium to 2-benzothiazolyllithium. This, as in the case of the decomposition of 2-benzothiazolyllithium would lead to an unlikely intermediate with two centers of negative charge very close together.



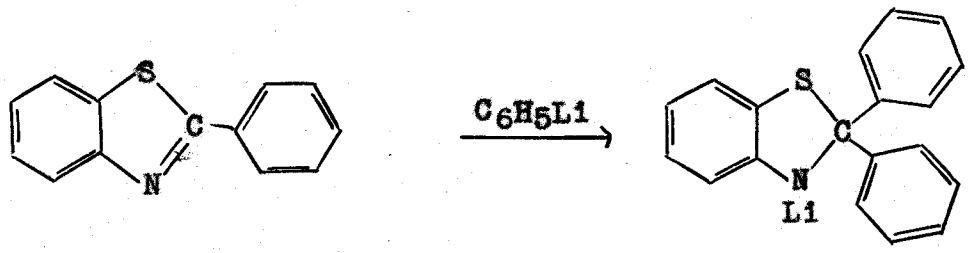
However, if there resulted a cleavage of the sulfur-carbon bond, the intermediate would have the charges more widely separated.

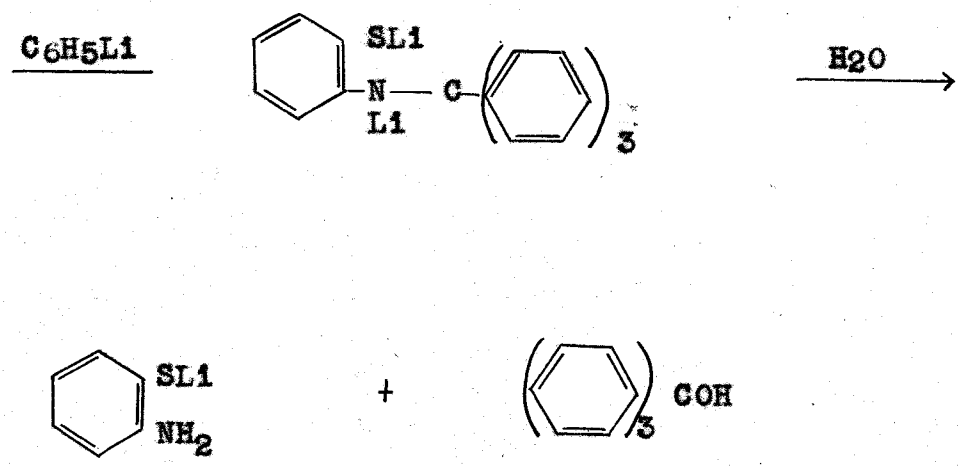


The possibility of stabilization by distribution of charge would be better, and the latter compound would also explain the water-solubility of the product on hydrolysis of the reaction mixture with water. Unfortunately, the experimental evidence does not permit more than suggesting possible mechanisms. An attempt to clarify the situation by treating 2-benzothiazolyllithium with phenyllithium from -75° to -10° resulted in about 70% recovery of benzothiazole and an intractable residue. More work on this approach would be of considerable interest.

Though the yields in these reactions of organolithium compounds with benzothiazole were poor, this reaction may still be of value in the preparation of 2-substituted benzothiazoles if an excess of RLi is used and if hydrolysis is effected by ammonium chloride solution.

Phenyllithium reacted with 2-phenylbenzothiazole to yield triphenylmethanol (8.4%) and bis-(o-aminophenyl) disulfide (7.7%). To get these products both addition to the azomethine linkage and cleavage of the sulfur-carbon bond had to be postulated.





The cleavage could just as well have occurred before the addition to the azomethine linkage. If addition is the first reaction, the intermediate is similar to the N-lithio-2,2-diphenyl-1,2-dihydroquinoline is obtained by the interaction of 2-phenylquinoline and phenyllithium.[1] Compounds like triphenylmethylaniline are easily hydrolyzed to triphenylmethanol and the amine.[231]

Phenylmagnesium bromide reacted with benzothiazole at -10° to yield 0.8% of 2-phenylbenzothiazole. Less than one third of the phenylmagnesium bromide reacted because on carbonation a 68.6% yield of benzoic acid was obtained. There was also a 54.2% recovery of benzothiazole. No benzothiazole-2-carboxylic acid was found. Ethylmagnesium bromide metalated benzothiazole according to Courtot and Tchelitcheff[5] so it

231. Gomberg, Ber., 35, 1822 (1902).

might be expected that phenylmagnesium bromide would also effect metalation. The 2-benzothiazolylmagnesium bromide might not be stable at -10°, however, which would account for the fact that no benzothiazole-2-carboxylic acid was isolated.

