116. *The 5- and 8-Bromination of Quinoline and Some of its Derivatives.*

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Quinoline (0·15 mole), bromine (0·1 mole), and silver sulphate in 98% sulphuric acid give 5- (28%) and 8-bromoquinoline (29%) with 5,8-dibromoquinoline (43%); the proportions of the products were determined by isotopic dilution. Altering the water content of the medium from 0 to 8% has little effect on the ratio of mono- to di-bromination. With an excess of quinoline, monobromoquinolines are the only products, and with bromine and silver sulphate in excess 5,8-dibromoquinoline is the major product. The last substance is similarly formed from 5- or 8-bromoquinoline; further bromination gives 5,6,8-tribromoquinoline. 3-Bromoquinoline likewise gives 3,5-dibromo- and 3,5,8-tribromo-quinoline. It is considered that both the initial and the subsequent bromination involve attack by a positively charged brominating species on the protonated forms of the bases. Such reactions should form good general routes to 5- and 8-bromoquinolines.

NITRATION of quinoline in sulphuric acid gives 5- and 8-nitroquinoline in similar amounts.[1] Under less acidic conditions,[2] other nitro-derivatives, including 3-nitroquinoline, can be obtained. It has been suggested [1] that the reactions in sulphuric acid involve electrophilic attack on the quinolinium cation, whereas the other reactions involve attack on the neutral quinoline molecule, either directly [3] or by addition followed by elimination.[2]

Quinoline and bromine at room temperature form a perbromide, probably $C_9H_7NBr^+Br_3^-$, which is reported to rearrange to 3,6,8-tribromoquinoline.[4] The initial substitution is presumably in the 3-position, since 3-bromoquinoline can be prepared by heating the perbromide of quinoline hydrobromide [5] at 200° and by brominating quinoline in acetic acid containing silver acetate.[3] Vapour-phase bromination of quinoline also gives 3-bromoquinoline at temperatures around 300°, though at higher temperatures 2-bromoquinoline is the main product.[6] Many derivatives of quinoline give corresponding reactions.[7]

By analogy with nitration, these 3-brominations can be considered to involve electrophilic attack on the neutral quinoline molecule,[3] although the exact reaction paths are uncertain. The results for nitration suggest also that bromination of the quinolinium cation should lead to 5- and 8-bromo-derivatives. No such brominations had been identified when the present work began. Contemporaneously with our preliminary communication,[8] which described the formation of 5- and 8-bromoquinoline by bromination in sulphuric acid according to the method given by Derbyshire and Waters,[9] R. D. Brown [3] presented in outline the results of some similar experiments.

EXPERIMENTAL

Quinoline was purified through the chlorozincate [10] or the phosphate.[11] The purified material had b. p. 236°/758 mm., m. p. −16°. Data concerning the bromoquinolines and their derivatives required as reference compounds are summarised in Tables 1 and 2; their properties accord adequately with values recorded in the literature.

[1] Dewar and Maitlis, *J.*, 1957, 2521.
[2] *Idem, ibid.*, p. 944.
[3] Brown, "Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 13.
[4] (*a*) Lubavin, *Annalen*, 1870, **155**, 311; (*b*) Claus and Caroselli, *J. prakt. Chem.*, 1895, **51**, 477.
[5] La Coste, *Ber.*, 1881, **14**, 915; Claus and Collischon, *Ber.*, 1886, **19**, 2763.
[6] Janse and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 699.
[7] Elderfield, "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 129.
[8] de la Mare, Kiamud-din, and Ridd, *Chem. and Ind.*, 1958, 361.
[9] Derbyshire and Waters, *J.*, 1950, 573.
[10] Mann and Saunders, "Practical Organic Chemistry," Longmans, Green and Co., 1938, p. 198.
[11] Swiss P. 258,296/1949; *Chem. Abs.*, 1950, **44**, 2041.

Bromination of Quinoline.—The method was essentially that described by Derbyshire and Waters.[9] The amine and an appropriate weight of silver sulphate were dissolved in sulphuric acid, and shaken with rather less than one equivalent of bromine (relative to the silver sulphate). After 3 hr., when most of the bromine had usually disappeared, the solution was filtered and any free bromine removed by addition of sodium sulphite. The precipitate of silver bromide was washed with water, and the combined filtrates were added to ice and worked up appropriately.

