## Summary

1. N-Succinyl-N-ethyl-3-bromomesidine has been prepared and resolved by the method previously described for the N-methyl compound. The half-life of the N-methyl was nine hours, of the N-ethyl twenty-eight hours, in boiling *n*-butanol, thus demonstrating the increased steric effect of the ethyl group.

2. 5-Methoxy-4-N-succinyl-4-methylamino-1,-3-dimethylbenzene was prepared and resolved. Its half-life was two and seven-tenths hours in boiling anhydrous methyl acetate (b. p. 56°) as compared with nine hours in boiling *n*-butanol for the half-life of N-succinyl-N-methyl-3-bromomesidine. The methoxyl has a much smaller steric effect than the methyl.


URBANA, ILLINOIS RECEIVED AUGUST 9, 1941

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

# Syntheses in the Quinoline Series. II. Some Derivatives of 4-Methylquinoline and a Study of their Structures

BY OSCAR H. JOHNSON[1] AND CLIFF S. HAMILTON

This investigation was undertaken with the object of introducing into the quinoline nucleus chemical groups known to have therapeutic activity. It was felt that if several of these groups could be introduced into one molecule in various combinations, an antimalarial of more general use or greater activity than those now known might be achieved.

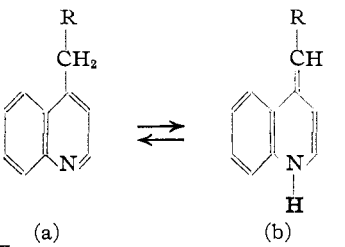
From the readily accessible acetoacetanilide were prepared in turn 2-hydroxy-4-methyl-, 2-chloro-4-methyl- and 4-methylquinoline (lepidine), following the procedures of Mikhailov.[2] Busch and Koenigs[3] nitrated lepidine to give as the major product a compound assumed to be 8-nitrolepidine. In this investigation a similar nitration was performed and the major product was shown to be 8-nitrolepidine by catalytic reduction to the amine followed by conversion to 8-chlorolepidine by a Gattermann diazo reaction. An authentic sample of 8-chlorolepidine was prepared from 2,8-dichlorolepidine.

8-Nitrolepidine was oxidized by selenium dioxide to 8-nitroquinoline-4-aldehyde.[4] This was condensed with nitroethane in a fashion similar to that employed by Kwartler and Lindwall[5] for the reaction of nitromethane with certain quinoline aldehydes. The α-nitroethyl-4-(8-nitroquinolino)-methanol thus obtained was reduced by catalytic means to α-aminoethyl-4-(8-aminoquinolino)-methanol. This compound has a side chain containing a secondary alcohol group and a basic nitrogen atom in the same relative positions as in quinine in addition to the 8-amino group found in the quinoline base from which plasmochin is derived.

The Grignard reaction was also investigated as a means for securing the secondary alcohol group of the quinine type. Quinoline-4-aldehyde was prepared by the Kwartler and Lindwall[5] method. This gave α-methyl-4-quinolinemethanol when treated with methylmagnesium iodide by standard Grignard procedure.

While this alcohol could not be dehydrated with formic acid and was unaffected by 48% aqueous hydrobromic acid, it did react readily with thionyl chloride to give 4-(α-chloroethyl)-quinoline. This compound was very resistant to alkaline hydrolysis and to conversion to 4-vinylquinoline.

The high reactivity of the alpha hydrogen atoms in the alkyl groups of certain homologs (a) of quinoline ($RCH_2$ group in the 2- or 4-position) has been explained[6] by the assumption of a tautomeric shift of one hydrogen atom to the tertiary nitrogen with a redistribution of double bonds to give a methylene form (b).




(a) (b)

(1) Parke, Davis and Company Fellow.

(2) Mikhailov, *J. Gen. Chem.* (U. S. S. R.), **6**, 511 (1936); *Chem. Abs.*, **30**, 6372 (1936).

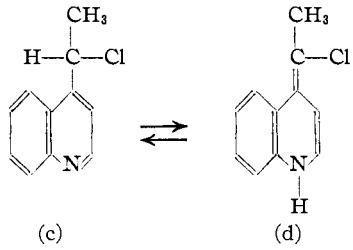
(3) Busch and Koenigs, *Ber.*, **23**, 2687 (1890).