It would be interesting to attempt this metalation by ethylmagnesium bromide, and if the yield were high, to find out how stable the resulting 2-benzothiazolylmagnesium bromide would be. If the same product were obtained at a low temperature as in the case of the decomposition of 2-benzothiazolyllithium, this would be evidence against decomposition by addition to the azomethine linkage because the Grignard reagent does not add to the azomethine linkage under these conditions. Also, the more negative 2-carbon atom in the 2-benzothiazolylmagnesium bromide would probably inhibit addition to the azomethine linkage.

Phenylmagnesium bromide did not react with 2-phenylbenzothiazole; after refluxing in ether for twenty-four hours a 92.8% recovery of 2-phenylbenzothiazole was obtained.

C. Organometallic Compounds and 2-Electronegatively Substituted Quinolines.

Because of the similarity of p-tolyl 2-quinolyl sulfide[212] to benzothiazole it was considered of interest to test the effect of organometallic reagents on this compound. Both benzothiazole and p-tolyl 2-quinolyl sulfide[212] contain the -N=C-S- grouping, but the latter open-chain compound differs

in that the carbon atom has no hydrogen attached to it, thus eliminating the possibility of metalation on that carbon atom.

The p-tolyl 2-quinolyl sulfide was mentioned in a British Patent,[212] but no preparation was given. We tried two methods in which we reacted 2-chloroquinoline with lead p-thiocrescxide and with lithium p-thiocresoxide. These methods gave p-tolyl 2-quinolyl sulfide in yields of 75% and 80%, respectively. In a preliminary experiment with phenyllithium at room temperature for four hours it was found that the p-tolyl 2-quinolyl sulfide was cleaved to yield p-thiocresol (57%) and 2-phenylquinoline (47%). This rather encouraging result suggested reactions with other electronegative groups in the 2- position of quinoline and with other organometallic reagents.

The organometallic compounds used in this work in order of decreasing reactivity were n-butyllithium, phenyllithium, phenylmagnesium bromide, and phenylcadmium chloride. In addition to p-tolyl 2-quinolyl sulfide the 2-substituted quinolines used were 2-phenoxyquinoline, 2-ethoxyquinoline, 2-chloroquinoline, 2-(N-piperidyl)quinoline, 2-benzyloxyquinoline, 2-allyloxyquinoline, and 2-benzylquinoline. Table V shows the results of reactions between phenyllithium and 2-substituted quinolines. In all but two experiments those with 2-(N-piperidyl)quinoline and with 2-benzylquinoline, there was some 2-phenylquinoline produced. The yields varied from 10.6% in the case of 2-allyloxyquinoline to 70.2% from

Table V

Reactions of Phenyllithium with 2-Substituted Quinolines

2-Substituted Quinoline	Yield of 2-phenylquinoline, %	Yield of cleavage product,%	Reaction time (hours)	T. °C.	Recovery of starting material, %
$CH_3C_6H_4S$	47.4	p-thiocresol (57)	5	28	____
C_6H_5O	70.2	phenol (72.3)	18	28	____
C_2H_5O	41.5	_____	18	28	54.8
Cl	65.7	_____	30	28	8.0
$C_5H_{10}N$	____	piperidine (trace)	18	28	10.0
$C_6H_5CH_2O$	12.2	benzyl alcohol (24.8)	6	0	17.
C_3H_5O	10.6	_____	18	28	15.6
$C_6H_5CH_2$	____	_____	18	28	82.6

2-phenoxyquinoline.

