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Studies with heterocyclic compounds containing the azomethine grouping

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STUDIES WITH HETEROCYCLIC COMPOUNDS CONTAINING THE AZOMETHINE GROUPING

by

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TABLE OF CONTENTS

Page

Page

Page

Page

Page

PART I. THE REDUCING ACTION OF THIOLS

I. INTRODUCTION

Although the oxidation of thiols to disulfides by inorganic reagents is a well-established reaction in organic chemistry[1], the interaction of a thiol with an organic compound to produce a disulfide and a hydrogenated compound has been observed in only a limited number of cases. Prior to the present study, the only systematic investigation of the latter type of reaction is the work of Gilman and Dickey[2], who found that p-thiocresol reduced benzalaniline, benzophenone-anil and azobenzene. A few scattered reports suggest that additional examples of the reducing action of thiols may have been noted, but among these the evidence, in some cases, is rather inconclusive.

The success obtained with benzalaniline and benzophenone-anil suggested further examination of the use of thiols as reductants for the azomethine linkage. With compounds like pyridine, quinoline and isoquinoline this would be of great preparative value, because at the present time there is no reagent

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1. Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, New York (1943), Vol. I, pp. 851, 854, 888.

2. Gilman and Dickey, J. Am. Chem. Soc., 52, 4573 (1930).

which is known to reduce preferentially the azomethine group in these compounds to their 1,2-dihydro derivatives. When quinoline derivatives are reduced with tin and hydrochloric acid, sodium and alcohol, 3% sodium amalgam[3] or hydrogen and nickel[4], 1,2,3,4-tetrahydroquinolines are produced. Heller[5] has obtained bi-1,2-dihydroquinaldine by the reduction of quinaldine with zinc and hydrochloric acid, but not the monomer. The 1,2-dihydroquinoline which Räth[6] claimed to have gotten from the condensation of o-toluidine and α -chloroacetaldehyde diethylacetal has been contested by Meisenheimer and Stotz[7], and shown by König and Bucheim[8] to have an entirely different structure. However, 1,4-dihydroquinoline (3% yield), together with its dimer and trimer, has been prepared by the electrolytic reduction of quinoline[9]. There are examples of 2-substituted dihydro compounds, but these have been prepared by the addition of organometallic compounds to the azomethine

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3. Cuisa and Barattini, Gazz. chim. ital., 56, 131 (1926) /C. A., 20, 2331 (1926)/

4. v. Braun, Ber., 55, 3779 (1922).

5. Heller, Ber., 44, 2106 (1911).

6. Räth, Ber., 57, 550 (1924).

7. Meisenheimer and Stotz, Ber., 58, 2330 (1925).

8. König and Bucheim, Ber., 58, 2868 (1925).

9. Levchenko, J. Gen. Chem. (U.S.S.R.), 11, 686 (1941) /C. A., 36, 39 (1942)/

linkage[10,11], rather than by the action of a reducing agent.

Unfortunately, under our conditions the simple systems did not undergo reduction, but acridine gave fairly good yields of biacridan, and in one experiment acridan was isolated. From the reaction with quinoxaline, a high melting compound was obtained which could not be identified.

A unique reaction was obtained with 2-styrylquinoline and with 4-styrylquinoline where the carbon-carbon double bond was hydrogenated in practically quantitative yields to 2-(β-phenylethyl)-quinoline and 4-(β-phenylethyl)-quinoline, respectively. Reductions were also attempted with compounds analogous to acridine and 2-styrylquinoline, but lacking the azomethine group, in an attempt to throw some light on the minimum structural requirements and mechanism of the reaction.

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10. Gilman, Towle and Spatz, J. Am. Chem. Soc., 68, 2017 (1946).

11. Geissman, et al, J. Org. Chem., 11, 741 (1946).

II. HISTORICAL

An unusual reaction has been described by Gilman and Dickey[2] in which benzalaniline was reduced to benzylaniline by p-thiocresol in refluxing xylene, with the thiol concomitantly oxidized to di-p-tolyl disulfide. Although the thiol was added in excess (a 3:1 mole ratio), the reduced anil was

$$2\ p\text{-}CH_3C_6H_4SH + C_6H_5CH\ NC_6H_5 \longrightarrow$$

$$C_6H_5CH_2NHC_6H_5 + p\text{-}CH_3C_6H_4SSC_6H_4CH_3\text{-}p$$

isolated in 76% yield with traces of aniline present. Likewise, benzophenone-anil was reduced to benzohydrylaniline, the latter isolated as both the free compound and combined as a molecular complex with unreacted benzophenone-anil (I).

$$\begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!>\!\!\begin{matrix} H\ H \\ C\text{-}NC_6H_5 \end{matrix} \cdot \begin{matrix} C_6H_5 \\ C_6H_5 \end{matrix}\!\!>\!\!C{=}NC_6H_5$$

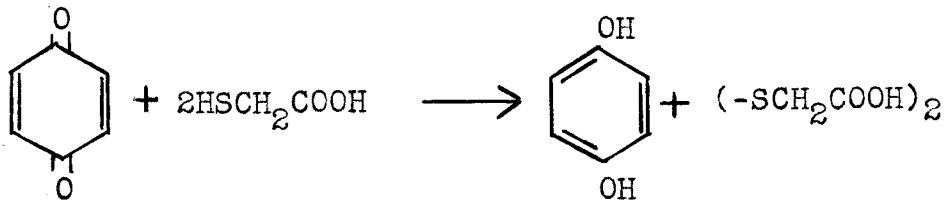
Azobenzene was reduced in good yield to aniline and hydrazobenzene. The authors are of the opinion that hydrazobenzene was formed at first and that this underwent decomposition, due to the forced conditions, to aniline and azobenzene. The azobenzene thus formed was then reduced by the same process

$$4\ C_6H_5\overset{H}{N}\text{-}\overset{H}{N}C_6H_5 \longrightarrow C_6H_5N{=}NC_6H_5 + 2\ C_6H_5NH_2$$

to aniline by the excess thiol present.

Curious to discover whether benzophenone and nitrobenzene would be reduced under the same forced conditions, they treated these compounds with p-thiocresol, but were able to recover the unreacted thiol in practically quantitative amounts, indicating that a reduction had not taken place.

In an early study, Bongartz[12] treated various aldehydes and ketones with thioglycolic acid to get the expected mercaptals and mercaptoles. With quinone an entirely different reaction took place. Instead of an addition product, he obtained hydroquinone and bisthioglycolic acid.

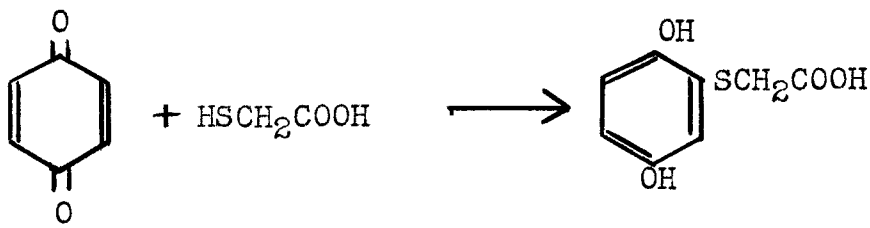


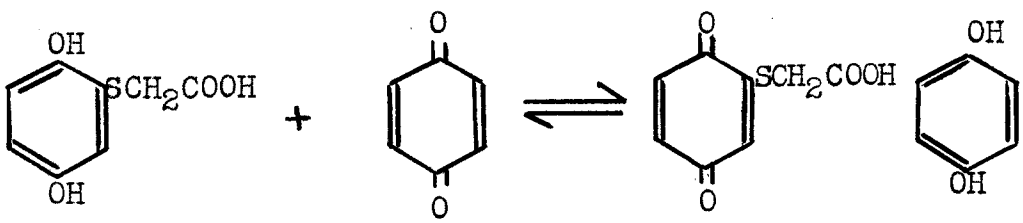
Similarly, anthraquinone and thioglycolic acid heated with zinc chloride at 200° gave him 9,10-dihydroxyanthracene. Another early evidence of the reducing action of thiols is

12. Bongartz, Ber., 21, 483 (1888).

reported by Tarbouriech[13], who obtained hydroquinone (isolated as the complex quinhydrone) by heating quinone with ethyl mercaptan in a bomb at 140°. He suggested, without presenting any experimental evidence, that the oxidation product was thioacetaldehyde.

Much later, Snell and Weissberger[14] investigated the quinone-thioglycolic acid reaction. In addition to hydroquinone they isolated quinone-α-mercaptoacetic acid. Their interpretation of this result is illustrated by the following reactions:

(1) 

(2) 

In reaction (1) the mercaptan probably adds to the quinone by 1,4-addition followed by a 1,3-shift of the proton to give the

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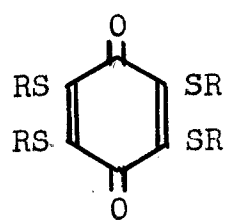
13. Tarbouriech, Bull. soc. chim., (3) 25, 313 (1901).

14. Snell and Weissberger, J. Am. Chem. Soc., 61, 450 (1939).

substituted hydroquinone. Excess quinone then oxidizes the sulfur-containing hydroquinone to the substituted quinone, it itself being reduced to hydroquinone. This postulation explains the formation of hydroquinone on the basis of oxidation potentials. Apparently the effect of the thioglycolic acid moiety in the ring is such that the substituted quinone has a lower potential than the parent quinone[15].

Snell and Weissberger[14] also were able to reduce duroquinone to durohydroquinone with thioglycolic acid in aqueous sodium carbonate solution. No mention is made of disulfide formation or of any other products. Schubert[16] found that by treating quinone with thioglycolic acid in hot water, a tetrasubstituted quinone was produced. The mechanism undoubtedly



(II)

involves reactions (1) and (2), with the overall reaction

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15. m-Directing groups, as well as chlorine, raise the oxidation potential, whereas, o-directing groups, in general, exert a potential-lowering effect. Fieser and Fieser, "Organic Chemistry," D. C. Heath and Company, Boston (1944), p. 729.

16. Schubert, J. Am. Chem. Soc., 69, 712 (1947).

represented thus:

$$4\ \text{Quinone} + 4\ \text{HSR} \longrightarrow (\text{II}) + 3\ \text{Hydroquinone}$$

Two different reactions, then, may result from quinones and thiols: (A), oxidation of the thiol to a disulfide with the reduction of the quinone to the hydroquinone; (B), addition of the thiol to the quinone and the subsequent oxidation of the adduct by the parent quinone which has a higher potential. Although (B) involves the reduction of quinone, (B) does not proceed through the formation of disulfide and therefore, strictly speaking, does not belong to the same category as reaction (A) and the reactions of Gilman and Dickey[2].

An interesting example of the reducing action of thiols is their physiological action on alloxan. Labes and Freisburger[17] found that when alloxan is administered to frogs, capillary paralysis sets in, the symptoms of which are convulsions, paralysis and intestinal hyperemia. Their contention is that capillary paralysis is caused by the oxidizing action of alloxan on the mercapto groups present in the tissue proteins, with the alloxan converted to murexide. They point out that other oxidants (anthraquinone, methylene ethers of various o-dihydroxyphenols and possibly barbituric acid) cause similar capillary paralysis in the intestinal walls.

Closely related to this is the work of d'Ouville, Myers

17. Labes and Freisburger, Arch. exp. Path. Pharmakol., 156, 226 (1930) [C. A., 25, 4046 (1931)]

and Connor[18] who attempted to prepare some mercaptoles from alloxan and then oxidize them to the sulfones. In one reaction with benzyl mercaptan, dibenzyl disulfide was isolated in addition to the hemimercaptole, 5-acetoxy-5-(benzylthio)-barbituric acid. However, the reduction product, dialuric acid (5-hydroxy-barbituric acid), which they expected to find, was not present among the reaction products. It is possible that the reduced alloxan had been converted to alloxantin which is formed very readily by the addition of alloxan to dialuric acid. In support of this, Ciamician and Silber[19] reported that alloxantin is produced from the oxidation of ethanol to acetaldehyde by alloxan in the presence of sunlight. It should also be pointed out that d'Ouville and his collaborators apparently made no attempt to exclude air from the alloxan-benzyl mercaptan reaction, which was carried out in a mixture of acetic acid and acetic anhydride and subjected to a prolonged period of refluxing. The disulfide could thus have arisen from air oxidation, although, admittedly, this is not as likely to happen in an acid medium as in a basic one. In other experiments they found that p-thiocresol did not react with alloxan either in dioxane or acetic acid. Catalysts used unsuccessfully to effect a reaction were anhydrous hydrogen chloride, concentrated sulfuric acid and zinc chloride.

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18. d'Ouville, Myers and Connor, J. Am. Chem. Soc., 61, 2033 (1939).

19. Ciamician and Silber, Ber., 36, 450 (1939).

The reduction of alloxan by a mercapto group is a property that one would predict from a knowledge of its role as a strong hydrogen acceptor. The oxidation of ethanol by alloxan has been mentioned, and Johnson[20] reported that hydrouracil can be quantitatively dehydrogenated to uracil with the aid of alloxan. Equally pertinent is the observation by Pellizzari[21] that hydrazobenzene is oxidized to azobenzene by alloxan. In the light of these facts it is rather surprising that d'Ouville, Myers and Connor[18] were unable to isolate any reduction products in any of their reactions. This seems particularly true when one compares two of these oxidation-reduction systems: the reduction of azobenzene to hydrazobenzene by p-thiocresol[2] and the reduction of alloxan by hydrazobenzene[21]. From a thermodynamic standpoint it would appear from the above that the difference of potentials between alloxan and p-thiocresol is great enough for oxidation to occur. However, other factors may be involved. This particular reduction may be possible only through a certain type of mechanism, the conditions for which have not been obtained in any of the previously attempted reactions.

Of especial relevance to this discussion of the reducing action of thiols is a reaction described in a patent[22] which

20. Johnson, J. Am. Chem. Soc., 63, 263 (1941).

21. Pellizzari, Gazz. chim. ital., 17, 256 (1888) [Chem. Zentr., 58, 1162 (1887)].

22. Williams and Allen, U. S. Patent 2,052,268 (Aug. 25, 1936) [C. A., 30, 7122 (1936)].

appeared in 1936. It is claimed that if hydrogen sulfide and an unsaturated hydrocarbon, containing at least six carbon atoms, are heated above 100°, under superatmospheric conditions, a saturated hydrocarbon is produced. Two examples of this reaction are the production of iso-octane from diisobutylene in 73.1% and 74% yields. The mechanism which the claimants have postulated is as follows:

(1) $C_nH_{2n} + H_2S \longrightarrow C_nH_{2n+2} + S$

(2) $C_nH_{2n} + H_2S \longrightarrow C_nH_{2n+1}SH$

(3) $C_nH_{2n} + 2\ C_nH_{2n+1}SH \longrightarrow (C_nH_{2n+1})_2S_2 + C_nH_{2n+2}$

These reactions are not fully substantiated by the experimental evidence. It is true that in other related reactions mercaptans (and thioethers) have been produced[22], but nowhere is the actual isolation of a disulfide mentioned. Furthermore, the authors did not test the validity of reaction (3) by attempting it under the specified conditions. It remains, however, an interesting postulate. Aside from the findings appearing in this dissertation, it is the only recorded instance of the reduction of a carbon-carbon double bond by a thiol. Nevertheless it must be emphasized that in this patent there is no rigorous proof of the reducing action of thiols. The possibility of hydrogen sulfide acting as a reductant, as illustrated in reaction (1), should not be overlooked.

Biological oxidation-reduction systems involving the mercapto group and the disulfide linkage are believed to play

an important part in both animal and plant metabolism. It has been suggested[23] that glutathione, glutamyl-cysteinyl-glycine, in the presence of the enzyme reductase reduces dehydroascorbic acid to ascorbic acid.

Dehydroascorbic acid + 2 GSH $\longrightarrow$ Ascorbic acid + GS-SG

Kendall and Nord[24] have an interesting theory regarding the thermodynamic reversibility of the -SH and -S-S- forms of glutathione. They believe that a third component is necessary -- a highly unstable oxygen addition complex of glutathione without which the system would not be reversible. For example, a deoxygenated solution of reduced (-SH) glutathione will not reduce indigo carmine. If oxygen is introduced, a complex is formed which reduces indigo carmine immediately. Hydrogen peroxide or sodium sulfide apparently have the same effect as oxygen. Their results indicate that reduced and oxidized forms of glutathione are relatively stable substances in which the atom of sulfur cannot change its state of oxidation with sufficient ease to influence a physiological process of oxidation and reduction. A similar active complex seems to be necessary for the system cysteine-cystine. Some of the dyes that are reduced by cysteine are dibromoindophenol,

23. Ref. 16, p. 1006.

24. Kendall and Nord, J. Biol. Chem., 69, 295 (1926).

naphthol indodichlorophenol and methylene blue.

An excess of another sulfhydryl compound may reduce a disulfide linkage by a mass action effect[25]. It is known that

$$RSSR + 2\ R'SH \longrightarrow 2\ RSH + R'SSR'$$

thioglycolic acid reacts with cystine in solution to give cysteine[26]. A similar reaction occurs between simple alkyl disulfides and mercaptans[27]. When mixtures of propyl disulfide and decyl mercaptan were heated in sealed tubes, a mole for mole exchange of propyl for decyl mercaptan occurred. The authors[27] believe that the reaction proceeds stepwise with the mixed disulfide formed at first. p-Thiocresol will similarly reduce dibenzothiazolyl disulfide to 2-mercaptobenzothiazole[28]. du Vigneaud[29] showed that insulin could be deactivated by cysteine and the reduced form of glutathione. The deactivation is believed to be due to the rupture of the disulfide linkage in the insulin molecule, although various attempts to restore the activity by reoxidizing the molecule resulted in failure.

25. Mirsky and Anson, Proc. Soc. Exp. Biol. Med., 28, 170 (1930).

26. Goddard and Michaelis, J. Biol. Chem., 106, 605 (1934).

27. Gorin, Dougherty and Tobolsky, J. Am. Chem. Soc., 71, 3551 (1949).

28. J. L. Towle, Unpublished studies, Iowa State College.

29. du Vigneaud, J. Biol. Chem., 94, 233 (1939).

III. EXPERIMENTAL

The same equipment set-up was used in all of the reactions involving thiols. This consisted of a two-necked flask with standard taper joints equipped with two Liebig condensers. The top of one condenser was connected to a source of oxygen-free nitrogen and the top of the second condenser was connected to an air trap[30]. Before starting a reaction the chemicals were placed in the flask and then the entire apparatus was flushed with nitrogen. This was essential to avoid air oxidation of the thiols, particularly at the temperatures employed.

Analyses for nitrogen were made by the micro Dumas method. The melting points are uncorrected.

p-Thiocresol and Quinoline (3:1 mole ratio, in xylene).- Thirty-nine g. (0.315 mole) of p-thiocresol and 13.5 g. (0.105 mole) of quinoline were dissolved in 200 ml. of xylene and refluxed for twenty-five hours. After the solution was cooled to room temperature, it was extracted with 10% sodium hydroxide. Acidification and cooling of the alkaline extract in an ice bath caused p-thiocresol to separate as large, easily filterable crystals. When dry, the thiol weighed

30. Gilman and Hewlett, Rec. trav. chim., 48, 1124 (1929).

38.0 g., representing a 95% recovery. It melted at 45-46° and did not depress the melting point of an authentic sample (m.p. 45-46°).

The xylene was distilled off and a portion of the liquid which remained was converted to the picrate. The melting point (202°) agreed with the reported value for quinoline picrate and its sharpness indicated the absence of possible contaminants such as dihydroquinoline.

p-Thiocresol and Quinoline (without solvent).-A mixture of 13.5 g. (0.105 mole) of quinoline and 26.0 g. (0.21 mole) of p-thiocresol was heated without a solvent (bath temperature 200°) for twenty-four hours. The reaction was worked up in the usual way by dissolving the mixture in ether, extracting with sodium hydroxide (95% thiol recovered), removing the ether by evaporation and converting the base to the picrate. The latter melted sharply at 202-203°, thus serving as an indication that contaminants which might have been formed by a reduction were not present. There was no depression in melting point when mixed with an authentic sample (m.p. 202-203°). In view of the good recovery of thiol and the apparent lack of contamination of recovered base by reduced products, a search for disulfide was considered unnecessary.

p-Thiocresol and Pyridine.-A mixture of 8.3 g. (0.105 mole) of pyridine and 39.0 g. (0.315 mole) of p-thiocresol was dissolved in 200 ml. of toluene and refluxed for twenty-five

hours. The solution was extracted with 10% sodium hydroxide to effect a recovery of 37.5 g. (96%) of thiol. It melted at 43-44° and its identity was established by a mixed melting point. Because of the excellent recovery of thiol, it was considered highly improbable that any reduction had occurred.

p-Thiocresol and Isoquinoline.-Thirty-nine g. (0.315 mole) of p-thiocresol and 13.5 g. (0.105 mole) of isoquinoline were refluxed in 200 ml. of xylene for twenty-five hours.

The reaction was worked up in exactly the same manner as in the attempted quinoline reduction. A recovery of 37.0 g. (95%) of thiol was effected. It was identified by a mixed melting point determination.

The melting point of the picrate of the residue, after the solvent was distilled off, was 224° and did not depress the melting point of an authentic sample of isoquinoline picrate (m.p. 224°).

p-Thiocresol and Benzothiazole.-A mixture of 60.0 g. (0.484 mole) of p-thiocresol and 15.0 g. (0.114 mole) of benzothiazole was heated for thirty-six hours at 190°. The reaction flask was cooled and ether added. Extraction with 10% sodium hydroxide effected a practically quantitative (98%) recovery of thiol. There was no evidence of any reaction.

p-Thiocresol and 2-Phenylquinoline.-Thirty-nine g. (0.315 mole) of p-thiocresol and 21.5 g. (0.105 mole) of 2-phenylquino-

line[31,32] were heated in 200 ml. of xylene under reflux for twenty-five hours. The reaction was worked up in the usual manner. Thirty-eight g. (97.4%) of thiol was recovered. There was no indication of reduction.

p-Thiocresol and 2-(p-Dimethylaminophenyl)-7-methylquinoline.-A mixture of 13.75 g. (0.053 mole) of 2-(p-dimethylaminophenyl)-7-methylquinoline[10] and 19.5 g. (0.156 mole) of p-thiocresol dissolved in 200 ml. of boiling xylene was refluxed for twenty-five hours.

After the reaction flask was cooled, a crystalline solid separated out. This was filtered off and washed with petroleum ether (b.p., 60-70°). It weighed 10.5 g. and melted sharply at 186-188°. This was recovered base (m.p. 187-188°) as shown by a mixed melting point.

The combined filtrate and washings were extracted with 10% sodium hydroxide. Acidification caused 18.7 g. of thiol to precipitate. This represents a 96% recovery. There was no evidence of any reduction.

p-Thiocresol and Acridine (3:1 mole ratio, in xylene).-A mixture of 39.0 g. (0.315 mole) of p-thiocresol and 18.8 g. (0.105 mole) of acridine was dissolved in 200 ml. of xylene and refluxed for twenty-five hours. During the reflux period a crystalline substance continually separated. This was

31. Ziegler and Zeizer, Ann., 485, 174 (1931).
32. Gilman and Gainer, J. Am. Chem. Soc., 69, 877 (1947).

filtered off and washed in turn with xylene and hot ethanol. The dried material weighed 6.0 g. Because of its extreme insolubility, attempts at purification through recrystallization did not lead to satisfactory results. The results of elemental analyses and melting point (m.p. 260-265°in a melting point block) suggested this compound might be the biacridan reported by Schlenk and Bergmann[33] and also by Bergmann and Blum-Bergmann[34].

Anal. Calcd. for $C_{26}H_{20}N_2$: C, 86.66; H, 5.59; N, 7.42. Found: C, 86.40, 86.72; H, 5.43, 5.47; N, 7.45.

A mixed melting point determination with a sample of Bergmann's[35] compound failed to establish clearly whether the compounds were identical. By heating the bath to 230° and then inserting the thermometer and samples, the following melting points were obtained: the compound prepared by the thiol reduction, m.p. 255-260°; Bergmann's biacridan, m.p. 245-249°; an equal mixture of the two compounds, m.p. 240-250°.

When the thermometer and samples were inserted in the bath at room temperature the melting points were as follows: our compound, m.p. 247-255°; Bergmann's compound, m.p. 225-233°; a mixture of the two compounds, m.p. 230-240°. Apparently the

33. Schlenk and Bergmann, Ann., 463, 300 (1928).

34. Bergmann and Blum-Bergmann, Ber., 63, 757 (1930).

35. We are grateful to Dr. Ernst Bergmann for samples of biacridan and 9,9'-dibenzoylbiacridan.

melting point is greatly influenced by the method used.

The failure to obtain an appreciable depression in melting point recalls the work of Lehmstedt and Hundertmark[36] whose method of preheating the bath was described above. They found their compound (m.p. 214°), which they believed to be biacridan, and isomeric with Bergmann's compound (m.p. 249° by the method of Lehmstedt and Hundertmark), failed to depress the melting point of the latter. In this case the Lehmstedt and Hundertmark compound melted at 214° with disproportionation and "the melt which results from the decomposition products, acridine and acridan, acts as a non-dissolving solution toward the higher melting isomer"[36].

Debye powder diagrams[37] of our compound and Bergmann's are identical. Lehmstedt and Hundertmark also state that their biacridan gives the same pattern as Bergmann's product.

The compound was finally identified by preparing the dibenzoyl derivative (described in the following experiment). A mixed melting point determination with a sample of the compound obtained by Schlenk and Bergmann[33] from the benzoylation of the sodium-adduct of acridine demonstrated the two to be identical. The yield of biacridan was 32%.

The original filtrate from which biacridan was separated

36. Lehmstedt and Hundertmark, Ber., 63, 1229 (1930).

37. We are indebted to Mr. Richard Raeuchle for the Debye powder diagrams.

was extracted with sodium hydroxide to recover 19.5 g. (50%) of unreacted thiol.

After standing over sodium sulfate, the xylene solution was evaporated to dryness leaving a crystalline residue. This was dissolved in ethanol and filtered. A small amount of unidentified yellowish material melting above 300° remained on the filter. The ethanolic filtrate was completely evaporated and the residue taken up in anhydrous ether. Ethanolic hydrogen chloride was added to precipitate acridine hydrochloride. This was removed by filtration and converted to the free base by trituration with aqueous sodium hydroxide. The dried material weighed 11.0 g. (58% recovery).

