[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

# Aza-Aromatic Substitution. I. The Selective Bromination of the Quinoline Nucleus[1]

JOHN J. EISCH

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The complex $C_9H_7NBr_2$(I), formed by the interaction of quinoline and bromine in inert solvents, displayed properties suggestive of the formulation, $C_9H_7N\rightarrow \overset{\delta+}{Br}\cdots\overset{\delta-}{Br}$. Sensitive to light and heat, I decomposed smoothly in the dark in refluxing chloroform or carbon tetrachloride to yield only 3-bromoquinoline and quinoline hydrobromide dibromide. Inclusion of pyridine as a hydrogen bromide scavenger gave excellent yields of the 3-bromo isomer exclusively. In glacial acetic acid decomposition of I led predominantly to 3,6-dibromo- and 3,6,8-tribromoquinolines, regardless of added sodium acetate. Preliminary indications are that the sites brominated are generally those possessing higher $\pi$-electron densities in the neutral quinoline molecule.

In comparison with the copious effort expended in elucidating the substitutional chemistry of aromatic hydrocarbons, aza-aromatic systems such as pyridine and quinoline have received considerable attention only recently.[2-5] Although the nitration[2] and the bromination[3,4] of quinoline in concentrated sulfuric acid (in both cases leading to the same ratio of 5- and 8- substitution) can be correlated admirably with the calculated localization energies of the quinolinium ion,[2] the substitutional behavior of quinoline under other experimental conditions is not well understood. For example, although calculations based upon various molecular orbital approximations suggest that the quinolinium ion should undergo electrophilic substitution at C-5 and C-8 and that neutral quinoline should undergo substitution at C-8, C-6, and C-3, the results of thermal bromination do not support these predictions.[5] Thus the heating of quinolinium tribromide at 200°[6a] and the vapor phase bromination of quinoline at 300°[6b] both lead to modest yields of solely 3-bromoquinoline.

In the present work the interaction of quinoline and bromine was studied under milder conditions to search for isomeric bromoquinolines and to learn more about the factors determining the sites of bromination on the unprotonated quinoline molecule. In the stringent bromination procedures previously reported[5,6] it was uncertain whether monobromoquinolines other than the 2- and 3-bromo isomers had been formed.

Admixture of equimolar quantities of quinoline and bromine in an inert solvent led to a quantitative precipitation of a new orange adduct, $C_9H_7NBr_2$(I), whose bromine was titrable by the iodine-sodium thiosulfate method.[7] As the complex I was sensitive to thermal and photochemical decomposition, spectral studies were performed on freshly prepared samples of I and exposure to light and heat was minimized. The infrared spectrum of the solid complex resembled that of quinoline, but noteworthy spectral shifts in quinoline's 940 cm.$^{-1}$ band (ring hydrogen deformations) and its 1600 cm.$^{-1}$ trio (C=N and C=C ring stretching vibrations) were observed.[8] Complex I exhibited its ring hydrogen deformation band at 950 cm.$^{-1}$, and the ring vibration trio at 1600 cm.$^{-1}$ was somewhat compressed (1595–1625 cm.$^{-1}$).

The exact nature of this quinoline-bromine complex may have an important bearing on the course of the selective and facile bromination uncovered in this study. Although the stoichiometry of the solid complex demonstrates the presence of equimolar proportions of quinoline and bromine, further work is underway to determine the stoichiometry and the structure of quinoline-bromine

(1) Presented at the 137th American Chemical Society Meeting, Cleveland, Ohio, April 5–14, 1960. A preliminary communication of a portion of this work appeared in *Chem. & Ind.*, 1449 (1959).

(2) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 944, 2518, 2521 (1957).

(3) (a) R. D. Brown, "Heterocyclic Chemistry," A. Albert, ed., Butterworths Scientific Publications, London, 1958, pp. 13–19; (b) R. D. Brown and R. D. Harcourt, *J. Chem. Soc.*, 3451 (1959); (c) *ibid., Tetrahedron*, **8**, 23 (1960).

(4) P. B. D. de la Mare, M. Kiamud-Din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960).