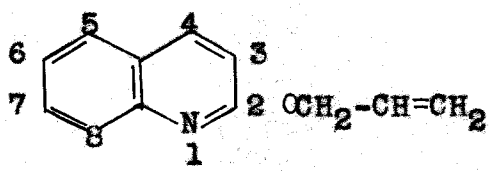
The reaction with 2-allyloxyquinoline was run to see if any allylbenzene might be formed as in the reaction of "hindered carbonyl compounds" with the Grignard reagent.[232] A typical reaction of this kind is the following:

$$(C_6H_5)_3\text{-}COCH_2\text{-}CH{=}CH_2 + C_6H_5MgBr \longrightarrow C_6H_5\text{-}CH_2\text{-}CH{=}CH_2 + (C_6H_5)_3\text{-}COOMgBr$$

Instead of the expected carbinol the magnesium salt of the acid

232. Arnold, Bank, and Liggett, J. Am. Chem. Soc., 63, 3444 (1941); Arnold and Liggett, ibid., 64, 2875 (1942); ibid., 67, 337 (1945).

and allylbenzene is obtained in good yield. The allyl esters which give this anomalous reaction have no hydrogen on the α-carbon of the ester, but 2-allyloxyquinoline does have a hydrogen atom on the 3-carbon which is analogous to the α-carbon of the ester.



Hindered allyl esters which have a hydrogen atom on the α-carbon have been shown recently to undergo an intramolecular rearrangement resulting in a α-allyl acid.[233]

In the reaction between 2-allyloxyquinoline and phenyllithium no allylbenzene was isolated, and no carbostyril was obtained indicating that an anomalous reaction did not occur. As no acidic material was found, the intramolecular rearrangement of hindered allyl esters with an α-hydrogen atom apparentyl did not take place. In this reaction, however, the yield of 2-phenylquinoline was 10.6% and the recovery of starting material was only 15.6%. There was a large amount of resinous material left after the distillation which indicated extensive reaction and probably polymerization.

2-Benzyloxyquinoline,[220] which should be similar to 2-allyloxyquinoline, gave only a 12.2% yield of 2-phenylquinoline and a 17% recovery of 2-benzyloxyquinoline. Another product, which melted at 110°, was isolated, but the nitrogen analysis did not check for any of the possible rearranged prod-

233. Arnold and Searles, Jr., J. Am. Chem. Soc., 71, 1150 (1949).

ucts. Arnold[232] did not report any rearrangement of hindered benzyl esters, though he said his results were inconclusive. It might also be mentioned here that these reactions of 2-allyloxy- and 2-benzyloxyquinoline were not run on a large scale; consequently small amounts of some products might have been overlooked.

The reaction of 2-ethoxyquinoline with phenyllithium was apparently not complicated with side reactions as the yield of 2-phenylquinoline and the recovery of 2-ethoxyquinoline total 95%. 2-Chloroquinoline gave a good yield (65.7%) of 2-phenylquinoline, and it is interesting to note that under similar conditions 2-chlorobenzothiazole and phenyllithium gave a 47.8% yield of 2-phenylbenzothiazole and a 39.1% recovery of 2-chlorobenzothiazole. This is rather anomalous in view of the fact that the halogen atom 2-chlorobenzothiazole is more reactive than the halogen atom in 2-chloroquinoline.

The reaction between 2-benzylquinoline[132] and phenyllithium resulted in an 82.6% recovery of 2-benzylquinoline. However, a Color Test I[205] at the end of eighteen hours was negative. This probably indicates that the phenyllithium metalated the 2-benzylquinoline on the methylene carbon atom of the benzyl group and that the resulting organometallic compound did not give a positive Color Test I.[205] This is not too surprising because somewhat similar organometallic compounds, 2-picolyllithium[130] and quinaldyllithium, do not give a Color Test I. Carbonation may have resulted in an

acid which was not isolated because of decarboxylation in working the material up. An acid of this type would be expected to decarboxylate easily at low temperature.[191]

The method used for preparing the 2-benzylquinoline involved the addition of benzylsodium[221] to the azomethine linkage of quinoline with subsequent oxidation. Attempts to prepare the compound by the reaction of benzylmagnesium chloride and 2-chloroquinoline resulted in tars. The only method for the preparation of 2-benzylquinoline to be found in the literature is that of Bergmann and Rosenthal,[132] who treated quinoline in dioxane with benzylmagnesium chloride. This resulted in a mixture of 2- and 4-benzylquinolines which were separated by fractional crystallization of the picrates from n-propyl alcohol. Obviously the method we used which gave a 34% purified yield of 2-benzylquinoline is a considerable improvement over the other methods. This yield assumes a 90% metalation of the toluene by the phenylsodium as reported by Gilman, Pacevitz, and Baine.[221]