After removal of the solvent by evaporation, the residue, weighing 8.5 g. was recrystallized from dilute ethanol. It was shown to be di-p-tolyl disulfide by comparison with an authentic sample.

9,9'-Dibenzoylbiacridan.-To 0.04 mole phenyllithium[38] in an ether-xylene solution was added 3.46 g. (0.1 mole) of biacridan and the mixture was refluxed for twenty-four hours. An excess of benzoyl chloride was then added and the refluxing continued for an additional six hours. The insoluble material was filtered off and washed thoroughly with acetone. The

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

crude product melted at 270-290°. After recrystallization from cumene it melted at 303-305°. Schlenk and Bergmann[33] report a melting point of 305°. A mixture of Bergmann's[35] compound and our preparation melted at 304-305°.

p-Thiocresol and Acridine (3:1 mole ratio, without solvent).-A mixture of 39.0 g. (0.315 mole) of p-thiocresol and 18.8 g. (0.105 mole) of acridine was heated, with the bath temperature at 170-180°, for twenty hours. To the cooled reaction flask was added 300 ml. of ether. The crystalline mass was easily broken up with a spatula, filtered on a sintered glass funnel and washed successively with hot ethanol and ordinary ether. The white crystalline product, 13.3 g. (72%) melted at 260-265°. It did not depress the melting point of biacridan prepared in the previous experiment.

Unreacted thiol was recovered by extracting the ethereal solution with 10% sodium hydroxide and acidifying the cooled extract. In this manner, 18.0 g. (46.2% of the original amount) was recovered.

After drying the ether solution over sodium sulfate and then evaporating to dryness, a residue was obtained which was transferred to a sintered glass funnel and washed quickly with petroleum ether (b.p. 28-30°). This treatment dissolved everything but di-p-tolyl disulfide which weighed 16.0 g. (0.065 mole). Evaporation of the ether from the filtrate left

a mixture of acridan and acridine weighing 5.2 g. These two compounds were separated by means of aqueous ethanolic hydrogen chloride. The insoluble acridan, weighing 4.0 g. (0.022 mole), was identified by a mixed melting point with an authentic specimen prepared by the sodium-amalgam reduction of acridine[39]. The remaining 1.2 g. was unreacted acridine.

p-Thiocresol and Acridan.-In 100 ml. of xylene, 11.5 g. (0.0927 mole) of p-thiocresol and 6.7 g. (0.0373 mole) of acridan were heated under reflux for twenty-four hours. During the reflux most of the solvent had distilled off through a loose fitting joint in the reaction flask. Most of the solid remaining was redissolved by the addition of ether. The very small amount which did not dissolve was filtered off and washed with ether. Apparently it was not biacridan because at 300° it did not melt. Further identification was not attempted. From this experiment it appears that biacridan is not formed from the reaction of p-thiocresol and acridan.

Pyrolysis of Biacridan.-A small amount of biacridan was placed in a test tube, fitted with a condenser, and heated in a metal bath under a nitrogen atmosphere for four hours at 300-320°. Acridine had formed and sublimed on the upper part of the tube. Its identity was established by a mixed melting point. There was no indication of acridan, which would be

39. Greabe and Caro, Ann., 158, 278 (1871).

expected from the decomposition of biacridan in an inert atmosphere.

p-Thiocresol and Acridine (3:1 mole ratio, in xylene, 36 hrs.).-A mixture of 78.0 g. (0.63 mole) of p-thiocresol and 37.6 g. (0.21 mole) of acridine dissolved in 300 ml. of xylene was refluxed for thirty-six hours. During the refluxing, biacridan separated as fine crystals. It was filtered off and washed with petroleum ether (b.p. 60-70°). The dried product weighed 19.0 g. (50%) and melted at 260-265°.

From the dark filtrate a small amount of crystals separated which were dissolved in ether and added to the combined filtrate and petroleum ether washings. Extraction with 10% sodium hydroxide and subsequent acidification and cooling of the extract effected a recovery of 38.0 g. (49%) of p-thiocresol.

The solution was dried over sodium sulfate and the solvent removed by distillation. A residue was obtained which was dissolved in anhydrous ether. Ethanolic hydrogen chloride was then added to precipitate greenish crystals. These weighed 11.0 g. and were shown to be acridine hydrochloride by converting to the free base with aqueous sodium hydroxide. The green filtrate, from which the hydrochloride was separated, was evaporated to dryness. The residue was recrystallized from 95% ethanol. A mixture of acridine and di-p-tolyl disulfide, weighing 29.0 g., was obtained. The latter was separated from

acridine by suspending the mixture in petroleum ether (b.p. 28-38°) and filtering. This treatment dissolved the disulfide and left 3.7 g. of acridine which was insoluble in this solvent. Evaporation of the petroleum ether, and recrystallization of the residue from dilute ethanol yielded 24.0 g. of di-p-tolyl disulfide. The identity of each of the compounds isolated was established by a mixed melting point determination.

p-Thiocresol and Acridine (1:1 mole ratio, in xylene).-A mixture of 17.9 g. (0.1 mole) of acridine and 12.4 g. (0.1 mole) of p-thiocresol, dissolved in 150 ml. of xylene, was refluxed for twenty-four hours. Within thirty minutes after the reflux commenced, insoluble biacridan began to separate. The crystals were filtered off and washed well with benzene and ether. The dried product weighed 8.0 g. (44.6%). It melted at 260-266°.

The filtrate was extracted with sodium hydroxide whereby 1.5 g. (12.1%) of p-thiocresol was recovered.

p-Thiocresol and Acridine (1:1 mole ratio, without solvent).-A mixture of 35.8 g. (0.20 mole) of acridine and 24.8 g. (0.20 mole) of p-thiocresol was heated (bath temperature, 200°) for twenty-four hours. Benzene was added to the cool reaction flask and the solid material broken up and separated by filtration. The product was washed thoroughly with benzene

and then with acetone. When dry it weighed 25.0 g. (70%) and melted at 260-265°. It did not depress the melting point of biacridan from a previous preparation. A recovery of 7.2 g. (30%) of the original thiol was obtained.

p-Thiocresol and 9-(o-Iodophenyl)-acridine.-One g. (0.00262 mole) of 9-(o-iodophenyl)-acridine[40] and 1.0 g. (0.0082 mole) of p-thiocresol were heated together at 200° for twenty-four hours. The acridine compound (m.p. 261-262°) did not dissolve in the molten thiol. A portion of the mixture was removed and washed with petroleum ether (b.p. 60-68°) to dissolve the thiol. The residue melted at 262° and was unreacted starting material, as evidenced by a mixed melting point determination.

The small amount of residue was returned to the reaction flask and a great excess of p-thiocresol (5.0 g.) was also added to serve as a solvent for the reaction. The mixture was heated again for twenty-four hours at the same temperature as in the first attempt. This time the result was a homogeneous melt. Two hundred ml. of petroleum ether (b.p. 60-70°) was then added to the cooled flask to bring everything into solution. Cooling caused tan crystals to separate. These were filtered off, washed with petroleum ether and dried in the desiccator. They weighed 0.95 g. and melted at 258°. A

40. We are indebted to Dr. C. Gardner Swain for a supply of 9-(o-iodophenyl)-acridine.

mixed melting point determination with 9-(o-iodophenyl)-acridine (m.p. 262°) was 261-262°, and indicated that the starting material was recovered in a practically quantitative amount.

p-Thiocresol and Anthracene.-To a solution of 29.1 g. (0.23 mole) of p-thiocresol in 200 ml. of xylene was added 17.9 g. (0.10 mole) of anthracene. The mixture was refluxed for twenty-four hours. The cooled reaction mixture was filtered and the residue washed with xylene. Extraction of the combined filtrate and washings with sodium hydroxide and subsequent acidification effected a recovery of 27.0 g. (93%) of thiol. Of the original anthracene 17.3 g. was recovered. The latter was subjected to a steam distillation, to determine whether any dihydroanthracene might be present. Apparently no reduction h had occurred, because dihydroanthracene, which is steam-distillable, was not obtained.

p-Thiocresol and Anthracene (with benzoyl peroxide catalyst).-A solution of 200 ml. of xylene containing 17.9 g. (0.1 mole) of anthracene, 12.4 g. (0.10 mole) of p-thiocresol and 0.5 g. (0.002 mole) of benzoyl peroxide was refluxed for twenty-four hours. When cool, anthracene crystallized from the solution. It was separated by filtration and washed thoroughly with toluene and petroleum ether (b.p. 28-38°). The filtrate and washings were extracted with 10% sodium hydroxide to recover 11.9 g. (96%) of thiol. The excellent

recovery of thiol did not seem to warrant the investigation of the recovered anthracene for any reduction products.

Preparation of Quinoxaline.-Quinoxaline was prepared according to the procedure of Hinsberg[41]. To a suspension of 50.0 g. (0.462 mole) of o-phenylenediamine in 350 ml. of water was added, with stirring, 145 g. (0.545 mole) of glyoxal-sodium bisulfite at a temperature of 50-60°. After ten minutes of stirring, everything was in solution. Solid potassium hydroxide pellets were added and an oil separated. This was taken up in ether and dried over potassium hydroxide pellets. The ether was removed by distillation and the product was collected over a range of 225-230° at atmospheric pressure. It weighed 47.6 g. (80%).

p-Thiocresol and Quinoxaline.-A solution of 78.0 g. (0.63 mole) of p-thiocresol and 13.5 g. (0.104 mole) of quinoxaline in 200 ml. of xylene was refluxed for thirty-six hours. The reaction mixture was cooled and filtered. A crystalline substance was separated on the filter. This was washed with xylene and dried. It weighed 4.1 g. (30.2% based on quinoxaline) and melted at 280-283°. An elemental qualitative analysis showed it to contain nitrogen but no sulfur. The crystals appeared to be black, but under the microscope they were seen to be dark green.

Two analyses showed a nitrogen content of 21.2% and

41. Hinsberg, Ann., 237, 334 (1887).

21.34%, respectively. The molecular weight (Rast method in camphor) was found to be 248.

The xylene filtrate was extracted with 10% sodium hydroxide. Acidification of the extract and cooling precipitated 62.0 g.(79.5%) of unreacted thiol. After evaporating the xylene solution to dryness, the residue was shaken with a mixture of petroleum ether (b.p. 60-70°) and dilute hydrochloric acid. In this manner unreacted quinoxaline was separated from di-p-tolyl disulfide. The latter was obtained after the petroleum ether extract was dried and evaporated. It weighed 4.2 g. (5.3%) and was identified by a mixed melting point determination with an authentic sample.

The molecular weight indicates a bis compound of some type or possibly a molecular complex of the type Gilman and Dickey[2] obtained from one of their reactions (see p. 4 of this thesis). However, the results of the reactions following directly are not in agreement with what one might expect from either of the types postulated above. This will be treated more fully in the Discussion part of the thesis.

Attempted oxidation with nitrobenzene.-The quinoxaline-p-thiocresol reduction product was dissolved in hot nitrobenzene and refluxed for thirty minutes. From the cold solution a brown material separated. A mixed melting point determination showed it to be starting material.

Attempted oxidation with mercuric oxide.-The compound was dissolved in methyl cellosolve and refluxed with mercuric oxide for four hours. The hot solution was separated from the mercuric oxide by filtration. A substance crystallized from the cold filtrate. This was shown to be unreacted starting material.

Attempted acetylation with acetic anhydride.-The compound was dissolved in an excess of hot acetic anhydride and the solution refluxed for two hours. Pyridine was added and the refluxing continued for an additional two hours. After cooling the solution, it was diluted with water. A crystalline substance separated. It was demonstrated to be the original compound by a mixed melting point determination.

p-Thiocresol and Quinoxaline (without solvent).-A mixture of 10.0 g. (0.077 mole) of quinoxaline and 40.0 g. (0.328 mole) of p-thiocresol was heated (bath temperature at 190-200°) for twenty-four hours. The reaction mixture was diluted with ether, triturated and filtered. The ether-insoluble black crystals were thoroughly washed with acetone. A yield of 5.0 g. (50%) was obtained. The melting point was 281-283°. A mixed melting point determination with the product obtained when xylene was used as a solvent was not depressed.

Preparation of 1,2,3,4-Tetrahydroquinoxaline.-The procedure that was followed for the reduction is essentially that

of Merz and Ris[42]. To a solution of 6.0 g. (0.046 mole) of quinoxaline in 250 ml. of ethanol, was added 34.0 g. (1.48 g. atoms) of sodium in small pieces. When the reaction was over, the entire mixture solidified. The color changes during the reduction were from dark blue to tan.

The mass was dissolved in a minimum amount of ethanol, diluted with water, made acidic with sulfuric acid and heated. A blue coloration developed. After continued heating, a tan material settled out. This was filtered off and the filtrate was made basic and extracted with ether. After drying over sodium sulfate, the solvent was removed. The residue was recrystallized from petroleum ether (b.p. 60-70°). The product, orange platelets, melted at 93-95° and weighed 0.7 g. (11.6%).

1,2,3,4-Tetrahydroquinoxaline and Quinoxaline.-In order to determine whether the product from the p-thiocresol-quinoxaline reaction might be a molecular compound formed from one molecule of tetrahydroquinoxaline and one of quinoxaline, the method of Allesandri[43], which he used to prepare other similar complexes of this type, was utilized in an attempt to obtain an authentic specimen.

A mixture of 0.7 g. (0.0054 mole) of 1,2,3,4-tetrahydroquinoxaline and 0.7 g. (0.0054 mole) of quinoxaline was

42. Merz and Ris, Ber., 20, 1196 (1887).

43. Allesandri, Gazz. chim. ital., 51, 1, 75 (1921) [C. A., 25, 4046 (1931)].

dissolved in 20 ml. of absolute ethanol and refluxed for twenty-four hours. At no time was any precipitate noticed. Since the product whose identification was being sought is insoluble even in boiling ethanol, it was certain it could not have been formed in the above attempted reaction.

Preparation of 2-Styrylquinoline.-A mixture of 66.0 g. (0.623 mole) of freshly distilled benzaldehyde, 89.2 g. (0.623 mole) of quinaldine and 63.5 g. (0.623 mole) of acetic anhydride was heated under reflux for ten hours. The temperature dropped from 155° to 145° during this time. The reaction mixture was added to twice its volume of water, made basic with ammonium hydroxide and stirred until the gummy product crystallized. It was stirred for an additional hour, filtered, and washed thoroughly with water. Trituration with 95% ethanol, filtering and washing the product with petroleum ether (b.p. 60-70°) removed practically all of the impurities. The product was recrystallized from 95% ethanol to give 105 g. (76%) of white crystals melting at 99-100°[44].

p-Thiocresol and 2-Styrylquinoline.-A mixture of 20.0 g. (0.0865 mole) of 2-styrylquinoline and 25.0 g. (0.205 mole) of p-thiocresol was heated for twenty-four hours, with the bath temperature at 200°. Standing at room temperature and then cooling in an ice bath failed to effect crystallization.

44. Skraup and Böhm, Ber., 59, 1013 (1926).

The melt was dissolved in ether and extracted with 10% sodium hydroxide. Acidification and cooling of the extract caused 3.5 g. (0.028 mole) of the thiol to separate. This is almost equal to the excess (0.032 mole) of thiol used in the reaction.

The ethereal solution was dried over sodium sulfate and evaporated to a viscous residue that resisted every attempt at crystallization. A portion of this residue was dissolved in ether and hydrogen chloride gas introduced. A red gummy material separated. The clear supernatant solution was decanted and evaporated to a deposit of white crystals. These melted at 45-46°, and a mixed melting point demonstrated the crystals to be di-p-tolyl disulfide.

The remainder of the viscous material was dissolved in anhydrous benzene and saturated with hydrogen chloride gas. Two layers formed which soon became homogeneous. Cooling overnight in the refrigerator caused a red mass of crystals to separate. This supposedly was the hydrochloride of the reduction product. After filtering and washing with dry benzene, the crystalline product, being somewhat hygroscopic, was not considered pure enough for analysis or a melting point determination. Therefore, it was dissolved in 95% ethanol and converted to the picrate by adding an ethanolic solution of picric acid. The yellow picrate which crystallized upon cooling melted at 135-136°. The results of a nitrogen analysis

corresponded to a monopicrate of reduced 2-styrylquinoline. (The picrate of 2-styrylquinoline melts at 230-232°).

Anal. Calcd. for $C_{23}H_{18}N_4O_7$: N, 12.10. Found: N, 12.39.

To determine if the reduction product might be a 1,2-dihydro compound, 8.0 g. of the picrate was converted to the free base by refluxing with 150 ml. of 5% sodium hydroxide for two hours. The red aqueous solution was cooled and extracted with ether. After drying over sodium sulfate, the extract was evaporated to an oily residue which failed to crystallize at 0°. It was heated with nitrobenzene, dissolved in 95% ethanol and treated with picric acid. The picrate that separated melted at 134-135°, and did not depress the melting point of the original picrate. Thus, the reduction product was not a 1,2-dihydro derivative. The other logical possibility was that it might be 2-(β-phenylethyl)-quinoline.

p-Thiocresol and 2-Styrylquinoline.-A mixture of 20.0 g. (0.0865 mole) of 2-styrylquinoline and 25.0 g. (0.205 mole) of p-thiocresol was heated (bath temperature at 200-205°) for twenty-four hours. The melt was dissolved in ether and the solution extracted with 10% sodium hydroxide. Acidification of the extract and cooling caused the separation of 2.4 g. (0.194 mole) of unreacted thiol.

Drying of the ethereal solution over sodium sulfate and subsequent evaporation of the solvent left a residue which

was taken up in dry benzene. Hydrogen chloride gas was introduced while the benzene solution was kept immersed in an ice water bath. The flask was then placed in the refrigerator overnight and the red crystalline precipitate, which had formed, was filtered off and washed with benzene. The crystals weighed 20.0 g. and represented a yield of 86.5%, if they are assumed to be pure 2-(β-phenylethyl)-quinoline hydrochloride.

The residue, which remained after distilling off the benzene, was extracted with petroleum ether (b.p. 60-70°). Removal of the petroleum ether by evaporation left a white crystalline solid weighing 20.0 g. and melting at 44-45°. It was shown to be di-p-tolyl disulfide by a mixed melting point determination.

The hydrochloride was suspended in benzene, and then ammonium hydroxide was added. The benzene layer containing the free base was washed with water and dried over sodium sulfate. After removal of the solvent by distillation, the product was distilled over at 160-165°/0.1 mm. Several days in the refrigerator caused the oil to crystallize. It melted at 27°. The picrate melted at 134-135°.

Preparation of 2-(β-Phenylethyl)-quinoline (by hydrogen iodide reduction of 2-styrylquinoline).-This method of preparation is essentially in accordance with the directions of Heymann and Koenigs[45].

45. Heymann and Koenigs, Ber., 21, 1427 (1888).

To a solution of 50.0 g. of glacial acetic acid saturated with 39.0 g. of anhydrous hydrogen iodide (at 0°), was added 1.6 g. of red phosphorus and 8.0 g. (0.035 mole) of 2-styryl-quinoline dissolved in 32 ml. of glacial acetic acid. The mixture was refluxed for twelve hours. Considerable hydrogen iodide was evolved. A white solid sublimed in the condenser which might have been phosphonium iodide. It reacted with water, giving off a gas with a garlic odor, probably phosphine.

The reaction mixture was diluted with water, and sodium bisulfite was added to decompose any periodide that might have formed. The solution was made basic with ammonium hydroxide, and then extracted with ether.

After the ether was removed from the extract by distillation, a portion of the residue was dissolved in 95% ethanol and treated with an ethanolic solution of picric acid. The first crop of crystals which separated was 2-styrylquinoline picrate (mixed melting point determination). Immediately after filtering off the first crop, a second crop of crystals precipitated. This melted at 133-134°, and was shown to be the same compound as the picrate of the thiol reduction product of 2-styrylquinoline by the method of mixed melting points.

Preparation of 2-(β-Phenylethyl)-quinoline (by reaction of quinaldyllithium with benzylchloride).-The method of

preparation follows in essential details that of Ziegler and Zeizer[31].

To an ethereal solution of phenyllithium, prepared from 31.4 g. (0.2 mole) of bromobenzene and 2.76 g. (0.4 g. atom) of lithium, was added 28.6 g. (0.2 mole) of quinaldine. The solution was stirred for one hour and then 25.0 g. (0.2 mole) of freshly distilled benzyl chloride, dissolved in 100 ml. of ether, was added slowly. A white precipitate of lithium chloride separated during the addition of the benzyl chloride. The reaction was hydrolyzed and the ether layer separated and dried over sodium sulfate.

After removal of the solvent by distillation, the product was distilled over a range of 165-175° at 0.1 to 0.2 mm. It weighed 30.0 g. (70%). The picrate melted at 134-135° and did not depress the melting point of the picrate of the reduction product of 2-styrylquinoline prepared with p-thiocresol.

Thiophenol and 2-Styrylquinoline.-A mixture of 5.0 g. (0.022 mole) of 2-styrylquinoline and 5.0 g. (0.044 mole) of thiophenol was heated (bath temperature at 190-200°) for twenty-four hours. The melt was dissolved in dry benzene and the solution saturated with anhydrous hydrogen chloride. It was then placed in the refrigerator overnight. A crystalline precipitate separated out. This was filtered off, washed with benzene and dissolved in 95% ethanol. The

ethanolic solution was treated with hot ethanolic picric acid. After several hours a red gum separated, which crystallized to yellow needles upon standing in the cold. These were filtered off and washed with 95% ethanol. The picrate melted at 134-135° and did not depress the melting point of the picrate of 2-(β-phenylethyl)-quinoline.

Preparation of 4-Styrylquinoline.-The procedure followed is essentially that of Kaslow and Staynor[46]. A mixture of 68.5 g. (0.48 mole) of lepidine, 90.0 g. (0.85 mole) of freshly distilled benzaldehyde and 8.0 g. of freshly fused zinc chloride was heated at 160° for eighteen hours. It was essential to allow some of the water formed in the reaction to escape as vapor in order to maintain the desired reaction temperature. The hot reaction mixture was poured into 180 ml. of warm 20% sodium hydroxide solution, cooled, and the supernatant oil separated and dissolved in 125 ml. of concentrated hydrochloric acid. Dilution of the acid solution with 400 ml. of water precipitated a yellow solid which was filtered off and suspended in 100 ml. of water. The suspension was made alkaline with dilute sodium hydroxide and then filtered . After drying and recrystallization from benzene-petroleum ether (b.p. 60-70°), the product melted at 91-92°. The yield was 68%.

46. Kaslow and Staynor, J. Am. Chem. Soc., 67, 1716 (1945).

p-Thiocresol and 4-Styrylquinoline.-After heating 15.0 g. (0.065 mole) of 4-styrylquinoline and 19.0 g. (0.153 mole) of p-thiocresol for twenty-three hours (bath temperature at 190-200°), the melt was cooled, dissolved in benzene and extracted with 10% sodium hydroxide to remove excess thiol. The benzene solution was dried over anhydrous sodium sulfate and then saturated with gaseous hydrogen chloride. After thorough cooling, the yellow, crystalline hydrochloride, which separated, was filtered off and washed with dry benzene. The hydrochloride was dissolved in 95% ethanol and neutralized with ammonium hydroxide. After the addition of an excess of water, an oil separated out. This was dissolved in hot dilute ethanol and cooled. The white crystals which precipitated melted at 101-103° and did not depress the melting point of an authentic specimen of 4-(β-phenylethyl)-quinoline.

The picrate melted at 188°. It did not depress the melting point of the picrate of 4-(β-phenylethyl)-quinoline prepared by the hydrogen iodide reduction of 4-styrylquinoline.

Anal. Calcd. for $C_{23}H_{18}N_4O_7$: N, 12.1. Found: N, 12.2.

Preparation of 4-(β-Phenylethyl)-quinoline.-This compound was prepared by the method of Heymann and Koenigs[45].

In a solution of 30 ml. of glacial acetic acid, saturated at 0° with 21.0 g. of hydrogen iodide, was dissolved 5.0 g. of 4-styrylquinoline. One g. of red phosphorus was added and the solution was refluxed for ten hours, cooled, and added to an

excess of water. A small amount of sodium bisulfite was added, followed by ammonium hydroxide until the solution was basic to litmus. The white substance that separated was recrystallized from 95% ethanol. It weighed 4.5 g. (90%) and melted at 100-101°.

p-Thiocresol and Styrene.-A mixture of 20.0 g. (0.19 mole) of styrene and 47.7 g. (0.38 mole) of p-thiocresol was heated at 190-200° for twenty-four hours. Though the boiling points of the reactants are considerably below the reaction temperature, there was no reflux, thus indicating a rapid reaction.

The cooled reaction mixture was dissolved in ether and extracted with 10% sodium hydroxide. Upon acidification, 22.8 g. (0.184 mole, 96%) of thiol was recovered.

After drying the ether solution over sodium sulfate, the solvent was removed by distillation. The residue, which was the styrene-p-thiocresol adduct, was characterized by oxidation to the sulfone in the manner described below.

Oxidation of p-Thiocresol-Styrene Adduct to p-Tolyl β-Phenylethyl Sulfone.-To a mixture of 22.5 ml. of acetic anhydride and 22.5 ml. of glacial acetic acid was added 10.3 g. (0.045 mole) of adduct (p-tolyl β-phenylethyl sulfide). This was treated with 12 ml. of 30% hydrogen peroxide (35% excess). During the addition of the peroxide, the flask was immersed in an ice bath. An oily layer separated out on top

immediately. After allowing the reaction to stand for twenty-four hours at room temperature, the solution became homogeneous. It was then thrown into ice water and a crystalline precipitate separated out. This was recrystallized from 95% ethanol. It melted at 72-73° and did not depress the melting point of an authentic sample of p-tolyl β-phenylethyl sulfone prepared by another method (following experiment).

Anal. Calcd. for $C_{15}H_{16}O_2S$: S, 12.3. Found: S, 12.1. This compound is not described in the literature.