(5) *Cf.* J. Eisch and H. Gilman, *Chem. Revs.*, **57**, 525 (1957), for a recent survey of aza-aromatic substitution.

(6) (a) A. Claus and F. Collischonn, *Ber.*, **19**, 2763 (1886); (b) H. E. Jansen and J. P. Wibaut, *Rec. trav. chim.*, **56**, 699 (1937).

(7) E. Grimaux, *Bull. Soc. Chim. Paris*, [2], **38**, 124 (1882), reported a red quinoline tetrabromide adduct and N. N. Lubavin, *Russ. J. Phys.-Chem. Soc.*, **18**, 434 (1886), obtained a product, $C_9H_7NBr_2$, m.p. 92–100°, by the action of bromine on quinoline hydrobromide and subsequent recrystallization from ethanol. As both Grimaux's and Lubavin's adducts were subjected to considerable heating, their products were probably perbromides of quinoline hydrobromide; $C_9H_7NHBr_3$ melts at 98°.

(8) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Wiley, New York, 1958, pp. 81–83. Bands in the 900–1000 cm.$^{-1}$ region are assignable to out-of-plane hydrogen deformations of the quinoline system. In the present work it was noted that quinoline methiodide and the 4-, 5-, and 8- bromoquinolines (vicinally trisubstituted benzene or pyridine systems) have their most prominent band in this region at 960 ± 10 cm.$^{-1}$. In comparison, the 2-, 3-, 6-, and 7-bromoquinolines (1,2,4-trisubstituted) display their corresponding band at 939 ± 4 cm.$^{-1}$.

TABLE I

THE DECOMPOSITION OF THE QUINOLINE-BROMINE COMPLEX(I)

| Moles of I | Reaction Conditions: Time, hr. | Temp. | Solvent | Products, %: 3-Bromo | 3,6-Dibromo | 3,8-Dibromo- | 3,6,8-Tribromo | Quinoline, recovered |
|---|---|---|---|---|---|---|---|---|
| 0.20 | 8 | 65 | $CHCl_3$ | 21 | — 12[a] | — | — | 63 |
| 0.20 | 5 | 70 | $CCl_4$ | 43 | 2 5[a] | — | — | 41 |
| 0.20 | 14 | 120 | HOAc | 3 | — 15[a] | — | 8 | 60 |
| 0.20 | 8 | 70 | HOAc + NaOAc (anhyd., 0.4 m.) | — | 8 | — | 7[b] | 51 |
| 1.00 | 3 | 190 ± 5 | Molten | 46 | + | 1 | [c] | 22 |
| 1.00 | 22 | 77 | $CCl_4 + C_5H_5N$ | 82 | 1.5 | + | + | 10 |
| 1.00 | 22 | 77 | $CCl_4 + C_5H_5N$[d] | 77 | + 5[a] | + | + | 8 |

[a] Combined amount of 3,6- and 3,8- dibromoquinolines. [b] *Ca.* 10% yield of polybromocarbostyrils was also isolated. [c] *Ca.* 5% yield of crude 3,6,8-tribromoquinoline admixed with ill-defined substances also obtained. [d] Light, moisture, and oxygen excluded.

complexes in solution.[9] Additional spectral study will aim at distinguishing among the following possibilities for the 1:1 quinoline-bromine complex in solution: a) coordination of the unshared electron pair of quinoline with the bromine molecule to form the structure $C_9H_7N\text{—}\overset{\delta+}{Br}\cdots\overset{\delta-}{Br}$ (analogous to $C_9H_7\overset{+}{N}\text{—}CH_2I^-$); b) charge-transfer bonding through the $\pi$-electron cloud of quinoline, $[C_9H_7N]^+ \rightarrow Br_2^-$[10]; c) dicoordinate complexation of the type $(C_9H_7N)_2Br^+Br_3^-$[11]: and d) 1,2- or 1,4-addition of bromine to quinoline.[12]