(a) *Preparation of 5- and 8-bromoquinoline.* Quinoline (65 g.), silver sulphate (17 g.), sulphuric acid (100 ml.), and bromine (5·2 ml.) were allowed to react. The filtrates were then made alkaline and distilled in steam. The steam-distillate was extracted with ether; the extract was dried (KOH) and fractionally distilled *in vacuo*. After removal of the excess of

TABLE 1. *Properties of quinoline, the monobromoquinolines, and some of their derivatives.*[a]

Quinoline deriv.	Method of prep.	B. p.	M. p.	Oxalate, m. p.	Picrate, m. p.	Dichromate, m. p.	Nitrate, m. p.	Ref.
(Quinoline)	From chlorozincate	236°	−16°	115°	201—202°	167°	—	A, B
2-Bromo	From 2-hydroxyquinoline [b]	—	49	—	238	—	—	C
3-Bromo	From 3-aminoquinoline	(274—276)	15	107	190—191	144—145	180°	D, E
4-Bromo	From 4-hydroxyquinoline [b]	(280)	(31)	—	(215)	—	—	F, G
5-Bromo	From 5-aminoquinoline [c]	—	47—48	152	238	134	186	H
6-Bromo	From picrate	—	(24)	(62)	215	(179)	(182)	D
7-Bromo	Skraup method, from *m*-bromoaniline	—	36	167	238	(202)	(205—206)	H
8-Bromo	From 8-aminoquinoline [c]	302—303	—	—	169	159—160	(90)	D, I

[a] Values in brackets are taken from the literature. [b] By reaction with PBr_5; cf. Fischer, *Ber.*, 1899, **32**, 1304; see also Young and Amstutz, *J. Amer. Chem. Soc.*, 1951, **73**, 4773; 4-bromoquinoline was not prepared in the present investigation. [c] Prepared by reduction of the corresponding nitro-compounds with iron and acetic acid; cf. Curd, Graham, Richardson, and Rose, *J.*, 1947, 1613.

A, Lellmann and Alt, *Annalen*, 1887, **237**, 323; B, Timmermans and Hennart-Roland, *J. Chim. 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, Elliott, and Rowe, *J.*, 1947, 437; I, Ukai, *J. Pharm. Soc. Japan*, 1927, 873.

TABLE 2. *Properties of some di- and tri-bromoquinolines and their derivatives.*

Quinoline deriv.	Method of prep.	M. p.	Nitrate, m. p.	Hydrochloride, m. p.	Ref.
3,5-Dibromo	From 5-bromoquinoline [a]	86°	147°	183°	J
3,6-Dibromo	From 6-bromoquinoline	126	158	(185)	J
5,8-Dibromo	From 2,5-dibromoaniline by Skraup method	129—130	—	(190—192)	K
3,5,8-Tribromo	From 5,8-dibromoquinoline [a]	171	—	—	L
3,6,8-Tribromo	[b]	170	—	—	L
5,6,8-Tribromo	From 6-bromoquinoline [c]	161—162	—	—	M

[a] By heating the perbromide; cf. ref. L. [b] By brominating 1,2,3,4-tetrahydroquinoline, and elimination of HBr; cf. ref. L. [c] By the method described in this paper.

J, Claus and Welter, *J. prakt. Chem.*, 1889, **240**, 391. K, Claus and Geisler, *ibid.*, p. 376. L, Claus and Heerman, *ibid.*, 1890, **242**, 335. M, Claus and Caroselli, *ibid.*, 1895, **251**, 481.

quinoline, the residue was treated in alcohol with an excess of oxalic acid in alcohol. 5-Bromoquinoline oxalate was precipitated, while 8-bromoquinoline remained in solution. The precipitate was recrystallised and then treated with excess of aqueous alkali. The white solid remaining (6·5 g.) was extracted with ether, recovered, and residue recrystallised from aqueous alcohol or acetone, giving 5-bromoquinoline (6 g.), m. p. 48°, not depressed on admixture with an authentic sample (see Table 1). The picrate, m. p. 238°, dichromate, m. p. 135°, and nitrate, m. p. 186°, were prepared. 5- and 2-Bromoquinoline are readily distinguished by infrared bands at 952 and 1082 $cm.^{-1}$, respectively.