Preparation of p-Tolyl β-Phenylethyl Sulfone.-To a solution of 20.5 g. (0.1 mole) of β-phenylethyl bromide in 200 ml. of absolute ethanol was added 17.8 g. (0.1 mole) of sodium p-toluenesulfinate. The mixture was refluxed for four hours, cooled and then filtered. The sodium bromide cake was washed with hot ethanol and a small amount of water was added to the ethanolic solution. The sulfone soon separated as white crystals. After recrystallization from 95% ethanol, the product melted at 72-73°.

p-Thiocresol and Stilbene.-A mixture of 9.0 g. (0.05 mole) of trans-stilbene and 13.4 g. (0.1 mole) of p-thiocresol was heated at 190-195° for twenty-four hours. The cooled mixture was dissolved in ether and extracted with 10% sodium hydroxide. Subsequent to acidification with hydrochloric acid and cooling, 12.5 g. of thiol was recovered. If the small amount of thiol that volatilized into the condenser is taken

into account, then the recovery can be considered practically quantitative. There was no evidence of addition or reduction.

p-Thiocresylmagnesium Bromide and 2-Styrylquinoline.-To 1.68 g. (0.07 g. atom) of magnesium turnings suspended in 100 ml. of anhydrous ether was added dropwise 7.6 g. (0.07 mole) of ethyl bromide dissolved in 25 ml. of ether. A solution of 8.7 g. (0.07 mole) of p-thiocresol in 100 ml. of ether was added slowly to the ethylmagnesium bromide. A reflux accompanied the addition, and after one-half of the thiol had been added, a white precipitate appeared. Sixteen g. (0.07 mole) of 2-styrylquinoline dissolved in ether was then added. There was no reflux. At the end of five hours of stirring, 250 ml. of dry xylene was added and the mixture refluxed for two hours. It was hydrolyzed and acidified with hydrochloric acid. A yellow precipitate separated. This was filtered off and washed thoroughly with petroleum ether (b.p. 28-38°). The combined washings and filtrate were extracted with 10% sodium hydroxide. Subsequent to acidification, 8.0 g. (91%) of thiol was recovered.

The yellow precipitate which separated was apparently a hydrochloride. It was converted to 2-styrylquinoline picrate and the identity of the latter was established by a melting point determination.

Experiments on the Separation and Identification of 2-Styrylquinoline and 2-(β-Phenylethyl)-quinoline.-A mixture

of 3.0 g. of 2-styrylquinoline and 3.0 g. of 2-(β-phenylethyl)-quinoline was dissolved in 75 ml. of dry benzene and saturated with anhydrous hydrogen chloride. After cooling overnight in the refrigerator, the precipitated hydrochlorides were filtered off, washed with dry benzene and then dissolved in boiling 95% ethanol. An ethanolic solution of picric acid was added and a precipitate separated immediately. After allowing the solution to cool to room temperature, the precipitate was filtered off. It melted at 242-245°, and did not depress the melting point of a sample of 2-styrylquinoline picrate.

The filtrate was allowed to stand for several hours and a second crop separated. This melted at 134-135° and was shown to be 2-(β-phenylethyl)-quinoline picrate by a mixed melting point determination.

The above procedure was repeated with a mixture of equal weights of 2-styrylquinoline, 2-(β-phenylethyl)-quinoline and di-p-tolyl disulfide. The results were the same. The presence of the disulfide did not affect the precipitation of the mixture of hydrochlorides from the benzene solution and their subsequent identification through their respective picrates.

p-Thiocresol and 2-Styrylquinoline (with hydroquinone).- In 8.05 g. (0.065 mole) of p-thiocresol heated to 170° was dissolved 0.5 g. (0.0045 mole) of hydroquinone. To this was added 15.0 g. (0.065 mole) of 2-styrylquinoline, and the mix-

ture heated for twenty-four hours at 200°. The mixture was dissolved in benzene and extracted with 10% sodium hydroxide. Acidification of the extract failed to precipitate any free thiol. After drying the benzene solution over sodium sulfate, the solvent was removed by distillation in a nitrogen atmosphere. An additional 8.05 g. (0.065 mole) of p-thiocresol was added and again the mixture was heated for twenty-four hours at 200°. After dissolving the melt in benzene, the solution was extracted with sodium hydroxide. No thiol was recovered from the extract after acidification.

The solution was allowed to stand over sodium sulfate and then saturated with anhydrous hydrogen chloride. A crystalline precipitate separated after several days in the refrigerator. This was filtered off, dissolved in 95% ethanol and treated with an ethanolic solution of picric acid. The yellow needles which separated melted at 132-134°, and did not depress the melting point of 2-(β-phenylethyl)-quinoline picrate.

p-Thiocresol and 2-Styrylquinoline (1:1 mole ratio).-A mixture of 10.0 g. (0.043 mole) of 2-styrylquinoline and 5.3 g. (0.043 mole) of p-thiocresol was heated at 190-200° for twenty-four hours. The melt was dissolved in benzene, extracted with 10% sodium hydroxide and dried over sodium sulfate. The extract was acidified with hydrochloric acid and

then cooled in an ice bath. There was no precipitate of thiol. After filtering off the drying agent, the benzene solution was saturated with dry hydrogen chloride. A precipitate separated which was removed by filtration, washed with benzene and then dissolved in 95% ethanol. An ethanolic solution of picric acid was added to cause a dense yellow precipitate to appear. This was filtered off and found to be 2-styrylquinoline picrate (m.p. 243-245°) by a mixed melting point determination. A second and a third crop were also the picrates of 2-styrylquinoline. There was no indication of reduced compound.

p-Thiocresol and 2-Styrylquinoline (1:1 mole ratio).-A mixture of 23.1 g. (0.1 mole) of 2-styrylquinoline and 12.4 g. (0.1 mole) of p-thiocresol was heated at 190-200° for twenty-four hours. It was then dissolved in benzene and extracted with 10% sodium hydroxide. Acidification of the extract did not produce any thiol. The solution was dried over sodium sulfate and then saturated with anhydrous hydrogen chloride. A precipitate separated. This was filtered off and washed with benzene. The filtrate was made basic with ammonium hydroxide and then extracted with 10% sodium hydroxide. Acidification again did not precipitate any thiol. After drying over sodium sulfate, the filtrate was evaporatively distilled to dryness in a nitrogen atmosphere. The residue was taken up in ether and treated with concentrated hydrochloric acid. A small amount of red gum separated. The supernatant

solution was decanted and evaporated to dryness. A residue was obtained which weighed 11.2 g. and melted at 44°. It was identified as di-p-tolyl disulfide by a mixed melting point with an authentic sample (m.p. 45-46°). The yield of disulfide was 90%.

The crystalline precipitate obtained from the benzene solution by the hydrogen chloride treatment was dissolved in hot 95% ethanol and treated with a boiling ethanolic solution of picric acid. A small precipitate separated immediately. This melted at 242-245° and was shown to be 2-styrylquinoline picrate by the method of mixed melting points. A second, a third and a fourth crop of crystals came down which, before melting at 245°, softened somewhat at 155-157°. They were different in crystal structure from the first crop (2-styrylquinoline picrate), and apparently were more soluble in ethanol. The crystals which softened at 155-157° were dissolved in nitrobenzene, heated on the steam bath, and then allowed to crystallize after the addition of cold ethanol. After this treatment they melted at 243-245°, without a prior softening in the vicinity of 155°. Furthermore, their crystal structure appeared to resemble that of 2-styrylquinoline picrate, and a mixed melting point with the latter compound was 245°. (See Discussion for the possible structure of this compound).

Anal. Calcd. for $C_{33}H_{19}N_4O_7$: N, 12.10. Found: N, 11.84.

IV. DISCUSSION

A. Attempted Reduction of Pyridine, Quinoline and Derivatives, Isoquinoline and Benzothiazole.

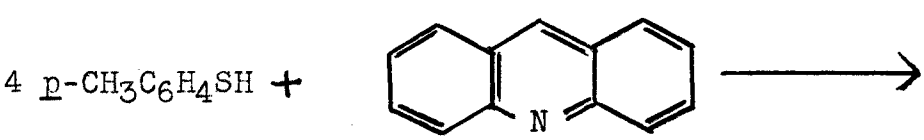
In contrast to the smooth reactions obtained with benzalaniline and benzophenone-anil[2], the simple heterocycles chosen for study were not reduced under any of the conditions which were employed. Two methods were used to determine if a reaction had occurred. First, the recovery of thiol was excellent evidence of the failure of a compound to undergo reduction. For this purpose p-thiocresol served nicely, because of the ease with which it could be extracted with dilute sodium hydroxide, and then precipitated as water-insoluble crystals by the addition of acid. Second, if a reaction had taken place, the presence of the reduction product, even in a small amount, would most likely lower the melting point of the recovered starting material.

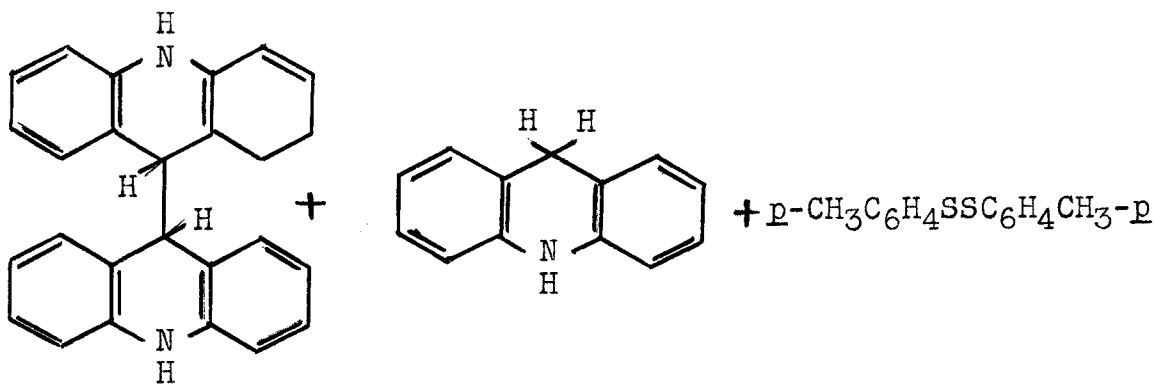
The reduction of quinoline was attempted under different conditions. The first attempt was patterned after Gilman and Dickey's[2] reactions. Quinoline and an excess of thiol were refluxed in xylene for the usual period. The excellent recovery of thiol and the melting point of the picrate indicated that a reaction had not taken place. More drastic conditions

were tried by heating the reactants without a solvent at an elevated temperature. Again the results were negative. Pyridine, isoquinoline and benzothiazole also were not acted upon by p-thiocresol. In an effort to determine whether a substituent in the 2-position might render the azomethine group more susceptible to reduction, 2-phenylquinoline and 2-(p-dimethylaminophenyl)-7-methylquinoline were treated with p-thiocresol. However, as with the unsubstituted compounds, there was no evidence that reduction had occurred. The increased inertness of the azomethine group in pyridine and quinoline can be correlated with the heightened resonance effect of a cyclic system. This is reflected in the failure of the simpler closed anils to react with p-thiocresol.

B. The Reactions of p-Thiocresol with Acridine

Acridine reacted with p-thiocresol in an unexpected manner to give biacridan (III) and di-p-tolyl disulfide. In one experiment, in addition to biacridan, acridan (IV) was also obtained, but in a much lower yield. The extent of the reaction was influenced by the experimental conditions.





(III) (IV)

It appears that the time factor is important, the yield being proportional to time. Heating the reactants without a solvent also increased the yields. The effect of the mole ratios of the reactants is somewhat unexpected. When the reaction was carried out in xylene, a 1:1 mole ratio of reactants produced a greater amount of biacridan than when a 3:1 mole ratio of thiol to acridine was used. However, when the reactants were heated without a solvent, the yield of biacridan was independent of the mole ratio.

A question arose as to the origin of the acridan which was obtained from the fusion reaction where a 3:1

mole ratio of p-thiocresol to acridine was used. Was acridine reduced directly to acridan, or did the latter arise from the disproportionation of biacridan to acridan and acridine? An attempt was made to answer this question by heating biacridan in a nitrogen atmosphere to determine if it would disproportionate into acridine and acridan. The only product isolated was acridine.[47] One might argue that in the original reaction, where acridan was isolated, an excess of thiol was present and consequently the conditions were not the same for the two reactions. In answer to this argument are the results of the fusion reaction where the reactants were added in a 1:1 mole ratio. Here no acridan was produced, and yet an excess of thiol was always present as evidenced by a 30% recovery of unreacted thiol. From the available evidence it was assumed that the acridan was formed as a result of the hydrogenation of acridine rather than through disproportionation.

The possibility that acridan was in some manner a precursor of biacridan was given attention in one

47. This is in disagreement with Lehmstedt and Wirth, Ber., 61, 2044 (1928), who reported that biacridan decomposed upon heating into acridine and acridan. It is possible that our temperature was too high and decomposed acridan as well.

experiment. Acridan and p-thiocresol were heated together under the usual conditions, but no product could be isolated which had the characteristics of biacridan.

The importance of the steric factor in the reactions of acridine derivatives with p-thiocresol became apparent in an attempted reduction of 9-(o-iodophenyl)-acridine. This reaction was undertaken as a result of a study made by Lingane, Swain, and Fields.[48] They tried to reduce 9-(o-iodophenyl)-acridine to 9-(o-iodophenyl)-9,10-dihydroacridine, and found that every chemical agent strong enough to hydrogenate the acridine nucleus also removed the iodine, to form 9-(phenyl)-9,10-dihydroacridine. The desired compound was finally obtained in a very small amount by a cathodic reduction with the mercury electrode. In view of the results obtained with acridine, it was considered worthwhile to determine if p-thiocresol would preferentially reduce the acridine ring and leave the o-iodophenyl group intact. It was reasoned that the presence of the large blocking group would hinder the formation of a biacridan type and instead favor reduction to the acridan compound. However, even drastic conditions, such as fusing the components at 200°

48. Lingane, Swain and Fields, J. Am. Chem. Soc., 65, 1348 (1943).

for twenty-four hours, failed to effect any reaction. The 9-(o-iodophenyl)-acridine was recovered in quantitative amount.

The bond structure of anthracene resembles that of acridine, yet p-thiocresol has no effect whatever on anthracene. This points out the importance of the azomethine group and that it is somehow intimately connected with the reducing action of p-thiocresol.

The findings of Kharasch[49] and other workers[50] suggest that thiols add to unsaturated systems through a free radical mechanism. In some reactions it was shown that the presence of a peroxide catalyst, which initiates the chain reaction, caused the addition to go to completion in three to five minutes, whereas under rigid antioxidant conditions, addition was completely inhibited. Therefore, the anthracene-p-thiocresol reaction was repeated with benzoyl peroxide catalyst, to see if the latter might induce the 1,4- addition of thiol to anthracene. Again the thiol was recovered in 96% yield, indicating that no addition had occurred.

The original biacridan was obtained by Schlenk and

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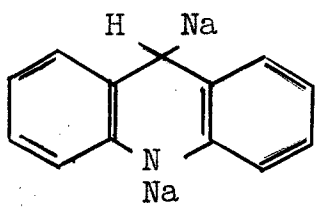
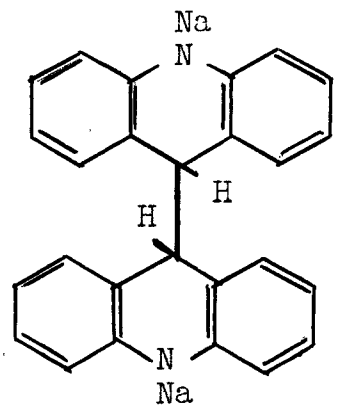
49. Kharasch, Read and Mayo, Chem. and Ind., 16, 752 (1938).

50. Jones and Read, J. Am. Chem. Soc., 60, 2452 (1938).

Bergmann[33] from the ethanolysis of the sodium-adduct of acridine. In addition to the biacridan (m.p. 260-265°), some acridan was also formed. When the sodium-adduct was treated with benzoyl chloride, a compound melting at 305° and corresponding to 9,9'-dibenzoylbiacridan was obtained. Carbonation of the adduct gave biacridan and 9-acridancarboxylic acid. From these facts it appears that the sodium added to acridine in two ways, giving (V) and (VI). 9,10-Disodioacridan (V) was undoubtedly formed



(V)



(VI)

through a 1,4- addition of sodium to acridine. The other product (VI) was probably formed by the dimerization of two radicals, which came into being as the result of the addition of an atom of sodium to the nitrogen of the acridine.

A little later, Lehmstedt and Wirth[47] reported that a

biacridan melting at 214° was obtained as a by-product in the preparation of 9-cyanoacridan. Reduction of 9,9'-biacridyl with zinc and acetic acid produced the same compound (m.p. 214°). However, the biacridan formed by the reduction of 9-cyanoacridan with sodium-amalgam melted at 249°.

Bergmann and Blum - Bergmann[34] were unable to repeat Lehmstedt and Wirth's[47] preparation of biacridan from 9-cyanoacridan and stated that the product which Lehmstedt and Wirth obtained from the zinc-acetic acid reduction of biacridyl, melted at 220° and not at 214° as Lehmstedt and Wirth had reported. Furthermore, the product melting at 220° was not the lower melting biacridan, but a mixture of unreacted biacridyl and higher melting biacridan (260-265°). The latter was also synthesized by Bergmann and Blum - Bergmann[34] by treating 9,9'-biacridyl with sodium and subsequently hydrolyzing the adduct.

In order to resolve the confusion originating in the inconsistencies of the melting points, a detailed study of the two biacridans (Lehmstedt and Wirth's melting at 214° and Schlenk and Bergmann's melting at 260-265°) was undertaken by Lehmstedt and Hundertmark.[36] In the first place, they disagreed with the melting point of 260-265° for the Schlenk and Bergmann compound. By their method

of preheating the melting point bath they obtained 249°. A mixture of both substances gave no noticeable depression. It started to melt at 214°, whereupon the second component (m.p. 249°) did not begin to melt until a higher temperature - above 240° - was reached. It was assumed that the absence of a melting point depression could be traced back to the fact that the melt which resulted from the decomposition products of the lower melting compound, acridine and acridan, acted as a non-dissolving medium towards the higher melting compound. When both samples were crystallized together from benzonitrile, the following melting points were observed: a 1:1 mixture melted at 215°; a mixture consisting of two parts of the compound melting at 214° and one part of the higher melting compound melted at 195°. From the melting point data they strongly suspected the two samples of biacridan were isomers, although crystallographically there was no detectable difference, and their Röntgen diagrams were also alike. In view of the identical Röntgen diagrams, Lehmstedt and Hundertmark[36] felt that stereoisomerism would have to lie in the different arrangements of the hydrogen atoms. They felt that X-rays would not be of any assistance in this respect because of the absence of sufficient scattering

power in hydrogen atoms.[51]

The difficulty that Lehmstedt[36] and his workers experienced in attempting to identify their biacridan by the method of mixed melting points was also encountered in the identification of the thiol-produced biacridan. A decision could not be made with the aid of the mixed melting point method and the problem was finally solved by preparing the dibenzoyl derivative. As described earlier, Schlenk and Bergmann[33] benzoylated the sodium-acridine adduct to get 9,9'-dibenzoylacridan. A sample for a mixed melting point was synthesized by treating biacridan with a great excess of phenyllithium and adding benzoyl chloride to the N,N'-dilithiobiacridan thus formed. The phenyllithium was used in great excess in order to avoid having any unreacted biacridan. Any benzophenone and triphenylcarbinol formed from the benzoylation of excess phenyllithium could easily be washed out with acetone, but the presence of insoluble biacridan would have been a great problem in the subsequent purification of the dibenzoyl derivative.

It is quite probable that isomerism does not exist

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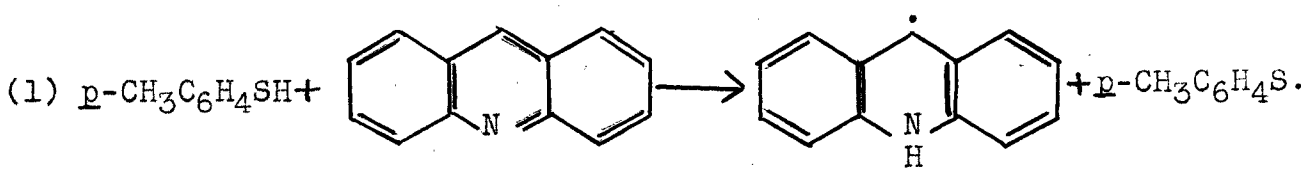
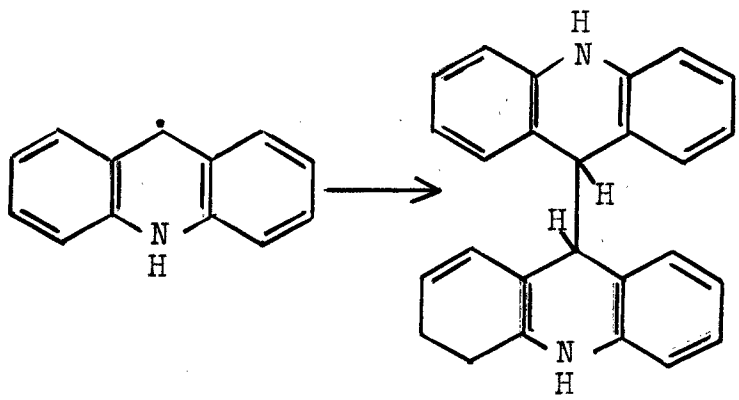
51. Dr. Robert E. Rundle has ventured the opinion that any isomerism due to the relative positions of the hydrogen atoms alone would probably change the shape of the molecule sufficiently to give rise to a somewhat different molecular packing, which would alter the X-ray diffraction pattern.

in the various specimens of 9,9'-biacridan that have been prepared. The different melting points that are reported may be due to two factors. In the first place, these melting points are not true melting points, but are decomposition points and probably more sensitive to catalytic traces of impurities. Secondly, biacridan itself is extremely insoluble in practically all solvents and therefore is not amenable to purification through recrystallization. Since these compounds were prepared by different methods, in all probability they would be contaminated by different substances, each contaminant having a different effect on the decomposition point. Another significant point is the variation of the melting point with its method of determination. In this laboratory a change of 5^{o} was observed by using two different methods.

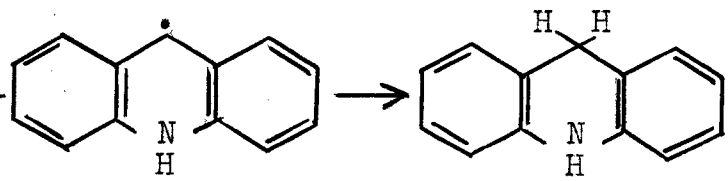
One mechanism that is suggested and which is entirely conjectural is based on the dimerization of free radicals:

(1) 

(2) 2 p-$CH_3C_6H_4S\cdot$ $\longrightarrow$ p-$CH_3C_6H_4SSC_6H_4CH_3$-p

(3) 2 

(III)

(4) p-$CH_3C_6H_4SH$+ 

+ p-$CH_3C_6H_4S\cdot$

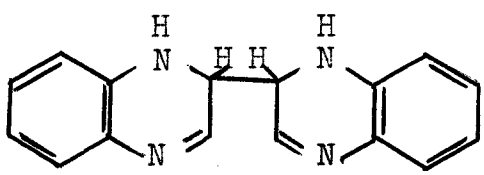
(IV)

C. The Reactions of p-Thiocresol with Quinoxaline.

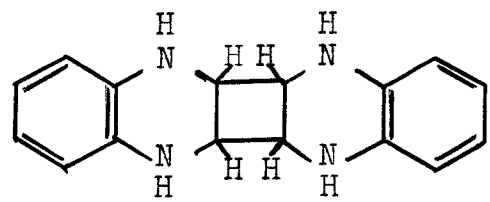
At the present time no structural formula can be written for the compound isolated from the quinoxaline-p-thiocresol reaction which is compatible with the experimental facts. The high melting, high molecular weight (M.W. 248) product indicated a bis compound of some type or a molecular complex similar to the one Gilman and Dickey[2] obtained from the thiol reduction of benzophenone-

anil. An attempt was made to prepare such a complex by heating quinoxaline and 1,2,3,4-tetrahydroquinoxaline in ethanol according to the method of Allesandri.[43] Since the compound in question is insoluble in alcohol and no alcohol-insoluble substance was produced, it was concluded that the possibility of it being a complex was unlikely.

Two postulated bis types are (VII) and (VIII). Neither of these compounds is reported, but certain of



(VII)



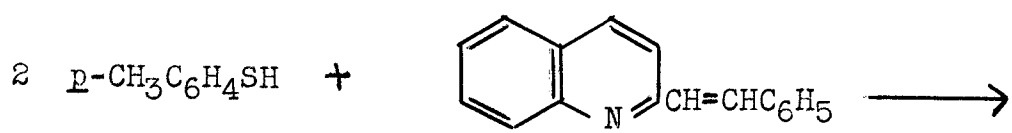
(VIII)

their properties can be predicted from the structures and from a comparison with analogous compounds which are known. One would expect, for instance, that both molecules would be subject to mild oxidation with reagents like nitrobenzene and mercuric oxide. Experiments demonstrated, however, that the unknown product was unaffected by both oxidizing agents. The presence of a secondary amino group would indicate the possibility of acetylation. As in the other reactions, the starting material was recovered un-

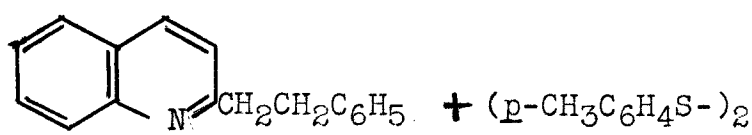
changed from one attempt to prepare an acetyl derivative with acetic anhydride.

D. The Reactions of p-Thiocresol with 2-Styrylquinoline and 4-Styrylquinoline.

From the standpoint of stoichiometry, the 2-styrylquinoline reduction is more amenable to interpretation than the acridine reduction. There is good reason to believe that the reaction goes to completion when a 2:1



(IX)



(X)

mole ratio of thiol to 2-styrylquinoline is added. In one experiment, where the thiol was added above the theoretical amount, the excess was recovered almost quantitatively. A major difficulty is the separation of

2-(β-phenylethyl)-quinoline (X) from di-p-tolyl disulfide. The method that was used in this work was to precipitate the insoluble hydrochloride from an anhydrous benzene solution. In this manner, an 86.5% yield of 2-(β-phenylethyl)-quinoline hydrochloride was isolated from one reaction. With an improved technique the yield could probably be increased.