In Table VI the experiments with n-butyllithium are shown. It is evident that the yields of 2-n-butylquinoline are not as high as the yields of 2-phenylquinoline and the recovery of starting material is lower. The reaction time for a negative Color Test I[205] was also much less, and in some cases lower temperatures were employed. Even at -75° n-butyllithium and p-tolyl 2-quinolyl sulfide yielded 13.3% 2-n-butylquinoline and 11.15% p-thiocresol. An 82.2% re-

Table VI

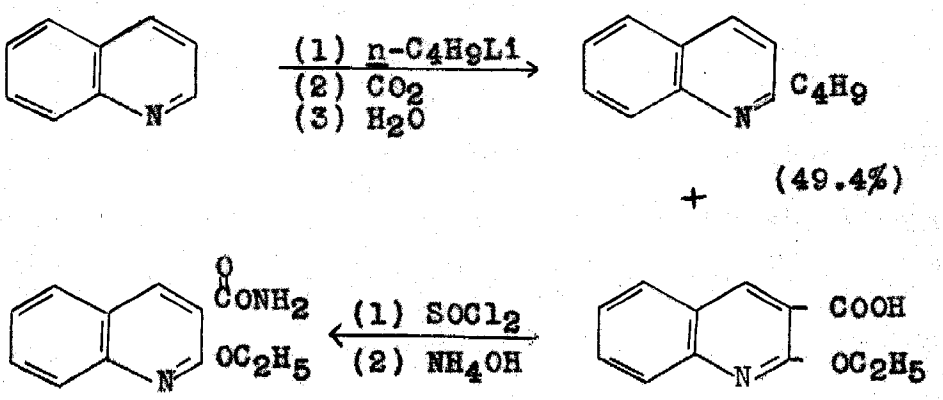
Reactions of n-Butyllithium with 2-Substituted Quinolines

2-Substituted Quinoline	Yield of 2-butylquinoline, %	Yield of cleavage product,%	Reaction time (hours)	T. °C.	Recovery of starting material, %
$CH_3C_6H_4S$	13.3	p-thiocresol (11.15)	.25	-75	82.2
$CH_3C_6H_4S$	63.8	p-thiocresol (35)	.1	28	____
C_6H_5O	9.6	phenol (62.6)	4.	28	14.9
C_2H_5O	49.4	_____	.3	28	14.9
Cl	11.4	_____	.3	0	____
Cl	52.2	_____	.6	-45	____
$C_5H_{10}N$	17.8	_____	4.	28	____

covery of starting material showed that the side reactions were definitely minimized at the lower temperature.

Evidence that metalation is one of the complicating side reactions was obtained with n-butyllithium and 2-ethoxyquinoline which yielded after carbonation 6.5% of 2-ethoxyquinoline-3-carboxylic acid.[217] This acid was identified by melting point and conversion to 2-ethoxyquinoline-3-carboxamide by thionyl chloride followed by concentrated ammonium hydroxide. A mixed melting point with an authentic specimen of the carboxamide[203, 218] showed no depression. This authentic specimen was prepared by Professor Hans Wojahn from 2-hydroxyquino-

line-3-carboxylic acid, which was obtained by a ring-closure reaction.



The orientation of the metalation is of particular interest. It has been found that metalation generally takes place ortho to the hetero element and that the order of decreasing influence of some hetero elements is O,S,N,P,As.[234] In this compound we have the nitrogen atom directing metalation to the 8- position and the oxygen atom directing to the 3- position. The isolation of the 2-ethoxyquinoline-3-carboxylic acid confirms the greater orienting effect of the oxygen atom. It is interesting to note that quinoline itself is metalated primarily in the 8- position by mercuric acetate.[4]

The 9.6% yield of 2-n-butylquinoline and the 62.2% yield of phenol from the reaction of 2-phenoxyquinoline was anomalous. A viscous yellow oil, which was not identified, was obtained.

234. Gilman and Bebb, J. Am. Chem. Soc., 61, 109 (1939).

Possibly there was more 2-n-butylquinoline which co-distilled with starting material, or the 2-n-butylquinoline formed may have reacted further with the n-butyllithium. The reaction time was considerably longer in this reaction than any other except the reaction with 2-(N-piperidyl)quinoline, in which case there was also a considerable amount of viscous yellow oil, which could not be identified.