Impure 8-bromoquinoline, recovered from the filtrate, gave, in alcohol, a picrate, m. p. 182—186°, which was fractionally crystallised. The least soluble fractions, m. p. >200°, were

discarded. Successive concentration and cooling of the mother-liquors gave fractions, m. p. 157—160°, 159—163°, and 161—164°. These on recrystallisation gave a picrate, m. p. 168°, not depressed on admixture with authentic 8-bromoquinoline picrate prepared as described in Table 1. The dichromate had m. p. 159—160°.

(b) *Preparation of* 5,8-*dibromoquinoline.* Quinoline (6·6 ml.), silver sulphate (16·5 g.), sulphuric acid (60 ml.), and bromine (5·2 ml.) were shaken until the bromine had reacted. The filtrate was brought to pH 2—3, and the white precipitate was filtered off, washed, and recrystallised from acetone, giving 5,8-dibromoquinoline (12·5 g.), m. p. and mixed m. p. 129—130°.

(c) *Reaction of quinoline* (0·15 *mole*) *with bromine* (0·1 *mole*). 5,8-Dibromoquinoline was separated from the reaction mixture by precipitation at about pH 2; then more alkali was added; an oily precipitate of monobromoquinolines began to appear at about pH 3. The 5- and 8-bromoquinolines were then extracted and separated as described above. Table 3

TABLE 3. *Yields in the reaction of bromine with a* 1·5-*fold excess of quinoline.*

Medium	5,8-Dibromo-quinoline (g.)	5-Bromo-quinoline (g.)	8-Bromo-quinoline (g.)
H_2SO_4, 5% SO_3	4·5	2·5	Picrate isolated
100% H_2SO_4 *	6·5	3·8	2·5
95% H_2SO_4	6·0	3·6	2·5
92% H_2SO_4	3·8	1·5	1·0
87% H_2SO_4	1·2	0	0
80% H_2SO_4	0	0	0

* We are indebted to Dr. R. J. Gillespie for this specimen.

summarises the yields obtained when the original reaction was carried out under various conditions. In each case, the reactants were quinoline (20 g.), silver sulphate (17 g.), and bromine (5·2 ml.) in sulphuric acid (100 ml.).

(d) *Isotope-dilution experiments.* The apparatus and general methods for using ^{82}Br have been described elsewhere.[12] Labelled bromine was prepared by warming bromine with irradiated $NH_4{}^{82}Br$ and removing the ^{82}Br by distillation *in vacuo*. This was allowed to react with the quinoline and silver sulphate as described above, and the mixture was diluted with the appropriate bromoquinoline, which was then recovered. Its radioactivity was determined after crystallisation (5-bromoquinoline generally as the oxalate, 8-bromoquinoline as the

TABLE 4. *Analysis, by the method of isotopic dilution, of the products of bromination of quinoline in* 98% *sulphuric acid.*

Expt.	Ratio, Quinoline : Bromine	Derivative produced: 5-Bromo (%)	8-Bromo (%)	5,8-Dibromo (%)
A	1·5 : 1	28	— [a, b]	43
B	1·5 : 1	29	29	— [a, c]
C	5 : 1	51	49	— [a, d]

[a] Not looked for. [b] By difference, 29%. [c] By difference, 42%. [d] By difference, 0%.

picrate) to constant specific activity, correction being made for radioactive decay. The total amount of mixed bromoquinolines produced was determined by extracting from an aliquot part of the reaction mixture all the organic product. This was made up to known volume in an appropriate solvent and its radioactivity was compared with that of a specimen of the original bromine, which had been converted into lithium bromide. The results of three experiments performed in this way are summarised in Table 4.

