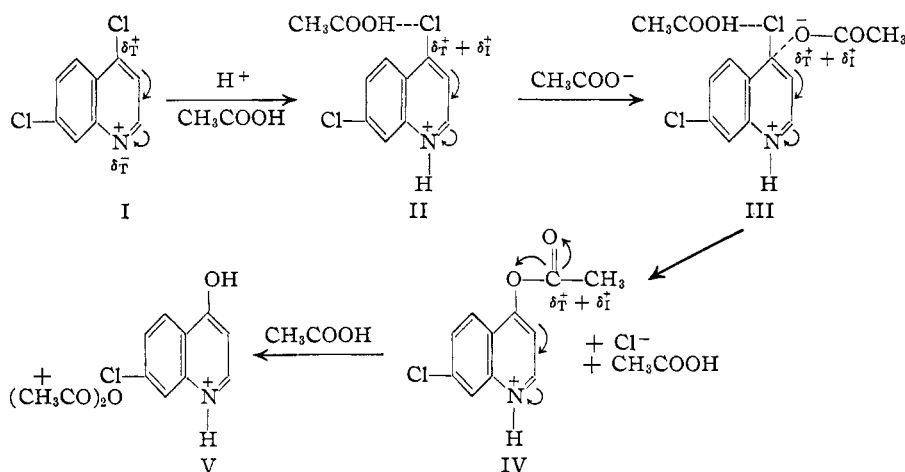


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## The Reaction of 4,7-Dichloroquinoline with Acetic Acid

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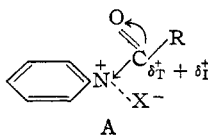
In the course of our work on the condensation of 4,7-dichloroquinoline (I) with various diamines, it was observed that when acetic acid was employed in the reaction some 7-chloro-4-hydroxyquinoline (V) was formed. Further investigation showed that 4,7-dichloroquinoline reacts readily with glacial acetic acid under anhydrous conditions to give 7-chloro-4-hydroxyquinoline hydrochloride. Some of the results of the present work are tabulated in Table I. On the basis of these data the formation of V can be formulated in the following manner



The normal activation ( $\delta_T^+$ ) of the 4-carbon atom is enhanced ( $\delta_I^+$ ) by protonization of the ring nitrogen as well as by solvation of the chlorine atom by acetic acid. A nucleophilic attack by acetate ion results in a loss of chloride ion with the formation of IV. The latter is a powerful acylating agent and reacts with a molecule of acetic acid (or acetate ion if available) to form V and acetic anhydride.<sup>1</sup>

Experimental evidence in support of the proposed mechanism was obtained by semi-quantitative methods. When a large excess of a tertiary

(1) A somewhat related example is the formation of acid anhydrides by the action of moisture (Wedekind, *Ber.*, **34**, 2070 (1901)) or organic acids (Tschitschibabin, *J. Phys. Chem. [U. S. S. R.]*, **33**, 404 (1901); *Chem. Centr.*, **72**, II, 543 (1901); see also Patent of Knoll and Co., *ibid.*, **72**, I, 347 (1901)) on N-acylpyridinium halide. In these cases the acylation can be explained by means of the intermediate A.



This type of intermediate is probably involved in the reaction of acid chlorides with amines and alcohols in the presence of pyridine or other tertiary amines.

base, N<sup>1</sup>,N<sup>1</sup>-diethyl-N<sup>4</sup>,N<sup>4</sup>-dimethyl-1,4-pentanediamine (no. 6, Table I), was employed in the reaction of I with acetic acid, only a trace of the product (V) was obtained. The strong base, while increasing the acetate ion concentration, greatly suppresses the concentration of protons available to the quinoline nitrogen.<sup>2</sup> However, when sufficient protons were made available, by means of a large excess of acetic acid, the presence of one equivalent of this base (no. 3) or of triethylamine (no. 2) resulted in higher yields of V than were obtained with acetic acid alone (no. 1).<sup>3</sup> In

these instances the bases maintain a high acetate ion concentration throughout the reaction by removing the hydrogen chloride as it was formed. These data would indicate that the activating effect of the protonized nitrogen is considerable.