(4) Koenigs, *ibid.*, **31**, 2364 (1898).

(5) Kwartler and Lindwall, THIS JOURNAL, **59**, 524 (1937).

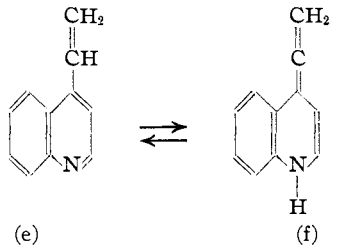
(6) Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, 1937, p. 558.

If a similar tautomerism occurred with 4-(α-chloroethyl)-quinoline, (c) there would result (d) in which the chlorine atom is held by an unsaturated carbon atom. Such a chloride is known to be quite stable to hydrolysis.



(c) (d)

In the case of 4-vinylquinoline (e) there would result a form (f) containing a system of cumulative double bonds.



(e) (f)

The high activity of 4-vinylquinoline as shown by its ability to add alcohols[7] indicates that such a system of twinned double bonds may exist. The addition of alcohols is suggestive of the similar addition to the cumulative system in allene.

Several workers[8,9] have found that the conjugation of an aromatic nucleus with an ethylenic linkage may give an active diene system. 4-Vinylquinoline was prepared by the method of Meisenheimer.[7] It reacted with maleic anhydride at 100° with rapid evolution of carbon dioxide. Lepidine and pyridine reacted similarly. Hence the reaction of 4-vinylquinoline with maleic anhydride probably involves the quinoline nucleus rather than the conjugated system terminating in the ethylenic linkage.

ω-Bromoacetoacetanilide and 2-hydroxy-4-(bromomethyl)-quinoline were prepared by the method of Chick and Wilsmore.[10] The halogen in the latter compound resisted hydrolysis when refluxed with 80% aqueous acetic acid. It reacted, however, with sodium methylate, with aniline and with *p*-anisidine to give the expected products. 2-Hydroxy-4-(methoxymethyl)-quinoline thus prepared was converted to 2-chloro-4-(methoxymethyl)-quinoline.

(7) Meisenheimer, *Ann.*, **420**, 190 (1919).
(8) Wagner-Jauregg, *ibid.*, **491**, 1 (1931).
(9) Cohen and Warren, *J. Chem. Soc.*, 1315 (1937).
(10) Chick and Wilsmore, *ibid.*, **97** 1981 (1910).

## Experimental

**8-Nitrolepidine.**—Sixty-five grams of lepidine dissolved in 180 g. of concd. sulfuric acid was nitrated at −5° by slow addition of a mixture of 75 g. of fuming nitric acid (d. 1.5) and 90 g. of concentrated sulfuric acid. The mixture was stirred constantly and held at 0° for two hours after all of the nitric acid had been added, then at room temperature for five hours. It was then poured on ice and the solution made alkaline with ammonium hydroxide to precipitate the product. After filtering and washing the solid, it was purified by two fractional recrystallizations from ethanol with application of charcoal; yield 44 g. (52%); m. p. 126°. Busch and Koenigs[3] reported m. p. 126°.

**8-Aminolepidine.**—Five grams of 8-nitrolepidine was dissolved in 100 cc. of ethanol at 75° and reduced with hydrogen at 45 pounds pressure in the presence of Raney nickel catalyst.[11] When the reduction was complete, the catalyst was removed by filtration, the filtrate concentrated and then diluted with water. The product thus obtained was recrystallized from benzene to give 3.5 g. (83% yield) of monoclinic plates; m. p. 84°.

*Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C 76.00, 76.02; H, 6.51, 6.43.

**8-Chlorolepidine. (1) From 8-Aminolepidine.**—One gram of 8-aminolepidine was dissolved in 7 cc. of concd. hydrochloric acid. It was treated at 0° with a solution of 0.4 g. of sodium nitrite in 2 cc. of water and when diazotization was complete, 1.5 g. of copper powder suspended in 5 cc. of 20% hydrochloric acid was added. After a few minutes, the reaction was heated to boiling, made alkaline by addition of ammonium hydroxide and cooled. The solid which separated was recrystallized from an ethanol–water mixture; yield 0.2 g. (20%); m. p. 107°.