(e) *Bromination of quinoline under other conditions.* No bromo-product was obtained by shaking quinoline, bromine, and acetic acid with silver acetate, or by heating quinoline and bromine in concentrated nitric acid with silver nitrate. When quinoline (60 g.) in hydrochloric acid (150 ml.) was heated under reflux for 24 hr. with bromine (5·2 ml.) in chloroform (100 ml.), there were recovered after removal of chloroform (i) 3,6,8-tribromoquinoline (1·5 g.) (precipitated from strongly acid solution), m. p. and mixed m. p. 170°, (ii) 3,6-dibromoquinoline (2·5 g.) (precipitated at about pH 2·5), m. p. and mixed m. p. 128°.

Bromination of Derivatives of Quinoline.—(a) 3-*Bromoquinoline.* From approximately equimolar amounts of 3-bromoquinoline (3·7 g.) and bromine (1·2 ml.) with silver sulphate in sulphuric acid, there were obtained (i) 3,5,8-tribromoquinoline (1 g.) (precipitated by diluting

[12] de la Mare and Harvey, *J.*, 1956, 36.

the reaction mixture), m. p. and mixed m. p. 171—172° (from alcohol or acetone), and (ii) 3,5-dibromoquinoline [precipitated at pH 3 after removal of (i)] (1·3 g.), m. p. and mixed m. p. 86° (from alcohol or acetone).

(b) 5-*Bromoquinoline and* 8-*bromoquinoline.* These, on treatment as before with one equivalent of bromine, both gave 5,8-dibromoquinoline, m. p. 129°.

(c) 5,8-*Dibromoquinoline.* This, on treatment as before with one equivalent of bromine, reacted slowly. After 6 hr., the mixture was filtered and diluted with water. The white precipitate was 5,6,8-tribromoquinoline, m. p. 160° (lit.,[4b] 161—162°). It depressed considerably the m. p. of 3,5,8-tribromoquinoline, and its structure is proved by the demonstration that it is identical with the tribromoquinoline prepared by the bromination of 6-bromoquinoline (see below).

(d) 6-*Bromoquinoline.* This was brominated as before with one equivalent of bromine. The filtered mixture, on dilution, gave a precipitate, which gave 5,6,8-tribromoquinoline, m. p. and mixed m. p. 161—162° (from acetone).

Discussion

Earlier investigators have shown that, when quinoline is heated with bromine, only 3-substituted derivatives of quinoline are obtained, so that the initial attack under these conditions is on the pyridine (Py) ring. This orientation is maintained even for bromination in concentrated hydrochloric acid, which has an acidity,[13] as measured by H_0, of about −4. Since the acidic dissociation constant of the quinolinium cation [14,15] has $pK_a \sim 5$, the ratio, $[Q] : [QH^+]$, of free base to conjugate acid under these conditions must be very small. It seems therefore that it is not easy to effect attack by molecular bromine on the benzene (Bz) ring of a quinolinium cation.

Bromination in sulphuric acid, however, gives a completely different result. The entire product of substitution involves attack on the Bz-ring, so that the products of mono-bromination are 5- and 8-bromoquinoline, formed in nearly equal amounts. Dibromination gives a nearly quantitative yield of 5,8-dibromoquinoline; and substitution in the Bz-ring remains substantially complete even for tribromination, which gives 5,6,8-tribromoquinoline. The reactions are so simply performed that they give preparative routes to 5-bromo-, 5,8-dibromo-, and 5,6,8-tribromo-quinoline which are in our opinion the best yet recorded; the same method has been applied to the bromination of some other bromoquinolines with equal success, and it is suggested that this method will prove generally applicable. The preparation of 8-bromoquinoline by this route, though practicable, involves rather more difficulty, because 8-bromoquinoline picrate and other derivatives which we have tried are less easy to separate from the corresponding derivatives of 5-bromoquinoline and of unchanged quinoline.

It seems almost certain that the entity undergoing substitution in the bromination of quinoline in sulphuric acid is the quinolinium cation. This conclusion accords with the results obtained by Dewar and Maitlis,[1,2] and also with the views expressed by R. D. Brown;[3] nitration in sulphuric acid, which presumably also involves the quinolinium cation, gives 5- and 8-nitroquinoline in equal amount, whereas with nitric acid under less acidic conditions, substitution in, and possibly addition to, the Py-ring supervene.

