

## THE 5-AND 8-CHLORINATION OF QUINOLINE AND SOME OF ITS DERIVATIVES

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Quinoline (0.1 mol.) and silver sulphate (0.05 mol.) in 98% sulphuric acid, and dry chlorine at room temperature give 5-chloroquinoline (17%), 8-chloroquinoline (21%) and 5:8-dichloroquinoline (32%); approximate proportions were determined from the isolated products. With an excess of quinoline the monochloroquinolines are the predominant products and with silver sulphate and dry chlorine for a prolonged period 5:8-dichloroquinoline is the major product. Further chlorination of 5-chloroquinoline and 8-chloroquinoline gives 5:8-dichloroquinoline in the like manner. It is considered that the positively charged chloronium ion ( $Cl^+$ ) and the protonated form of the bases are the main species involved in the initial and the subsequent chlorination. Such reactions should form convenient preparative routes to the mono- and dichlorination of quinoline.

### Introduction

In a mixture of nitric and sulphuric acids, quinoline gives 5- and 8-nitroquinolines in almost equal quantities.<sup>1</sup> Nitration under less acidic<sup>2</sup> conditions gives 3-nitroquinoline including other nitro derivatives. It has been suggested that reactions in strongly acid conditions, involve electrophilic attack on the quinolinium cation,<sup>1</sup> whereas other reactions occur due to the attack on neutral quinoline molecule either directly<sup>3</sup> or by addition followed by elimination.<sup>2</sup>

Bromination of quinoline in 98% sulphuric acid containing silver sulphate gives 5- and 8-mono-bromoquinolines in equal amounts and 5:8-dibromoquinoline in variable quantities according to the proportion of the reagents used. It has been observed that the bromination involves electrophilic reaction between positively charged bromine ( $Br^+$ ) and quinolinium cation.<sup>4-5</sup>

Similarly quinoline and silver sulphate in sulphuric acid with solid iodine at 200°C, gives 5-iodo, 8-iodo and 5:8-diiodoquinoline.<sup>6</sup> The course of reaction and the species involved in the iodination are identical with those of nitration<sup>1</sup> and bromination.<sup>4,5</sup>

Sulphonation also takes place at 5- and 8-positions forming 5- and 8-monoisomers and 5:8-diisomer.

The results of nitration, bromination, iodination and sulphonation indicate that chlorination of quinoline by positive chlorine ( $Cl^+$ ) may be possible under similar conditions and the reaction should lead to the formation of 5- and 8-chloro derivatives. Our preliminary communication<sup>7</sup> described the formation of 5- and 8-chloroquinoline in sulphuric acid, the process being a modification of that used by Derbyshire and Waters.<sup>8</sup>

### Experimental

Quinoline was purified through chlorozincate<sup>9</sup> or phosphate.<sup>10</sup> The purified material had b.p. 236°/758 mm., m.p., -19°C. Sulphuric acid and silver sulphate were of the analytical grade. Gaseous chlorine was prepared by oxidising concentrated hydrochloric acid with potassium permanganate and was purified by passing through a series of bubblers containing water and concentrated sulphuric acid respectively. Chloroquinolines required as reference materials were prepared by the standard method. Data concerning the prepared chloroquinolines and their derivatives are shown in Table I. Their properties are in good agreement with the values recorded in the literature.

#### METHOD OF CHLORINATION

The method of chlorination is that of Derbyshire and Waters<sup>8</sup> and was modified according to the requirements of the reactions. The base quinoline or its derivatives and an appropriate quantity of silver sulphate were dissolved in concentrated sulphuric acid. Dry Chlorine prepared as above was passed, with vigorous shaking, through the mixture for one to two hours. After any necessary filtration, the filtrate and the washings were treated with 5% sodium sulphite solution containing crushed ice to remove any free chlorine. The reaction mixture was then basified, extracted with solvent or steam distilled and worked up suitably.