If the reaction rate is dependent upon the attack of II by acetate ion then it should be possible to slow up the reaction by suppressing the acetate ion concentration with hydrogen chloride. This was actually demonstrated for when one mole of hydrogen chloride was present (no. 7) no product (V) was isolated.

TABLE I

THE REACTION OF 4,7-DICHLOROQUINOLINE (I) WITH GLACIAL ACETIC ACID AT 125° FOR FIFTEEN MINUTES

No.	Acetic acid, moles <sup>a</sup>	Reagents added, moles	Products, % V	I
1	6.5		40.5 <sup>b</sup>	55.5
2	6.5	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> N (1)	54.0	42.5
3	6.5	Diamine <sup>c</sup> (0.5)	53.5	42.5
4	6.5	CH <sub>3</sub> CO <sub>2</sub> Na (1)	50.5 <sup>d</sup>	47.0
5	2.5		48.5	49.0
6	2.5	Diamine <sup>c</sup> (2.6)	Trace	85.0
7	6.5	HCl <sup>e</sup> (1)	None <sup>f</sup>	90.0

<sup>a</sup> Molecular equivalents, based on amount of 4,7-dichloroquinoline. <sup>b</sup> After one hour the yield was 91% and 3.5% of I was recovered. <sup>c</sup> N<sup>1</sup>,N<sup>1</sup>-diethyl-N<sup>4</sup>,N<sup>4</sup>-dimethyl-1,4-pentanediamine. <sup>d</sup> After one hour the yield was 94%. <sup>e</sup> Added as 4,7-dichloroquinoline hydrochloride. <sup>f</sup> After one hour the yield was 18%.

(2) The solvolytic effect of acetic acid is also affected.

(3) The lower yield in no. 1 as compared to no. 5 is probably due to the decreased acetate ion concentration of the former caused by increased dilution of the reaction mixture.

According to the proposed mechanism two moles of acetic acid are required. This was shown by the reaction in which one mole of acetic acid was employed. In this case the yield of V was only 46% or approximately one-half that obtained when two moles of acetic acid were used.

The acetic anhydride which is formed in the last step was identified by diluting the reaction mixture with anhydrous ether, filtering off the 7-chloro-4-hydroxyquinoline hydrochloride and then adding pyridine and aniline to the filtrate. Acetanilide was obtained after allowing the mixture to stand at room temperature for one hour. Under similar conditions, in the absence of acetic anhydride no acetanilide could be isolated.

### Experimental

**7-Chloro-4-hydroxyquinoline Hydrochloride.**—The following is a general method for the preparation of 7-chloro-4-hydroxyquinoline hydrochloride by the action of glacial acetic acid on 4,7-dichloroquinoline.

A mixture of 4,7-dichloroquinoline and 6.5 molecular equivalents of glacial acetic acid was placed in a round-bottomed flask, fitted with a drying tube, and heated, by means of an oil-bath, at 125° for one hour.<sup>4</sup> Separation of a white solid product usually occurred within twenty to thirty minutes after heating was started. Dry ether was added to the cooled reaction mixture and the white solid was filtered off to give an 88.5% yield of 7-chloro-4-hydroxyquinoline hydrochloride, m. p. 252–255°. A mixed melting point with an authentic sample was not depressed. The free base, obtained from the above hydrochloride, was identical with 7-chloro-4-hydroxyquinoline.<sup>5</sup>

The 7-chloro-4-hydroxyquinoline hydrochloride was purified by recrystallization with glacial acetic acid containing one equivalent of ethanolic hydrogen chloride.<sup>6</sup> The pure hydrochloride separated as glistening white needles, m. p., 265–266.5° dec. (cor.).

*Anal.* Calcd. for  $C_9H_6ClNO \cdot HCl$ :  $Cl^-$ , 16.41. Found:  $Cl^-$ , 16.19.

When the above reaction was run using only one mole of acetic acid a 46% yield of the hydroxyquinoline hydrochloride resulted. The use of two moles of acetic acid increased the yield to 80%.

In order to establish that the reaction occurred under anhydrous conditions, the following experiment was performed. A mixture of 4 cc. of glacial acetic acid and 1 cc. of acetic anhydride, contained in a 50-cc. round-bottomed flask fitted with a drying tube, was heated thirty minutes at 125°. Purified 4,7-dichloroquinoline (1.98 g.) (0.01 mole) was added and the heating continued for one hour to give an 84% yield of 7-chloro-4-hydroxyquinoline hydrochloride.