**(2) From 2,8-Dichlorolepidine.**—Two grams of 2,8-dichlorolepidine with 2 g. of granulated tin, 35 cc. of concentrated hydrochloric acid and 20 cc. of water was heated at 80° for twelve hours with constant stirring. Upon cooling, the stannous chloride addition product settled out and was filtered off, dissolved in warm water and the solution saturated with hydrogen sulfide. After removing the stannous sulfide by filtration, the filtrate was made alkaline with ammonium hydroxide and the precipitate recrystallized from an ethanol–water mixture to give triclinic needles; yield 0.9 g. (54%); m. p. 107°. A mixed melting point with a sample from (1) showed no depression.

*Anal.* Calcd. for $C_{10}H_8NCl$: Cl, 19.96. Found: Cl, 19.70, 19.62.

**8-Nitroquinoline-4-aldehyde.**—Five and one-half grams of 8-nitrolepidine and 3.5 g. of selenium dioxide were dissolved in 75 cc. of ethanol and refluxed for eight hours. After treating with charcoal, the hot solution was filtered and the ethanol removed by distillation. The residue was recrystallized twice from toluene to give 3.1 g. (53% yield) of the aldehyde; m. p. 175° as reported by Koenigs,[4] who prepared this compound by another method.

**α-Nitroethyl-4-(8-nitroquinolino)-methanol.**—Two and one-half grams of 8-nitroquinoline-4-aldehyde was dis-

(11) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

solved in 100 cc. of absolute ethanol and to this was added 3 cc. of nitroethane and 15 drops of diethylamine at room temperature. After standing for three days, the precipitated product was filtered off and washed with ethanol. It was found to be pure by analysis. Attempts to recrystallize the substance led to decomposition. There was obtained 2.75 g. (80% yield) of monoclinic plates; m. p. 180–190° dec. (depending upon the rate of heating).

*Anal.* Calcd. for $C_{12}H_{11}O_5N_3$: C, 51.99; H, 4.00. Found: C, 51.84, 51.63; H, 3.92, 3.82.

**α-Aminoethyl-4-(8-aminoquinolino)-methanol.**—Two grams of 8-nitro-α-nitroethyl-4-quinolinemethanol was suspended in 30 cc. of methanol and reduced with hydrogen at 40 pounds pressure in the presence of Raney nickel catalyst. After the reduction was complete the catalyst was removed and the filtrate evaporated to dryness. The substance was purified by dissolving in cold methanol, thus separating it from the relatively insoluble impurities, applying charcoal and filtering, and evaporating the filtrate to dryness. This gave 0.8 g. (51% yield) of an amorphous brown powder of m. p. 82–84°.

*Anal.* Calcd. for $C_{12}H_{15}ON_3$: C, 66.34; H, 6.96. Found: C, 66.34, 66.34; H, 6.87, 6.64.

**α-Methyl-4-quinolinemethanol.**—A Grignard solution was prepared from 50 g. of methyl iodide and 8.6 g. of magnesium turnings in 100 cc. of ethyl ether. To the cooled mixture was added 42 g. of quinoline-4-aldehyde in 100 cc. of ether and stirring was continued for one-half hour after addition was complete. The complex was hydrolyzed by slow addition of a solution of ammonium chloride. After distilling with steam to remove the unreacted aldehyde, the mixture was evaporated to dryness and the product extracted with hot toluene. Concentration of this extract gave 25.5 g. (55% yield) of tetragonal prisms, m. p. 125°.

*Anal.* Calcd. for $C_{11}H_{11}ON$: N, 8.09. Found: N, 7.92, 7.98.

The picrate of the alcohol precipitated from ethanol has a melting point of 181°.

Attempts to dehydrate this alcohol by means of anhydrous formic acid were unsuccessful at temperatures up to 150°. At higher temperatures the formic acid caused reduction to 4-ethylquinoline which was identified by its chloroplatinic acid derivative.[12] Treatment of the alcohol with 48% aqueous hydrobromic acid at temperatures up to 100° resulted in no reaction.