2-Styrylquinoline contains a carbon-carbon double bond conjugated with two aromatic systems - a quinoline nucleus and a benzene ring. The addition of thiols to olefinic compounds has been observed in a number of instances and, therefore, the possibility of reduction proceeding through a prior addition to the olefinic bond in 2-styrylquinoline was considered. Styrene, and especially stilbene, have conjugated systems analogous to 2-styrylquinoline and at least styrene is known to form adducts with thiols.[49] A forced reaction between an adduct and a thiol would be interesting on two accounts. First, a reaction of this type has never been reported and therefore the possibility of obtaining reduction was still open to question; second, it might throw some light on the role of the azomethine group in the reduction of 2-styrylquinoline. Accordingly, p-thiocresol and styrene, in a 2:1 mole ratio, were heated for twenty-four hours

under the usual conditions. There was no indication of interaction between the adduct formed and p-thiocresol. The excess of the latter was recovered in 96% yield, and characterization of the sulfide was accomplished by oxidizing it to the sulfone with hydrogen peroxide, followed by a mixed melting point determination with the identical sulfone prepared from β-phenylethyl bromide and sodium p-toluenesulfinate. It is interesting to note that the addition of p-thiocresol to styrene was in a manner contrary to Markownikoff's rule, and in agreement with the findings of Kharasch[49] and other investigators.[50]

With stilbene, neither addition nor reduction was observed. It is clear from these two reactions that the azomethine group is essential for reduction. Whether conjugation of the azomethine group with the olefinic bond is absolutely necessary has never been proved. The vinylog of 2-styrylquinoline, 4-styrylquinoline, was hydrogenated by thiocresol to 4-(β-phenylethyl)-quinoline. In this connection it is unfortunate that 3-styrylquinoline, which is not conjugated in the sense mentioned above, is not available for study.

Keeping in mind Kharasch's[49] demonstration that the reversed addition (and in certain cases the normal addition as well) could be suppressed by the presence of an

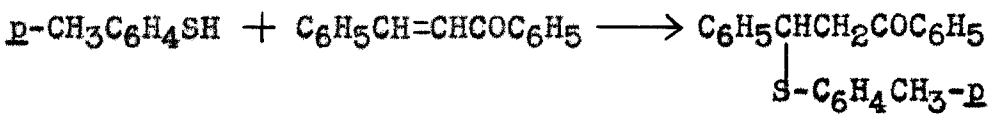
antioxidant, the reduction of 2-styrylquinoline was attempted in the presence of hydroquinone. The reaction apparently was not affected by the antioxidant. This piece of evidence does not seem to agree with the postulation of an intermediately formed adduct.

Comparisons have frequently been made of α,β-unsaturated ketones in the aquo system with those in the ammono system, e.g., 2-styrylquinoline. The resemblances between these two classes of compounds are striking. The preparation of benzalacetophenone, for instance, involves the Claisen condensation of benzaldehyde with acetophenone. Quinaldine undergoes a similar reaction with benzaldehyde to form 2-styrylquinoline. Grignard reagents undergo nuclear-lateral addition to 2-styrylquinoline[52]; they also add 1,4- to benzalacetophenone.[53] Of particular interest is the reversibility of the addition reactions of benzalacetophenone and 2-styrylquinoline. The investigations of Nicolet[54] indicate that in the reaction shown below, the equilibrium is shifted far to the left in the presence of a base.

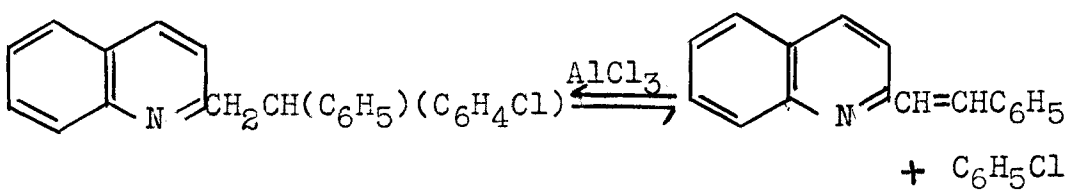
52. Fuson, Farlow and Evans, J. Am. Chem. Soc., 55, 2000 (1933).

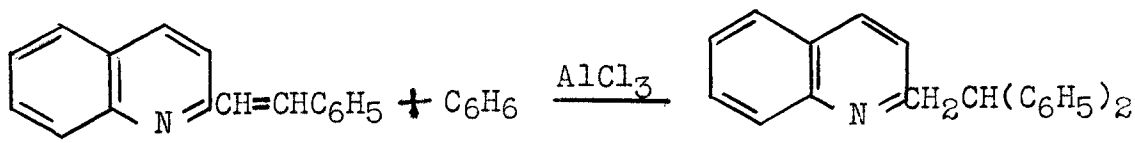
53. Kohler, Am. Chem. J., 38, 511 (1907).

54. Nicolet, J. Am. Chem. Soc., 53, 3066 (1931).



Fuson[55] treated 2-p-chlorostyrylquinoline with benzene and aluminum chloride in a typical Friedel-Crafts reaction and obtained benzohydrylquinaldine. This is interpreted by the following reversible reaction.





In view of these remarkable similarities, it is interesting to compare the reactions of thiols with both classes of compounds. A mole per mole reaction of thiol with benzalacetophenone, for instance, results in addition across the olefinic bond to form a sulfide.[56] If an excess

55. Fuson, et al., J. Am. Chem. Soc., 55, 3798 (1933).

56. Posner, Ber., 35, 799 (1902).

of thiol is used, a mercaptole is formed after the first mole of thiol has added to the carbon-carbon double bond. This elimination of the carbonyl group, through mercaptole formation, may account for the fact that reduction by thiols has never been observed with α,β-unsaturated compounds in the aquo system, as they have been in the ammono system.

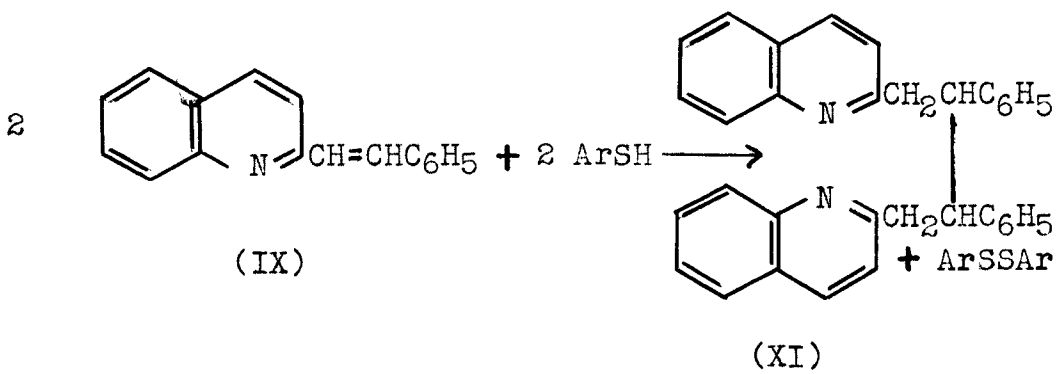
Several attempts were made to prepare a p-thiocresol adduct of 2-styrylquinoline, with the object of studying it as a possible intermediate in the reduction reaction. The addition of RSMgX compounds, by Gilman and King[57], to benzalacetophenone and the 1,4- nuclear-lateral addition of RMgX compounds to 2-styrylquinoline,[52] suggested that p-thiocresylmagnesium bromide might also add 1,4- to 2-styrylquinoline to give, subsequent to hydrolysis, the desired compound. After refluxing a mixture of p-thiocresylmagnesium bromide and the quinoline compound in an ether-xylene medium for two hours, it was found that addition had not occurred.

Another attempt to prepare the adduct was made by heating together equimolar amounts of thiol and 2-styrylquinoline. Although no thiol was recovered, the first, second and third crops of picrate which separated

57. Gilman and King, J. Am. Chem. Soc., 47, 1136 (1925).

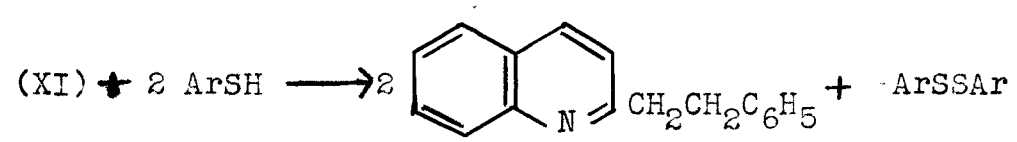
were those of the unreduced styryl compound. There was no indication of any reduced compound. This was difficult to explain because with artificial mixtures, it was shown that 2-styrylquinoline could be effectively separated from 2-(β-phenylethyl)-quinoline through the fractional crystallization of the picrates. Therefore, the reaction was repeated and much greater care was taken in working it up. This time di-p-tolyl disulfide was isolated in 90% yield. In addition to 2-styrylquinoline picrate (m.p. 245°), three successive crops of crystals were obtained, which, although melting at 245°, first softened somewhat at 155-157°. These crystals differed in crystalline structure from 2-styrylquinoline picrate. After treating them with nitrobenzene, they melted at 245° without a preliminary softening at 155-157°, and had the appearance of 2-styrylquinoline picrate. No picrate of 2-(β-phenylethyl)-quinoline was isolated. From these facts, it appears that the compound softening at 155-157° might be the picrate of a dihydro compound, or that of a dimer formed through a bimolecular reduction. The softening at 155-157°, and the change in crystalline structure and absence of softening after nitrobenzene treatment, can be attributed to an unstable compound that can be converted to 2-styrylquinoline picrate by the application of heat or by mild oxidation.

Unfortunately, not enough of the material was available for a molecular weight determination. The assumption of such a compound seems to be the only way in which the production of disulfide and the absence of 2-(β-phenylethyl)-quinoline can be accounted for. It is quite possible that this unstable compound is an intermediate in the reduction of 2-styrylquinoline to 2-(β-phenylethyl)-quinoline. It will be recalled that in the experiment where hydroquinone was added, the reaction was carried out stepwise. First, one mole of thiol was added and then another. Since no thiol was recovered at the interruption of the reaction, it must have been oxidized to the disulfide. The addition of the second mole of thiol may have reduced the intermediate further to 2-(β-phenylethyl)-quinoline.

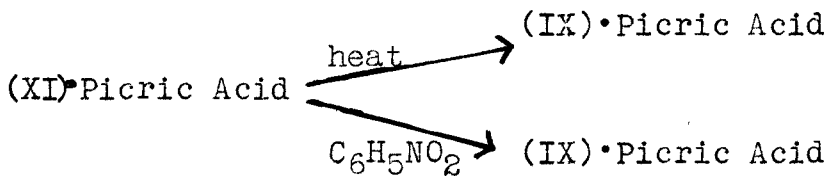


(IX)

(XI)


(XI) + 2 ArSH
2
N
$CH_2CH_2C_6H_5$
+ ArSSAr


(XI) + Picric Acid
(XI)•Picric Acid


heat
(IX)•Picric Acid
(XI)•Picric Acid
$C_6H_5NO_2$
(IX)•Picric Acid

V. SUMMARY

1. A general review has been given of the reactions in which thiols act as reducing agents.
2. Several unsuccessful attempts have been made to reduce pyridine, quinoline and derivatives, isoquinoline and benzothiazole with p-thiocresol.
3. Acridine was bimolecularly reduced to biacridan by p-thiocresol, with the latter oxidized to di-p-tolyl disulfide. Acridan also was isolated in one experiment.
4. 2-Styrylquinoline and 4-styrylquinoline were hydrogenated to 2-(β-phenylethyl)-quinoline and 4-(β-phenylethyl)-quinoline, respectively.
5. The importance of the azomethine linkage was demonstrated by the failure to obtain reduction under forced conditions, with anthracene, styrene and stilbene.
6. An unidentified product was obtained from quinoxaline.
7. There are indications that the hydrogenation of 2-styrylquinoline proceeds through the formation of an unstable intermediate, possibly of a bimolecular structure.

PART II. THE SYNTHESES OF SOME HYDROXYL-CONTAINING HETEROCYCLES

I. INTRODUCTION

There exists a large array of chemicals, both organic and inorganic, that possess antiseptic action. Of the synthetic organic compounds, the greatest successes have been obtained with phenols, carboxylic acids, dyes, quaternary compounds and the sulfonamides. One of the objectives of this work was to study further a class of phenolic compounds in which only a slight beginning has been made. These are the hydroxystyryl heterocycles.

The investigation itself is more or less of an exploratory nature, with the object of uncovering any latent possibilities which might lead to synthetic developments of even greater promise. As a working foundation, however, the molecules have been designed so that they contain several groups which, separately, have been shown to possess strong antibacterial action. Phenols and alkylated phenols have been used as antiseptic agents for over three-quarters of a century.

Browning and his coworkers[58, 59, 60] have demonstrated that styrylpyridines and styrilquinolines, as well as their anil analogs, possess marked antiseptic and trypanocidal activity. Therefore, the incorporation of these groups into one structure ought to prove interesting.

On the basis of recent theories regarding the mode of action of 8-hydroxyquinoline as a bacteriostatic agent, the syntheses of several metal-chelating agents was undertaken. Some of these new derivatives are built around the structures of known and proven compounds; others are departures from the accustomed architectural types. The further application of 8-hydroxyquinoline and its derivatives as analytical reagents has elicited continued interest. The fact that a greater selectivity for the metals with which its complexes is obtained when this reagent is substituted in the 2-position, suggests that other innovations in the structure of the molecule might augment this property to an even greater extent.

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58. Ashley, Browning, Cohen, and Gulbranson, Proc. Roy. Soc., B113, 293 (1933) [C. A., 27, 5363 (1933)].

59. Browning, Ellingsworth, and Gulbranson, J. Path. Bact., 27, 121 (1924) [C. A., 18, 2019 (1924)].

60. Browning, Cohen, Ellingsworth, and Gulbranson, Brit. Med. J., 326 (1923) [C. A., 18, 1146 (1924)].

It might be of interest, therefore, to test the metal-chelating compounds that were prepared, for analytical purposes as well as for antiseptic properties.

Incidental to the preparatory work, some new reactions were attempted with the object of improving general techniques in this field of synthesis. Since all of the compounds synthesized contain phenolic hydroxyl groups, a brief survey of the antiseptic properties of phenol derivatives is included in the Historical section. The Claisen reaction, which was used extensively in the preparation of the methoxystyryl intermediates, is reviewed rather thoroughly.

II. HISTORICAL

Phenol was recognized as possessing valuable bactericidal properties by Lister in 1865[61] who used it with marked success as an antiseptic agent in surgery. In 1906 the investigation of other phenolic compounds was undertaken by Ehrlich and his co-workers.[62] They found that the introduction of halogen atoms or methyl groups increased materially the effectiveness of phenol and also of β-naphthol. Further interest in the relationship between structure and bactericidal activity was stimulated by the work of Johnson and Lane[63] on the 4-alkylresorcinols. Since 1921, literally hundreds of papers and patents have appeared dealing with new phenolic compounds and their mode of action.

A. Phenol Derivatives.[64]

1. Alkyl Phenols. The antibacterial activity of a series of alkylphenols was found to increase with the

61. Dunker, J. Chem. Ed., 15, 58 (1938).

62. Bechold and Ehrlich, Z. physiol. chem., 47, 173 (1906).

63. Johnson and Lane, J. Am. Chem. Soc., 43, 348 (1921).

64. For a more detailed review of this subject see Suter, Chem. Revs., 28, 269 (1941).

length of the chain, the maximum activity being reached with the n-amyl group (phenol coefficient[65] 104, B. typhosus).[66] It appears that the position of the alkyl group is of no importance. The three cresols are 2.5 times as effective as phenol. Branching of the chain reduces the activity; a primary alkyl group has more effect than a secondary or tertiary alkyl group of the same weight.

An aralkyl group improves the activity of the parent phenol as Table I[67] indicates.

The introduction of two alkyl groups in the phenol nucleus yields effective compounds,[66] but water solubility is decreased. For the lower molecular weight

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65. The phenol coefficient represents the ratio of the highest dilution of the agent, in whose subculture no growth occurs, to the corresponding figure for phenol after definite time intervals of exposure. With the efficiency of phenol arbitrarily chosen as 1.0, a phenol coefficient of 6.0, for example, indicates that under similar conditions a compound is six times as powerful as phenol. Since a figure may vary greatly with the type of organism, usually the recorded values are accompanied by the name of the organism. The bacteria most commonly used for testing purposes are: B. typhosus, Staph. aureus, E. typhi, Strep. hemolyticus, B. coli, E. parodysenteriae and Mycob. smegmatis. A procedure adopted by the United States Food and Drug Administration is commonly employed. U. S. Dept. of Agriculture Circular No. 198 (1931).
For other methods of testing antiseptics and disinfectants see Porter, "Bacterial Chemistry and Physiology," John Wiley and Sons, Inc., New York, 1946, pp. 225-229.

66. Coulthard, et al., J. Chem. Soc., 280 (1930).

67. Klarman, J. Am. Chem. Soc., 48, 791, 2358 (1926).

compounds, a greater activity is achieved when a given number of carbon atoms is present in one chain than when distributed among two or more chains. This is reversed

Table I[67]

Activities of Aralkyl Compounds

p-Benzylphenol	4.6	
4-Benzylresorcinol	22	phenol coefficients determined against B. typhosus
4-β-Phenylethylresorcinol	40	
4-γ-Phenylpropylresorcinol	31	

in some cases, with the higher alkyl groups. Coulthard[66] found the most satisfactory method of preparing the n-alkylphenols was a Clemmenson reduction of the respective ketone. Of the different methods he used to prepare the ketone, the Fries rearrangement of the aryl ester led to the best results.

2. Polyhydroxy Phenols. Inexplicably, the simple polyhydroxyphenols show little or no activity, although hydroquinone exhibits anomalous behavior in that its activity is high against B. typhosus (phenol coefficient, 12) and low against Staph. aureus (0.4).[68] Pyragallol is practically inactive and resorcinol has a phenol

68. Klarman, J. Am. Chem. Soc., 54, 298, 1204 (1932).

coefficient of 0.4. Catechol is inferior to phenol against both B. typhosus and Staph. aureus. Phloroglucinol does not possess germicidal properties.[68]

3. Alkyl Polyhydroxy Phenols. 4-Alkyl resorcinols and pyrogallols are generally strong antibacterial agents with the phenol coefficients ranging between 15 and 50.[69] The effectiveness of the higher alkyl polyhydroxyphenols against B. typhosus is practically nil, but against Staph. aureus an amazing value of 980 is attained with 4-n-nonylresorcinol.

The syntheses of the primary 4-alkylresorcinols, both normal and branched chain, are readily accomplished by the Nencki condensation, which consists of heating the phenol with the proper fatty acid in the presence of zinc chloride,[70,71] and then followed by a Clemmenson reduction. The secondary and tertiary compounds are derived directly by condensing olefins, alkyl halides or alcohols with resorcinol.[72, 73] Substitution in the 2-[74] and

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69. Dohme, J. Am. Chem. Soc., 48, 1688 (1926).

70. Dohme, U. S. Patent 1,649,672, Nov. 15, 1928 [C. A. 22, 481 (1928).

71. Johnson, J. Am. Chem. Soc., 35, 1014 (1913).

72. Niederl, Natelson and Beekman, ibid., 55, 2571 (1933).

73. Robinson and Hester, U. S. Patent 2,008,337, July 16, 1935 [C. A., 29, 5926 (1935)].

74. Russell, J. Am. Chem. Soc., 62, 1441 (1940).

5-[75] positions is rather involved and requires a long series of reactions.

The activities of the dialkylresorcinols are not consistent. 4,6-Di-n-butylresorcinol is equal in activity to the 4-n-butyl compound, but the 4,6-di-n-hexyl derivative is less than one-half as active as 4-n-hexylresorcinol.[66]

Di-sec- and di-tert-alkylpyrogallols[76] have been prepared by condensing the respective alcohols with pyrogallol in the presence of zinc chloride. The structures are not definitely established. Their activities are usually high, ranging from 100 (di-tert-amyl derivative) to 215 (di-1-methylbutyl). The tert-butyl and isoamyl derivatives are less effective (5 and 11, respectively). Among the n-alkylpyrogallols the maximum value was obtained with the di-n-heptyl compound (360, B. typhosus).

4. Halogen Derivatives. The presence of a halogen atom invariably increases the bactericidal property of a phenolic compound.[77] This increase is greater for the

75. Suter, J. Am. Chem. Soc., 56, 2470 (1934).

76. Rawlins and Hamilton, U. S. Patent 2,107,307, Feb. 8, 1938 [C. A., 32, 2692 (1938)].

77. Klarman, J. Bact., 17, 440 (1929).

para position than for the *ortho*. In general, bromine is more effective than chlorine and very little is known about the effect of iodine.

The enhancing effect of halogens is less for resorcinol than it is for phenol. Resorcinol, 4-chlororesorcinol, 4,6-dichlororesorcinol and 2,4,6-trichlororesorcinol have phenol coefficients of 0.4, 0.7, 3.2 and 5.0, respectively, while the values of halogenated phenols vary from 4 to 24.[77]

Since alkyl groups and halogen atoms separately increase the bactericidal power of a phenol, it is interesting to note that the presence of both groups in a molecule produces a cumulative effect. In a series of *o*-alkyl-*p*-chlorophenols, which Klarman[78] prepared, the hexyl or heptyl compounds showed the highest activity depending on the organism employed for testing. The maximum values were obtained with *Staph. aureus* (1500), *Strep. hemolyticus* (2220) and *Mycobium smegmatis* (1250). Against *E. typhi* they were less effective (23-150).

For the preparation[78] of the normal alkyl chlorophenols, two methods were employed. One was the Friedel-Crafts condensation of the alkyl chloride, and the other was an aluminum chloride catalyzed rearrangement of the

78. Klarman, Shternov and Gates, *J. Am. Chem. Soc.*, *56*, 2576 (1934).

aryl esters, followed by a reduction of the respective ketone. Branched chain derivatives were synthesized by the condensation of a primary alcohol in the presence of concentrated sulfuric acid.

The p-alkyl-o-halophenols[79] were not as active as the previously described isomers. For example, p-n-hexyl-o-bromophenol is just one-half as active as the isomer with the bromine in the para position.

An increase in the number of alkyl groups in the halophenols did not materially improve the bactericidal activity. Perhaps the expected increase was compensated by a decrease in water solubility.

5. Hydroxyaryl Ethers and Sulfides. The inclusion of an oxygen atom between the phenol nucleus and an alkyl group reduces the antibacterial activity. A parallel effect is incurred by the presence of oxygen as an alcohol or ether group in the side chain. In contrast, a sulfur atom between the aryl and alkyl group increases the germicidal action.[80]

As in the case of the alkyl chlorophenols, the para and meta isomers give markedly higher values than the

79. Blicke and Stockhaus, J. Am. Pharm. Assoc., 22, 1090 (1933).

80. Suter, et al., J. Am. Chem. Soc., 54, 4100 (1932).

Table II[80]

Phenol Coefficients Against B. typhosus

Substituent	Sulfide	Ether
methyl	4	1
ethyl	12	1.5
n-propyl	25	4.1
n-butyl	60	9.3
n-hexyl	150	30
n-heptyl	200	100

ortho isomers. This lower activity of the ortho isomers may be due to hydrogen bonding between the hydrogen of the phenolic group and the electronegative chlorine and oxygen atoms.[68]

Table III[68, 81]

Phenol Coefficients of Hydroxyphenyl Ethers Against Staph. aureus

	para	meta	ortho
n-amyl	30	36	23
n-hexyl	100	125	28
n-heptyl	200	330	37
n-octyl	360	580	37
n-nonyl	360	600	37

81. Klarman, Gatyas and Shternov, J. Am. Chem. Soc., 53, 3399 (1932).

6. Hydroxy Derivatives of Diphenyl Methane. Table IV[82] is a list of compounds prepared by Klarman. Here, again, the necessity of taking into account the type of organism is strikingly illustrated.

Table IV[82]

Diphenyl Methane Derivatives

Substituted hydroxy compound	E. typhi.	Strep. hemolyticus
3-Chloro-4-	36	165
3-Chloro-2-	24	94
5-Chloro-2-	74	245
4'-Chloro-4-	83	165
3-Bromo-4-	57	175
5-Bromo-2-	19	185
3,4'-Dichloro-4-	26	310
3,5-Dichloro-2-	41	175
3-Chloro-4'-bromo-4-	22	250
5-Chloro-3-methyl-2-	17	565
4'-Chloro-3-methyl-2-	16	300
5-Chloro-4-methyl-2-	16	260
5-Chloro-4,6-dimethyl-2-	17	455
4'-Bromo-4,6-dimethyl-2-	31	785
5-Chloro-3-isopropyl-6-methyl-2-	16	38

If the methylene group is replaced by a longer aliphatic chain, enhanced bactericidal activity results.[83] Branching of the chain, as has been observed with other series, lowers the activity below the normal straight chain compounds. When the compound contains no other

82. Klarman, J. Am. Chem. Soc., 54, 3315 (1932).

83. Heineman, J. Lab. Clin. Med., 29, 254 (1944).

group but hydroxyl, then the position of the latter does not influence the activity to any extent. Ehrlich and his co-workers discovered that when two benzene rings, one bearing a hydroxyl group, were separated by the ketone, sulfone or carbinol grouping, the antibacterial activity was lower than the diphenylmethane analog.

7. Other Phenols. All three nitrophenols are stronger bactericides than phenol.[84] o-Aminophenol and its n-alkyl derivatives have been reported to be active germicidal agents, but they have not been investigated extensively.[85] Phenolsulfonic acids are of doubtful germicidal value, although n-hexylresorcinolsulfonic acid has been patented as a germicidal agent.[86]

8. Heterocycles Containing Phenolic Hydroxyl Groups. A series of hydroxystilbazoles were prepared by Chiang and Hartung[87] with the intention of augmenting the antiseptic activity of the quaternary pyridinium salts with the hydroxystyryl and the hydroxyphenylethyl groups.

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84. Mazzetti, Boll. soc. ital. biol. sper., 3, 1198 (1928); ibid., 6, 1108 (1931) [C. A., 24, 879 (1930); C. A., 26, 2761 (1932)].

85. Ostromislensky, U. S. Patent 2,040,183, May 12, 1936 [C. A., 30, 4629 (1936)].

86. Legerlotz, Austrian Patent 151,971, Dec. 27, 1937 [C. A., 32, 3095 (1938)].

87. Chiang and Hartung, J. Org. Chem., 10, 21 (1945).

The preliminary tests have not shown great activity. Other related types have been prepared such as 2-(p-dimethylaminostyryl)-6-hydroxyquinoline[88] and 4-substituted derivatives of 2-(3',4'-dihydroxystyryl)-6-methoxyquinoline.[89] Reports on their activity have not, as yet, been published.

