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SOME PROBLEMS IN THE SYNTHESIS OF AN ANTIMALARIAL INTERMEDIATE

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INTRODUCTION

Intensive research carried out in this country during World War II and the years following showed the marked antimalarial activity of 4-amino-7-chloroquinoline derivatives. The ready preparation of these compounds from 4,7-dichloroquinoline led to much investigation of new procedures for the synthesis of this intermediate. Several preparations have been developed but a shorter, more economical method remains desirable. Although the purpose of this investigation was to develop a new method of synthesizing 4,7-dichloroquinoline, a large part of the work has been concerned with the preparation of intermediate compounds and derivatives of 4,7-dichloroquinaldine. Some of these are new.

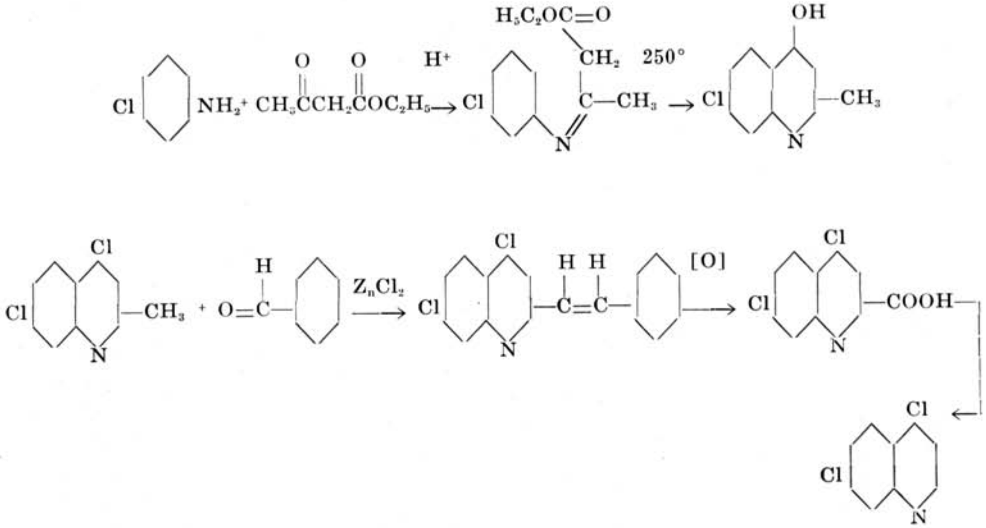
Since, in previous syntheses, one of the principal disadvantages had been the formation of a mixture of isomers in the step involving ring closure, a likely road to the compound seemed to lie in Price, Leonard and Reitsema's (1946:1256) method of condensation of *m*-chloroaniline with acetoacetic ester in the presence of a few drops of concentrated hydrochloric acid as catalyst followed by ring closure in boiling Dowtherm A. Although there is a possibility of the formation of the 5- and 7- isomers in this reaction, only the 7- is formed and this is 70% yield.

After replacing the 4-OH by means refluxing with phosphorus oxychloride in the manner of Ainley and King (1938:73), there seemed to be three possible routes to 4, 7-dichloroquinoline from 4, 7-dichloroquinaldine: 1) direct oxidation to convert the methyl group to -COOH followed by decarboxylation; 2) condensation with an aldehyde to form an unsaturated compound with subsequent oxidation to the acid and decarboxylation; and 3) halogenation of the methyl group followed by hydrolysis and decarboxylation.

RESULT OF THE STUDY

Direct oxidation of 4, 7-dichloroquinaldine using potassium permanganate in hot pyridine according to the manner of Ainley and King (1938:72) produced no apparent effect on the compound.

Condensation with benzaldehyde using the essential method of Rabe (1931:2487), heating in an open flask in the presence of zinc chloride at a temperature of 105°, for 7.5 hours resulted in average 62% yields of the 2-styryl compound (m.p.126°). This, when oxidized by potassium permanganate in cold acetone formed 4,7-dichloroquinaldic

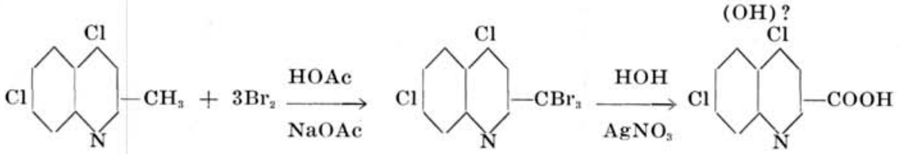


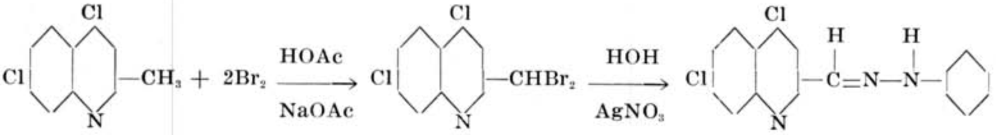
acid (m.p.183°) which, upon decarboxylation in boiling Dowtherm A according to the method of Surrey (1946:113), produced quantitative yields of 4, 7-dichloroquinoline (m.p. 83-84°).