Table VII shows the results of reactions with phenylmagnesium bromide. This reagent of lower reactivity than

Table VII

Reactions of Phenylmagnesium Bromide with 2-Substituted Quinolines

2-Substituted Quinoline	Yield of 2-phenylquinoline, %	Yield of cleavage product,%	Reaction time (hours)	T. °C.	Recovery of starting material,%
$CH_3C_6H_5S$	3.1	4.2	18	28	74.6
C_6H_5O	2.6	____	48	28	84.7
C_2H_5O	____	____	18	28	90.8
Cl	31.2	____	48	28	50.6
$C_5H_{10}N$	____	____	60	28	78.8

n-butyllithium and phenyllithium showed little reaction even during extended period of forty-eight to sixty hours at room temperature. There was no reaction with 2-ethoxyquinoline or 2-(N-piperidyl)quinoline. 2-Chloroquinoline, however, showed a particularly high reactivity with the Grignard reagent and

formed 2-phenylquinoline in 31.2% yield. The high recovery of starting material also indicated the absence of side reactions. A slightly higher yield of 2-phenylquinoline by refluxing 2-chloroquinoline and phenylmagnesium bromide had been obtained recently by Heuser and Weiss,[235] but they reported no recovery of 2-chloroquinoline.

Phenylcadmium chloride,[219] an organometallic compound of still lower reactivity, showed no reaction with 2-chloroquinoline or 2-ethoxyquinoline under corresponding conditions. Phenylcadmium chloride did not react with quinoline at room temperature to yield any 2-phenylquinoline as would be expected. However, the black color of the phenylcadmium chloride turned to white on stirring with quinoline. Probably a complex was formed as in the case of the Grignard reagent. This phenylcadmium chloride-quinoline complex might be converted to 2-phenylquinoline by heating to a higher temperature, hydrolyzing, and oxidizing with nitrobenzene.

These reactions confirm the relative reactivities of organometallic compounds as n-butyllithium was most reactive, followed by phenyllithium, phenylmagnesium bromide, and phenylcadmium chloride. The yields in the reactions with n-butyllithium are lower, however, than with phenyllithium because of more extensive side reactions. This is shown by the considerably greater reactivity of n-butyllithium at -75° at which tem-

235. Hauser and Weiss, J. Org. Chem., 14, 310 (1949).

perature side reactions were minimized.

The reactivity of the 2-substituted quinolines in these reactions may be indicated qualitatively as follows:

$Cl\text{-} \rangle CH_3\text{-}C_6\text{-}H_4\text{-}S\text{-} \rangle C_6H_5\text{-}O\text{-} \rangle C_2H_5O\text{-} \rangle C_3H_5O\text{-} \rangle C_6H_5\text{-}CH_2\text{-}O \rangle C_5H_{10}N\text{-} \rangle C_6H_5\text{-}CH_2$.

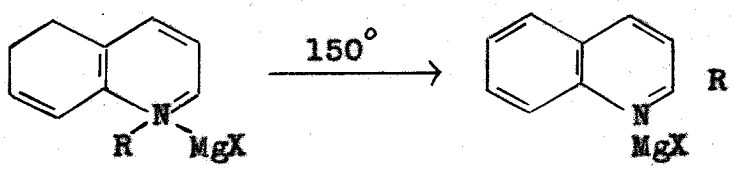
Obviously there are many complications involved in placing the various groupings in this order. For example, the 2-allyloxy- and 2-benzyloxyquinolines, which appear toward the end of the list, were quite reactive, but the yield of cleavage products was low because of side reactions.

The considerable body of literature about quinoline and organometallic compounds is concerned chiefly with the addition of the RM compound to the azomethine linkage of quinoline.[1] Any substitutents on the quinoline were of such a nature that they did not affect the addition which is smooth and rapid even at low temperatures with organolithium reagents. For example, a 93% yield of 2-n-butylquinoline[3] was obtained from n-butyllithium and quinoline at -35°, and in this work we found the yield of 2-n-butylquinoline from the same reagents at -75° for fifteen minutes to be 73%. A subsequent experiment at -75° for thirty minutes improved the yield of 2-n-butylquinoline to 84.2%.