8-Hydroxyquinoline has been used as an antiseptic for over a half century, but it appears, from recent investigations, that its mode of action is entirely different from other phenolic compounds. In the following section on Mode of Action, a discussion of this compound and its derivatives will be given somewhat in detail.

B. Mode of Action.

In the light of present knowledge, it is generally agreed that the mode of action of antiseptic compounds is due to a combination of the physico-chemical properties of the molecule as a whole, and to the specific action of certain functional groups. A theory[90] that has gained

88. Brohmachari and Bholtacharjee, J. Ind. Chem. Soc., 7, 527 (1930).

89. Renfrew, J. Am. Chem. Soc., 69, 711 (1946).

90. Stearn and Stearn, J. Bact., 9, 491 (1924).

wide acceptance is based fundamentally on some very simple chemical reactions. The basic or acidic groups in the cell protein combine with the opposite groups (acidic or basic) of the antiseptic to form un-ionized complexes. This interferes with the vital enzymic processes to cause metabolic disturbances in the organism and eventually its death. The postulates of this theory divide antiseptics into two categories -- cationic and anionic. The cationic antiseptics are the neutral salts of bases of high molecular weight, and include all the basic dyes such as polyphenylmethane antiseptics (brilliant green, auramine, crystal violet) and the acridine antiseptics (proflavine, acriflavine) as well as higher aliphatic amines ("Zephiran"). The equilibrium between cation and protein is represented by the following reaction:

$$P\text{-}COOH + BH^+ + Cl^- \rightleftharpoons P\text{-}COOBH + H^+ + Cl^-$$

The anionic protein is designated as P-COOH and the salt-like un-ionized complex as P-COOBH. It is evident from the equation that a high hydrogen ion concentration will favor formation of undissociated protein and dissociated base (ammonium ion). Conversely, an increase in hydroxyl ion concentration will produce the opposite

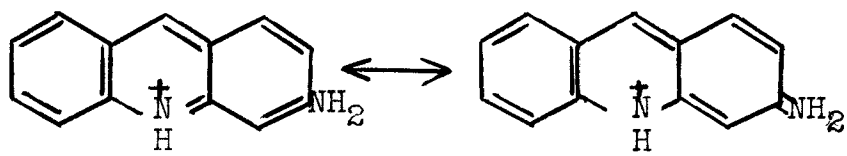
effect. This is actually reflected in the increasing bactericidal effectiveness of cationic antiseptics as the pH is raised.

A corollary of this hypothesis was enunciated by Stearn and Stearn[90] in 1924, "For any closely related series of dyes or other basic substances, the bacteriostatic index should increase with the basic strength." This is based on two premises. First, that the salts of stronger bases would ionize more readily and thus increase interaction with the protein of the bacteria; secondly, the cation of a stronger base would tend to form a complex more resistant to hydrolysis. A correlation of basic strength among aminoacridines and bacteriostatic property is presented in Table V.[91]

The unusually high indices for 2-amino-, 2,8-diamino- and 5-aminoacridines in comparisons with their isomers are directly related to the dissociation constants. The striking differences in dissociation constants (or basic strengths) is explicable in terms of a heightened resonance effect. Amino groups in the 2-, 5- and 8- positions permit stabilization of the ion relative to the free base because of the greater number of limiting

91. Albert, Rubbo and Goldacre, Nature, 147, 332, 709 (1941).

structures that contribute to the resonating system. Two of the contributing structures for 2-aminoacridine are (XII) and (XIII). If the amino groups are in the 1-, 3-, 4-, 6-, 7- and 9- positions, however, it is impossible



(XII) (XIII)

to write an amine structure comparable to (XIII), and consequently an increased stability of the ion due to resonance is not possible.

The anionic antiseptics are the neutral or faintly alkaline sodium salts of acids of high molecular weight, such as soap, ammonium mandelate and the neutral "acid dyes", an example of which is acid fuchsin. The mode of action is exactly analogous to that of the cationic antiseptics. This class of antibacterial agents function better in slightly acid medium -- a condition which is illustrated by the reaction:

$$P\text{-}NH_2 + Na^+ + A^- + HOH \rightleftharpoons R\text{-}NH_3A + Na^+ + OH^-$$

Table V[91]

Correlation of Bacteriostasis and Basic Strength Among Aminoacridines

Substance	Medium : 10% serum-broth (pH 7.2) Cl. Welchii	Strep. haem.	Staph. aureus	E. coli	Proteus vulgaris	Bacteriostatic index (sum of inhibitory dilutions)	Dissociation constant at 25°C. (x 10^{-1})
5-Amino acridine	7[+]	6	3	3	4	23	300
2,8-Diamino-acridine (Proflavine)	7	6	3	3	2	21	120
2-Amino-acridine	7	4	3	4	3	21	12
4-Amino-acridine	5	2	1	1	0	9	0.03
3-Amino-acridine	5	2	1	0	0	8	0.01
Acridine	3	1	1	0	1	6	0.002
1-Amino-acridine	2	1	1	0	0	4	0.001

[+]Key to dilutions: 1 = 1g. antiseptic prevents growth in 5000 c.cm. of medium. Similarly, 2 = 1 in 10,000; 3 = 1 in 20,000; 4 = 1 in 40,000; up to 7 = 1 in 320,000. 0 signifies no inhibition at 1 in 5000.

Anionic agents are useful in the urinary tract where a lower pH is present. They are not as important as the cationic type because bacteria contain an excess of acidic groups over basic groups.

Phenols, due to the slightly acidic hydroxyl group, have been regarded at times as of the anionic type.

From a number of studies it was shown that a relationship exists between surface activity and bactericidal action of phenols. Table VI[92] shows how the phenol coefficient is a function of the surface tension. The larger the alkyl group, the lower is the surface tension and the greater is the antiseptic action. There are some who hold the opinion that the action of phenols is related to the oil/water partition coefficient. This latter viewpoint had some support in the much earlier work of Meyer[93] who showed in the aliphatic narcotics that strength of narcotic action was approximately due to the distribution coefficient. Whatever the exact nature of the surface action, it in itself cannot be responsible for the antibacterial action of phenols. It is very likely that the initial action is to render the cell proteins more accessible to further chemical action

92. Frobisher, J. Bact., 13, 163 (1927).

93. Meyer, Arch. exp. Path. Pharmak., 42, 109, 119 (1899).

Table VI[92]

Relation of Phenol Coefficient to Surface Activity in Alkyl Resorcinols

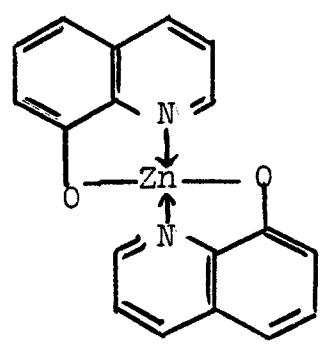
Substance	Phenol Coefficient	Surface Tension (1/10,000 dilution) (Dynes per cm.) (aid/water)
Resorcinol	0.3	76
Propylresorcinol	5	73
Butylresorcinol	22	66
Amylresorcinol	33	60
Hexylresorcinol	50	54
Heptylresorcinol	30	43

by increasing the permeability of the lipoid-protein cell membrane. The exact nature of this secondary chemical action is still undetermined. Possibly it is merely the interaction between the hydroxyl of the phenol and a functional group of the protein, probably the amino group. Rideal[94] has pointed out that although hydroxyl groups are not ordinarily classed as highly reactive in reactions occurring in the bulk phase, their reactivity may be much greater when oriented at a surface layer. Neutral detergents which cannot combine with carboxyl or amino groups of cellular proteins are non-bactericidal.[95]

94. Rideal and Schulman, Nature, 144, 100 (1939).

95. Work and Work, "The Basis of Chemotherapy," Oliver and Boyd Ltd., London, 1948, p. 329.

A very interesting theory has been put forward regarding the mode of action of the class of antibacterial compounds related to 8-hydroxyquinoline. It has been suggested that their activity is due to the ability to combine with metabolically important trace metals on the surface of the bacterium. The chemical process itself is called chelation and occurs with compounds containing groups which are so placed that they can form feebly dissociated cyclic complexes with various metals. The zinc complex with 8-hydroxyquinoline (oxine), for example, has the following structure.



The zinc atom has replaced hydrogen from the hydroxyl group and is linked to the oxygen by a primary valence and to nitrogen by a secondary (coordinate) valence.

Zentmyer[96] in 1944 suggested that oxine acts on fungi

96. Zentmyer, Science, 100, 294 (1944).

through chelation with essential metals, and Albert[97] soon after entertained the same idea regarding its action as an antiseptic. When it was discovered[98] that 1-hydroxyacridine, which has all the requisites for metal chelation, showed antibacterial activity in excess of that which could be predicted from its ionization constant, a detailed investigation of this ehtire subject was undertaken.[99]

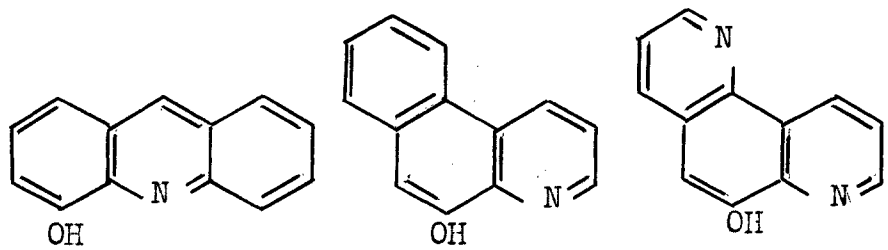
From experiments[99] with a considerable number of compounds, it became clear that although chelation is essential, the architecture of the drug molecule as a whole is equally important. It appears that the 8-hydroxyquinoline structure, or some derivative of it, is necessary. 2- and 8-Quinolinecarboxylic acids chelate with metals but neither of them is antibacterial. Furthermore, if a group is present which might sterically interfere with chelation, then the activity falls off. 2-Methyl-8-hydroxyquinoline is less active than both the parent molecule and its 5-methyl isomer. 2,3-Benzo-8-hydroxyquinoline (1-hydroxyacridine) (XIV) is less active than 8-hydroxyquinoline giving further proof of the

97. Albert, Med. J. Aust., 245 (1944).

98. Albert, et al., Brit. J. Expt. Path., 26, 160 (1945).

99. Albert, et al., ibid., 28, 69 (1947).

importance of the steric factor. However, the spatially removed groups in 5,6-benzo-8-hydroxyquinoline (XV) and in 6-hydroxy-m-phenanthroline (XVI) do not exert this adverse effect.



(XIV) (XV) (XVI)

8-Methoxyquinoline is inactive as are all the seven isomers of 8-hydroxyquinoline, chelation being impossible with any of them. 1-Hydroxyphenazine is somewhat active while 8-mercaptoquinoline, a strong chelating agent, shows high activity. N-alkylation, as in a quaternary salt, destroys the chelating power, by making unavailable for coordination the electron pair on the nitrogen, and thus also destroys antibacterial activity.

There is insufficient evidence upon which to base a decision as to the identity of the trace metals. Preliminary experiments indicate that zinc, iron, copper, and cobalt are involved. Regarding the question as to whether these chelating agents act by removing the

essential metals from the growth medium or by abstracting them from the bacterial surface, the fact that many compounds of chelate properties are non-active is rather convincing evidence for the second alternative.

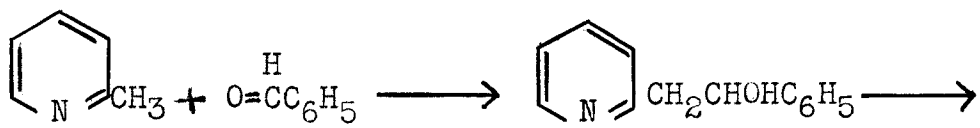
There are several theories[100] which have been advanced to explain bacterial inhibition of the sulfonamides. The one that correlates best with experimental observations is based on the fact that p-aminobenzoic acid, an essential metabolite for bacterial growth, counteracts the antibacterial action of sulfanilamide. It is believed that there is a competition between these two structurally similar compounds for an enzyme surface. In the absence of p-aminobenzoic acid, sulfanilamide reacts temporarily with the enzyme but because it is sufficiently unrelated to the essential amino acid, it cannot replace the function of the latter, and instead interferes with the metabolism of the cell and causes inhibition.

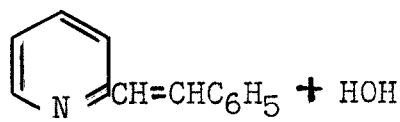
C. The Aldol and Claisen Reactions of Methyl Groups α- and γ- to the Azomethine Linkage of Nitrogen-Containing Heterocycles.

Methyl groups in the α-(2-) and γ-(4-) positions

100. See Ref. 95, Ch. V; also Henry, "The Mode of Action of Sulfonamides", Josiah Macy, Jr. Foundation; New York, 1944.

in quinoline and in pyridine react with aldehydes to form aldols. In the majority of cases, usually in the presence of a catalyst, a secondary reaction may occur and water is split out to form an unsaturated compound. The overall reaction is called the Claisen condensation. A methyl





group in the β-(3-) position is incapable of being activated by the azomethine grouping and consequently does not undergo the aldol and Claisen reactions.

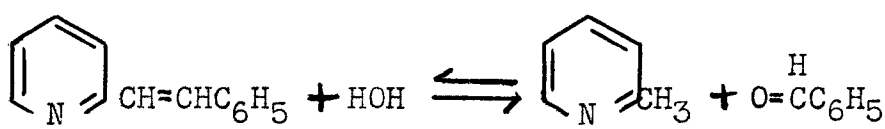
1. Formation of Carbinols (or Aldols). The simpler aliphatic aldehydes, like acetaldehyde[101, 102] and propionaldehyde,[98] condense with 2-picoline to give the corresponding carbinols in poor yields. Chloral reacts to form trichloromethyl-2-picolyl methanol in 70% yield. If quinaldine and chloral are heated on a water bath,

101. Leonigs and Happe, Ber., 35, 1343 (1902).

102. McElvain and Johnson, J. Am. Chem. Soc., 63, 2213 (1941).

γ-trichloro-β-hydroxy-α-(2-quinolyl)-propane is formed. This can be converted by mild hydrolysis to β-(2-quinolyl)-lactic acid[103] or, under more drastic conditions, to β-(2-quinolyl)-acrylic acid.[104]

2-Picoline forms the alkine 2-(β-hydroxy-β-phenylethyl)-pyridine[105] if it is heated with benzaldehyde for ten hours at 140-160° in the presence of a small amount of water. Shaw and Wagstaff[106] have shown that the aldol reaction is reversible by isolating benzaldehyde and picoline after heating pure stilbazole and water at 140° for ten hours.



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

104. von Miller and Spady, Ber., 19, 130 (1886).

105. Bach, Ber., 34, 2231 (1901).

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

Tipson[107] investigated the reversible quinaldine-p-dimethylaminobenzaldehyde reaction for the purpose of establishing the conditions for maximum yield. The best yield of the styryl derivative, which he obtained after heating for four and one-half hours at 255°, was 44%. When the reaction was interrupted at the end of two hours at 275° to remove the products, water and styryl compound, and then the unreacted materials heated for an additional two hours at the same temperature, the yield was increased to 86%. Thus, by removing two of the components of the equilibrium, a greater yield was obtained by forcing the reaction to proceed in the desired direction.

2. Condensing Agents. The carbinols which are formed exclusively in some reactions can be converted to the alkene or styryl compound by several different methods. Heating[108] the molten carbinol will usually effect dehydration; refluxing with acetic anhydride is even more efficient.[108] A trace of acid is all that is necessary to lead directly to the styryl derivative in some condensations.[108] Other catalysts that have been successfully used in Claisen condensations are sodium hydroxide, sodium alkoxides, diethylamine, piperidine, zinc chloride,

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

108. Walton, Tipson and Cretcher, ibid., 67, 1501 (1945).

hydrochloric acid, sulfuric acid and potassium acid sulfate.[109] Aluminum chloride[110] was effective in the condensation of quinaldine and Michler's ketone.

A comparison of the relative effectiveness of several condensing agents can be found in a study by Tipson.[107] In the reaction of quinaldine and p-dimethylaminobenzaldehyde, the following yields of styryl derivatives were obtained: acetic anhydride, 13%; hydrochloric acid, 51%; zinc chloride, 68%; "Drierite" (2 hours at 150°), 0%. Gilman and Karmas,[111] however, found acetic anhydride to be superior to zinc chloride in condensations of quinaldine, lepidine and picoline. Spallino and Cucchiaroni[112] stated that zinc chloride was harmful and caused resinification. In the reaction between 2-phenyllepidine and benzaldehyde, John[113] was unable to isolate any product when he used zinc chloride and potassium acid sulfate as catalysts. The condensation was finally accomplished by heating in a sealed tube without a catalyst at 200-210°.

109. Bergstrom, Chem. Revs., 35, 181 (1944).

110. Kehlstadt, Helv. Chim. Acta., 27, 685 (1945).

111. Gilman and Karmas, J. Am. Chem. Soc., 67, 342 (1945).

112. Spallino and Cucchiaroni, Gazz. chim. ital., 42, 517 (1912) [C. A., 6, 2419 (1912)].

113. John, Ber., 59, 722 (1926).

Chiang and Hartung,[87] in their reactions of picoline and hydroxyaldehydes, found acetic anhydride superior to zinc chloride and hydrochloric acid.

With more reactive aldehydes, piperidine is sufficient as a condensing agent. Quinaldine and m-nitrobenzaldehyde were converted to the corresponding styryl compound in a yield of 70%.[114]

Occasionally benzylidenediquinaldine, $C_6H_5CH(CH_2C_9H_6N)_2$, is obtained as a by-product in the preparation of benzalquinaldine.[115] If two moles of quinaldine are used to one mole of aldehyde, then the diquinaldine compound is the main product.[115, 116] Tipson[107] found that decreasing the amount of condensing agent increases the yield of by-product; for instance, one mole of quinaldine heated with one mole of benzaldehyde and one-half mole of zinc chloride gives a greater proportion of the diquinaldyl compound than that of the styryl derivative.

3. Quaternary Salts. The quaternary salts are much more reactive than the free bases. p-Nitrosodimethylaniline, for instance, which is inert towards picoline, condenses

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114. Graef, Fredericksen and Burger, J. Org. Chem., 11, 257 (1945).

115. Henze, Ber., 70, 1273 (1937).

116. Hamer, J. Chem. Soc., 123, 256 (1926).

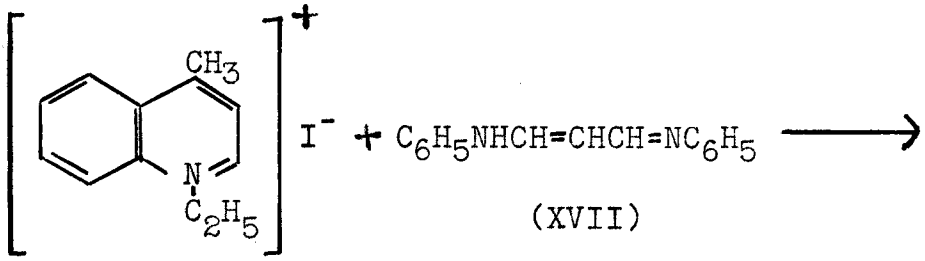
very readily with the methiodide in boiling ethanol.[115, 117] Usually a few drops of piperidine is added as a catalyst. Mills and Pope[118] found that p-dimethylaminobenzaldehyde forms the corresponding styryl derivative from 2-picoline methiodide in boiling ethanol. Ordinarily this rather weak electrophilic agent requires a condensing agent like zinc chloride or acetic anhydride at elevated temperatures. Another example is the reaction of quinaldine methiodide and p-methoxycinnamaldehyde[119] in boiling ethanol. The methyl ether was subsequently hydrolyzed with hydrobromic acid in glacial acetic acid to give the free hydroxy compound.

A striking illustration of the increased reactivity of the quaternary salts is the condensation of the ethiodides of quinaldine, lepidine and 2-methylbenzothiazole with ammono dialdehyde ethers of the general formula, $R\text{-}NCH(CH\ CH)_n\text{-}NR_2$.[109] Lepidine ethiodide and β-anilinoacrolein anil (XVII) react as follows:

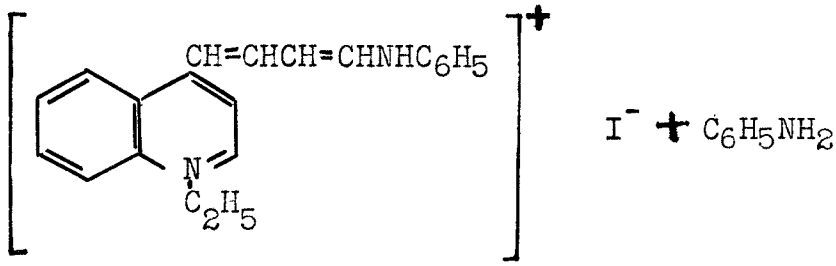
117. Kaufmann and Vallette, Ber., 45, 1737 (1912).

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

119. Schneider and Pothmann, Ber., 74, 471 (1941).



(XVII)



4. Relative Reactivity of 2- and 4-Methyl Groups. The greater reactivity of the 2- over the 4-methyl group has been established by a number of experiments. When 2,4-lutidine was heated with benzaldehyde in the presence of acetic anhydride, the 2-styryl compound and the 2,4-distyryl derivative were formed in a ratio of two to one, respectively.[120] Eibner[121] heated quinaldine and lepidine with benzaldehyde in parallel experiments, and obtained 7.95 grams of 2-styrylquinoline to 1.0 gram of 4-styrylquinoline hydrochloride.

When an excess of fo maldehyde was heated with quinaldine or lepidine, tris(hydroxymethyl)quinaldine

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

121. Eibner, Ber., 37, 3609 (1904).

was formed from the former, and only bis(hydroxymethyl)-lepidine from the latter.[122, 123] Kaslow and Staynor[46] treated 2,4-dimethylquinoline with benzaldehyde for thirty hours at 130°, with one drop of 10% sodium hydroxide catalyst, and obtained a 74% yield of 2-styryllepidine, thus showing the lesser reactivity of the 4-methyl group.

With a sufficient amount of aldehyde both methyl groups in 2,6-lutidine condense to form distyryl derivatives. With p-nitrobenzaldehyde[124] and acetic anhydride, a 54% yield was obtained. p-Anisaldehyde gave a 61% yield of 2,6-di-(p-methoxystyryl)-pyridine.[125] There are other examples in the literature which demonstrate the equivalence of the methyl groups in 2,6-lutidine and present, therefore; strong evidence against a static bond structure.

5. Other Heterocycles in the Claisen Reaction. The aldol and Claisen reactions are not limited to the homologues of quinoline and pyridine. 1-Methylisoquinoline condenses with benzaldehyde in the presence

122. Koenigs, Ber., 34, 4322 (1901).

123. Methner, Ber., 27, 2689 (1894).

124. Royer, J. Chem. Soc., 560 (1947).

125. Lee and Freudenberg, J. Org. Chem., 9, 537 (1944).

of zinc chloride at 100° to give a good yield of 1-styrylisoquinoline.[126] The aldol reaction does not occur with the isomeric 3-methylisoquinoline.[126] 2-Methylbenzothiazole is also readily condensed; for example, when it is heated with p-dimethylaminobenzaldehyde, at 100° for sixteen hours with concentrated hydrochloric acid, it gives a 78% yield of the styryl derivative.[127] Likewise, benzaldehyde and 2-methylbenzothiazole with zinc chloride gives 2-styrylbenzothiazole.[128] 2-Benzylbenzothiazole condenses with both benzaldehyde and p-nitrosodimethylaniline, the latter forming the anil.[44] Only one of the methyl groups in 2,5-dimethylbenzimidazole reacts with aldehydes,[129] while 2-benzylbenzimidazole forms α-phenylstyrylbenzimidazole.[44]

It is interesting to note the activating effect of the phenyl grouping in these reactions. 2-Methyl- and 2-ethylbenzoxazole do not react with benzaldehyde, but 2-benzylbenzoxazole condenses with both benzaldehyde and

126. Mills and Smith, J. Chem. Soc., 121, 2726 (1922).

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

128. Ochiai and Nizizawa, J. Pharm. Soc. Japan, 60, 132 (1940) [C. A., 34, 5082 (1940)].

129. Bamberger and Berle, Ann., 273, 277 (1893).

the much less reactive p-nitrosodimethylaniline.[44] 9-Methylacridine with benzaldehyde forms the 9-styryl derivative; when the methyl grouping is replaced with ethyl, no reaction occurs.[44]

Bennett and Willis[130] made a study of the reactions of 2-methylquinoxaline and 2,3-dimethylquinoxaline. They used an excess of acetic anhydride as a condensing agent, and generally heated the reactants for a four-hour period at the reflux temperature. Some of the yields were as low as 10% and in several instances, when dimethylquinoxaline was used, a mixture of the mono- and di-substituted products were obtained.

6. Aldehydes with other Functional Groups. Aldehydes containing reactive centers other than the aldehyde group condense with varying degrees of facility. p-Cyanobenzaldehyde[131] reacts with 2-picoline in the presence of acetic anhydride over a ten-hour reflux period to give a 42% yield of the corresponding p-cyano derivative. Both carbonyl groupings of isophthalaldehyde[132] condense with quinaldine to form α,α'-isophthalylidenediquinaldine.

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130. Bennett and Willis, J. Chem. Soc., 1960 (1928).

131. Gregory and Holt, ibid., 87 (1947).

132. Steinkopf, Leitsmann, Müller and Wilhelm, Ann., 541, 260 (1939).

Harris and Lenhart[133] heated 2-picoline and pyridine-2-aldehyde in a bomb for twenty-four hours with zinc chloride to obtain 1,2-di-(α-pyridyl)-ethane. A similar reaction occurs in the quinoline series. Kaplan and Lindwall[134] condensed quinaldine and quinoline-2-aldehyde by refluxing for six hours in ethanol. The corresponding carbinol was isolated in 75% yield, and then quantitatively dehydrated to the ethene with acetic anhydride. Quinaldine condenses with quinoline-4-aldehyde, and lepidine reacts with the 2-aldehyde, but not with the 4-aldehyde.

