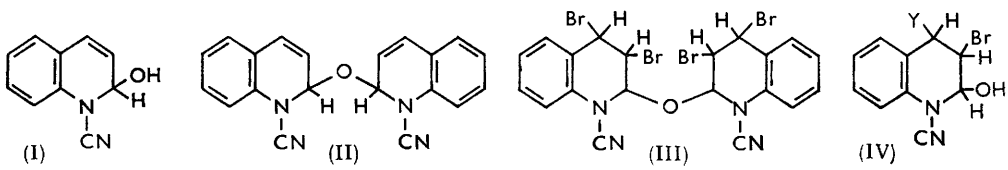
48. N-*Substituted Quinolinium Ions. Part II.*[1] *The Mechanism of Formation of Bromoquinolines from the* N-*Cyanoquinolinium Ion.*

By M. D. Johnson and J. H. Ridd.

The reaction of the *N*-cyanoquinolinium ion with aqueous solutions of bromine is ascribed to the intermediate formation of the pseudo-base, 1-cyano-1,2-dihydro-2-hydroxyquinoline (I). The bromination of this pseudo-base has been studied in a number of media; the initial reaction leads to a mixture of tetrahydroquinolines, resulting from the addition of a bromine cation at the 3-position and a nucleophile (*e.g.*, bromide ion, acetate ion, or hydroxide ion) at the 4-position. In acidic media these tetrahydroquinolines undergo elimination to give 3-bromoquinoline in about 50% yield. With an excess of bromine, substitution occurs also at the 6- and the 8-position. Related reactions of the pseudo-base (I) in chloroform are complicated by the formation and bromination of the corresponding ether (II). These reactions are discussed in relation to the bromination of quinoline at low acidities.

The bromination of quinoline in media of moderate or low acidity leads to substitution at the 3-, 6-, and 8-position in that order and affords a considerable amount of 3,6-dibromoquinoline even when equivalent quantities of the reagent are used. Two explanations have been suggested for this orientation: one involves the bromination of the neutral quinoline molecule;[2] the other requires formation of a quinolinium ion, followed by reaction with a nucleophile at the 2- or the 4-position to give a substituted dihydroquinoline;[3,4] this is then assumed to undergo bromination at the stated positions. Recent arguments[3] have favoured the second hypothesis and the present study has been designed to test this hypothesis by experiments with the *N*-cyanoquinolinium ion.

No reaction between bromine and the *N*-cyanoquinolinium ion in concentrated perchloric acid was observed in a period of hours, but, with an equivalent concentration of bromine in *ca.* 2M-perchloric acid, the disappearance of the bromine was instantaneous and the products were 3-bromoquinoline (*ca.* 47%), 3,6-dibromoquinoline (*ca.* 26%), and unchanged quinoline (*ca.* 16%). The results in Part I[1] have shown that, at low acidities,



the *N*-cyanoquinolinium ion reacts with water to form the corresponding pseudo-base (I) and that this undergoes an acid-catalysed decomposition to quinoline. An acid-catalysed reaction to the corresponding ether (II) can also be observed; this ether undergoes acid-catalysed decomposition to quinoline. Both the pseudo-base (I) and the ether (II) react very readily with bromine and this presumably explains the apparent reactivity of the *N*-cyanoquinolinium ion at low acidities.

The reaction of the pseudo-base (I) with bromine has been studied in buffer solutions to minimise the acid-catalysed decomposition and etherification. Under these conditions, and with an equimolar solution of bromine, the first product involves addition to the 3,4-double bond, not substitution at the 3-position. Usually a mixture of addition

[1] Part I, preceding paper.
[2] Brown, "Current Trends in Heterocyclic Chemistry," Butterworths Scientific Publ., London, 1958, p. 13.
[3] Dewar and Maitlis, *J.*, 1957, 944.
[4] Brown and Harcourt, *J.*, 1959, 3451.

products is obtained, depending on the conditions of reaction. The three results described below are selected from a large number of similar experiments and illustrate some of the products. All the addition products from the pseudo-base (I) were viscous liquids that decomposed readily and were difficult to purify.