It has been suggested[3] that the high proportion of di- and tri-bromination often observed in substitution in quinoline arises (as it almost certainly does in the bromination of aniline [16]) from the fact that the conjugate acid of the monobromo-product is a stronger acid than that of the starting material, so that dibromination, involving the monobromo-derivative as the free base, can compete with monobromination. It seems unlikely, however, that this explanation can apply to the experiments which we have carried out with anhydrous and slightly aqueous sulphuric acid as solvent. For, if formation of dibromoquinoline involved the free base of monobromoquinoline, the proportion of dibromination

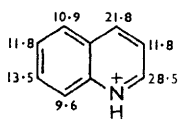
[13] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[14] Albert and Goldacre, *Nature*, 1944, **153**, 468.
[15] Knight, Willic, and Bowen, *J. Amer. Chem. Soc.*, 1954, **76**, 3780.
[16] Cf. de la Mare and Ridd, "Aromatic Substitution," Butterworths, 1959, p. 109.

should be substantially increased by increasing the water content of the medium. A change from anhydrous to 92% sulphuric acid should then increase considerably the proportion of free 5(or 8)-bromoquinoline, which accumulates during the reaction, whereas it would not change the amount of the quinolinium cation, since this is the bulk component of the protonation equilibrium. In fact, the results in Table 3 show that the ratio of di- to mono-bromination is little changed by altering the water content of the medium, though the total yield is reduced by making the reaction mixture sufficiently aqueous.* So probably both dibromination and monobromination involve entities of the same charge-type, and therefore both probably involve the conjugate acid.

The results in Table 4 show that the rates of monobromination in the 5- and the 8-position are the same, and also that 5- and 8-bromoquinoline must be brominated at almost equal rates, since the ratio of 5- to 8-bromoquinoline formed in the reaction is almost independent of the extent of dibromination. If the partial rate factors for bromination in the 5- and the 8-position were quite independent of the presence of a bromine substituent at the other position, then substitution in these positions could be considered independently, and the reaction of equimolar amounts of bromine and quinoline should lead to the formation of 25% of dibromoquinoline. Since the observed dibromination (43%) is substantially greater than this, in spite of the presence of a slight excess of quinoline, it follows that, under the experimental conditions described, the presence of a 5- or 8-bromine must increase the partial rate factor for substitution at the other position. This is somewhat surprising, since the usual effect of a bromine substituent is to reduce the rate of electrophilic substitution in the aromatic ring by a factor of about 10, both for bromination by molecular bromine and for nitration by the nitronium ion.[17] It is possible that the present divergence arises because the reaction mixture is heterogeneous.

The electrophilic reagent involved in attack on the quinoline under the conditions used in this work is almost certainly a positively charged species. Derbyshire and Waters [9] assumed that, for bromination in 90% sulphuric acid, the effective reagent is Br^+ or $BrOH_2^+$. It seems rather less likely that the latter ion is concerned in the present experiments, particularly those in which 100% sulphuric acid and oleum (5% SO_3) were used as solvents. It is possible that the Br^+ cation is associated covalently with sulphuric acid, perhaps as $BrH_2SO_4^+$, or $BrSO_3^+$.

In sulphuric acid as solvent, the isomeric proportions produced in nitration and bromination accord excellently. Dewar and Maitlis [1] calculated the π-electron contribution to the activation energy for nitration of the quinolinium ion, and obtained the results (in kcal. mole^{-1}) shown in the annexed diagram. Since the product of 8-substitution is formed in amount considerably smaller than would be predicted from the calculations, these authors suggest that the discrepancy is to be attributed to the electrostatic and inductive effect of the positive charge on the nitrogen atom in the quinolinium ion. Presumably this effect would also be significant at the 3-position, so the preference for the entry of the third halogen into the 6-rather than the 3-position may be explained similarly. The results of the present investigation accord with the theoretical calculations to the same degree of approximation as is found for nitration.



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* It should be appreciated that dibromoquinoline is isolated in these preparative experiments more readily than the monobromoquinolines.

[17] Cf. de la Mare and Robertson, *J.*, 1948, 100.