(a) *Preparation of 5- and 8-chloroquinoline.*—Dry chlorine was passed for one hour through a mixture of quinoline (64.5 g.), silver sulphate (15.6g.), sulphuric acid 150 ml. The filtered reaction mixture was poured into ice cold sodium sulphite solution, basified and steam distilled. The steam distillate was extracted with ether and the ether extract was dried over anhydrous sodium sulphate

TABLE I.—PROPERTIES OF QUINOLINE, THE MONOCHLOROQUINOLINES AND SOME OF THEIR DERIVATIVES.

| Products               | Method of preparation                      | mp/bp                             | Picrate       | Oxalate             | Dichromate | Nitrate | Methio-iodide.    | Hydro-chloride | Chloro-platinate  | Reference |
|------------------------|--|-----------------------------------|---------------|---------------------|------------|---------|-------------------|----------------|-------------------|-----------|
| Quinoline              | From Chlorozincate                         | -19°m.p.<br>236°b.p.              | 201-2°        | 115°                | 167°       | —       | 133°              | 94°            | 227-5°            | A.B.      |
| 2-Chloroquinoline      | From 2-hydroxy(b) quinoline                | 37-8°m.p.<br>266-7°b.p.           | 122°          |                     |            |         |                   |                |                   | C.        |
| 3-Chloroquinoline      | From 3-amino(a) quinoline                  | b.p.255°/<br>743mm                | 182°          |                     | 125-6°     |         | 276°<br>(sublime) | 210°           | 300°              | D.E.      |
| 4-Chloroquinoline      | From 4-hydroxy(b) quinoline                | m.p. 31°<br>b.p. 261°/<br>744mm   |               | 212-3°<br>(decomp.) |            |         |                   |                | 278°-9°           | F.G.      |
| 5-Chloroquinoline      | From 5-amino(a) quinoline                  | 45°                               | 222-23°       | 145°                | 121°       | 160-61° | 170-73°           |                | 255°              | H.        |
| 6-Chloroquinoline      | From Picrate                               | m.p. 41°<br>b.p. 261-2°/<br>740mm |               |                     |            | 176°    | 248°<br>(decomp.) |                |                   | D.        |
| 7-Chloroquinoline      | Skraup method from m-chloroaniline         | m.p. 31-2°<br>b.p.267-8°          | 225°          | 155°                | 172-8°     | 199°    | 250°<br>(decomp.) |                | 253°<br>(decomp.) | H.        |
| 8-Chloroquinoline      | From 8-amino(a) quinoline                  | b.p. 288°                         | 177*-78°      |                     | 160-61°    |         | 165°              |                |                   | D.I.      |
| 5:8-Dichloro-quinoline | From 2,5-dichloro-aniline by skraup method | 97-98°                            | **<br>150-51° |                     | 130-31°    |         |                   |                |                   | J.        |

\* 8-Chloroquinoline picrate is not mentioned in the literature. It is a new compound.

\*\* 5:8-Dichloroquinoline picrate is also a new compound.

(a) Prepared by reduction of the corresponding nitro compound with iron and acetic acid of Curds, Graham, Richardson and Rose, J, 1947, 1613;

(b) By reaction with phosphorous pentachloride; cf. Fisher, Ber., 1899, 32,1304;

A, Lellman and Alt, Annalen, 1887,237,323; B, Timmermans and Hennart-Roland, J. Chem. Phys. 1937,34,733; C, Claus and Pollitz, J. prakt-chem, 1889,41,41; D, Claus and Tornier, Ber; 1887,20,2872; E, Jansen and Wibaut, Rec. Trav. Chim, 1937,56,699,709; F, Claus and Frobenius, J Prakt. chem, 1897,56,192; G, Nakayama, J. Pharm. Soc., Japan, 1951,71,1088, H, Bradford, Elliot and Rose J, 1947,437; I, Ukai, J. Pharm. Soc., Japan, 1927, 873; J, Claus and Geisler, J. Prakt. Chem., 1889,240,376,

and fractionally distilled *in vacuo* to remove unreacted quinoline completely. The residue left after the removal of excess quinoline was taken in dilute sulphuric acid and treated with picric acid solution. The precipitated picrate was filtered, dried and dissolved in acetone. On fractional crystallisation, the first crop of crystals recrystallised from acetone or alcohol had m.p. 222-23°. On further concentration, the mother liquor gave a second crop of crystals which recrystallised from acetone or alcohol melted at 177-78°.