It has been shown that 1,2-addition is the predominant reaction with organolithium compounds even if there is an aryl group in the 2- position of quinoline.[1] Thus, 2,2-di-

phenyl-1,2-dihydroquinoline is obtained from the reaction between phenyllithium and 2-phenylquinoline. No 1,4-addition, which was previously thought to be a side reaction in the addition of an RLi reagent to quinoline, is obtained. Addition to the azomethine linkage of quinoline must, therefore, be taken into account in any reaction of an RLi compound with a substituted quinoline.

Grignard reagents also react with quinoline though usually a higher temperature is required to cause the initially-formed adduct to rearrange.[236]



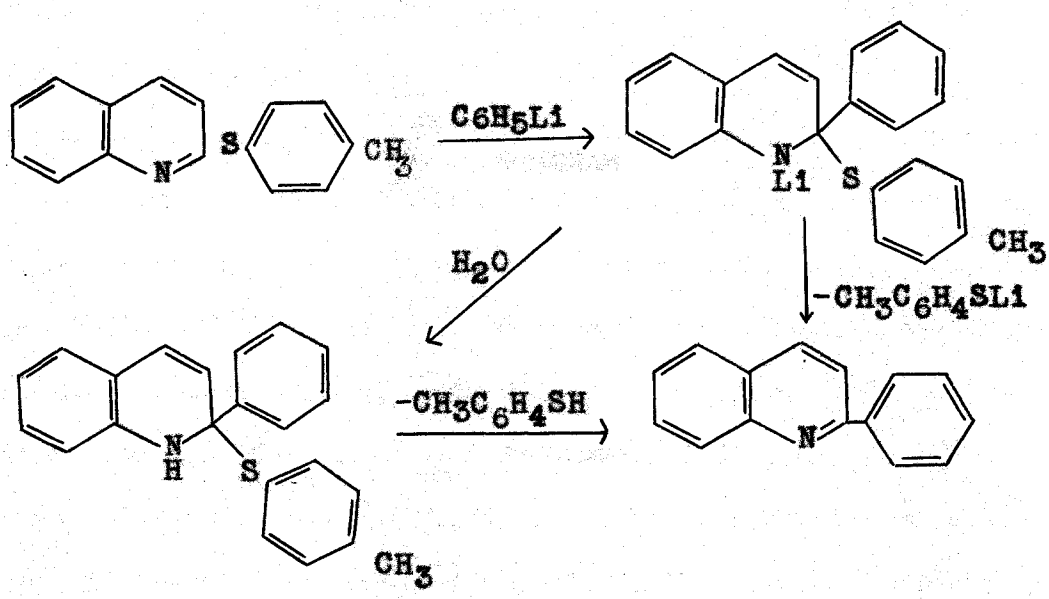
Gilman and Gainer,[237] however, have obtained 2-phenylquinoline in about 7% yield by the reaction of phenylmagnesium bromide and quinoline at the reflux point of ether for twenty-four hours.

In view of this strong tendency toward addition to the azomethine linkage of quinoline, addition may be intermediate in the formation of the cleavage products obtained from RM compounds and 2-substituted quinolines. In the case of p-tolyl

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

237. Gilman and Gainer, J. Am. Chem. Soc., 71, 000 (1949).

2-quinolyl sulfide the addition complex could decompose before hydrolysis with the elimination of lithium p-thiocresoxide or, after hydrolysis, with the elimination of p-thiocresol as shown below.



The permanganate to red color of the ethereal reaction mixture might be evidence in favor of the preliminary addition, but no other evidence was obtained.

In the reaction of the Grignard reagent with 2-ethoxyquinoline and 2-phenoxyquinoline a white precipitate was formed. These precipitates, however, gave no Color Test I[205] and on treatment with water yielded 2-ethoxyquinoline and 2-phenoxyquinoline, respectively, and were apparently complexes of the ethers with magnesium bromide from the Grignard reagent.

Another possible mechanism is the nucleophilic displacement of the 2-substituent by the carbanion of the organometallic used. This might be more likely in view of the

postulated deactivation of the azomethine linkage by chlorine,[3] and which, if true, could be extended to the other electronegative substituents employed in this work. At the present time, however, there is not sufficient evidence to prove either mechanism.

It is interesting to note that the 4-halogen is unaffected by phenyllithium if the 2- position is open. 4,7-Dichloroquinoline reacted with phenyllithium at 0° to yield 2-phenyl-4,7-dichloroquinoline[222] in 84.9% yield. Reactions of phenyllithium with 2-phenyl-4,7-dichloroquinoline and also with 2-phenyl-4-ethoxy-7-chloroquinoline gave mixtures of products which have not been separated.