(*a*) Bromination of the pseudo-base (I) in aqueous methanol buffered with disodium hydrogen phosphate gave a product analysing approximately for the addition of hypobromous acid, but with too high a content of carbon. A small quantity of the tetrabromo-ether (III) was afterwards obtained from the viscous product by chromatography.

(*b*) Bromination in anhydrous methanol buffered with sodium acetate and saturated with sodium bromide gave a product whose analysis agreed fairly well with addition of molecular bromine. This compound was particularly unstable and readily lost hydrogen bromide and cyanogen bromide on warming or at very low pressures.

(*c*) Bromination in anhydrous methanol buffered with sodium acetate and saturated with lithium chloride gave a product whose analyses were accurate for addition of bromine chloride. This compound was markedly more stable than that from (*b*) above.

Fragmentary evidence was obtained for the formation of other addition products. Thus bromination of the pseudo-base (I) in anhydrous methanol saturated with sodium acetate probably involved mainly the addition of bromine acetate, for the product obtained gave evidence of carbonyl absorption in the infrared spectrum and methyl absorption in the proton magnetic resonance spectrum. One other addition product was described in Part I; it was obtained crystalline on bromination of the *N*-cyanoquinolinium ion in acetic anhydride and its analyses were correct for an acetoxy-dibromo-cyanotetrahydroquinoline, but the positions of the added groups are not known.

All these addition products from the pseudo-base (I) and that from the *N*-cyanoquinolinium ion undergo a double elimination in strongly acidic media, to give 3-bromoquinoline in 30—72% yield; the bromine atom can therefore be assigned to the 3-position. Most of these addition products can therefore be written as (IV) where Y is a nucleophilic group or atom (OH, OAc, Br, Cl). They are presumably formed by electrophilic attack of bromine at the 3-position, followed by the addition of one or other of the available nucleophiles in the medium to the 4-position. This addition can gave rise to four possible geometrical isomers, each existing as a number of non-separable conformational isomers. The fact that the addition compounds were nearly all obtained as viscous liquids suggests that several geometrical isomers are present in each case; this point is being investigated further.

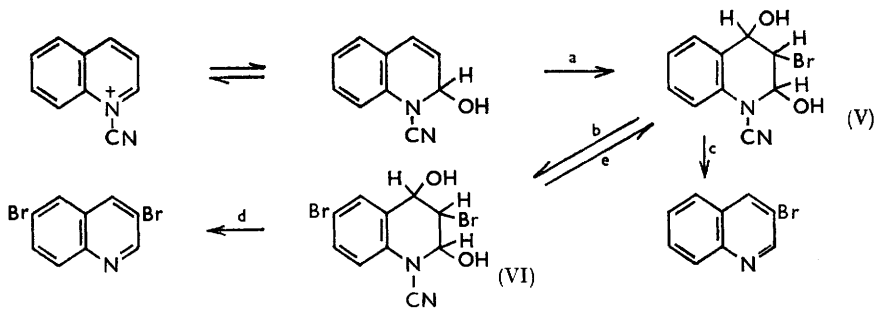
In the presence of an excess of bromine the initial fast reaction of the pseudo-base (I) to give the addition products (IV) is followed by slower substitution in the homocyclic ring. When a solution of the pseudo-base in aqueous ethanol buffered with disodium hydrogen phosphate is treated with a two-fold excess of bromine and then made strongly acidic, the product is a mixture of 3-bromo- and 3,6-dibromo-quinoline. A similar result is obtained by treating the addition products (IV) with an equimolar amount of bromine under similar conditions. The direction of electrophilic attack to the 6-position can therefore be considered to be a property of the preliminary addition product (IV). When a solution of the pseudo-base in aqueous ethanol is treated with a large excess of bromine under similar conditions and then made strongly acidic, the main product is 3,6,8-tribromoquinoline.