Warming dry solutions of the quinoline-bromine complex (I) in the dark caused decomposition with resulting facile bromination of the quinoline nucleus under 100°. The hydrogen bromide liberated protonated the unchanged quinoline-bromine complex according to Equation 1:

$$2C_9H_7NBr_2 \xrightarrow[\Delta]{} \underset{\text{II}}{C_9H_6NBr} + C_9H_7NHBr_3 \quad (1)$$

The monobromo product II proved to be exclusively 3-bromoquinoline by comparison of its infrared spectrum with authentic spectra of the seven isomeric bromoquinolines. Depending upon experimental conditions, varying amounts of polybromination accompanied reaction 1. The products found in these cases were always 3,6-dibromoquinoline, 3,8-dibromoquinoline, and 3,6,8-tribromoquinoline, together with polybromocarbostyrils in certain runs. An excellent preparative procedure for the selective bromination of the quinoline nucleus at C-3 consisted in decomposing the complex I in a carbon tetrachloride slurry while slowly adding one equivalent of pyridine as a hydrogen-bromide scavenger:

$$C_9H_7NBr_2 + C_5H_5N \xrightarrow[\Delta]{} C_9H_6NBr + C_5H_5NHBr \quad (2)$$

The results of decomposing I in solution and in the molten state are given in Table I. Three trends in the nature of the products are noteworthy: a) the sites of bromination are consistently the 3-, 6-, and/or 8- positions of quinoline, to the exclusion of the other possible sites; b) the 3- position is by far the most readily brominated under these conditions, no other monobromoquinoline being detected; and c) glacial acetic acid pronouncedly favors polybromination in the decomposition of I, while decomposition in carbon tetrachloride, chloroform, or in the molten state leads to facile and selective monobromination at C-3, with very minor amounts of polybromination.

The ease with which quinoline undergoes nuclear bromination with bromine alone below 100° is at variance with the previous opinion[6] that the bromination of quinoline is very slow below 200°. In this study it was shown that quinoline-bromine solutions do undergo a photocatalyzed bromination reaction. However, the fact that the quinoline-bromine complex(I) decomposes smoothly in a thermal process, even when light and oxygen are excluded and highly purified reagents are used, suggests that a polar bromination process may predominate in the dark. Although a decision between a radical or polar process cannot be made unequivocably at this time, certain other factors also support a polar process for the dark reaction. In the concentrated solutions or slurries employed, the quinoline-bromine complex(I), $C_9H_7N \rightarrow \overset{\delta+}{Br}\cdots\overset{\delta-}{Br}$, is probably an important molecular species. This potential source of a positively polarized bromine moiety could permit electrophilic attack upon uncomplexed quinoline in equilibrium with I:

(9) Quinoline and bromine have been shown to form an equimolar complex in carbon tetrachloride solution. An ultraviolet study of the formation constant of this complex, as well as the search for other intermediates in the bromination of quinoline, is currently being conducted by Dr. Bruno Jaselskis and the present worker in these laboratories.

(10) W. Slough and A. R. Ubbelohde, *J. Chem. Soc.*, 911 (1957).

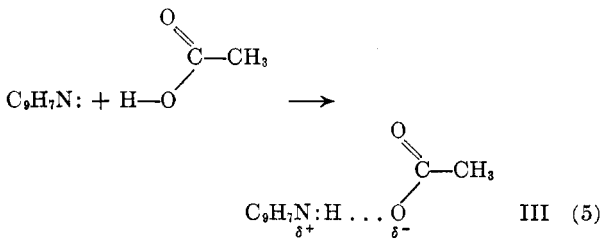
(11) *Cf.* P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *Chem. & Ind.*, 727 (1959), for the preparation of the perchlorates of the diquinoline- and diisoquinolinebromine cation.