The fact that the reactions of p-tolyl 2-quinolyl sulfide with phenyllithium forms p-thiocresol and 2-phenylquinoline does not shed much light on the reaction between phenyllithium and benzothiazole. In the first place no evidence for addition to the azomethine linkage of p-tolyl 2-quinolyl sulfide was obtained except the intense permanganate color of the solution which may have indicated an adduct of some kind. In the second place in the case of p-tolyl 2-quinolyl sulfide we may have been dealing with an entirely different sort of reaction because metalation on the 2-carbon atom could not have occurred. However, the latter reaction does show that the "cleavage" reaction is the main result whether it occurs by addition or by some other mechanism, and that the same type of reaction could be expected from phenyllithium and benzo-

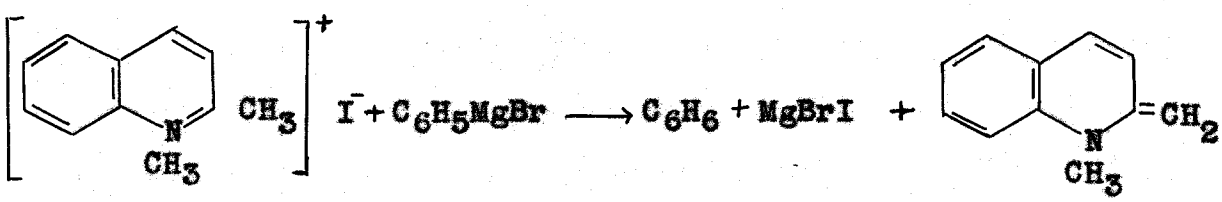
thiazole provided metalation did not occur first. It is possible too that, if temperature had more effect on the rate of the cleavage reaction than on the metalation reaction, the rate of the cleavage reaction might increase to the point at which it could compete successfully with the metalation reaction.

D. Reactions of Organometallic Compounds with Some Quaternary Salts.

As the formation of the quarternary salt enhances the activity of substituents in the 2- position of quinoline,[8] it was considered of interest to attempt some reactions of organometallic compounds with certain quaternary salts. Meisenheimer, Stotz, and Bauer[223] found that phenylmagnesium bromide reacted vigorously with quinoline methiodide to yield N-methyl-2-phenyl-1,2-dihydroquinoline. We found that phenylcadmium chloride[219] also reacted with quinoline methiodide in eighteen hours to give 57% of N-methyl-2-phenyl-1,2-dihydroquinoline. As phenylcadmium chloride is of lower reactivity than phenylmagnesium bromide, as shown by the fact that the organocadmium compound is easily formed by the reaction of the Grignard reagent with anhydrous cadmium chloride,[219] we tried the reaction with some organometallic compounds of extremely low reactivity. The organometallic compounds used were phenylmercuric bromide and diphenyl mercury. In both cases there was not a trace of reaction with the quinoline

methiodide.

We attempted a reaction between phenylmagnesium bromide and quinaldine methiodide to see if it were possible to obtain N-methyl-2-methyl-2-phenyl-1,2-dihydroquinoline, but only a red solid was obtained. It was suspected that this might be the polymeric decomposition product of the methylene base of quinaldine which might have been formed as follows:



According to Rosenhauer[225] the methylene base of quinaldine is extremely unstable and polymerizes to a red solid.

V. SUMMARY

1. A general discussion has been made on the activation toward nucleophilic reagents of the 2- and 4- positions of pyridine and quinoline, the 2- position of benzothiazole, and the 1- position of isoquinoline.
2. The chemistry of alkyl and halogen substitutents in these positions has been discussed in some detail.
3. To a lesser extent the chemistry of the amino, alkoxy, thiol, hydroxy, carboxy, and carbonyl derivatives has been outlined.
4. A generalized comparison of the activity of the 2- and 4- positions of quinoline has been made.
5. Several attempts to prepare organometallic derivatives of benzothiazole have been made. The optimal conditions for the metalation of benzothiazole by n-butyllithium have been determined. The metalation, as determined by carbonation, proceeds to about 90% of the theoretical amount.
6. 2-Benzothiazolyllithium has been found to be normal in its reactions with nitriles, aldehydes, ketones, and carbon dioxide. Several secondary and tertiary 2-benzothiazole methanols have been prepared. 2-Benzothiazolyllithium is not stable above -35° (bath temperature) so the reactions must be carried out below that temperature. 2,2'-Bibenzothiazole is one of the products formed by the decomposition of 2-benzothiazolyllithium. A mechanism for the formation

of this product has been proposed.