Comparison of the infrared spectra of the bromo-compounds obtained under all the above conditions with those for 6-bromo-, 8-bromo-, 6,8-dibromo-, and 3,8-dibromoquinoline indicated that no detectable amount of these other bromoquinolines is formed. In the pseudo-base (I), the 3-position is therefore the most reactive centre for electrophilic attack, and in the addition products (IV) the reactivity of the 6-position considerably exceeds that of the 8-position. The preferential reactivity of the 3-position is unchanged when the pseudo-base is brominated in aqueous acetic acid containing sodium acetate, although the yield of 3-bromoquinoline may be somewhat reduced owing to the instability

of the pseudo-base in this medium. Under all the conditions studied, the formation of the addition products (IV) appeared to be almost instantaneous but the subsequent reactions in the homocyclic ring are very much slower.

Bromination of the pseudo-base (I) in chloroform leads mainly to the tetrabromo-ether (III). This is not unexpected because of the rapid acid-catalysed etherification of the pseudo-base in the absence of bromine. The tetrabromo-ether has also been prepared by the direct bromination of the ether (II). A competitive bromination of anisole and the pseudo-base in chloroform solution gave no bromoanisoles, but a somewhat reduced yield of the tetrabromo-ether, illustrating the high reactivity of the 3,4-double bond in the pseudo-base.

The above experiments make it possible to set out the annexed fairly detailed scheme for the formation of bromoquinolines from the *N*-cyanoquinolinium ion in aqueous solution. It is considered that a small equilibrium concentration of the pseudo-base is formed and with bromine rapidly forms the substituted tetrahydroquinoline (V). These tetrahydroquinolines appear to be much more stable to acid than the pseudo-base [*i.e.*, reaction (c) is slow] and hence the concentration of the tetrahydroquinoline (V) should soon exceed that of the pseudo-base. Thus, although the rate coefficient for reaction (b) is much less than for (a), the build-up of the tetrahydroquinoline (V) is sufficient to allow the reaction (b) to take place to an appreciable extent. Reactions (c), (d), and (e) are much slower than (a) and (b) and so the amounts of 3-bromo- and 3,6-dibromo-quinoline formed are directly proportional to the concentrations of the intermediate tetrahydroquinolines (V) and (VI) respectively. The larger the build-up of the tetrahydroquinoline (VI), the greater the amount of 3,6-dibromoquinoline in the final product.



The interest in this reaction scheme comes from the possibility that bromination of quinoline at low acidities (*e.g.*, in acetic acid) follows a related scheme, with possibly the *N*-bromoquinolinium ion taking the place of the *N*-cyanoquinolinium ion and other nucleophiles taking the place of the hydroxide ion. The following points support this suggestion: (1) The orientation in the bromination of the *N*-cyanoquinolinium ion and the relative reactivity of the carbon atoms is the same as in the bromination of quinoline, and the extensive formation of polybromoquinolines is also common to both reactions.[5] The slightly greater proportion of polybromoquinolines in the bromination of quinoline is to be expected because of an additional equilibrium between quinoline and the *N*-substituted quinolinium ion, which increases the relative build-up of the tetrahydroquinolines of the type (IV). (2) The formation of tetrahydroquinolines related to (IV) is not limited to aqueous solution, for a similar intermediate has been detected in the bromination of the *N*-cyanoquinolinium ion in acetic anhydride. (3) The high reactivity of the pseudo-base (I) towards bromine is probably characteristic of other 1,2-dihydroquinolines and so only traces of such compounds would have to be formed to determine the products.