Konig and Treichel[135] have remarked that p-aminobenzaldehyde condensed readily with quinaldine methiodide, but the ortho isomer is not as reactive. The inclusion of a vinyl grouping, as occurs in cinnamaldehyde, does not seem to interfere in most reactions. p-Nitrocinnamaldehyde[136] reacts with quinaldine in 90% yield, when acetic anhydride is used as a catalyst. In contrast to this smooth reaction, however, Brooker and Sprague[127] reported that they

133. Harries and Lenhart, Ann., 410, 95 (1915).

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

135. Konig and Treichel, J. prakt. Chem., [2] 102, 80 (1921).

obtained only a 9% yield of product from quinaldine and p-dimethylaminocinnamaldehyde with hydrochloric acid catalyst.

Hydroxyaldehydes were condensed with picoline for a study of the antiseptic action of hydroxystilbazoles and their quaternary salts. Chiang and Hartung[87] found that acetic anhydride gave better yields and cleaner products, although saponification with sodium hydroxide was necessary to free the hydroxy compound from its acetoxy derivative. The condensation of hydroxyaldehydes goes even smoother with the quaternary salts.[137]

7. Heterocycles Containing Functional Groups. The presence of other active groups in quinaldine and lepidine generally does not interfere in aldol condensations. In the case of the 4-hydroxyquinaldine type there are two contradictory reports. Myer and Maurin[138] state that this compound will not condense with benzaldehyde, but the quaternary salt, in the presence of piperidine, forms a colored styryl derivative. p-Nitrosodimethylaniline fails to react with the quaternary salt of 4-hydroxyquinaldine, but does condense with the

136. Mathur and Robinson, J. Chem. Soc., 1520 (1934).

137. Phillips, J. Org. Chem., 12, 333 (1947).

138. Myer and Maurin, Compt. rend., 200, 931 (1935).

salt of the methoxyl derivative. In disagreement with the findings of Myer and Maurin is the work of Renfrew,[89] who obtained a 50% yield of 2-(3',4'-dioxymethylenestyryl)-4-hydroxy-6-methoxyquinoline from the condensation of 4-hydroxy-6-methoxyquinaldine and piperonaldehyde, using acetic anhydride as a condensing agent. Tröger and Dunker[139] were also successful in reacting 4-hydroxyquinaldine with various aldehydes. They used zinc chloride and obtained a crystalline product from the reaction with benzaldehyde, but the o-hydroxy-, o-methoxy- and p-methoxy-styryl derivatives were amorphous, high melting compounds.

There are several other examples of condensations of hydroxy derivatives of quinaldine and lepidine. Clapp and Tipson[140] obtained 4-(p-dimethylaminostyryl)-6-(β-hydroxyethoxy)-quinoline in low yield from 6-(β-hydroxyethoxy)-lepidine and the respective aldehyde. 6-Hydroxyquinaldine and p-dimethylaminobenzaldehyde were condensed by boiling for ten minutes in ethanol without a catalyst.[88] The following aldehydes were condensed by Phillips and his collaborators[141] with 8-hydroxyquinaldine:

139. Tröger and Dunker, J. prakt. Chem., 109, 88 (1925).

140. Clapp and Tipson, J. Am. Chem. Soc., 68, 1332 (1946).

141. Phillips, Elbinger and Merritt, ibid., 71, 3986 (1949).

benzaldehyde, m-tolualdehyde, p-anisaldehyde and piperonaldehyde. The yields varied from 30% to 50%.

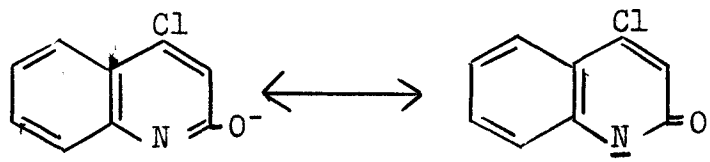
3-Hydroxyquinaldine and salicylaldehyde gave an amorphous product, and the product from the condensation of anisaldehyde and benzaldehyde was also amorphous and resisted all attempts at crystallization.[139]

In an attempt to react 2-methoxylepidine with aromatic aldehydes Tröger and Dunker[139] found that, instead of the expected aldol condensation, demethylation occurred to give 2-hydroxylepidine. As an alternative method, they reacted the free hydroxy compound with various aldehydes, using zinc chloride catalyst, and were able to effect the desired condensations. Products obtained by this method were the following derivatives of 2-hydroxyquinoline: 4-o-hydroxybenzal-, p-methoxybenzal-, and 3-methoxy-4-hydroxybenzal-, all of them amorphous powders melting above 360°.

The reactivity of the methyl group in 2-hydroxylepidine is rather surprising in view of the fact that the halogen in 2-hydroxy-4-chloroquinoline is unreactive. For instance, aniline and 4-chloroquinoline, when heated, yield 4-anilinoquinoline.[142] 2,4-Dichloroquinoline gives 2,4-dianilinoquinoline.

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

2-Hydroxy-4-chloroquinoline does not react with aniline to give 2-hydroxy-4-anilinoquinoline, nor with boiling alcoholic solutions of sodium alkoxides to give the 4-ethers.[143] Thus, the hydroxyl grouping in the 2-position deactivates the 4- halogen. This deactivation has been attributed by Bergstrom[109] to the resonance of the unperturbed form (XVIII), which stabilizes the molecule so that the reaction is hindered.



(XVIII)

An unusual reaction between 4-methoxyquinaldine and anisaldehyde has been reported by Tröger and Dunker.[144] If the condensation is carried out *in vacuo*, the normal product is obtained, but if it is attempted under pressure at 185-190°, a rearrangement occurs to give 2-*p*-methoxystyryl-N-methyl-4-quinolone (XIX). The normal product can be converted to (XIX) by heating it in the molten state with methyl iodide.

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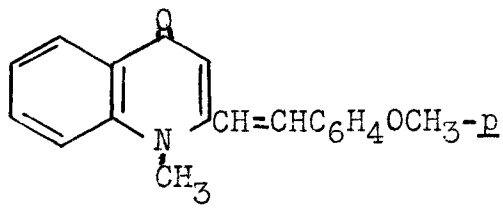
143. Friedländer and Muller, *Ber.*, *20*, 2009 (1887).

144. Tröger and Dunker, *J. prakt. Chem.*, *112*, 196 (1926).



(XIX)

6-Methoxyquinaldine-4-carboxylic acid[145] and 6-methoxyquinaldine-4-sulfonic acid[146] both condense with benzaldehyde in fairly good yields. Other compounds containing acidic groupings which undergo the aldol reaction are 3-acetamidoquinaldine,[147] 4-acetamidoquinaldine,[148] 4-sulfonamidophenylamino-6-methoxyquinaldine[147] and 4-chloro-6-acetamidoquinaldine.[149]

Many aldol and Claisen condensations have been successfully carried out with basic nitrogen groups in the molecule of quinaldine. If acetic anhydride is used

145. Swiss Patent 126,074 (Sept. 7, 1926) [C. A., 23, 851 (1929)].

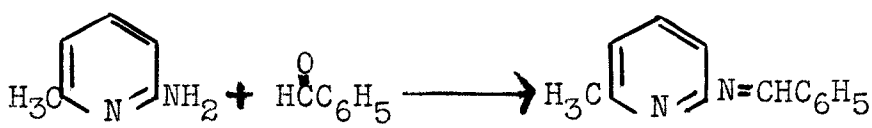
146. Rubtzov and Arendaruk, J. Gen. Chem. (U.S.S.R.), 16, 215 (1946) [C. A., 41, 128 (1947)].

147. Clemo and Swan, J. Chem. Soc., 867 (1945).

148. British Patent 282,143 (Sept. 11, 1926) [C. A., 22, 3735 (1928)].

149. Rubtzov and Burrina, J. Gen. Chem. (U.S.S.R.), 14, 1128 (1944) [C. A., 40, 7194 (1946)].

as a condensing agent and a primary or secondary amino group is present, then a secondary process of acetylation will occur. Amino compounds that have been reported to condense are 4-amino-[148] and 4-hydrazinoquinaldine,[148] 4-(1-methyl-4-diethylaminobutylamino)-6-methoxyquinaldine,[146] 4-amino-6-methoxyquinaldine[89] and 3-dimethylaminoquinaldine.[147] Feist, Awe and Kuklinski[150] studied the reactions of aminopicolines, and their results are not in accord with what one might expect from the above reported reactions. 6-Methylamino- and 6-dimethylamino-α-picoline did not react with benzaldehyde. 6-Amino-α-picoline condensed to form an anil rather than the styryl derivative.



Active halogens in the quinoline nucleus are not affected by the aldol reaction. 3,4-Dibromoquinaldine[151] and 4-chloro-6-methoxyquinaldine[152] were condensed with

150. Feist, Awe and Kuklinski, Arch. Pharm., 274, 419 (1936).

151. Kaslow and March, J. Org. Chem., 12, 456 (1947).

152. Eislet, German Patent 540,699 (Dec. 7, 1929) [C. A., 26, 2199 (1932)].

benzaldehyde and cinnamaldehyde, respectively.

8. Mechanism. The mechanism of the aldol and Claisen reactions of the α- and γ-methyl groups in azomethine compounds has received various interpretations. Analogous reactions occur with the methyl ketones in the aquo system and with certain aromatic compounds like 2,4-dinitrotoluene. It is from the activating effect of these electronegative groups, azomethine, carbonyl and nitro, that the methyl groups derive their reactivity.

Certain reactions of methyl ketones are related to the formation of enols.[153, 154] According to modern theory,[155] the base catalyzed condensations of acetone involve the addition of one polarized molecule of acetone to the conjugate base (carbanion) of another, the latter formed by the removal of a proton by the catalyst.

The condensation of 2,4-dinitrotoluene with benzaldehyde, as depicted by Remick,[156] is a

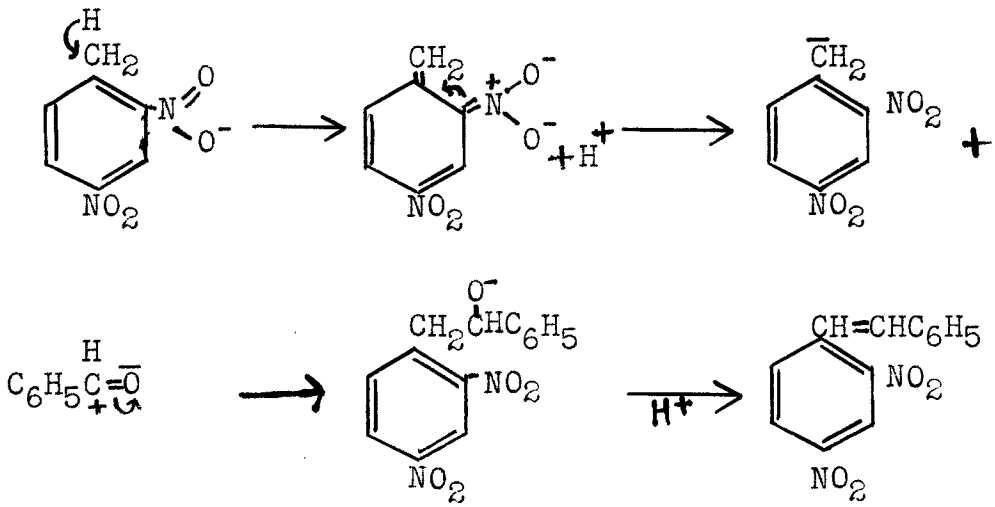
153. Lapworth, J. Chem. Soc., 85, 30 (1904).

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

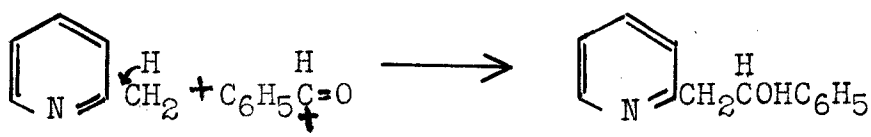
155. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Company, Inc., New York, 1940, p. 344.

156. Remick, "Electronic Interpretations of Organic Chemistry", John Wiley and Sons, Inc., New York, 1943, p. 130.

nucleophilic attack on the positively charged carbon of the polarized carbonyl group. Here the nitro groups activate the methyl group in the following manner:



By similar reasoning, the activation in azomethine heterocycles is due to a -I effect of the nitrogen atom,

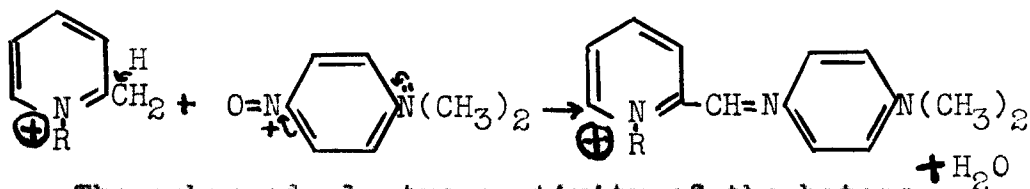


which is brought into play by the approach of a nucleophilic condensing agent (piperidine).

Obviously, this effect can be relayed (principle of vinylogy) to the γ-position in pyridine and quinoline but not to the β-position. Similarly, only the 1-methyl group is active in isoquinoline, the 2-methyl in 2,4-dimethylthiazole and only one of the methyl

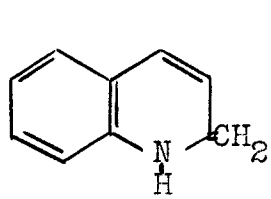
groups in dimethylbenzimidazole.[129]

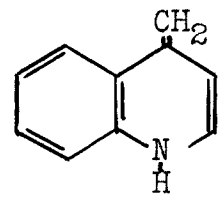
This same principle explains the failure of p-nitrosodimethylaniline to condense with 2-picoline, in contrast to its smooth reaction with the quaternary salt. Picoline, itself, is too weakly nucleophilic to attack the positive pole of the nitroso nitrogen, because of the partial neutralization of the latter by the conjugative relay of electrons from the dimethylamino group. The positive charge, conferred on the hetero atom through salt formation, increases its electronegativity and renders the reaction possible.



The enhanced electronegativity of the hetero nitrogen by salt formation probably accounts for the readiness of the intermediately formed aldol to be dehydrated in the presence of acids. Here, the positively charged nitrogen induces dehydration by a process which can be thought of as a type of β-elimination.

Several investigators[157, 158, 159] have suggested that quinaldine, lepidine and related active methyl compounds react with aldehydes in their isomeric enamic forms. Although no direct proof for the existence of





these modification has been obtained by experiment, the methylene bases derived from quaternary salts have, in a few cases actually been isolated. With one of these, (XX), derived from β-naphthaquinaldine ethiodide, Mills was able to show with convincing evidence the nature of the condensation of quaternary salts with aldehydes.

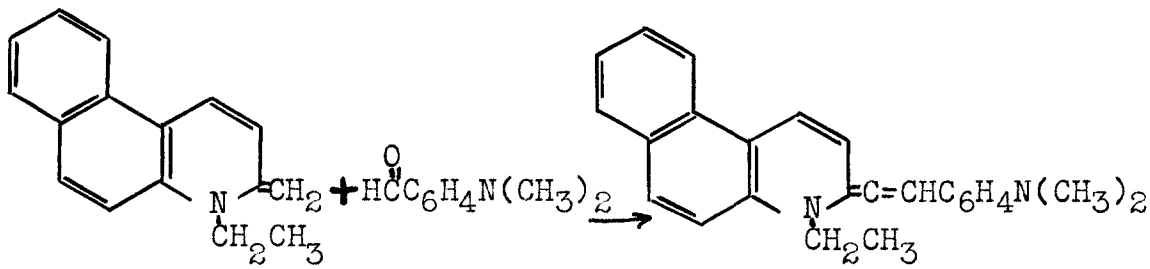
From the interaction of this methylene base and p-dimethylaminobenzaldehyde, he isolated an oxygen-free compound that corresponded to structure (XXI). When this compound was treated with hydriodic acid, he obtained p-dimethylaminobenzal-β-naphthoquinaldine

157. Chichibabin, Ber., 60, 1607 (1927).

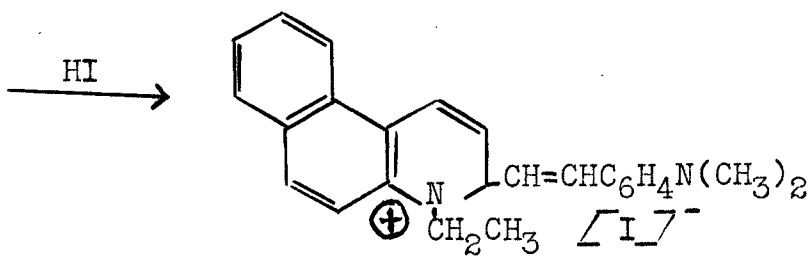
158. Mills and Raper, J. Chem. Soc., 127, 2466 (1925).

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

ethiodide. This product was identical with the one obtained from the condensation of the aldehyde and β-naphthaquinaldine ethiodide in the presence of piperidine. Furthermore, compound (XXI) was shown to remove hydriodic acid from piperidine hydroiodide to form (XXII).



(XX) (XXI)

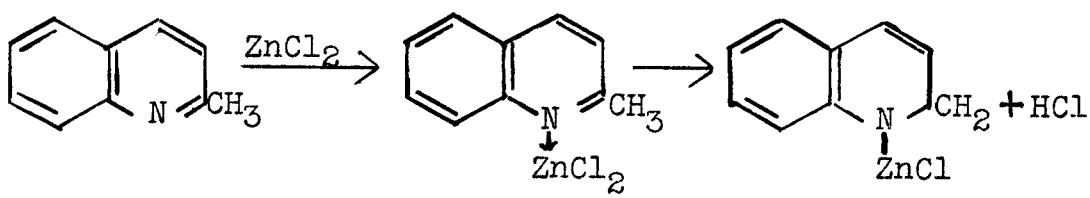


(XXII)

From these observations, the sequence of reactions which occur in a condensation of a quaternary salt in the presence of piperidine can be formulated in the following manner: at first, the abstraction of hydrogen iodide from the quaternary salt by piperidine to form

the methylene base; next, the reaction of the methylene base and the aldehyde to give the allene compound; and thirdly, the interaction of piperidine hydroiodide and the allene to give the styryl compound and regenerated piperidine.

With the striking experiments of Mills[158] in mind, Sidgwick, Taylor and Baker[159] have suggested that the role of acid condensing agents as hydrochloric acid and zinc chloride may well be to first form a quaternary compound, and, then, at elevated temperatures the latter lose hydrogen chloride to give the reactive methylene base. This point of view formulates a mechanism almost identical with that for the reactions of the quaternary salts.



III. EXPERIMENTAL

Preparation of 2-Styrylbenzothiazole.- A mixture of 14.9 g. (0.1 mole) of 2-methylbenzothiazole, 10.6 g. (0.1 mole) of benzaldehyde and 10.2 g. (0.1 mole) of acetic anhydride was refluxed for eighteen hours. The reaction mixture was diluted with 100 ml. of 50% ethanol and stirred very thoroughly. After filtration, the product was washed with dilute ethanol, dilute ammonium hydroxide and then water. The crude material weighed 20.0 g. (84.5%) and melted at 109-110°. Recrystallization from ethanol increased the melting point to 112-113°.[160]

Action of Hydriodic Acid on 2-Styrylbenzothiazole.- To 30 ml. of 47% hydriodic acid (stabilized with 4-4.5% hypophosphorous acid) and 30 ml. of glacial acetic acid was added 5.0 g. of 2-styrylbenzothiazole. The mixture was refluxed for twenty-four hours, diluted with water and made basic with ammonium hydroxide. A white precipitate separated which weighed 4.7 g. when dry and melted at 112-113°. Apparently the compound was unaffected by the hydrolytic agents under these forced

160. Mills and Whitworth, J. Chem. Soc., 2738 (1927), report a melting point of 112-113°.

conditions.

2-(p-Methoxystyryl)-benzothiazole (with piperidine).- A mixture of 14.9 g. (0.1 mole) of 2-methylbenzothiazole and 13.6 g. (0.1 mole) of p-anisaldehyde, with ten drops of piperidine as a catalyst, was heated at 170-180° for ten hours in a nitrogen atmosphere. The mixture was subjected to a distillation at 0.5 mm. Except for a small amount (1.0 g.), the entire mixture distilled at 75-82°. Apparently a condensation had not occurred to any appreciable extent, because the product would certainly be a solid at room temperature or at least not distillable at 75-82°. The residue was recrystallized from 95% ethanol to melt at 142-143°. A mixed melting point determination with the product obtained from the reaction, where acetic anhydride was used as the condensing agent (following experiment), showed the small residue to be 2-(p-methoxystyryl)-benzothiazole. The yield was 3%.

2-(p-Methoxystyryl)-benzothiazole (with acetic anhydride).- A mixture of 14.9 g. (0.1 mole) of 2-methylbenzothiazole, 13.6 g. (0.1 mole) of p-anisaldehyde and 10.2 g. (0.1 mole) of acetic anhydride was refluxed for twelve hours in a nitrogen atmosphere. When cool, the reaction mixture crystallized. An attempt was

made to purify it by distillation. At a bath temperature of 175° and a pressure of 1.0 mm., only a very small amount of material was distilled over. It had the odor of acetic anhydride. In order to avoid any possible decomposition due to higher distillation temperatures, a different method of purification was used. This consisted of removing the impurities by triturating with 95% ethanol, filtering and washing with 80% ethanol. It was recrystallized from ethanol to melt at 142-144°. The weight was 15.0 g. (58%).

Anal. Calcd. for $C_{16}H_{13}NOS$: S, 11.95. Found: S, 12.00.

2-(p-Hydroxystyryl)-benzothiazole.- In a mixture of 100 ml. of 47% hydriodic acid (stabilized with hypophosphorous acid) and 100 ml. of glacial acetic acid was dissolved 7.5 g. of 2-(p-methoxystyryl)-benzothiazole and refluxed for twenty-four hours. It was then diluted with water and made basic with ammonium hydroxide. Crystals separated (m.p. 211-212°) which were filtered off and washed with water. The product was dissolved in 5% sodium hydroxide, treated with "Norite" and filtered. Acidification with acetic acid caused precipitation. After recrystallization from ethanol, the melting point was 212-213°. The weight was 6.0 g. (84.5%).

The light yellow crystals did not give a positive ferric chloride test for the phenolic hydroxyl group.

Anal. Calcd. for $C_{15}H_{11}NOS$: S, 12.65. Found: S, 12.68.

2-(2',3'-Dimethoxystyryl)-benzothiazole.- A mixture of 14.9 g. (0.1 mole) of 2-methylbenzothiazole, 16.6 g. (0.1 mole) of 2,3-dimethoxybenzaldehyde and 10.2 g. (0.1 mole) of acetic anhydride was refluxed for twenty-four hours. It was diluted with 75 ml. of 50% ethanol and cooled. The product which crystallized was separated by filtration and washed with 50% ethanol. The crude yield was 26.0 g. (88%) and melted at 85-87°. Recrystallization from aqueous methanol raised the melting point to 90-91°.

Anal. Calcd. for $C_{17}H_{15}NO_2S$: S, 10.80. Found: S, 10.64.

2-(2',3'-Dihydroxystyryl)-benzothiazole.- To a solution of 150 ml. glacial acetic acid and 75 ml. of hydriodic acid (d. = 1.5) was added 10.0 g. of 2-(2', 3'-dimethoxystyryl)-benzothiazole. The mixture was refluxed for twenty-four hours, diluted with an equal volume of water and made basic with ammonium hydroxide. An amorphous substance separated. This was filtered off, washed with water and dried. The weight was 8.0 g.

It was purified by dissolving in hot glacial acetic acid, treating with "Nuchar" and adding to water. The product precipitated as a yellow amorphous powder which weighed 5.5 g. (52%) and melted with decomposition at 185-190°.

Anal. Calcd. for $C_{15}H_{11}NO_2S$: S, 11.89. Found: S, 11.65.

2-(3',4'-Dimethoxystyryl)-benzothiazole.- A mixture of 10.0 g. (0.06 mole) of 3,4-dimethoxybenzaldehyde, 9.0 g. (0.06 mole) of 2-methylbenzothiazole and 6.1 g. (0.06 mole) of acetic anhydride was heated for twenty hours with the bath temperature at 185-210°. The molten reaction mixture was poured into a crystallizing dish, whereby it soon solidified. The crystalline mass was broken up and triturated with cold 50% ethanol. After filtering, the product was washed with 50% ethanol and recrystallized from 95% ethanol. It weighed 12.0 g. (67%) and melted at 150-151°.

Anal. Calcd. for $C_{17}H_{15}NO_2S$: S, 10.75. Found: S, 11.00.

2-(3',4'-Dihydroxystyryl)-benzothiazole.- To a solution of 100 ml. of hydriodic acid (d. = 1.5) and 150 ml. of glacial acetic acid was added 8.0 g. of 2-(3',4'-dimethoxystyryl)-benzothiazole. The clear solution was refluxed for thirty-six hours at the end of which time a

red-orange precipitate had formed. After dilution with water, ammonium hydroxide was added in slight excess. The precipitate which separated was filtered off and washed with water. It was purified by dissolving in hot glacial acetic acid, treating with "Nuchar" and adding to an excess of water. A crystalline product separated which weighed 5.0 g. (62%) and melted with decomposition at 220-230°.

Anal. Calcd. for $C_{15}H_{11}NO_2S$: S, 11.89. Found. S, 11.69.

Preparation of 2,6-Di-(p-methoxystyryl)-pyridine[125].- A mixture of 21.4 g. (0.2 mole) of 2,6-lutidine, 54.4 g. (0.4 mole) of p-anisaldehyde and 40.8 g. (0.4 mole) of acetic anhydride was refluxed for eighteen hours. The viscous mass was triturated with 50% ethanol and this effected crystallization. A thick crop of crystals was filtered off. After thorough washing with 50% ethanol, the product was recrystallized from a benzene-petroleum ether (b.p. 60-70°) mixture. The white crystals melted at 183-185° and weighed 30.0 g. (43.8%).

2,6-Di-(p-hydroxystyryl)-pyridine.- To a mixture of 100 ml. of hydriodic acid (d. = 1.5) and 200 ml. of glacial acetic acid was added 10.0 g. of 2,6-di-(p-methoxystyryl)-pyridine. After refluxing for twenty-four

hours, water was added and then ammonium hydroxide in slight excess. A red-orange precipitate separated, which weighed 10.0 g. when dry. The material was triturated with 10% sodium hydroxide and filtered leaving a residue weighing 1.3 g. The latter was probably unreacted dimethoxy compound. For further purification, the product was dissolved in hot methyl cellosolve, treated with activated carbon and filtered. The addition of water caused a flocculent suspension to appear, which did not settle out very readily. Therefore, the suspension was centrifuged, and after decanting the supernatant solution, more water was added and again decanted after centrifugation. The amorphous residue was removed mechanically from the centrifuge tubes and placed on a porous plate to dry. The final yield was 5.0 g. (47%) and melted with decomposition at 235-240°.