7. Several attempts have been made to prepare 2-substituted benzothiazoles by the addition of organolithium compounds to benzothiazole. The best yield of 2-phenylbenzothiazole obtained in this was 44% (crude). The reaction may not proceed by normal addition to the azomethine linkage.
8. 2-Electronegatively-substituted quinolines have been cleaved by organometallic compounds to form alkyl- and arylquinolines. The electronegative groups involved were Cl-, CH_3-C_6H_5-S-, C_6H_5O, C_2H_5O-, C_3H_5O, C_6H_5-CH_2-O-, and $C_5H_{10}N$-. The reaction may proceed by initial addition to the azomethine linkage of the 2-substituted quinoline.
9. The best yields of 2-alkylquinolines were obtained with phenylithium. n-Butyllithium effected the cleavage, but side reactions were extensive. For example, a 6% yield of 2-ethoxyquinoline-3-carboxylic acid was obtained from the reaction with 2-ethoxyquinoline followed by carbonation.
10. Phenylcadmium chloride has been found to react with quinoline methiodide to yield 58% of N-methyl-2-phenyl-1,2-dihydroquinoline. Phenylmercuric bromide and diphenylmercury did not react with quinoline methiodide under corresponding conditions.

VI. APPENDIX

The following communication from E. J. Crane, editor of Chemical Abstracts, was received in reply to inquiries regarding the nomenclature of certain compounds.

COPY

November 24, 1948

Dr. John A. Beel,
Chemistry Department,
Iowa State College,
Ames, Iowa.

Dear Dr. Beel:

When your letter of November 14 arrived I turned it over to Dr. Leonard T. Capell of this office to ask him, please, to suggest answers to your four queries. Doctor Capell specializes in the organic side of our work and he is more familiar with organic nomenclature than I am. I can answer your letter in no better way than by reproducing his comment. Here it is.

The following names are formed in accordance with Chemical Abstracts rules and should be acceptable to the Journal of the American Chemical Society.

1. 2,2'-Bibenzothiazole is preferred over 2,2'-bibenzothiazolyl (The use of radical names with bi- is confined to a few of the commoner radicals --- otherwise bi- is prefixed to the name of a compound. This is especially true with heterocyclic compounds. Thus bipyridine and bibenzothiazole are preferred names.)

2. We prefer the alphabetical order of radicals, thus 2-benzothiazolyl phenyl ketone is the preferred order. See section 77, page 5878, of the Introduction to Volume 39 Subject Index.

3. We prefer methanol over carbinol as the name of the

Dr. John A. Beel

parent compound.

4. This is a case where the additive name benzothiazolemethanol is better than the substitutive name benzothiazolylmethanol. In the former name the whole name represents the parent compound whereas in the second name the parent compound is the methanol. The advantages of the additive name are soon evident when one begins to name the related compounds, especially if one considers the inverted forms of the names. Thus one has 2-benzothiazolemethanol, α-methyl-α-phenyl-2-benzothiazolemethanol (2-Benzothiazolemethanol, α-methyl-α-phenyl-), α-butyl-2-benzothiazolemethanol (2-Benzothiazolemethanol, α-butyl-). (Cf. section 62, page 5876 of the Introduction to Volume 39 index to Chemical Abstracts). If a name like benzothiazolylmethanol is used, the parent compound is methanol (or whatever the alcohol part of the name is). Thus one has 2-benzothiazolylmethanol (Methanol, 2-benzothiazolyl-), α-2-benzothiazolyl-α-methylbenzyl alcohol (Benzyl alcohol, α-2-benzothiazolyl-α-methyl-), and 1-(2-benzothiazolyl)-1-pentanol (1-Pentanol, 1-(2-benzothiazolyl)-). The additive names make the use of the table very easy, since all the compounds may be named as derivatives of 2-benzothiazolemethanol.

Sincerely yours,

signed E. J. Crane

EJC/ES

cc/Dr. Austin Patterson