The argument that derivatives of 1,2-dihydro- and 1,2,3,4-tetrahydro-quinoline are intermediates in the bromination of quinoline at low acidities is in agreement with the

[5] Ridd and Smith, unpublished observations.

suggestions by Dewar and Maitlis,[3] but differs from the more recent conclusions of Brown and Harcourt.[4] The last two authors have discounted the role of substituted 1,2-dihydroquinolines in these reactions partly because they believe that weak nucleophiles should react with *N*-substituted quinolinium ions at the 4-position and partly because calculations of charge densities suggest that substituted 1,2-dihydroquinolines should undergo preferential reaction with electrophilic reagents in the homocyclic ring. The first point has been discussed in Part I, and the second appears to underestimate the reactivity of the isolated double bond. Nevertheless, we do not wish to emphasise the importance of the initial 1,2-addition, because, where a 1,2,3,4-tetrahydroquinoline derivative is formed, the question of orientation of the initial addition is probably less important as far as the overall product is concerned than the nature and direction of the two acid-catalysed eliminations from the tetrahydroquinoline derivative. This argument suggests that several new factors including the stereochemistry of addition and conformational control of elimination can in principle influence the products of electrophilic substitution of quinoline.

Experimental

In the following work, quinoline and 3-bromo-, 3,6-dibromo-, and 3,6,8-tribromo-quinoline were identified by comparison of their infrared spectra and m. p.s (or the m. p. of the corresponding picrate) with those of authentic samples. In each case, no evidence could be obtained for 5-, 6-, or 8-bromoquinoline, 3,8-, or 5,8-dibromoquinoline, or 3,5,8-tribromoquinoline, though their infrared spectra were available.

Bromination of the N-*Cyanoquinolinium Ion in Perchloric Acid.*—(a) *In* 72% *perchloric acid.* Bromine (0·8 g., 0·005 mole) was added to a solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (0·86 g., 0·005 mole) in 72% perchloric acid (10 ml.). After 1 hr. the bromine was removed by warming under reduced pressure, and water (50 ml.) was added. The solution was boiled for 1 hr., made alkaline, and extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and on evaporation gave only pure quinoline.

(b) *In* 2M-*perchloric acid.* *N*-Cyanoquinolinium fluoroborate (1·21 g., 0·005 mole) in 60% perchloric acid (35 ml.) was added to a solution of bromine (0·8 g., 0·005 mole) and 60% perchloric acid (61 ml.) in water (350 ml.) with stirring. The bromine colour disappeared almost immediately to give a faint yellow-green solution. After a further ½ hour's stirring the solution was heated on a water bath for 3 hr., then extracted with ether. Dilute alkali was added to the aqueous solution until the acid concentration was approximately 0·5M, and the solution was again extracted with ether. The ethereal extract, when worked up in the usual way, gave mainly 3,6-dibromoquinoline with a trace of 3-bromoquinoline. The aqueous phase was again treated with alkali (to pH 3) and extracted with ether. The ethereal extract afforded 3-bromoquinoline with a trace of quinoline. The aqueous phase was made alkaline to pH 10 and extracted with ether; the product removed was quinoline. Approximate yields were 3,6-dibromoquinoline 0·38 g. (26%), 3-bromoquinoline 0·5 g. (47%), quinoline 0·1 g. (16%), each ±10%.

Bromination of 1-*Cyano*-1,2-*dihydro*-2-*hydroxyquinoline.*—(a) *In phosphate-buffered aqueous methanol.* Bromine (0·48 g.) was added to a solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (0·52 g.) in 1 : 1 v/v aqueous methanol (10 ml.) in the presence of an excess of disodium hydrogen phosphate (1 g.; anhydrous). The solution was poured into water (250 ml.) and extracted with chloroform. The chloroform solution was washed with dilute potassium hydrogen carbonate solution and with very dilute hydrochloric acid, and dried (Na_2SO_4). On evaporation a highly viscous liquid was produced (0·57 g., 72%, based on the addition of BrOH) (Found: C, 46·3; H, 4·3; Br, 29·6; N, 9·6. Calc. for $C_{10}H_9BrN_2O_2$: C, 44·6; H, 3·4; Br, 29·7; N, 10·4%).