Anal. Calcd. for $C_{21}H_{17}NO_2$: N, 4.45. Found: N, 4.31.

2,6-Di-(2',3'-dimethoxystyryl)-pyridine.- A mixture of 21.4 g. (0.2 mole) of 2,6-lutidine, 66.4 g. (0.4 mole) of 2,3-dimethoxybenzaldehyde, and 40.8 g. (0.4 mole) of acetic anhydride was refluxed for twenty-four hours. It was diluted to three times the original volume with 50% ethanol and cooled. A crystalline

precipitate separated, which was filtered off and washed with 50% ethanol and then with 95% ethanol. The weight of crude product, melting at 135-137°, was 40.2 g. (50%). It was purified by suspending it in hot 75% ethanol and filtering rapidly. The residue, which weighed 36.0 g., was recrystallized to a constant melting point from a benzene-petroleum ether (b.p. 60-70°) mixture, m.p. 140-141°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: N, 3.48. Found: N, 3.62.

2,6-Di-(2',3'-dihydroxystyryl)-pyridine (attempted).- To a mixture of 50 ml. of hydriodic acid (d. = 1.5) and 75 ml. of glacial acetic acid was added 5.0 g. of 2,6-di-(2',3'-dimethoxystyryl)-pyridine. The mixture was refluxed for twenty-four hours, cooled, diluted with water and then made basic with ammonium hydroxide. A precipitate formed which was filtered off, washed with water and dried. The purification was carried out precisely in the same manner as for 2,3-di-(p-hydroxystyryl)-quinoxaline. After drying in the Abderhalden apparatus, the product was analyzed.

Anal. Calcd. for $C_{21}H_{1}NO_4$: N, 4.05. Found: N, 3.21, 4.83. Apparently the material was non-homogeneous and not the desired product.

2,6-Di-(3'-methoxy-4'-hydroxystyryl)-pyridine.- A mixture of 15.2 g. (0.1 mole) of vanillin, 5.35 g. (0.05 mole) of 2,6-lutidine and 15 ml. of acetic anhydride was refluxed for twenty-four hours. After cooling, the reaction mixture solidified. It was dissolved in 10% sodium hydroxide and filtered. The filtrate was acidified with dilute acetic acid whereby a precipitate separated. It was filtered off, washed thoroughly with water and dried in the desiccator to a constant weight of 9.5 g. (39.5%). The dark yellow powder was recrystallized from 95% ethanol. It melted at 173-175°.

Anal. Calcd. for $C_{23}H_{21}NO_4$: N, 3.73. Found: N, 4.00.

Preparation of 2,3-Di-(p-methoxystyryl)-quinoxaline[130].- A mixture of 7.4 g. (0.05 mole) of 2,3-dimethylquinoxaline, 13.6 g. (0.1 mole) of p-anisaldehyde and 10.6 g. (0.1 mole) of acetic anhydride was refluxed for twenty-four hours. The contents of the flask were poured into a beaker and allowed to crystallize. The crystalline cake was broken up and after trituration with 50% ethanol, it was filtered and washed with 95% ethanol. The crude product weighed 17.0 g. (86%). A small portion was recrystallized from benzene. It melted at 163-164°.

The remainder of the product was digested in boiling

methanol to separate it from the more soluble 2-methyl-3-(p-methoxystyryl)-quinoxaline, and then filtered. The portion that did not dissolve in the methanol weighed 14.0 g. (71%)[161] and melted at 163°.

2,3-Di-(p-hydroxystyryl)-quinoxaline.- To a solution of 50 ml. of hydriodic acid (d. = 1.5) and 75 ml. of glacial acetic acid was added 5.0 g. of 2,3-di-(p-methoxystyryl)-quinoxaline and refluxed for eleven hours. After dilution with water, the solution was made basic with ammonium hydroxide. The precipitate which formed was filtered off, washed with water and redissolved in 10% sodium hydroxide. The solution was treated with activated carbon, filtered and neutralized with acetic acid. A gelatinous precipitate formed which did not settle out after twenty-four hours. Therefore, it was centrifuged, and after decanting the supernatant solution, fresh water was added to the residue and again centrifuged. This process of washing the precipitate was repeated two more times and then the precipitate was removed and placed in the desiccator to dry. In this manner an amorphous, dark tan product was obtained

161. 2,3-Di-(p-methoxystyryl)-quinoxaline[130] was reported in 10% yield (m.p. 163°); the methanol soluble 2-methyl-3-(p-methoxystyryl)-quinoxaline was also obtained in 10% yield (m.p. 122.5°).

which weighed 8.5 g. (50%) and melted with decomposition at 220-225°.

Anal. Calcd. for $C_{24}H_{18}N_2O_2$: N, 7.65. Found: N, 7.88.

Preparation of 2,3-Di-(3',4'-dimethoxystyryl)-quinoxaline[130].- A mixture of 7.4 g. (0.05 mole) of 2,3-dimethylquinoxaline, 16.6 g. (0.1 mole) of 3,4-dimethoxybenzaldehyde and 10.6 g. (0.1 mole) of acetic anhydride was refluxed twenty-four hours. The addition of 50% ethanol caused the reaction mixture to crystallize. It was then broken up with a spatula and triturated with additional 50% ethanol. After the product was separated by filtration, it was washed with 75% ethanol. Recrystallization from benzene and petroleum ether (b.p. 60-70°) resulted in yellow crystals melting at 196-197°. The weight was 13.5 g. (64%).

Because this compound was reported to melt at 208° by Bennett and Willis,[130] who obtained it in 10% yield, our product was analyzed to determine if it might be 2-methyl-3-(3',4'-dimethoxystyryl)-quinoxaline which is not reported.

Anal. Calcd. for $C_{28}H_{26}N_2O_4$: N, 6.17. Found: N, 6.39. Calcd. for $C_{19}H_{18}N_2O_2$: N, 9.15. Found: N, 6.39.

From the analysis it appears that the product is not the monosubstituted compound but rather the disubstituted compound. It is possible that the reported value is a typographical error.

2,3-Di-(3',4'-dihydroxystyryl)-quinoxaline (attempted).- In a solution of 100 ml. of hydriodic acid and 150 ml. of glacial acetic acid was dissolved 5.5 g. of 2,3-di-(3',4'-dimethoxystyryl)-quinoxaline and refluxed for twenty-four hours. The clear solution was diluted with water and neutralized with ammonium hydroxide. The precipitate was filtered off, washed with water and dried. It weighed 4.2 g. and gave a positive ferric chloride test.

It could not be crystallized from any of the solvents that were tried and was therefore dissolved in sodium hydroxide, treated with "Nuchar", and filtered. Acidification with acetic acid caused a gelatinous precipitate to appear. This was centrifuged and washed in the previously described manner and then spread on a porous plate to dry. The material changed to a black powder which did not analyze correctly and was apparently non-homogeneous.

Anal. Calcd. for $C_{24}H_{18}N_2O_4$: N, 7.05. Found: N, 7.39, 5.32.

6-Methoxyquinaldine.- To 250 ml. of an ether solution of methyllithium, prepared from 3.05 g. (0.44 g. atom) of lithium and 31.2 g. (0.22 mole) of methyl iodide, was added at room temperature, 20.0 g. (0.126 mole) of 6-methoxyquinoline in 50 ml. of ether. The addition was accompanied by a steady reflux and a dark yellow precipitate began to separate. The reaction mixture was stirred overnight and then hydrolyzed with water. After the ether layer was separated, it was dried over sodium sulfate and then evaporatively distilled. The oily residue was dissolved in ethanol and oxidized by heating on the steam plate overnight with an equivalent amount of mercuric oxide. The amalgam-like mixture of mercury and mercuric oxide was separated by filtration, and the ethanolic filtrate was concentrated by evaporation on the steam place. The residue weighed 11.0 g. (50%) and was an oil which crystallized when cooled. It melted at 56°.[162] It was used as such without further purification.

Preparation of 4-Hydroxy-6-methoxyquinaldine.- This procedure is an adaptation of the method described by Reynolds and Hauser[163] for the preparation of

162. Rubtsov, J. Gen. Chem. (U.S.S.R.), 13, 593 (1943) [C. A., 39, 705 (1945)] reports a crude melting point of 58°.

163. Reynolds and Hauser, Org. Syn., 29, 70.

4-hydroxyquinaldine.

To 250 ml. of refluxing diphenyl ether, contained in a one-liter, three-necked flask equipped with a dropping funnel, mechanical stirrer and air condenser, was added rapidly 100 g. of molten ethyl β-anisidino crotonate,[164] the latter diluted with a little diphenyl ether. The mixture was stirred under reflux for fifteen minutes and then allowed to cool. It was diluted with 300 ml. of petroleum ether (b.p. 60-70°) and the yellow crystalline solid was separated on the filter. Thorough washing with 200 ml. of petroleum ether (b.p. 60-70°) was followed by air drying. The product was purified by dissolving in 5% hydrochloric acid, treating with charcoal and precipitating with ammonium hydroxide. A 92% yield was obtained. It melted with decomposition at 304-305° and was characterized by converting a portion to the 4-chloro derivative, m.p. 98-100°.[165] Slater[166] reported a lower melting point, 296-298°, for 4-hydroxy-6-methoxyquinaldine.

Preparation of 6-Methoxyquinaldine.- The procedure followed is that of Rubtsov.[162]

164. Coffey, et al., J. Chem. Soc., 856 (1936).

165. Conrad and Limpach, Ber., 21, 1651 (1888).

166. Slater, J. Chem. Soc., 107 (1931).

Twenty-five g. (0.12 mole) of 4-chloro-6-methoxyquinaldine[165] was added to a mixture of 250 ml. of concentrated hydrochloric acid and 330 ml. of water. Thirty-three g. (0.278 g. atom) of tin was added, and the flask was heated for ten hours at 90-95°. The flask was cooled and the yellow complex which crystallized out was filtered off, washed with ethanol and dried. It weighed 35.0 g. and melted at 158-159°.

The complex was converted to the free base by heating it on the steam plate with 30.0 g. of sodium hydroxide and 70 ml. of water. Extraction with ether and evaporation of the latter left a residue which weighed 13.0 g. (62%). This soon crystallized and melted at 58°.

2-(p-Methoxystyryl)-6-methoxyquinoline.- A mixture of 11.0 g. (0.0635 mole) of 6-methoxyquinaldine, 8.7 g. (0.0635 mole) of p-anisaldehyde and 6.5 g. (0.0635 mole) of acetic anhydride was refluxed for twenty-four hours. At room temperature the mixture had solidified to a crystalline mass. It was recrystallized from 95% ethanol to give 14.0 g. (76%) of yellow crystals melting at 161-162°. Recrystallization from a mixture of benzene and petroleum ether (b.p. 60-70°) raised the melting point to 162-163°.

Anal. Calcd. for $C_{19}H_{17}NO_2$: N, 4.82. Found: N, 5.00.

2-(p-Hydroxystyryl)-6-hydroxyquinoline.- To a mixture of 75 ml. of hydriodic acid (d. = 1.5) and 300 ml. of glacial acetic acid was added 5.0 g. of 2-(p-methoxystyryl)-6-methoxyquinoline. After refluxing for twenty-four hours, the reaction mixture was diluted with water and neutralized with ammonium hydroxide. The product which precipitated was filtered off and washed with water. It was purified by dissolving in dilute sodium hydroxide and precipitating with dilute acetic acid. The weight was 3.0 g. (58%), m.p. 270-275° (dec.).

Anal. Calcd. for $C_{17}H_{13}NO_2$: N, 5.35. Found: N, 5.15.

2-(3',4'-Dimethoxystyryl)-6-methoxyquinoline.- A mixture of 13.0 g. (0.075 mole) of 6-methoxyquinaldine, 12.5 g. (0.075 mole) of 3,4-dimethoxybenzaldehyde and 10.2 g. (0.1 mole) of acetic anhydride was refluxed for thirty-six hours. The mixture was diluted with 75 ml. of 50% ethanol and left in the refrigerator for two days. A crystalline precipitate appeared which was collected on the filter and washed with 95% ethanol. It weighed 18.0 g. (75%) and was recrystallized to a constant melting point from aqueous ethanol. The light tan

crystals melted at 137-138°.

Anal. Calcd. for $C_{20}H_{19}NO_3$: N, 4.36. Found: N, 4.31.

2-(3',4'-Dihydroxystyryl)-6-hydroxyquinoline (attempted).- The demethylation was carried out in exactly the same manner as described previously for the hydroxystyryl compounds. The product, which separated upon neutralization of the acidic solution, was a brick-red material, which could not be crystallized from any of the solvents that were tried. It was soluble in dilute sodium hydroxide, but the addition of acid caused the separation of a dark, almost-black semi-solid substance. Repeated attempts to work up this product resulted in failures.

2-(2',3'-Dimethoxystyryl)-4-hydroxy-6-methoxyquinoline.- A mixture of 18.9 g. (0.1 mole) of 4-hydroxy-6-methoxyquinaldine, 16.6 g. (0.1 mole) of 2,3-dimethoxybenzaldehyde and 43.2 g. (0.42 mole) of acetic anhydride was heated under reflux for twenty-four hours. It was then diluted with 100 ml. of 50% ethanol and placed in the refrigerator overnight. The product which separated was collected on the filter and washed with warm 95% ethanol. It weighed 20.0 g. (60%) and melted at 275-278°. Recrystallization from methyl cellosolve to a constant

melting point of 278-280° yielded yellow crystals, which gave a negative color test with ferric chloride.

Anal. Calcd. for $C_{20}H_{19}NO_4$: N, 4.15. Found: N, 4.27.

2-(2',3'-Dihydrosystyryl)-4-hydroxy-6-hydroxyquinoline (attempted).- The demethylation was carried out in the usual manner. The analysis of the product did not give consistent results. It is apparent that decomposition of the product, which probably occurred during purification, was the cause.

Anal. Calcd. for $C_{17}H_{13}NO_4$: N, 4.75. Found: N, 3.19, 2.07.

2-(8-Quinolyloxy)-tetrahydropyran (attempted).- The procedure is similar in essential details to the method used by Parham and Anderson[167] with aryl- and alkylhydroxy compounds.

To 16.8 g. (0.2 mole) of dihydropyran (Du Pont) was added four drops of concentrated hydrochloric acid and then 14.5 g. (0.1 mole) of 8-hydroxyquinoline. There was no apparent evolution of heat. After standing overnight at room temperature, the mixture was warmed on the water bath, whereby complete solution was effected. Crystals separated from the cooled solution. Without

167. Parham and Anderson, J. Am. Chem. Soc., 70, 418 (1948).

separating them, the solution and crystals were dissolved in 200 ml. of ether. The addition of 100 ml. of 10% sodium hydroxide caused a precipitate to separate immediately. This was filtered off and washed with acetone and then ether. A portion of the dry material (11.0 g.) was ignited, and the residue, which remained, indicated the product to be the sodium salt of 8-hydroxyquinoline. This was confirmed by suspending the precipitate in water and carefully neutralizing with hydrochloric acid. The free hydroxy compound was filtered off, washed with cold water and dried. A mixed melting point determination with 8-hydroxyquinoline was not depressed.

An attempt was made to react dihydropyran with 8-hydroxyquinoline hydrochloride. The conditions were the same as for the previous reaction. A few drops of hydrochloric acid were added to insure the presence of an acid catalyst. After neutralization, 8-hydroxyquinoline was recovered unchanged.

Preparation of 8-Methoxyquinoline.- To 30.0 g. (0.207 mole) of 8-hydroxyquinoline, dissolved in 330 ml. of warm water containing 23.1 g. (0.414 mole) of potassium hydroxide, was added 32.3 g. (0.207 mole) of dimethyl sulfate. The addition was carried out dropwise,

and the color of the solution changed from dark yellow to dark red.

After stirring for an hour, the aqueous solution was extracted with benzene. The extract was dried over sodium hydroxide and then the solvent was removed by distillation. The product was distilled at 110-114°/ 2 mm., as a yellow oil, which soon crystallized. A yield of 18.0 g. (54.5%) was obtained. The melting point, 45-46°, was in agreement with the reported value.[168]

2-(o-Hydroxyphenyl)-6-methoxyquinoline.- To 0-lithio-o-hydroxyphenyllithium,[169] prepared from 13.3 g. (0.077 mole) of o-bromophenol (in 75 ml. of ether) and 0.154 mole of n-butyllithium[170] (in 167 ml. of ether), was added 8.0 g. (0.05 mole) of 6-methoxyquinoline dissolved in 50 ml. of ether. The addition was accompanied by a reflux and an orange precipitate appeared. After stirring for one hour, the reaction mixture was hydrolyzed with water. A yellow crystalline precipitate separated after twenty-four hours. After filtration a second crop

168. Kaufmann and Rothlin, Ber., 49, 581 (1916).

169. Gilman and Arntzen, J. Am. Chem. Soc., 69, 1537 (1947).

170. Gilman, Beel, Brannen, Bullock, Dunn and Miller, ibid., 71, 1499 (1949).

precipitated in the filtrate. In order to free the product from its lithium salt, the latter was dissolved in concentrated hydrochloric acid and neutralized with ammonium hydroxide. The product was filtered off, washed thoroughly with water, dried, and recrystallized from toluene. The yellow crystals melted at 159-160° and weighed 5.0 g. (40%).

Anal. Calcd. for $C_{16}H_{13}NO_2$: N, 5.52. Found: N, 5.63.

2-(o-Hydroxyphenyl)-6-hydroxyquinoline.- In a mixture of 15 ml. of 47% hydriodic acid and 16 ml. of glacial acetic acid, was dissolved 3.0 g. (0.0118 mole) of 2-(o-hydroxyphenyl)-6-methoxyquinoline. The solution was refluxed for twenty-four hours, diluted with water, and neutralized with ammonium hydroxide. A light orange product separated. This was filtered off, washed with water and recrystallized from dilute ethanol. The orange crystals melted at 205-207° and weighed 2.2 g. (77.5%).

Anal. Calcd. for $C_{15}H_{11}NO_2$: N, 5.89. Found: N, 5.61.

2-(o-Hydroxyphenyl)-8-methoxyquinoline.- To 0-lithio-o-hydroxyphenyllithium,[169] prepared from 0.372 mole of n-butyllithium[170] and 30.0 g. (0.174 mole) of o-bromophenol, was added 18.0 g. (0.113 mole) of 8-methoxyquinoline dissolved in 100 ml. of ether. The

reaction was stirred overnight and then hydrolyzed with water. After several days, a precipitate separated. This was a lithium salt; it did not melt at 300° and gave a residue upon ignition. The weight was 15.0 g.

The lithium complex was converted to the free hydroxy compound by dissolving it in hydrochloric acid and carefully neutralizing with ammonium hydroxide. A yellow precipitate separated, which weighed 11.0 g. when dry. It was crystallized from ethanol to a constant melting point, m.p. 162-164°. The orange needles, when dissolved in dilute ethanol, did not give a ferric chloride test.

Anal. Calcd. for $C_{16}H_{13}NO_2$: N, 5.58; active hydrogen 1.00. Found: N, 5.62; active hydrogen, 1.03.

A picrate was made which melted at 232-235°.

The active hydrogen was determined by the semi-micro Zerewitinoff method. The solvent used was dry xylene, and the Grignard reagent was a di-n-butyl ether solution of methylmagnesium iodide.

Demethylation of 2-(o-Hydroxyphenyl)-8-methoxyquinoline (attempted).- To 35 ml. of 48% (d. = 1.5) hydrobromic acid was added 5.0 g. of 2-(o-hydroxyphenyl)-8-methoxyquinoline, and then refluxed for four hours. The cooled solution was diluted with water and neutralized carefully with ammonium hydroxide. After the precipitate

was filtered off, it was washed with water and dried. It gave only a slight test with ferric chloride and was insoluble in sodium hydroxide. The melting point after crystallization from ethanol was 155-160°. A mixed melting point with the starting material was 155-160°. A picrate of the precipitate melted at 225-230°. This did not depress the melting point of the picrate of the starting material (m.p. 232-235°). Apparently the ether had not been cleaved.

The ether cleavage was attempted again with 2.0 g. of the methoxy compound in 20 ml. of glacial acetic acid and 15 ml. of hydriodic acid (d. = 1.5). After a five-hour reflux period, the starting material was recovered unchanged.

2-(o-Hydroxyphenyl)-8-hydroxyquinoline.- To a mixture of 30 ml. of glacial acetic acid and 30 ml. of 47% hydriodic acid was added 5.0 g. of 2-(o-hydroxyphenyl)-8-methoxyquinoline. After refluxing for forty-eight hours, the solution was diluted with an equal volume of water and made basic with ammonium hydroxide. The product which separated was filtered off and washed with water. It weighed 4.2 g. (89%). After recrystallization from ethanol, it melted at 219-221°. The compound was soluble in dilute sodium hydroxide and gave a

positive test for the phenolic hydroxyl group with ferric chloride.

Anal. Calcd. for $C_{15}H_{11}NO_2$: N, 5.91. Found: N, 5.79.

2-(o-Hydroxyphenyl)-8-hydroxyquinoline (direct synthesis).- To O-lithio-o-hydroxyphenyllithium,[169] prepared from 0.178 mole of n-butyllithium[170] and 15.4 g. (0.089 mole) of o-bromophenol (in 100 ml. of anhydrous ether), was added at room temperature 4.2 g. (0.029 mole) of 8-hydroxyquinoline. During the addition a white precipitate separated. Immediately after addition, Color Test I[171] was very positive; after nineteen hours of refluxing, the color test was very faint; after forty hours, it was negative.

The mixture was hydrolyzed with water and left overnight without separating the layers. A yellow precipitate of the lithium salt separated. This was filtered off, washed with ether, dried and suspended in concentrated hydrochloric acid. Addition of ammonium hydroxide converted it to an orange powder, which weighed 2.5 g. (36.5%) when dry. After recrystallization from ethanol it melted at 219-221°. A mixed melting point with the product obtained from the demethylation of

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

2-(o-hydroxyphenyl)-8-methoxyquinoline (p. 137) was not depressed.

8-Hydroxyquinaldine.- To 25.0 g. (0.173 mole) of 8-hydroxyquinoline, dissolved in 200 ml. of ether, was added at room temperature 0.346 mole of titrated methyllithium, contained in an ether solution of 375 ml. volume. During the addition of the first equivalent of methyllithium, methane was evolved and a considerable reflux accompanied the addition. A gummy precipitate, presumably the lithium salt of 8-hydroxyquinoline, had settled out. Color Test I[171] was negative.

The addition of the remainder of the organolithium compound caused the precipitate to slowly disappear and the supernatant solution turned orange. After stirring the reaction for twelve hours, the color test was negative and an orange precipitate had appeared. It was hydrolyzed in water and allowed to stand overnight. A precipitate separated. This was filtered off and washed with ether. An ignition test showed it to be a lithium salt. It was converted to the free phenol by dissolving in concentrated hydrochloric acid, and carefully neutralizing with ammonium hydroxide. The yellow product was recrystallized from ethanol. A yield of 11.0 g. (37.6%), melting at 72-73°[172] was obtained.

2-(p-Dimethylaminophenyl)-6-methoxy-8-aminoquinoline (attempted).- To 11.6 g. (0.066 mole) of 8-amino-6-methoxyquinoline, dissolved in 50 ml. of ether, was added dropwise 0.20 mole (based on an estimated 80% yield) of p-dimethylaminophenyllithium,[173] at 0°, over a six-minute period. A red amorphous precipitate appeared and this was stirred for ten minutes at room temperature. The reaction was hydrolyzed with ice water and the ether layer separated and dried over sodium sulfate. After removal of the ether by evaporation, the dimethylaniline was distilled over with the aid of a vacuum pump. The residue was converted to the hydrochloride by the addition of a small amount of hydrochloric acid. A yellow crystalline product formed, which was filtered off, washed with cold ethanol and dried. The weight was 14.0 g. and it melted at 230°.[174] A mixed melting point with an authentic sample of the hydrochloride of 8-amino-6-methoxyquinoline was not depressed. Based on the weight of hydrochloride,

172. Merritt and Walker, Ind. Eng. Chem., Anal. Ed., 16, 387 (1944).

173. Gilman, Zoellner and Selby, J. Am. Chem. Soc., 55, 1252 (1933).

174. Misani and Bogert, J. Org. Chem., 10, 356 (1944), report 228-230°.

the starting material was recovered in 85% yield.

2-Phenyl-6-methoxy-8-aminoquinoline (attempted).- To 0.15 mole of a 1.0 molar solution of phenyllithium,[38] was added 22.5 g. (0.129 mole) of 6-methoxy-8-aminoquinoline dissolved in 100 ml. of anhydrous ether. The solution turned dark at first, then orange-red, finally an orange precipitate separated. The addition was accompanied by a reflux. Color Test I[171] was negative. Color Test II[175] was also negative; an olive colored precipitate appeared.

Another 0.15 mole of phenyllithium was added. The orange precipitate changed to a very deep red. Immediately after the addition Test IV[176] could not be applied because the precipitate was also insoluble in petroleum ether (b.p. 60-70°). Refluxing for forty minutes caused Color Test I[171] to become negative.

Additional phenyllithium (0.15 mole) was added, and the mixture was refluxed for one hour and hydrolyzed in water. The ether layer was separated, dried over sodium sulfate, and evaporatively distilled. A residue remained, which was shown to be a practically quantitative recovery of 6-methoxy-8-aminoquinoline. It was

175. Gilman and Swiss, J. Am. Chem. Soc., 62, 1847 (1940).
176. Gilman and Woods, ibid., 65, 33 (1943).

identified through the hydrochloride (m.p. 230-232°) and the picrate (m.p. 207-209°). Mixed melting points were taken with authentic samples.

2-Methyl-6-methoxy-8-acetamidoquinoline (attempted).- To 10.8 g. (0.05 mole) of 6-methoxy-8-acetamidoquinoline[177] suspended in 200 ml. of ether was added 0.05 mole of 0.7 molar titrated methyllithium. A flocculent white precipitate formed in the supernatant solution. Color Test I[171] was negative. Immediately after the addition of another 0.05 mole of methyllithium, Color Test I was positive, but during a one-hour reflux period, the color test became less intense and finally negative.