**4-(α-Chloroethyl)-quinoline.**—Five grams of α-methyl-4-quinolinemethanol in 10 cc. of ethyl ether was treated with 10 cc. of thionyl chloride. When the vigorous reaction had ceased the mixture was heated on a water-bath for one hour, then poured on ice. The aqueous solution was made alkaline with ammonium hydroxide and extracted with ether. Upon drying with anhydrous potassium carbonate and evaporating the solvent there was obtained 4.2 g. of a brown liquid (70% yield). The picrate crystallized from hot aqueous solution and was recrystallized from benzene; m. p. 180°.

*Anal.* (picrate): Calcd. for $C_{17}H_{13}O_4N_4Cl$: Cl, 8.02. Found: Cl, 8.02, 7.97.

(12) Reher, *Ber.*, **19**, 2999 (1886).

The halogen in this compound was resistant to hydrolysis in a boiling water–dioxane solution of sodium hydroxide; attempts to convert it to 4-vinylquinoline by refluxing with potassium hydroxide in acetone, as well as in higher boiling solvents, were only partially successful.

**2-Hydroxy-4-(methoxymethyl)-quinoline.**—To a solution of 9 g. of sodium in 100 cc. of methanol was added 1.7 g. of 2-hydroxy-4-(bromomethyl)-quinoline. After refluxing four hours the alcohol was distilled and the residue dissolved in water. The product was precipitated by acidification with hydrochloric acid and recrystallized from ethanol and benzene to give 10.5 g. (78% yield) of tetragonal plates; m. p. 171°.

*Anal.* Calcd. for $C_{11}H_{11}O_2N$: N, 7.40. Found: N, 7.40, 7.42.

**2-Chloro-4-(methoxymethyl)-quinoline.**—A mixture of 11 g. of 2-hydroxy-4-(methoxymethyl)-quinoline and 20 cc. of phosphorus oxychloride was heated at 130° for one hour, then poured on ice, neutralized with ammonium hydroxide and the product purified by steam distillation. A low yield of white tetragonal rods was obtained; m. p. 64°.

*Anal.* Calcd. for $C_{11}H_{10}ONCl$: N, 6.74. Found: N, 6.62, 6.62.

**2-Hydroxy-4-(anilinomethyl)-quinoline.**—A mixture of 20 cc. of aniline and 10 g. of 2-hydroxy-4-(bromomethyl)-quinoline was refluxed five hours, then cooled and made alkaline with ammonium hydroxide. The excess aniline was removed by steam distillation and the residual solid dissolved in warm 6 *N* hydrochloric acid and treated with charcoal. The cooled filtrate was made alkaline with ammonium hydroxide and the precipitated solid was recrystallized from an ethanol–water mixture to give 8 g. (87% yield) of a white, amorphous powder; m. p. 238–240°.

*Anal.* Calcd. for $C_{16}H_{14}ON_2$: N, 11.19. Found: N, 11.08, 10.83.

**2-Hydroxy-4-(*p*-anisylaminomethyl)-quinoline.**—A mixture of 4.8 g. of 2-hydroxy-4-(bromomethyl)-quinoline, 5 g. of *p*-anisidine and 25 cc. of *n*-amyl alcohol was refluxed for four hours. After diluting with petroleum ether, the solid was filtered and washed well with water. Recrystallization from a dioxane–water mixture gave 4 g. (64% yield) of tan monoclinic plates; m. p. 206–207°.

*Anal.* Calcd. for $C_{17}H_{16}O_2N_2$: N, 9.99. Found: N, 9.81, 9.84.

## Summary

1. The major product from the nitration of lepidine was shown to be 8-nitrolepidine.

2. 8-Nitroquinoline-4-aldehyde, prepared by a new method, was condensed with nitroethane and the product reduced to give a substance of possible value as an antimalarial.

3. Quinoline-4-aldehyde was found to undergo a normal Grignard reaction to give a secondary alcohol which was difficult to dehydrate and easy to reduce. The chloride derived from this alcohol was very difficult to hydrolyze. Some of these unusual chemical properties were interpreted in terms of possible molecular structures.

4. 4-Vinylquinoline, lepidine and pyridine were found to react with maleic anhydride with evolution of carbon dioxide.

