

THE 5-AND 8-IODINATION OF QUINOLINE AND SOME OF ITS DERIVATIVES

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Quinoline (0.3 mole) and silver sulphate (0.2 mole) in 98 percent sulphuric acid at 150-200°C., and iodine (0.2 mole) give 5-iodoquinoline (20 percent), 8-iodoquinoline (18 percent) and 5:8-diiodoquinoline (35 percent), the approximate proportions were determined from the products isolated. With an excess of quinoline, monoiodoquinolines predominate and with silver sulphate and iodine in excess, 5:8-diiodoquinoline is the major product. 5-iodo and 8-diiodoquinolines are similarly iodinated to form 5:8-diiodoquinoline. It is considered that the positively-charged iodonium ion (I^+) and the protonated form of the bases are the principal species involved in the initial and the subsequent iodination. Such reactions should form convenient preparative routes to mono and diiodination of quinoline.

Quinoline with a mixture of nitric and sulphuric acids gives 5- and 8-nitro quinolines in similar amounts.¹ Nitration under less acidic² 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,¹ whereas other reactions occur due to the attack on neutral quinoline molecule either directly³ or by addition followed² by elimination.

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

Similarly quinoline and silver sulphate in sulphuric acid give with gaseous chlorine 5-chloro, 8-chloro and 5:8-dichloroquinoline.⁶ The course of reaction and the species involved in the chlorination are identical with those of nitration¹ and bromination.^{4,5} As for iodination, Cleinberg and coworkers⁷ reported some reaction of quinoline and iodine at room temperature but no products had been isolated. Edinger⁸ prepared triiodoquinoline of unknown orientation by heating quinoline, iodine and sulphuric acid at 100° for several hours.

The results of nitration, bromination and chlorination indicate that iodination of quinoline by positive iodine (I^+) may be possible under similar conditions and the reaction should lead to the production of 5- and 8-iododerivatives. No such iodination reactions have so far been reported. Our preliminary communication⁹ described the formation of 5- and 8-iodoquinoline in sulphuric acid at 200°C., the process being a modification of that used by Derbyshire and Waters.¹⁰

Experimental

Quinoline was purified through chlorozincate¹¹ or phosphate.¹² The purified material had b.p. 236°/760 mm., m.p. -19°C. Iodine, sulphuric acid and silver sulphate were of analytical grade. Iodoquinolines required as reference substances were prepared by standard methods. The data concerning the prepared iodoquinolines and their derivatives are shown in Table 1; their properties are in good agreement with values recorded in the literature.

Method of Iodination.—In principle the method is that of Derbyshire and Waters¹⁰ and was modified according to requirements of the reactions. The base quinoline or its derivative and an appropriate quantity of silver sulphate were dissolved in concentrated sulphuric acid and heated to 150-200°C. About one equivalent of iodine relative to silver sulphate was gradually added with thorough shaking, in about an hour time. After filtration of the resultant silver iodide precipitate the filtrate and the washings were treated with sodium sulphite solution containing crushed ice to 5 percent remove any free iodine. The reaction mixture was then basified, extracted with solvent or steam-distilled and worked up suitably.

(a) *Preparation of 5- and 8-iodoquinoline.*—Quinoline (33 g.) and silver sulphate (16.5 g.) in sulphuric acid (98%, 100 ml.) at 150-200°C. were allowed to react with iodine (6.5 g.) added small quantity at a time. The reaction was indicated by the appearance of silver iodide precipitate and was complete in an hour. The filtered reaction mixture was poured into ice-cold sodium sulphate solution, basified and steam-distilled. The ether extract of the steam distillate was dried and fractionally distilled in vacuum. After removal of the excess of quinoline the residue was redissolved in sulphuric acid. The solution was treated with sodium hydroxide, 5-iodoquinoline was precipita-

TABLE I.—PROPERTIES OF SOME OF THE IODOQUINOLINES AND SOME OF THEIR DERIVATIVES.

Quinoline	Method of preparation	M.P.	Methiodide M.P.	Hydrochloride	Chloroplatinate	Reference
Quinoline	From Chlorozincate	16.5 (B.P. 236°)	133°	94°	227.5°	A.B.
2-iodoquinoline	From 2-hydroxyquinoline ^a	52.53°	211-2°	—	—	C
4-iodoquinoline	From 4-hydroxy ^a quinoline	97°	251°	—	185°	D
5-iodoquinoline	From 5-Amino ^b quinoline	100°	245°	235°	263	E
6-iodoquinoline	From 6-hydroxy ^a quinoline	91°	300°	210°	265°	E
8-iodoquinoline	From 8-amino ^b quinoline	36°	200°	—	251	F
(5-6-diiodoquinoline) ^c	—	125°	—	—	—	G
(5:7-diiodoquinoline) ^c	—	132°	—	—	—	H
5:8-diiodoquinoline	From 5-and 8-diiodoquinoline	162°	—	—	—	I

(a) by reaction with red phosphorus and iodine; (b) prepared by reduction of the corresponding nitrocompounds with iron and acetic acid; (c) the values of the compounds within brackets are taken from literature; (d) prepared by method described in this paper.