(b) *In acetate-buffered anhydrous methanol in the presence of an excess of bromide ion.* Bromine (2·9 g.) was added to a solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (3·19 g.), sodium acetate (1·0 g.), and sodium bromide (saturated solution). The solution was poured into water and extracted with chloroform. The chloroform solution was worked up as described above, to give a highly viscous liquid (Found: C, 37·4; H, 3·1; Br, 47·7; N, 8·4. Calc. for $C_{10}H_8Br_2N_2O$: C, 36·2; H, 2·4; Br, 48·2; N, 8·4%). Attempts to prepare products with

improved analytical figures were unsuccessful, for in the recovery procedure hydrogen bromide and cyanogen bromide were readily liberated, even when washing was avoided.

(c) *In acetate-buffered anhydrous methanol in the presence of an excess of chloride ion.* Reaction was effected as described in (b) above, but in the presence of lithium chloride in place of sodium bromide. The product from the chloroform extract was a highly viscous liquid (3·12 g.) (Found: C, 41·3; H, 3·35; N, 9·9; Hal., 40·1. Calc. for $C_{10}H_8BrClN_2O$: C, 41·8; H, 2·8; N, 9·75; Hal., 40·3%). The infrared spectra of intermediates (b) and (c) were consistent with the addition of bromine and bromine chloride, respectively.

(d) *In acetate-buffered anhydrous methanol.* Reaction was effected as described in (b), but with sodium acetate (5 g.) in place of sodium bromide. The product was a highly viscous liquid (4·05 g., 70% based on BrOAc addition) (Found: C, 47·1; H, 3·4; Br, 31·0; N, 10·4. Calc. for $C_{12}H_{11}BrN_2O_3$: C, 46·3; H, 3·6; Br, 25·7; N, 9·0%). This liquid was partially dissolved in acetone and the insoluble crystalline residue was filtered off. The filtrate was evaporated to dryness to give a viscous liquid (3·54 g., 61% based on BrOAc addition) (Found: C, 46·6; H, 3·6%). The residue after recrystallization from benzene had m. p. 156—157° (0·5 g.) (Found: C, 37·8; H, 1·6; Br, 47·0; N, 8·9%).

(e) *In chloroform.* Bromine (0·48 g.) was added to a stirred solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (0·52 g.) in chloroform (30 ml.). A slight orange residue was filtered off and the filtrate was evaporated to dryness under reduced pressure. The white crystalline residue had m. p. 100—108° (0·74 g., 79%) (Found: C, 37·7; H, 3·2; Br, 46·4; N, 8·9. Calc. for $C_{20}H_{14}Br_4N_4O$: C, 37·2; H, 2·2; Br, 49·4; N, 8·7%). On recrystallization from acetone the product had m. p. 124—126° (Found: C, 40·4; H, 3·4; Br, 44·5; N, 8·1%). The initial product lost bromide ion readily in solution, as shown by the immediate precipitation of silver bromide from aqueous-methanolic silver nitrate.

(f) *In chloroform in the presence of sodium acetate.* Reaction as described for (e), but with sodium acetate suspended in the solution, gave an identical product (0·75 g.).

Decomposition of the Intermediates.—The intermediates were warmed for upwards of 1 hr. with concentrated hydrochloric acid, then diluted with an equal volume of water and filtered. The filtrate was extracted with ether, made alkaline, and again extracted with ether. This latter extract was worked up for quinoline and 3-bromoquinoline as described above. Products obtained were:

Intermediate	a	b	c	d	e	g	h
3-Bromoquinoline (%; ± ~10%)	32	43	62	50	49	55	72
Quinoline (%; ± ~5%)	4	5	4	7	10	0	—

The intermediate (g) was obtained by treatment of the intermediate (d) with silver nitrate in aqueous methanol. The precipitate of silver bromide was filtered off and the filtrate was poured into water and extracted with ether. The ether extract was worked up as described above to give the intermediate (g). The intermediate (h) is the acetoxy-dibromo-cyano-tetrahydroquinoline described in Part I.