(12) *Cf.* P. B. D. de la Mare, M. D. Johnson, and J. H. Ridd; *Chem. & Ind.*, 1505 (1960).

$$C_9H_7NBr_2 \rightleftharpoons C_9H_7N + Br_2 \quad (3)$$

$$C_9H_7N\overset{\delta+}{Br} \ldots \overset{\delta-}{Br} + C_9H_7N \longrightarrow C_9H_6NBr + C_9H_7NHBr \quad (4)$$

The equilibrium indicated in Equation 3 should be strongly dependent upon the solvating properties of the solvent employed. In glacial acetic acid the dissociation of I should be promoted by the hydrogen-bond solvation between quinoline and the acid (Equation 5)[13]:



$$C_9H_7N: + H{-}O(C{=}O){-}CH_3 \longrightarrow C_9H_7N{:}H \ldots O(C{=}O){-}CH_3 \quad \text{III} \quad (5)$$

As a result molecular bromine should be present to a large extent in acetic acid. It is believed that the greater amount of polybromination in this solvent, compared with chloroform or carbon tetrachloride, is due to the attack of the more reactive (hence less selective) free bromine on the quinoline nucleus. In acetic acid, moreover, the species undergoing bromination would be solvated quinoline III. This positively polarized entity should be less receptive to attack by a polarized bromine molecule ($\overset{\delta+}{Br} \cdots \overset{\delta-}{Br} \cdots$ HOAc) than uncomplexed quinoline. It is reasonable to assume that the 3-bromoquinoline (or the 6- and 8-isomers) produced upon bromination is solvated less firmly by acetic acid and hence less deactivated to further bromination than is quinoline itself. This follows from the observations that quinoline is 150 times stronger as a base in water than 3-bromoquinoline[14] and that the extent of hydrogen bonding between an amine and methanol is a function of the amine's basicity.[15] Hence, in acetic acid the monobromoquinolines are brominated to dibromo- and tribromoquinolines preferentially.

An alternative explanation for the polybromination in glacial acetic acid might appear to be the protonation of the unreacted quinoline by the hydrogen bromide liberated in the formation of a monobromoquinoline,[3a] as in Equation 4. The unprotonated bromoquinoline might then undergo further bromination faster than quinoline hydrobromide, resulting in much recovered quinoline and extensive polybromination. That this viewpoint is inadequate was demonstrated by decomposing the complex I in glacial acetic acid containing anhydrous sodium acetate. Such a buffer system would be expected to scavenge any hydrogen bromide liberated. Again, however, polybromination predominated (51% recovered quinoline), accompanied by small amounts of polybromocarbostyrils.

The treatment of quinoline derivatives with bromine in carbon tetrachloride with the slow introduction of pyridine as a hydrogen bromide scavenger has proved to be a superior method for brominating the 3-position in high yield under mild conditions. Indeed, the bromination of other aza-aromatic heterocycles such as pyridine and isoquinoline as well as aromatic amines by this method shows great promise.[1] It is interesting to note that 6- and 8-bromoquinolines were readily brominated by this technique, whereas 3-bromoquinoline was almost wholly untouched under the same experimental conditions. This indicates that the 3,6- and 3,8-dibromoquinolines isolated from decomposing I in carbon tetrachloride probably arose from the further bromination of small amounts of 6- and 8-bromoquinolines initially formed, rather than from the continued bromination of 3-bromoquinoline.

The sites undergoing bromination in quinoline can be correlated better with the sites of enhanced $\pi$-electron charge density in the ground state of this heterocycle[5] than with the localization energies of quinolinium-like species.[2] For the neutral quinoline molecule approximate molecular-orbital calculations[16] suggest an order of decreasing $\pi$-electron densities of C-8 > C-6 > C-3. Indeed, bromination was observed only at these positions in the decompostion of I. Indicative, however, that other factors besides $\pi$-electron density must be operative in the transition state of bromination is the selective attack at C-3 when the complex I is decomposed under aprotic conditions. If one pleads that C-8 should be more sensitive to steric hindrance, still the greater reactivity of C-3 over C-6 remains to be brought into consonance with theory. To account for the selective attack on the pyridinoid ring in the high-temperature bromination of aza-aromatic heterocycles, various investigators[1,2,5] have proposed addition-elimination mechanisms. In the case of quinoline this suggestion has taken two forms: a) the 1,2- addition of hydrogen bromide to the azomethine linkage, followed by 3,4- addition of bromine and the elimination of two molecules of hydrogen bromide[2]; or b) the 3,4- addition of bromine to the styrene-like double bond of quinolinium bromide and the subsequent elimination of hydrogen bromide.[5] The recent observation[12] that the treatment of 1-cyano-2-hydroxy-1,2-dihydroquinoline in aqueous

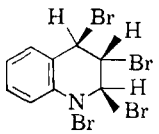
(13) *Cf.* J. A. Gardner, *Ber.*, **23**, 1587 (1890), for the behavior of pyridine toward glacial acetic acid.