A, Lellmann and Alt. *Annalen*, 1887, 237, 323; B, Timmermans and Hennart-Roland, *J. Chim. Phys.*, 1937, 34, 733; C, Friendlander and Weinberg, *Ber.*, 1885, 18, 1531; D, Claus and Frobenius, *J. Pract. Chem.*, 1897, 56, 193; E, Claus and Gran, *J. Pract. Chem.*, *Ann.* 1893, 48, 167; F, Howitz, Fraenkel, Schroeder, 1913, 396, 57; G, Howitz, Fraenkel, Schoeder, *Ann.*, 1913, 396, 73; H, Wellgerodt and Arnold, *Ber.*; 1901, 34, 3349; I, Howitz, Traankel, Schroeder, *Ann.*, 1913, 396, 61.

ted at pH 3.5 and 8-iodoquinoline remained in solution. The precipitate (2 g.) was filtered, extracted with ether, the extract dried with anhydrous sodium sulphate, ether removed and the residue recrystallised from alcohol or acetone giving 5-iodoquinoline, m.p. 100°C; no depression of mixed melt with authentic specimen, methiodide m.p. 245°, hydrochloride m.p. 235°, chloroplatinate m.p. 263°, picrate m.p. 234°. * Infrared spectra of the 5-iodoquinoline was identical with the spectra of 5-iodoquinoline prepared from 5-aminoquinoline.

The filtrate was basified and extracted with ether. The ether extract gave impure 8-iodoquinoline. It was purified through picrate or methiodide which on decomposition gave 8-iodoquinoline m.p. 36°C., methiodide m.p. 200°C., picrate m.p. 171°C., ** chloroplatinate m.p. 251°C.

(b) *Preparation of 5:8-Diiodoquinoline.*—Quinoline (6 g.) in sulphuric acid (75 ml. 98%) containing silver sulphate (16 g.) was heated at 150-200°C.

*5-iodoquinoline picrate is not mentioned in literature and is a new compound.

**8-iodoquinoline picrate is also a new compound.

with iodine (6 g.) until the reaction was complete. The filtered reaction mixture after treatment with sodium sulphite was brought to pH 2 and the resultant white precipitate was filtered, washed and recrystallised giving 5:8-diiodoquinoline m.p. 162°. No depression of mixed melt with a specimen obtained by iodination of 5-and 8-iodoquinoline.

(c) *Reaction of Quinoline (.15 mole), Iodine (.1 mole) and Silver Sulphate (1 mole) in Sulphuric Acid with Increasing Water Content.*—The quantities of quinoline, iodine 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-diiodoquinoline, 5-iodoquinoline and 8-iodoquinoline were isolated as described above. Table 2 summarises the yields of iodoquinolines obtained when the reaction was carried out under various conditions. In such case, the reactants were quinoline (19.5 g.), silver sulphate (31 g.), iodine (12.7 g.) and sulphuric acid 100 ml.

Iodination of Quinoline under other Conditions.—(a) No iodo-product was obtained by treatment of quinoline and iodine in acetic, nitric or hydrochloric acids with the corresponding silver salt.

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

Medium	5:8-diiodoquinoline g.	5-iodoquinoline g.	8-iodoquinoline g.
H ₂ SO ₄ , 5% SO ₃	0	0	0
100% H ₂ SO ₄	2.4	1.5	1
95% H ₂ SO ₄	2.1	1.1	0.98
90% H ₂ SO ₄	1.2	0.8	0.5
80% H ₂ SO ₄	0	0	0

(b) At ordinary temperature quinoline (12 g.) in perchloric acid (10%, 100 ml.) when reacted with hypoiodous acid gave a white precipitate. The precipitate was unstable and decomposed by either heating or treatment with alkali giving back quinoline. It could neither be crystallised nor be reoriented to any iodoquinoline when treated under different conditions.

Iodination of the Derivatives of Quinoline.—(a) 5-iodoquinoline: Approximately equivalent amounts of 5-iodoquinoline (10.2 g.) silver sulphate (24.5 g.) in sulphuric acid (50 ml. 98%) at 200°C. were reacted with iodine (10.2 g.). The reaction mixture after the usual treatment as before gave 5:8-diiodoquinoline (6.6 g.) m.p. 162°. (C, 27.99, H, 1.40, N, 3.57, 1, 67.38% calculated for C, 28.34, H, 1.31, N, 3.57, 1, 66.66%)

(b) 8-iodoquinoline: Equimolecular amount of 8-iodoquinoline (10.2 g.), silver sulphate (24.5 g.) in sulphuric acid (50 ml.) and iodine (10.2 g.) were used in the same way as before. The product obtained was 5:8-diiodoquinoline (6.1 g.) m.p. 162°C.