However, since a more economical method was sought and benzaldehyde is expensive, similar condensations were tried with formaldehyde and acetaldehyde. The former resulted in polymerization and the latter in no identifiable product but considerable amounts of the starting materials.

Bromination of the 4, 7-dichloroquinaldine in the presence of benzoyl peroxide, phosphorus oxychloride or ultra violet light, all resulted in very good yields of the ∂-tribromo-derivative of 4, 7-dichloroquinaldine. The method of Hammick (1923:2882) was used. In a three-necked, round-bottom flask, fitted with a condenser, calcium chloride tube, mechanical stirrer and dropping funnel, were placed 27.5 ml. of glacial acetic acid, 11.8 gms. of anhydrous sodium acetate, and 5 gms. of 4, 7-dichloroquinaldine. The mixture was heated in a water bath at 70-75°, and 3.7 ml. of bromine in 18 ml. of glacial acetic acid were added from the dropping funnel during 20 minutes. The temperature of the bath was raised to 90-95° and heating was continued for one hour. The reaction mixture was allowed to stand overnight and then was filtered. The white solid so obtained was triturated with 200 ml. of water, the mixture filtered, and the solid collected and dried. The product weighed 9.5 gms. (m.p. 110-116°). This represents an 89% yield. Two recrystallizations from 95% ethyl alcohol raised the melting point to 143°. (Analysis: $C_{10}H_4N$ Cl_2Br_3 : Calculated: C 26.7, H 0.89, N 3.12. Found: C 25.76, H 0.87, N 3.29).

Hydrolysis by means of refluxing for four hours with silver nitrate as suggested by Krahler and Burger (1942) resulted in low yields of an





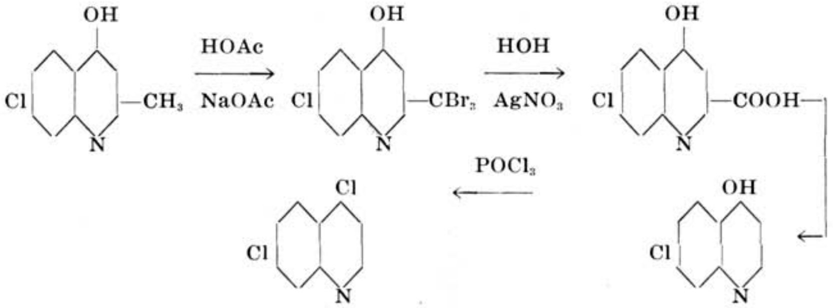
acid with carbon, hydrogen and nitrogen content very close to that of 4, 7-dichloroquinaldic acid. (Analysis: $C_{10}H_5O_2N\ Cl_2$: Calculated: C 49.6, H 2.08, N 5.70. Found: C 49.1, H 2.30, N 6.00). However, the melting point (245-248°) is much closer to that of 4-OH-7-Cl-quinaldic acid (m.p. 277°).

This posed the question as to whether or not the 4-Cl had been removed by the silver nitrate hydrolysis. Decarboxylation of the acid produced a small amount of white solid (m.p. 278°) which corresponds to the melting point of 4-0H-7-Cl-quinoline (m.p. 277-279°) and also indicates that the 4-Cl has probably been removed.

As a further test to determine the position of the bromine and to see whether or not the 4-Cl had retained its position, the dibromo product (m.p. 190°) was prepared in the same manner as the tribromo derivative. (Analysis: $C_{10}H_5N\ Cl_2Br_2$: Calculated: C 32.46, H 1.36, N 3.78. Found: C 32.82, H 1.33, N 3.90). Silver nitrate hydrolysis of the dibromo derivative led to the formation of low yields of 4, 7-dichloroquinaldehyde (m.p. 153-155°) which was converted directly to the corresponding phenylhydrazone (m.p. 210-213°) according to the method of Shriner and Fuson (1948:68). (Analysis: $C_{16}H_{11}N_3Cl_2$: Calculated: C 60.77, H 3.50, N 13.29. Found: C 60.60, H 3.60, N 13.20). Further work is being done to increase the yields and to determine the exact nature of the hydrolysis products.

Because the 4-Cl seems to be affected by the silver nitrate and because the 4-chloro compounds are quite soluble and difficult to isolate, a similar investigation is being carried out to effect the same reactions on the 4-OH-7-Cl-quinaldine. These compounds are more stable and much less soluble than the corresponding 4-Cl compounds.

Quantitative yields of the tribromo derivative of 4-OH-7-Cl-quinaldine (m.p. 326°) have been produced. Attempts are being made to hydrolyze the bromination product to determine the difference between the effect of the 4-OH and the 4-Cl. Should the hydrolysis of the tribromo derivative of the 4-OH compound prove to be more readily accomplished, the replacement of the 4-OH by -Cl could easily be effected by the action of phosphorus oxychloride on the decarboxylation product.



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