(14) S. B. Knight, R. H. Wallick, and J. Bowen, *J. Am. Chem. Soc.*, **76**, 3780 (1954).

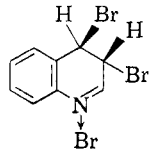
(15) M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, *J. Am. Chem. Soc.*, **76**, 3984 (1954).

(16) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947). Others have suggested the order, $C_8 > C_3 > C_6$: C. Sandorfy, C. Vroelant, P. Yvan, O. Chalvet, and R. Daudel, *Bull. soc. chim. France*, **17**, 304 (1950). In any event the $\pi$-electron densities at these positions would be quite close.

methanol with bromine and then with acid results in 3-bromoquinoline lends support to pathway *a* for hypobromous acid brominations in polar protic systems. For the selective and facile bromination of quinoline in carbon tetrachloride observed in this study analogous 1,2,3,4-tetrabromo adducts of quinoline(IV) or 3,4- adducts of $C_9H_7N$ or $C_9H_7N \rightarrow Br_2$(V) suggest themselves. The usual elimination of hydrogen bromide by a *trans* process would not be possible if the bromine addition takes a *trans*

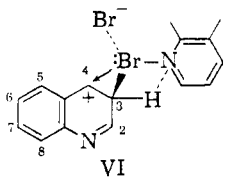


IV



V

course. Consequently, it would appear that elimination of hydrogen bromide might occur by preliminary ionization of the benzylic C-4—Br bond and the stabilization of the C-4 carbonium ion by the neighboring participation of the bromine on C-3. Hence, it is conceivable that a polarized $Br^{\delta-} \ldots Br^{\delta+}—N$ attacks quinoline directly and forms a bridged bromonium ion transition state. It is proposed that electrophilic attack by $C_9H_7NBr_2$(I) on quinoline or I occurs preferentially at C-3 because a particularly favorable bridged bromonium-ion transition state(VI) can be formed. This configuration would derive added stabilization by the coordination of the unshared electron pair of $:\ddot{Br}^+$ with the electron paucities at C-2 or especially C-4. (Calculations suggest that $\pi$-electron densities are at a minimum at C-2 and C-4 even in the ground state of quinoline.[16]) The carbon atoms vicinal to C-6 and C-8 cannot furnish similarly low charge densities for such stabilization.



VI

## EXPERIMENTAL[17]

*Starting materials.* The quinoline employed for preparative brominations was Eastman White Label synthetic grade, previously dried over pellet potassium hydroxide and fractionally distilled under reduced pressure just before use. For spectral and catalytic studies this quinoline was freshly distilled through a 1 × 50 cm. heated fractionation column packed with 1/8-in. glass helices, b.p. 127–128° (31 mm.), $n^{30}D$ 1.6210, $n^{20}D$ 1.6267 (lit.[18] $n^{25}D$ 1.6240).

The bromine was Merck reagent grade; for spectral work this was distilled once from phosphorus pentoxide and then distilled twice from dried, powdered potassium bromide (reagent grade). Moisture was excluded from the distillation apparatus and no lubricant was applied to the ground-glass joints.[19]

Solvents used were of reagent grade and were fractionally distilled before use. The pyridine was stored over potassium hydroxide pellets, subsequently refluxed over barium oxide, and finally distilled to obtain an anhydrous product. The carbon tetrachloride employed in the spectral studies was purified according to a published procedure.[20]