**The Effect of Acid and Bases on the Reaction of 4,7-Dichloroquinoline with Glacial Acetic Acid.**—A series of seven experiments were run simultaneously (see Table I) in order that the effect of acid and varying amounts of bases might be studied.

In each of six consecutively numbered test-tubes was

(4) At steam-bath temperatures the reaction is much slower. The separation of solid from the reaction mixture was noted after two and one-half hours. In six hours the yield of VI was 88%.

(5) Surrey and Hammer, *THIS JOURNAL*, **68**, 113 (1946).

(6) The 7-chloro-4-hydroxyquinoline hydrochloride tends to lose hydrogen chloride.

placed 1.98 g. (0.1 mole) of 4,7-dichloroquinoline and 2.34 g. (0.01 mole) of 4,7-dichloroquinoline hydrochloride in the seventh. Glacial acetic acid in amounts as indicated in Table I was pipetted into each tube and additional reagents, as listed, were added. The test-tubes were stoppered and placed in a rack which, at zero time, was lowered into an oil-bath maintained at  $125 \pm 2^\circ$ . The rack was shaken for a few minutes in such a manner as to insure homogeneous mixing<sup>7</sup> of the contents of the tube. At the end of fifteen minutes, the rack of test-tubes was removed and immediately placed in ice water.

The contents of each tube was rinsed into a beaker with 80 cc. of 10% sodium hydroxide solution and the resulting mixture was thoroughly stirred and chilled in ice. The unreacted 4,7-dichloroquinoline (I) was filtered off, washed with water and dried. Treatment of the filtrate with acetic acid precipitated the 7-chloro-4-hydroxyquinoline (V) which was filtered off, washed with water and dried. In most cases approximately 95% of the starting material could be accounted for either as product (V) or unreacted I.

**Proof of the Formation of Acetic Anhydride: The Preparation of Acetanilide.**—A mixture of 4,7-dichloroquinoline (0.01 mole) and 2 ml. (0.035 mole) of glacial acetic acid was heated as previously described for one hour at 125°. The cooled solid was slurried with anhydrous ether (dried over sodium) and filtered immediately into a flask containing 4 cc. of pyridine and 1.5 cc. of aniline. The resulting solution was allowed to stand one hour at room temperature and the ether evaporated *in vacuo* at room temperature. The residual oil was treated with 50 cc. of ice cold 1 N hydrochloric acid solution and, after standing one-half hour, the crystalline acetanilide was filtered off; yield, 0.5 g., m. p. 112–114°. A mixed melting point with an authentic sample of acetanilide was not depressed. In another experiment the reaction mixture was diluted with 25 cc. of dry pyridine and analyzed.<sup>8</sup> This analysis indicated that 66% of the theoretical amount of acetic anhydride was present.

**$N^1, N^1$ -Diethyl- $N^4, N^4$ -dimethyl-1,4-pentanediamine.**<sup>9</sup>—This compound was prepared from Noval diamine by alkylation with formaldehyde and formic acid. Any primary or secondary amine present in the product was removed by reaction with *p*-toluenesulfonyl chloride. The yield was 59%; b. p., 87° at 5 mm.;  $n_D^{25}$  1.4393.

*Anal.* Calcd. for  $C_{11}H_{23}N_2$ : N, 15.04. Found. N, 14.65.

**Acknowledgment.**—The authors are indebted to Mr. M. E. Auerbach of the analytical staff of these laboratories for the analyses performed.

### Summary

A study of the reaction of 4,7-dichloroquinoline with acetic acid is reported.

A mechanism for the formation of 7-chloro-4-hydroxyquinoline hydrochloride and acetic anhydride is proposed.

RENSSELAER, NEW YORK RECEIVED JANUARY 17, 1950

(7) In the case of no. 4 the mixture was not homogeneous. As the sodium acetate gradually disappeared, sodium chloride separated from the reaction mixture.

(8) "Determination of Acetic Anhydride. Aniline Method," Scott's Standard Methods of Chemical Analysis, 5th edition, Vol. II, D. Van Nostrand Co., Inc., New York, N. Y., p. 2248.

(9) This compound was prepared in connection with other unpublished work.