(c) 5:8-diiodoquinoline: Attempts were made to iodinate 5:8-diiodoquinoline (10 g.) under similar conditions with equivalent and variable quantities of the reagents. The reaction did not proceed satisfactorily and no definite product could be isolated from the reaction mixture.

From the results of nitration and bromination, the earlier investigators have shown that with neutral quinoline molecule the initial attack takes place on the pyridine ring. This orientation is maintained in bromination in concentrated hydrochloric acid which has acidity¹³ as measured

by Ho, of about -4. Also as the ratio, (Q): (QH) of free base to conjugate acid is small owing to the fact that acidic dissociation constant of quinolinium cation^{14,15} has pKa -5, it seems rather unlikely that molecular iodine like molecular chlorine and bromine should attack on the benzene ring of quinolinium cation.

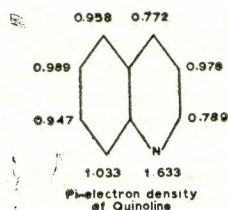
A completely different orientation is observed in nitration, bromination and chlorination of quinoline in sulphuric acid. The substitution reaction involves attack exclusively on the benzene ring. The iodination with similar reagents also maintains the same orientation but reaction occurs only at elevated temperatures, and 5-iodoquinoline and 8-iodoquinoline are produced in almost similar amounts. Further iodination of 5- and 8-iodoquinolines gives 5:8-diiodoquinoline in very good yield providing a further evidence that 8-position of 5-iodoquinoline and 5-position of 8-iodoquinoline are the most reactive points. The reactions are satisfactory enough to give a preparative route to 5- and 8-iodoquinoline and 5:8-diiodoquinoline and in our opinion the best yet recorded.

The works on nitration by Dewar and Maitlis,¹ bromination by de La Mare, Kiamuddin and Ridd,^{4,5} chlorination by Kiamuddin and Chowdhury⁶ and the views expressed by Brown,³ have shown that in sulphuric acid substitution takes place at 5- and 8-positions of the benzene ring of quinoline and the entity undergoing substitution is the quinolinium cation. Our results of iodination of quinoline in sulphuric acid at 200°C. support the above views in that the iodination involves the attack of positively charged iodine on protonated form of quinoline giving 5- and 8-iodoquinoline.

The dominant di- and tri-derivatives observed in substitution in quinoline series¹ is attributed³ to the fact that, since conjugate acid of mono-substituted quinoline is a stronger acid than that of quinoline, the di-substitution can compete with mono-substitution. The same may be the factors contributing to the formation of greater proportion of diiodoquinoline when molecular proportions of the reagents are used. The results in Table 2 show that the amount of diiodoquinoline is greater than that of mono-iodoquinoline and the ratio of mono to di-derivatives is little changed by altering the water content of sulphuric acid upto a certain extent, though the total yield is reduced and the reaction finally stopped when the reaction medium is made sufficiently aqueous.

Monoiodoquinoline is easily converted into diiodoquinoline and the reactions appear to be more complete in respect of yield. But diiodoquinoline could not be converted into triiodoquinoline under the experimental conditions whereas 5:8-dibromoquinoline was easily brominated to 5:6:8-tribromoquinoline.⁴ It is almost certain that positively charged species is the electrophilic reagent involved in the attack on quinoline under the conditions used in this work. The effective reagent would more likely be I^+ and not IOH_2^+ . It seems less likely that the latter ion is involved in the present iodination experiments, because in such media as 100% H_2SO_4 and oleum (5% SO_3), occurrence of IOH_2^+ does not seem feasible. It is agreed that in strongly acid medium the effective electrophilic reagents are the anhydrous positive ions such as Br^+ , Cl^+ and I^+ and not their hydrated forms- $BrOH_2^+$, $ClOH_2^+$ and IOH_2^+ .

Our results also support the view that in strongly acid medium the electrophilic attack by positively charged species takes place at the 5-and 8- positions of quinoline. Such observations are in complete agreement with localisation energies but in partial disagreement with the charge densities on the carbon atoms as calculated by Longuet-Higgins¹⁷ by molecular orbital method shown in the following diagram. According to



this the 3-and 6-position would be more reactive than the 5 position to electrophilic reagent. This discrepancy was explained by Dewar and Maitlis¹ and attributed to electrostatic and inductive effects of the positive charge on the nitrogen atom in the quinolinium ion. The results of the present

investigation accord with the theoretical calculations to the same degree of approximation as is found for nitration and bromination.

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