*Reference compounds: bromoquinolines.* For spectral comparison pure, authentic samples of the seven isomeric bromoquinolines were required. 2-Bromoquinoline was prepared from the reaction of carbostyril and phosphorus pentabromide at 140° (72% yield, m.p. 48.5–49.5°).[21] Authentic 3-bromoquinoline was obtained by the diazotization reaction with 3-aminoquinoline[22] or the pyrolysis of quinoline hydrobromide perbromide at 180–200°. In the latter reaction the large quantity of unchanged quinoline could be separated most efficiently by extracting it from the crude product with warm, aqueous tartaric acid solution. Fractionation of the remaining oil gave pale yellow 3-bromoquinoline, b.p. 128° (7 mm.), m.p. 14–16°, $n^{30}D$ 1.6592, $n^{20}D$ 1.6652. 4-Bromoquinoline was prepared from kyanurin and phosphorus pentabromide in 21% yield,[23] b.p. 140–142° (7 mm.), $n^{23}D$ 1.6662. Large amounts of 3,4-dibromoquinoline, m.p. 80–81°, were isolated as a side-product.

By a modified Skraup reaction on the bromoanilines the other bromoquinolines were obtained. Nitrobenzene proved to be a suitable oxidizing agent in this reaction,[24] as the by-product quinoline could be readily separated from the bromoquinolines by distillation. From *p*-bromoaniline the 6-bromoquinoline was obtained in 45% yield, b.p. 162–164°, (22 mm.), $n^{25}D$ 1.6605; from *o*-bromoaniline a 45% yield of 8-bromoquinoline, b.p. 112–113° (0.5 mm.), $n^{30}D$ 1.6674; and from *m*-bromoaniline a 61% yield of a mixture of 5- and 7-bromoquinolines, b.p. 131–139° (11 mm.). The 5 and 7-bromo isomers were separated from each other by fractional crystallization of their nitric acid salts from hot water.[25] Recrystallized from petroleum ether (b.p. 30–60°) 7-bromoquinoline formed colorless needles, m.p. 34–35.5° (lit. m.p. 34°). 5-Bromoquinoline yielded pale cream-colored prisms, m.p. 45–47° (lit. m.p. 48°).

*Quinoline-bromine complex* (I). *a. Preparation.* With the exclusion of moisture and light equimolar quantities of pure quinoline and bromine in carbon tetrachloride were mixed slowly at room temperature. The orange precipitate was collected, washed with fresh solvent, and then stored in a desiccator over a mixture of potassium hydroxide pellets and paraffin shavings. After the orange solid had dried in the dark, it was analyzed for "available" bromine. Tared samples were treated with 15 ml. of 40% potassium iodide solution and 15 ml. of 5 *N* acetic acid, and the liberated iodine was titrated with standardized sodium thiosulfate solution.

*Anal.* Calcd. for $C_9H_7NBr_2$: Br, 55.30. Found: Br, 55.14.

(17) All melting points are corrected. Infrared spectra were recorded with either a Perkin-Elmer Model 21 or Model 137 spectrophotometer.

(18) F. Krollpfeiffer, *Ann.*, **430**, 208 (1922).

(19) W. H. Bauer and F. Daniels, *J. Am. Chem. Soc.*, **56**, 378 (1934).

(20) A. I. Popov and N. E. Skelly, *J. Am. Chem. Soc.*, **77**, 3722 (1955).

(21) O. Fischer, *Ber.*, **32**, 1304 (1899), used *N*-methylquinolone in place of carbostyril.

(22) A. Claus and V. Tornier, *Ber.*, **20**, 2872 (1887).

(23) A. Claus and H. Howitz, *J. prakt. Chem.*, **50**, 232 (1894).

(24) Modified procedure of W. La Coste, *Ber.*, **15**, 559 (1882).

(25) A. Claus and G. N. Vis, *J. prakt. Chem.*, **38**, 387 (1888).

The orange adduct (I) melted at 81–84° dec. Treatment with sodium sulfite and ammonia solutions regenerated quinoline. Upon standing in air, I slowly lost bromine vapor and developed yellow flecks.