The picrate, m.p. 222-23°, was treated with alkali (5% solution) and steam distilled. A white product (1.556 g.) was obtained from the distillate. Recrystallised from ether, the substance melted at 45° (lit. m.p. 44-45°), not depressed on admixture with an authentic sample of 5-chloroquinoline prepared from 5-aminoquinoline. Their infra-red spectra were identical (Fig. 1). The prepared 5-chloroquinoline gave picrate m.p. 222-23° (lit. m.p. 222-23°); oxalate m.p. 145° (lit. m.p. 145°), dichromate m.p. 160-61° (lit. m.p. 161°), methiodide m.p. 172-73° (lit. m.p. 170-73°).

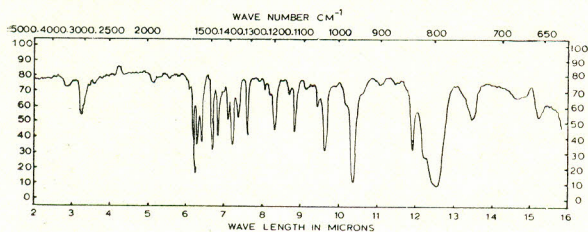


Fig. 1.—I.R. of 5-chloroquinoline.

The picrate m.p. 177-78° (no lit; a new compound) was treated with sodium hydroxide solution (5%) and steam distilled. Ether extraction of the aqueous distillate gave an oily product (1.667 g.) b.p. 288°. Its infrared spectra was identical with the spectra of 8-chloroquinoline prepared from 8-aminoquinoline. 8-chloroquinoline picrate m.p. 177-78° showed no depression of melting point when admixed with an authentic specimen. Their infrared spectra were identical, (Fig. 2). 8-Chloroquinoline nitrate, m.p. 165° (lit. m.p. 165°) was prepared.

(b) *Preparation of 5:8-dichloroquinoline.*—Quinoline (12.9 g.) in sulphuric acid (100 ml. 98%) containing silver sulphate (15.6 g.) was allowed to react with dry chlorine for two hours. The filtered reaction mixture after treatment with sodium sulphite was brought to pH 2-3. The

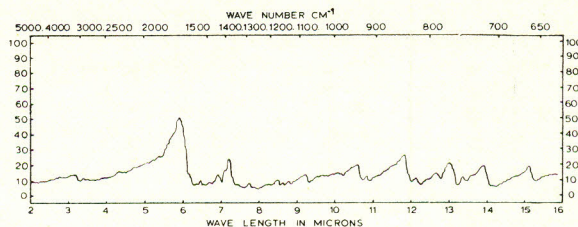


Fig. 2.—I.R. of Picrate of 8-chloroquinoline.

resultant white precipitate was filtered, washed and recrystallised from acetone or alcohol giving 5:8-dichloroquinoline (2.25 g.), m.p. 97-98°. No depression of mixed melt with a specimen was obtained from 2,5-dichloroaniline. Picrate, m.p. 150-51° (no lit. a new compound), and a dichromate, m.p. 130-31°, were prepared. Infra-red spectrum of 5:8-dichloroquinoline is identical with that of the authentic sample prepared from 2,5-dichloroaniline (Fig. 3).

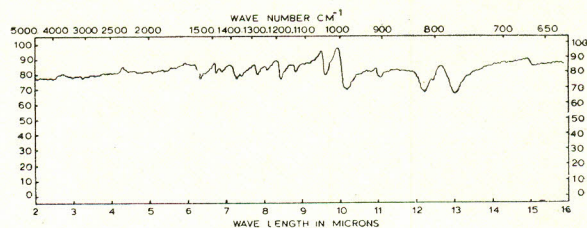


Fig. 3.—I.R. of 5:8-dichloroquinoline.