5. Several new quinoline compounds were prepared from 2-hydroxy-4-(bromomethyl)-quinoline.

LINCOLN, NEBRASKA RECEIVED JULY 28, 1941

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

# Syntheses in the Quinoline Series. III. The Nitration of 2-Chloro-4-methylquinoline and the Preparation of Some 2-Hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines

BY OSCAR H. JOHNSON[1] AND CLIFF S. HAMILTON

The introduction of a hydroxy group in the 2-position of certain pyridine and quinoline arsonic acids has been shown to have a beneficial effect upon the activity of these compounds as therapeutic agents.[2] Hence it seemed of interest to study the effect of such a group upon the antimalarial activity of 8-(dialkylaminoalkyl)-aminoquinolines.

Nitration of 2-chloro-4-methylquinoline gave the 8-nitro derivative as the major product together with some of the 6-nitro isomer. The structures were proved by conversion to known quinoline derivatives and comparison with authentic samples. 2-Chloro-4-methyl-8-nitroquinoline was reduced to the corresponding amine with the aid of Raney nickel catalyst. Treatment with sodium methylate then gave 2-methoxy-4-methyl-8-aminoquinoline which was found satisfactory for side chain condensations. While seeking other means for obtaining 2-methoxy-4-methyl-8-aminoquinoline, several new quinoline compounds were prepared.

The hydrobromides of β-N-diethylaminoethyl bromide and γ-N-diethylaminopropyl bromide were prepared by application of the method of Cortese.[3] Condensation of these halides with 2-methoxy-4-methyl-8-aminoquinoline followed by cleavage of the methoxy group gave the desired 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines. Condensation of the same quinoline amine with quinoline-4-aldehyde gave the expected anil.

## Experimental

### Nitration of 2-Chloro-4-methylquinoline and Separation of the Products

A mixture of 140 cc. of concentrated sulfuric acid and 80 cc. of fuming nitric acid (d. 1.5) was cooled to −5°. To this was added, with mechanical stirring and over a two-hour period, 50 g. of 2-chloro-4-methylquinoline. The mixture was allowed to stand at room temperature for two hours, then poured on ice and the solid product separated by filtration and washed well with ammonium hydroxide and with water.

In order to separate the isomeric products, the crude material was extracted with five 250-cc. portions of hot ethanol. The combined extract was diluted with water and filtered. This solid was then recrystallized from benzene to give 38 g. (63% yield) of white hexagonal needles, m. p. 135°. This was found to be **2-chloro-4-methyl-8-nitroquinoline.**

*Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: Cl, 15.92. Found: Cl, 16.02, 16.01.

The residue from the alcohol extraction was recrystallized from benzene to give 6.5 g. of white hexagonal needles (12% yield) melting at 212–213°. This was identified as **2-chloro-4-methyl-6-nitroquinoline.**

*Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: Cl, 15.92. Found: Cl, 15.71, 15.58.

### Structure Proof of the Nitration Products

**2-Chloro-4-methyl-6-nitroquinoline.**—A mixture of 29 g. of 2-hydroxy-4-methyl-6-nitroquinoline[4] and 50 cc. of phosphorus oxychloride was heated under reflux on an oil-bath for one hour. The mixture was poured on ice and the solution neutralized with ammonium hydroxide. The solid which separated was recrystallized from benzene to give 28.5 g. (90% yield) of white hexagonal needles, m. p. 212–213°. Balaban[4] reported a melting point of 207° for this compound. A mixed melting point with the minor product of the nitration of 2-chloro-4-methylquinoline showed no depression.

**2-Chloro-4-methyl-8-aminoquinoline.**—Eight grams of 2-chloro-4-methyl-8-nitroquinoline, the predominant isomer from the nitration of 2-chloro-4-methylquinoline, was dissolved in a mixture of equal portions of dioxane and methanol at 50° and reduced with the aid of Raney nickel catalyst and mechanical shaking. It was necessary to add fresh catalyst and reheat to 50° twice in order to complete the reduction. The catalyst was filtered from the warm solution and the filtrate concentrated and diluted with water to give the product which was recrystallized from ethanol giving 5.7 g. (83% yield) of monoclinic rods, m. p. 102°.

(1) Parke, Davis and Company Fellow.
(2) Binz and Rath, *Biochem. Z.*, **203**, 218 (1928).
(3) Cortese, THIS JOURNAL, **58**, 191 (1936).
(4) Balaban, *J. Chem. Soc.*, 2346 (1930).