Dibromination of 1-Cyano-1,2-dihydro-2-hydroxyquinoline.—Bromine (1·9 g., 0·012 mole) was added to a stirred solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (1·0 g., 0·006 mole) in ethanol (40 ml.) and water (50 ml.) in the presence of an excess of disodium hydrogen phosphate (4 g., anhydrous). After 15 min. the solution was poured into water (1200 ml.) and extracted with ether. The extract was evaporated to dryness and the residue heated for ½ hour with concentrated hydrochloric acid (10 ml.) on the water bath. The solution was diluted with an equal volume of water and extracted with ether. The aqueous phase was then worked up by extraction with ether at pH 0—1 and pH 3, to give 3,6-dibromo- (0·43 g., 26%) and 3-bromo-quinoline (0·32 g., 26%), respectively.

Tribromination of 1-Cyano-1,2-dihydro-2-hydroxyquinoline.—Bromine (9·0 g., 0·056 mole) was added to a stirred solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (0·5 g., 0·0029 mole) in ethanol (100 g.) and N/15-disodium hydrogen phosphate (150 ml.). After 30 min., concentrated hydrochloric acid (100 ml.) was added and the ethanol was evaporated. The insoluble portion was filtered off and the filtrate was diluted to an acid concentration of about 1·5M. The precipitate was filtered off and recrystallized from acetone to give pure 3,6,8-tribromoquinoline (0·49 g., 50%). The acid filtrate gave 3,6-dibromoquinoline (0·11 g., 10%).

Bromination of 1-Cyano-1,2-dihydro-2-hydroxyquinoline in Competition with Anisole.—Bromine (0·5 g., 0·0037 mole) was added to a stirred solution of 1-cyano-1,2-dihydro-2-hydroxyquinoline (0·64 g., 0·0037 mole) and anisole (0·40 g., 0·0037 mole) in chloroform (30 ml.). The

orange precipitate was filtered off and the filtrate evaporated to dryness. To the residue was added anhydrous methanol (3 ml.), and the crystals were filtered off, washed with anhydrous methanol (2 ml.), and dried *in vacuo* [yield 0·41 g., 35%; identical with the intermediate (e)]. The filtrate and washings were evaporated to dryness and extracted with hot water. The aqueous solution was cooled, filtered, and extracted with ether. The extract afforded only unchanged 1-cyano-1,2-dihydro-2-hydroxyquinoline and no bromoanisoles could be detected. A control experiment in the absence of anisole gave the intermediate (e) in 65% yield.

Bromination of Di-(1-cyano-1,2-dihydro-2-quinolyl) Ether.—Bromine (0·19 g.) was added to a solution of the ether (0·2 g.) in chloroform (30 ml.). The product was worked up as described for the intermediate (e) and shown to be identical with that intermediate.

Acid-catalysed Etherification of 1-Cyano-1,2-dihydro-2-hydroxyquinoline.—1-Cyano-1,2-dihydro-2-hydroxyquinoline (0·5 g.) in chloroform (30 ml.) was treated with a trace of dry hydrogen bromide. After 2 min., light petroleum (b. p. 60—80°) was added and the precipitate was filtered off. The filtrate was evaporated to dryness; the crystalline, residue when washed with ethanol, was shown to be di-(1-cyano-1,2-dihydro-2-quinolyl) ether (m. p.; infrared spectrum) (0·07 g., 15%).

This work was carried out during the tenure of an I.C.I. Fellowship by one of us (M. D. J.). We thank Professor P. B. D. de la Mare for many helpful discussions.

William Ramsay and Ralph Forster Laboratories,
University College, Gower Street,
London, W.C.1.

[*Received, August 17th,* 1961.]