(c) *Reaction of Quinoline (0.10 mole), Gaseous Chlorine, Silver Sulphate (0.1 mole.) in Sulphuric Acid with Increasing Water Content.*—The quantities of quinoline, chlorine and silver sulphate were fixed and the strength of sulphuric acid was varied. The reaction mixture was processed in the usual way and 5:8-dichloroquinoline, 5-chloroquinoline and 8-chloroquinoline were isolated as described above. Table 2 summarises the yields of chloroquinoline obtained when the reaction was carried out under various conditions. In such case, the reactants were quinoline (12.9 g.), silver sulphate (15.6 g.), and chlorine and sulphuric acid (100 ml.).

*Chlorination of Quinoline under other Conditions.*—(a) No chloro product was obtained by the treatment of quinoline and chlorine in acetic, nitric or hydrochloric acids with the corresponding silver salts.

(b) When dry chlorine was passed through quinoline in chloroform at room temperature,

TABLE 2.—YIELDS IN THE REACTION OF QUINOLINE AND CHLORINE IN THE VARIOUS CONDITIONS (SULPHURIC ACID OF DIFFERENT CONCENTRATIONS).

| Medium                         |                                | 5:8-dichloroquinoline (g.) | 5-chloroquinoline (g.) | 8-chloroquinoline (g.) |
|--------------------------------|--------------------------------|----------------------------|------------------------|------------------------|
| H <sub>2</sub> SO <sub>4</sub> | 15%SO <sub>3</sub>             | 0                          | 0                      | 0                      |
| 100%                           | H <sub>2</sub> SO <sub>4</sub> | 0.8523                     | 0.5531                 | 0.6471                 |
| 98%                            | H <sub>2</sub> SO <sub>4</sub> | 0.7637                     | 0.5404                 | 0.5651                 |
| 95%                            | H <sub>2</sub> SO <sub>4</sub> | 0.5203                     | 0.4981                 | 0.5012                 |
| 90%                            | H <sub>2</sub> SO <sub>4</sub> | 0.3230                     | 0.3674                 | 0.4126                 |
| 80%                            | H <sub>2</sub> SO <sub>4</sub> | 0.2301                     | 0.2720                 | 0.2815                 |
| 70%                            | H <sub>2</sub> SO <sub>4</sub> | —                          | —                      | —                      |

heavy precipitations occurred, but no product could be separated by ordinary the crystallisation methods.

*Chlorination of the Derivatives of Quinoline.*—(a) 5-Chloroquinoline: Approximately equivalent amounts of 5-chloroquinoline (1.635 g.) and silver sulphate (3.12 g.) in sulphuric acid (40 ml. 98%) were reacted with dry chlorine at room temperature for one hour. The reaction mixture after the usual treatment as before gave 5:8-dichloroquinoline (1.442 g.) m.p. 97-98°, C., 54.52, H, 2.53, N, 7.072, Cl, 35.92. Calculated for C<sub>9</sub>H<sub>5</sub>NCl<sub>2</sub> C, 54, 54, H, 2.52, N, 7.07, Cl, 35.85.

(b) 8-chloroquinoline: Equimolecular quantity of 8-chloroquinoline (1.635 g.), silver sulphate (3.12 g.) in sulphuric acid (40 ml., 98%) were chlorinated in the same way as before. The product obtained was 5:8-dichloroquinoline (1.4034 g.), m.p., 97-98°.

(c) 5:8-dichloroquinoline: Attempts were made to chlorinate 5:8-dichloroquinoline (1.98 g.) under similar conditions. No definite products could be obtained from the reaction mixture.

Earlier investigators have shown that electrophilic substitution such as nitration and bromination takes place with neutral quinoline molecule and the orientation is at the pyridine ring. Bromination in concentrated hydrochloric acid having acidity,<sup>11</sup> as measured by H<sub>0</sub>, of about -4 produced similar orientation. The acidic dissociation constant of the quinolinium cation<sup>12,13</sup> has p<sub>k</sub>a -5. Consequently the ratio, (Q): (QH<sup>+</sup>) of base to conjugate acid must be very small. Under such conditions the attack of molecular bromine and iodine on quinolinium cation was considered unlikely.<sup>4,6</sup> The same argument holds good for molecular chlorine.