The reaction mixture was hydrolyzed in water. A small amount (1.3 g.) of material, which was insoluble in both the ether and aqueous layers, was identified by the method of mixed melting points, as 6-methoxy-8-acetamidoquinoline. The ether layer was dried over sodium sulfate and then evaporatively distilled. A few crystals separated. The liquid portion was identified as 6-methoxy-8-aminoquinoline by a mixed melting point determination of the picrate. Without separating the crystals, the entire mixture was hydrolyzed by boiling with 400 ml. of 10% sodium hydroxide for twelve hours.

177. Robinson and Tomlinson, J. Chem. Soc., 1527 (1934).

The basic solution was extracted with ether and after drying over sodium sulfate, the solvent was removed by distillation. The residue was converted to the picrate and identified as 6-methoxy-8-aminoquinoline. There was no indication of a 2-methyl substituted product.

2-(p-Diethylaminophenyl)-8-hydroxyquinoline[141].- To 14.0 g. (0.0965 mole) of 8-hydroxyquinoline, dissolved in 150 ml. of ether, was added p-diethylaminophenyllithium, prepared from 50.0 g. (0.22 mole) of p-bromodiethylaniline and 3.4 g. (0.44 g. atom) of lithium. The usual precipitate of O-lithio-8-hydroxyquinoline appeared upon the addition of the first portion of organolithium compound. Further addition of p-diethylaminophenyllithium caused the precipitate to disappear. The now bright-orange solution was hydrolyzed with water. The precipitate, which appeared at the ether-water interface, was filtered off. This was suspended in water and neutralized with hydrochloric acid. After recrystallization from ethanol it weighed 13.0 g. (48%) and melted at 94-95°. This is also the reported value.

2-n-Hexyl-6-(o-methoxyphenyl)-pyridine (attempted).- To an ethereal solution of 0.09 mole of o-methoxyphenyllithium[173] was added 16.3 g. (0.1 mole) of 2-n-hexylpyridine (Reilly) dissolved in 50 ml. of ether. There was

no reflux, precipitation, or any other evidence of reaction. The solution was then refluxed for four hours, during which time the color of the mixture changed from amber to dark brown. Color Test I[171] was positive at the end of the reflux period. The reaction mixture was hydrolyzed with water and worked up in the usual way. After removing the ether by distillation, the residue was distilled with the aid of a water pump. Everything came over at a temperature not above 123° at 18 mm. Since 2-(o-methoxyphenyl)-pyridine[178] distills at 137° under a pressure of 2.0 mm., it was considered unlikely that any of the desired product, which probably boils at a higher temperature, was present in the mixture. An attempt was made to form a picrate from the substances which were distilled over, but nothing separated from the ethanolic solution

178. Geissman, et al., J. Org. Chem., 11, 741 (1946).

IV. DISCUSSION

A. Hydroxystyryl Compounds

The preparation of hydroxystyryl derivatives of nitrogen heterocycles have been accomplished by several different methods. The direct condensations of α- and γ-picolines with the appropriate hydroxyaldehyde, in the presence of a condensing agent, was used by Chiang and Hartung[87] to prepare o- and p- hydroxystilbazoles. The products were obtained in yields ranging from 48% to 72%, and were crystalline compounds that could be purified more or less readily from ethanol. Tröger and Dunker[139] utilized the same method to prepare a series of hydroxystyryl derivatives of quinoline. Zinc chloride was used as a catalyst. Most of these compounds contained two hydroxyl groups - one in the styryl group and one in the pyridine ring. They did not form crystalline salts, and, with a few exceptions, were amorphous powders which were difficult to purify. A third method[179] involved the preparation of the nitrostyryl derivative, which was subsequently reduced to the amino compound with iron and water. This was followed by

179. Simpson, J. Chem. Soc., 673 (1946).

diazotization and hydrolysis, whereby the desired hydroxystyrylpyridine was obtained. o-Hydroxystyrylpyridine, which Simpson[179] synthesized by this scheme, melted at 143-144°. Chiang and Hartung[87] have reported a melting point of 130-132° for the same compound and Butter[180a] reported 131-133°. The last two melting points are of products obtained from the Claisen condensation of 2-picoline and salicylaldehyde. The high melting point of Simpson's product is not a typographical error because he mentions the difference in melting points, although he offers no explanation for the discrepancy.

Other reducing agents that have been used to convert the nitrostyryl derivatives to the amino compounds are iron and hydrochloric acid in ethanol (60% yield),[136] stannous chloride and hydrochloric acid,[114] and hydrogen with a nickel or Adams catalyst.[111] A palladium charcoal catalyst hydrogenates the olefinic bond as well as the nitro group.[114]

A unique synthesis of a dihydroxystyryl compound was reported by Renfrew.[89] 4-Hydroxy-6-methoxyquinaldine and piperonaldehyde were condensed in 50% yield to form the styryl derivative. Treatment with phosphorous

180a. Butter, Ber., 23, 2697 (1890).

oxychloride chlorinated both the quinoline nucleus and the dioxymethylene group to give 2-(3',4'-dichlordioxymethylenestyryl)-4-chloro-6-methoxyquinoline. Hydrolysis with dilute sodium carbonate opened the dioxymethylene ring, to form 2-(3',4'-dihydroxystyryl)-4-chloro-6-methoxyquinoline. The latter was then converted to the 4-amino and 4-p-tolylmercapto derivatives by reaction with ammonia and p-thiocresol, respectively. Still another method is that of Schneider and Pothmann,[119] who reacted p-methoxycinnamaldehyde with quinoline ethiodide, and then removed the methyl group with hydrogen bromide and glacial acetic acid to get the corresponding hydroxy compound.

A cursory examination of the four methods, that have been described, would suggest that the method of choice is that of heating together the appropriate hydroxyaldehyde with the active methyl compound, and thus obtain directly the desired product. With the monohydroxy compounds, this method, which Chiang and Hartung[87] used to such advantage, is undoubtedly superior from the point of view of economy of materials and time. However, a few preliminary experiments indicated that this method was not entirely suitable for the preparation of polyhydroxy compounds. As Tröger

and Dunker[139] discovered, their products were amorphous and extremely difficult to purify, and, except for a few cases, were not obtained in the crystalline state. Therefore, it was decided to adopt the alternative method of preparing the methoxy derivatives first, and then hydrolyze them to the hydroxy compounds. The methoxystyryl compounds can be crystallized nicely from various solvents, and thus separated from the tarry materials, which are formed in Claisen condensations, even under the most favorable conditions. Any unreacted methyl ether from the subsequent hydrolysis could be separated from the hydroxy compound through the solubility of the latter in sodium hydroxide.

The prolonged treatment with hydriodic or hydrobromic acids that is required frequently to split the methoxy group, when it is contained in certain heterocycles, raised the question of what effect these forced conditions might have on the rest of the molecule. Tipson[107] exposed 2-(p-dimethylaminostyryl)-quinoline to concentrated hydrochloric acid at room temperature for fifty-five days, and then to 3 N. hydrochloric acid at the reflux temperature for three hours, and found no evidence of cleavage. As a

precautionary measure it was decided to treat 2-styryl-benzothiazole with 47% hydriodic acid (stabilized with hypophosphorous acid) in glacial acetic acid to determine if reduction or any other untoward effects might be produced. The conditions were identical with those which were intended to be used in the contemplated ether cleavages. Since the starting material was recovered unchanged, the proposed syntheses were undertaken without further concern over side-reactions during demethylation.

In the Claisen condensation of 2-methylbenzothiazole and p-anisaldehyde, a low yield (3%) resulted when piperidine was used as a catalyst. Acetic anhydride improved the yield to 58% and gave a nice clean product without excessive tar formation. The demethylation was effected by hydriodic acid in glacial acetic acid to give an easily crystallizable compound. The presence of two hydroxyl groups in the styryl group, however, presented great difficulties in the purification process. 2-(2',3'-Dihydroxystyryl)-benzothiazole could not be crystallized from any of the solvents that were tried, and was finally analyzed as an amorphous yellow powder. 2-(3',4'-Dihydroxystyryl)-benzothiazole was crystallized in an unconventional manner by

dissolving it in hot glacial acetic acid and adding the solution to an excess of water.

Several of the intermediate methoxy compounds have been prepared previously by other workers, but in lower yields. Bennett and Willis[130] obtained 2,3-di-(3',4'-dimethoxystyryl)-quinoxaline in 10% yield using a four to six-hour reflex period, and a great excess of acetic anhydride as a condensing agent. By reducing the amount of acetic anhydride to two moles, which is the stoichiometric equivalent necessary for dehydration, and increasing the reaction time to twenty-four hours, yields as high as 64% and 71% were obtained. It is very likely that an excessive amount of condensing agent lowered the reflux temperature of the reaction, and thus gave Bennett and Willis poorer yields. The same authors report 208° as the melting point for 2,3-di-(3',4'-dimethoxystyryl)-quinoxaline, which is not in agreement with the value (196-197°), obtained in this work. Therefore, the product was analyzed to determine if it might be the monosubstituted compound, but the results of the analysis indicated a distyryl compound. The recorded value may be a typographical error.

The attempted demethylations of four polymethoxy-

styryl compounds resulted in the failure to obtain a single product which analyzed correctly. This may be due to complete decomposition of the products or the presence of foreign materials from which they could not be separated. The intermediates involved are 2,6-di-(2',3'-dimethoxystyryl)-pyridine, 2,3-di-(3',4'-dimethoxystyryl)-quinoxaline, 2-(3',4'-dimethoxystyryl)-6-methoxyquinoline, and 2-(2',3'-dimethoxystyryl)-4-hydroxy-6-methoxyquinoline. Since it was shown, by experiment, that the quinoline nucleus and the styryl group were stable to conditions of ether cleavage, it is felt that the difficulty resided in the method of purification. Because these compounds could not be crystallized from any of the solvents tried, it was necessary to separate them from their parent methoxy compounds by extraction with sodium hydroxide solution. The addition of dilute acid then caused them to precipitate as very light jell-like substances, which did not settle even after standing for several days. When they were finally obtained as dry powders, analyses showed them to be non-homogeneous. None of the analyses agreed with the calculated values. It is quite possible that oxidation of the ortho dihydroxy compounds to quinoidal compounds occurred during the sodium hydroxide

extraction. The long exposure of the precipitated jells to air oxidation may also be responsible for some decomposition.

It is interesting that in compounds where there was only one hydroxyl group on the styryl residue decomposition did not occur. 2,6-Di-(p-hydroxystyryl)-pyridine and 2,3-di-(p-hydroxystyryl)-quinoxaline were purified through sodium hydroxide extraction and yet were obtained as clean products which analyzed correctly.

6-Methoxyquinaldine was prepared by two different methods. The first consisted of adding methyllithium to 6-methoxyquinoline in the conventional manner, while the second method was the reduction of 4-chloro-6-methoxyquinaldine, according to the method of Rubtsov.[162] Both of these methods have merit, and the question of preference depends largely on the availability of starting materials.

The synthesis of 2-(p-hydroxystyryl)-6-hydroxyquinoline, starting with 6-methoxyquinaldine, presented no difficulties except that the final product could not be crystallized. It was purified by dissolving in sodium hydroxide and precipitating with acid.

B. Reactions of Organolithium Compounds with Quinoline Derivatives Containing Active Hydrogen.

The addition of organolithium compounds to the azomethine linkage of 8-hydroxyquinoline was first demonstrated by Gilman, Towle and Spatz.[10] This was accomplished by adding two moles of RLi compound to one of 8-hydroxyquinoline, with the first mole of organometallic compound reacting with the hydroxyl group and the second mole adding to the azomethane linkage. Later, other investigators[141] applied this method successfully, but the yields were seldom better than 30-35%, and the method was uneconomical with respect to the amount of organometallic compound used.

In certain cases, when the organometallic compound is expensive or difficult to prepare, it is advantageous to block off the hydroxyl group by methylation. For this purpose dimethyl sulfate and sodium hydroxide is perhaps the best reagent. Although diazomethane is being used increasingly as a methylating agent, one study made by Marion and Cockburn[180b] revealed that with pyridine compounds it is not very efficient. The best yield of 2-methyl-5-methoxypyridine, that was obtained from the methylation of 2-methyl-5-hydroxypyridine with diazomethane, was 40%. A combination of methyl iodide

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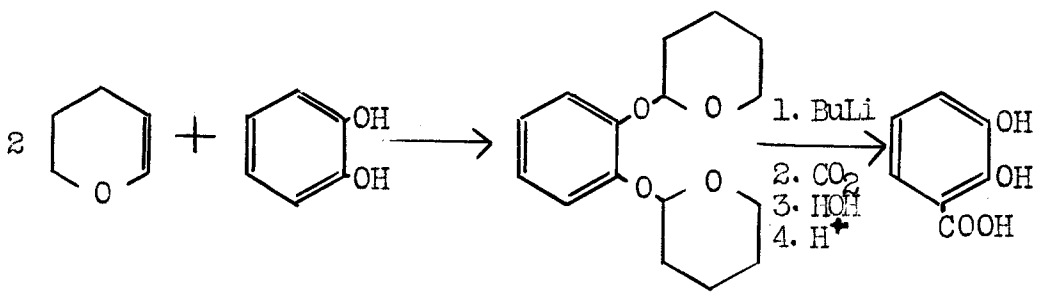
180b. Marion and Cockburn, J. Am. Chem. Soc., 71, 3402 (1949).

and potassium hydroxide gave very poor yields of 3-methoxyquinaldine, according to Tröger and Dunker.[139]

A novel method of protecting the hydroxyl group in 8-hydroxyquinoline was suggested by the work of Parham and Anderson,[167] who treated alcohols and phenols with dihydropyran in the presence of acid catalyst to form the corresponding 2-tetrahydropyranyl ethers. Subsequent reactions as hydrolysis and metalation were carried out successfully with the adduct obtained in this manner. To remove the protecting group it was merely necessary to shake the adduct with 2 N. hydrochloric acid, whereby the free alcohol or phenol was readily obtained. This method can be applied only with reactions which are effected in a basic media.



Two unsuccessful attempts were made to add 8-hydroxyquinoline to dihydropyran. In the first attempt, the usual few drops of hydrochloric acid were added as a

catalyst, but since no reaction occurred, it was inferred that its catalytic action was interfered with by forming a hydrochloride salt with the basic nitrogen of the 8-hydroxyquinoline. Therefore, in the following experiment, 8-hydroxyquinoline hydrochloride itself was treated with dihydropyran and, in addition, a few drops of acid were added to insure the presence of the necessary catalytic agent. Again, no reaction was observed. As yet, the dihydropyran reaction has not been studied very extensively and, therefore, it is difficult to ascribe any reason for this anomalous result. Two other compounds that did not form the expected acetals with dihydropyran, in a study by Hofferth,[181] are 2,4,6-tribromophenol and 2,4-dibromo-1-naphthol. The failure to obtain a reaction with 8-hydroxyquinoline is disappointing, because it would have augmented nicely the use of organometallic compounds in the syntheses of quinoline derivatives.

It is interesting to note that when the hydroxyl group is replaced by a primary amino group, anil-addition does not take place, even when an excess of organolithium compound is used. Phenyllithium and p-dimethylaminophenyllithium failed to add to

181. Hofferth, B., Doctoral Dissertation, Iowa State College, (1950).

6-methoxy-8-aminoquinoline in two experiments. An N,N-dilithio compound was formed, after the second mole of phenyllithium was added, as evidenced by Color Test I[171] being negative. The only apparent explanation for this anomalous behavior is that the red N,N-dilithio salt is so insoluble in the ether medium that further reaction with the organolithium compound is prevented. It should be pointed out, however, that in the halogen-metal interconversion of p-bromoaniline, an N,N-dilithio salt, N,N-dilithio-p-bromoaniline,[182] does undergo reaction with butyllithium to form N,N-dilithio-p-aminophenyllithium. Further speculation on the failure of organolithium compounds to add to the azomethine linkage of 6-methoxy-8-aminoquinoline led to a consideration of the electrostatic interaction of the negatively charged ions. The phenyl carbanion and the anion, formed as a result of the dissociation of N,N-dilithio-6-methoxy-8-aminoquinoline, could exert a mutual repulsion which would prevent their subsequent reaction. This idea, however, seems unlikely in the light of several other reactions which occur between ions of like charges. The halogen-metal exchange reaction of p-bromoaniline

182. Gilman and Stuckwisch, J. Am. Chem. Soc., 71, 2933 (1949).

and butyllithium[182] has already been mentioned. Also pertinent are the reactions of the lithium salts of 6-methoxy-8-acetamidoquinoline,[183] 8-hydroxyquinoline and 6-methoxy-8-(3'-diethylamino)-propylaminoquinoline[182] with organolithium compounds. Most important, perhaps, is the addition of O-lithio-o-hydroxyphenyllithium to the lithium salt of 8-hydroxyquinoline. Here a doubly charged anion reacts with another anion to form an azomethine adduct.

In connection with this theory of ionic repulsion, it is of interest to consider the coupling reactions of diazonium ions with aromatic amines and phenols. These are carried out in basic media and Alexander,[184] has pointed out that this may be necessary for two reasons. First, in an acid or neutral medium the substituted anilinium ion is of a like charge and, hence, would tend to repel the diazonium cation; second, and perhaps even more important, the resonance of the anilinium ion deactivates the aromatic nucleus and decreases its nucleophilic character. The same line of reasoning can be used to explain the coupling reactions with phenols.

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183. Elderfield, et al., J. Am. Chem. Soc., 68, 1589 (1946).

184. Alexander, "Principles of Ionic Organic Reactions", John Wiley and Sons, Inc., New York, 1950, p. 268.

There is a greater tendency for the diazonium ion to react with the oppositely charged phenoxide ion than with the free phenol. Furthermore, due to the greater resonance of the phenoxide ion there is an increased density of electrons in the ortho and para positions which favors reaction with the electrophilic diazonium ion. Therefore, due to the contributing factor of a heightened resonance effect in a basic medium, it is difficult to ascribe the greater reactivity of the free base and of the phenoxide ion entirely to a favorable interionic interaction.

Elderfield[183] also was unable to add phenyllithium to 6-methoxy-8-aminoquinoline, but he found that the secondary amino group in 6-methoxy-8-(3'-diethylaminopropylamino)-quinoline ("Plasmocide") did not interfere with addition to the azomethine linkage, provided a sufficient amount of phenyllithium was used. It is very likely that in this case a monolithium salt forms, which is soluble enough to react further with phenyllithium in an anil- addition.

If the amino group in 6-methoxy-8-aminoquinoline is first acetylated and then treated with two moles of phenyllithium, reaction occurs to give a 47% yield of 2-phenyl-6-methoxy-8-acetamidoquinoline.[183] Here again

the monolithium salt may be soluble enough to permit anil-addition. The N-acetyl derivative of "Plasmocide" underwent both anil-addition and deacetylation when treated with phenyllithium.[183] In one experiment, methyllithium, under the same conditions, did not form the expected 2-methyl-6-methoxy-8-acetamidoquinoline. This result is somewhat incongruous, but another attempt should be made before any final decision is reached on the possibility of success with this reaction. This is particularly true because methyllithium was added to 8-hydroxyquinoline in a 2:1 mole ratio to give 8-hydroxyquinaldine in a 37.6% yield. This latter reaction is another example of the advantage of the organometallic technique over ring closure methods[172] in the syntheses of 2-substituted quinoline compounds. 8-Hydroxyquinaldine has been prepared previously by the cyclization of o-aminophenol and crotonaldehyde.[172] The subsequent isolation and purification of the product was both tedious and time-consuming, with the overall yield less than 28%.

8-Hydroxyquinaldine exhibits properties which promise its use as an analytical reagent.[141] Possibly, because of the steric effect of the methyl group, it shows greater selectivity as a chelating agent than does

8-hydroxyquinoline. Aluminum ions, which react with 8-hydroxyquinoline, are not precipitated by the 2-substituted compound. This difference in behavior has been utilized to separate zinc from magnesium, from aluminum and from magnesium and aluminum. A solution containing zinc and aluminum ions, for example, can be treated with 8-hydroxyquinaldine to precipitate the zinc complex salt, which may be weighed directly or determined volumetrically by titration with potassium bromate. 8-Hydroxyquinoline is then added to the filtrate, whereby the complex salt of aluminum is separated.

The observation that a methyl group in the 2-position prevented the complexation of aluminum, while a methyl group in the 3- or 4- position did not exert this effect, suggested that the presence of groups of larger size than methyl might impart even greater selectivity. Therefore, Phillips[141] prepared a series of eleven variously substituted 2-aryl- and 2-styryl-8-hydroxyquinolines. Tests with a few representative ions, however, did not show any improvement in selectivity.

A variation in structure that may bring about the desired steric effect is a 2-(o-hydroxyphenyl)-quinoline with a substituent in the 8- position. The o-

hydroxyphenyl group is properly situated with respect to the nitrogen atom to form a six-membered cyclic complex with metal ions, and a peri substituent of adequate size may interfere with chelation with the larger ions. The substituent could either be an alkyl or aryl group or an ether prepared from the readily available 8-hydroxyquinoline. 2-(o-Hydroxyphenyl)-8-methoxyquinoline, which is described here, may well fit these specifications.

Several new hydroxy compounds were prepared with metal-chelating properties. 2-(o-Hydroxyphenyl)-6-hydroxyquinoline was synthesized by adding O-lithio-o-hydroxyphenyllithium to 6-methoxyquinoline, followed by hydrolysis of the ether group. It will be interesting to see if this compound, which may be considered an "open model" of a derivative of 1-hydroxyacridine, possesses antiseptic properties. The presence of the phenolic hydroxyl group in the 6- position may augment its bactericidal activity.

2-(o-Hydroxyphenyl)-8-hydroxyquinoline was synthesized in two ways. The first method consisted of treating 8-methoxyquinoline with O-lithio-o-hydroxyphenyllithium and then removing the methyl group by hydriodic acid cleavage. It appears that the presence

of the o-hydroxyphenyl group must hinder, in some way, the ether cleavage, because it was necessary to reflux the sol tion for twenty-four hours, after two previous attempts at four and five hours failed to remove the methyl group. Phillips[141] found it was not possible to cleave the 8-methoxy group of 2-(phenyl)-, 2-(o-methoxyphenyl-, 2-(m-methoxyphenyl- and 2-(p-methoxyphenyl)-8-methoxyquinoline with hydriodic acid, hydrobromic acid or potassium hydroxide and ethylene glycol under ordinary pressures. 8-Methoxyquinoline itself, however, has been reported to have been hydrolyzed in four hours with aqueous hydrobromic acid[185] (d. = 1.5).

A more direct synthesis of 2-(o-hydroxyphenyl)-8-hydroxyquinoline was the addition of O-lithio-o-hydroxyphenyllithium to the lithium salt of 8-hydroxyquinoline, followed by hydrolysis of the adduct.

The object of the attempted preparation of 2-n-hexyl-6-methoxyphenyl)-pyridine was to obtain 2-n-hexyl-6-(o-hydroxyphenyl)-pyridine, through the subsequent

185. King and Sherred, J. Chem. Soc., 415 (1942).

hydrolysis of the methyl ether. A molecule with this structure potentially possesses characteristics which have proved to be valuable in other antiseptic agents. The o-hydroxyphenyl group, in conjunction with the nitrogen of the pyridine ring, has chelating properties. In addition, the hexyl group should impart a certain amount of surface activity to the molecule, which heretofore has not been present, as such, in chelate compounds that exhibit antibacterial action.

The failure of the organolithium compound to add to 2-n-hexylpyridine is difficult to explain, unless metalation of the α-methylene group occurred instead. Some basis for this assumption is the reported metalation of 2-n-amylpyridine with phenyllithium by refluxing for two hours.[186] The 2-n-(α-lithioamyl)-pyridine, thus formed, was treated with acetonitrile to give, subsequent to hydrolysis, 3-(2-pyridyl)-2-heptanone in 10% yield. The metalation of 2-n-propyl-3,5-diethylpyridine has been accomplished, also with phenyllithium, by Haskelberg.[187] The conditions of the experiment were not given. It must not be inferred from the above that metalation occurs invariably when a 2-alkylpyridine is

186. Burger and Ullyot, J. Org. Chem., 12, 342 (1947).

187. Haskelberg, Chem. and Ind., 13, 261 (1935).

reacted with an organolithium compound. When 2-n-butylpyridine was treated with n-butyllithium anil-addition took place to form 2,6-di-n-butylpyridine.[31] Tsuda[188] similarly added n-butyllithium to 2-n-propylpyridine. Each of these addition reactions was carried out at room temperature and then heated in sealed tubes, presumably to split out lithium hydride.

There was no apparent evidence of reaction, at first, when o-methoxyphenyllithium was added to 2-n-hexylpyridine. An anil-addition almost always entails an immediate color change, a reflux and usually the precipitation of the highly colored adduct. None of these occurrences were observed. But after the mixture was refluxed, a gradually darkening color developed, reminiscent of picolyllithium and quinaldyllithium. From the limited evidence, it seems that at room temperature neither metalation nor anil-addition was obtained. After refluxing the solution, however, some metalation may have occurred. Ordinarily, the lateral metalation of compounds like picoline and quinaldine with phenyllithium occurs instantaneously. The relative slowness with which higher members of the series, such as n-amyl- and n-hexylpyridine, undergo α-metalation can be

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

attributed to the electron-repelling effect of the alkyl group. The activating influence of the azomethine linkage is thus somewhat nullified, and this in turn decreases the acidity of the -hydrogen atoms.

V. SUMMARY

1. The antibacterial activity of phenol derivatives has been briefly reviewed.
2. A discussion has been made on the mode of action of antiseptic agents.
3. The aldol and Claisen reactions of heterocycles, containing active methyl groups, have been discussed in some detail.
4. Some mono- and di-hydroxystyryl derivatives of pyridine, quinoline, benzothiazole and quinoxaline were prepared.
5. Reactions of organolithium compounds with quinoline derivatives containing active hydrogen were studied. When the hydroxyl group was present in the 8-position in quinoline, anil-addition took place readily. However, a primary amino group in the 8-position prevented addition to the azomethine linkage, presumably, because of the great insolubility of the N,N-dilithio salt.
6. Several new metal-chelating compounds were prepared. These are to be assayed as anti-bacterial agents, and also investigated for their possible utilization as reagents for inorganic analysis.

7. Two unsuccessful attempts were made to add 8-hydroxyquinoline to dihydropyran for the purpose of blocking off the hydroxyl group to prevent its interference in subsequent anil-addition reactions.
8. o-Methoxyphenyllithium was found not to add to 2-n-hexylpyridine. It is possible that metalation of the side-chain occurred instead.