A quite different orientation is observed in nitration,<sup>1</sup> bromination and iodination of quinoline in sulphuric acid.<sup>4</sup> The substitution reaction involves an attack exclusively on the benzene ring. Chlorination with similar reagents maintains the same orientation giving 5-chloroquinoline and 8-chloroquinoline in almost similar yield. Further chlorination of 5- and 8-chloroquinolines gives 5:8-dichloroquinoline, supporting the evidence for orientation at 5- and 8-positions. This route of preparation of 5- and 8-chloroquinoline and 5:8-dichloroquinoline is the best yet recorded.

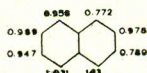
The present work shows that though the heteronitrogen atom deactivates the molecule, quinoline is effectively chlorinated in a high concentration of sulphuric acid, better yield being obtained in 100%. It is evident from the progressively lower yield, that the chlorinating species loses its efficiency in acid containing increasing proportion of water and in 70% acid, chlorination does not take place at all. Also in the presence of sulphur trioxides, chlorination does not occur. In the absence of silver sulphate, no reaction takes place with quinoline and chlorine in 98% sulphuric acid.

The work on nitration by Dewar-Maitles,<sup>1</sup> bromination by de-la-Mare Kiamuddin and Ridd<sup>4</sup> and the views expressed by R.D. Brown<sup>3</sup> have shown that in sulphuric acid, substitution takes place at 5- and 8-position of the benzene ring of quinoline and the entity undergoing substitution is the quinolinium cation. The results of the chlorination of quinoline in sulphuric acid support the above views in that the chlorination involves the attack of positively charged chlorine on the protonated form of quinoline and gives 5- and 8-chloroquinolines.

The numbers of the di and tri-derivatives exceeds mono substitution products in quinoline series.<sup>3</sup> The reason is that conjugated acid of mono substituted quinoline is a stronger acid than that of quinoline; hence disubstitution can compete with mono substitution and 5:8-dichloroquinoline is formed in greater proportion. Results in Table 1 show that the amount of dichloroquinoline is greater than that of monochloroquinoline when the reaction is carried out in concentrated sulphuric acid with reagents in molecular proportions. The ratio of mono-to di-derivatives is little changed by altering the water content of sulphuric acid; but the total yield goes on decreasing with increasing water and the reaction is finally stopped when the medium is made sufficiently aqueous. Therefore, the effective reagents for chlorination would be more likely Cl<sup>+</sup> and not (ClOH<sub>2</sub>)<sup>+</sup>. It seems less likely that the (ClOH<sub>2</sub>)<sup>+</sup> is involved in the present chlorination experiments, because

in such a medium as 10-98% sulphuric acid, occurrence of  $(\text{ClOH}_2)^+$  does not seem feasible. It is, therefore, agreed that in a strongly acid medium the effective electrophilic reagents are the anhydrous positive ions as brominium  $\text{Br}^+$ , chloronium  $\text{Cl}^+$ , iodonium  $\text{I}^+$  and nitronium  $\text{NO}_2^+$ , and not their hydrated forms  $\text{BrOH}_2^+$ ,  $\text{ClOH}_2^+$ , and  $\text{IOH}_2^+$  etc. Thus the results support the view that in strongly acid medium the electrophilic attack by positively charged species take place at the 5- and 8-position of quinoline.

Longuet-Higgings<sup>15</sup> and Coulson have calculated the charge densities at the different carbon atoms of quinoline by molecular orbital methods and the results are shown to follow the order  $8 > 6 > 3 > 5 > 7 > 2 > 4$ .



The charge densities at different carbon atoms predict that reactivity at 8-position should be greater than any other carbon atom and the next reactive points should be 6- and 3-positions. On the other hand, localisation energy suggests a slightly different order of reactivity of the carbon atoms of quinoline; the order is  $8 > 5 > 6 = 3 > 7 > 4 > 2$ .

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Scientific and Industrial Research, Chittagong, the authors completed it. Thanks are due to Dr. S.A. Warsi, Director, North Regional Laboratories, Pakistan Council of Scientific and Industrial Research, Peshawar, for his keen interest and providing facilities for this work.

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