*b. Infrared measurements.* Because of the "available" bromine in I, mineral oil and other mulling agents could not be used. In addition, solutions were considered unsatisfactory for infrared spectral work, as I tends to dissociate in solution. Acceptable spectral curves could be obtained by mulling I in carbon tetrachloride, transferring the suspension to the sodium chloride windows, and allowing the solvent to evaporate. The observed bands in I were verified by checking spectra of mulls of I in pure quinoline for new bands. The new bands in I occurred at 770(s), 950(s), 1220(w), 1260(s), and 1458(s) cm.$^{-1}$. Quinoline bands at 940, 1040, 1400, and 1440 cm.$^{-1}$ had almost vanished in the spectrum of I and the usual trio in quinoline's spectrum between 1579 and 1625 cm.$^{-1}$ appeared at 1595, 1602, and 1625 cm.$^{-1}$.

*c. Photocatalyzed decomposition.* Two samples of a carbon tetrachloride solution (in Pyrex volumetric flasks), $2.0 \times 10^{-4}$ *M* in quinoline and $2.7 \times 10^{-4}$ *M* in bromine, were placed equidistant (13 cm.) from an unfrosted 60-W light source. The one sample was completely exposed while the other was coated with aluminum foil. The uncovered sample became turbid and the bromine disappeared almost completely after 10 hr. The contents gave a pronounced acid reaction to moistened blue litmus paper. Neither the covered control of the quinoline-bromine solution nor an illuminated solution of bromine alone in carbon tetrachloride showed any change in the same period of time.

*d. Pyrolysis of the complex* I. The slow addition of 1.0 mole of bromine to 1.0 mole of quinoline with ice-bath cooling caused the exothermic formation of an orange-red mass. The semisolid mass was heated at 190 ± 5° for 3 hr. (hardly any bromine vapor!). The cooled residue was decomposed with dilute ammonium hydroxide, the liberated bases extracted with ether, and the ether extracts stored over anhydrous calcium sulfate. After solvent removal, the residue gave upon successive fractional distillations through a 12-in. packed column 29 g. of recovered quinoline and 96 g. of 3-bromoquinoline, 46% yield, b.p. 151–153° (16 mm.), $n^{26}$D 1.6633. By careful examination of the infrared spectrum of this product and comparison with the authentic spectra of the known bromoquinolines, no bands characteristic of any bromoquinoline other than the 3-isomer were found (*cf.* section *f*).

Extraction of the distillation residue with ether left 12.4 g. of insoluble brown solid melting over the range 140–155° and resembling impure 3,6,8-tribromoquinoline in its infrared spectrum. Evaporation of the ether extract and several recrystallizations of the residue from petroleum ether (b.p. 30–60°) yielded 2.0 g. of colorless needles, m.p. 99–102°. By mixture melting point and infrared spectral comparison with an authentic sample this was shown to be 3,8-dibromoquinoline.

*e. Decomposition of the complex* I *in solvents.* In Table I are indicated the experimental conditions and the yield of products for the decomposition of 0.2 mole of I in 150 ml. of various solvents. Except with carbon tetrachloride, a solution was obtained initially, but precipitation occurred as the reaction proceeded. The reaction mixture was worked up in one of two ways: either the solvent was removed and the residue was treated as in section *d* above; or the reaction precipitate was filtered off and worked up separately. Two types of work-up deserve special comment. First, upon decomposing the complex in a carbon tetrachloride slurry and filtering the residue consisted of 42 g. of orange solid, composed mostly of quinoline hydrobromide perbromide and undecomposed I. Decomposition of this solid separately with sodium hydroxide and usual work-up gave after distillation: 10.7 g. (41%) of quinoline, b.p. 105–109° (11 mm.), $n^{25}$D 1.6235; 2.61 g. of crude 3-bromoquinoline, b.p. 135–147°, (11 mm.), $n^{25}$D 1.6220 (infrared spectral identification), and 3.0 g. of semisolid residue (spectrally shown to be impure 3,6-dibromoquinoline). Removal of the solvent from the original carbon tetrachloride filtrate and fractional distillation of the residue yielded 10.9 g. of 3-bromoquinoline, b.p. 139–143° (10 mm.), $n^{25}$D 1.6640. Recrystallization of the distillation residue from petroleum ether (b.p. 30–60°) gave 0.8 g. of 3,6-dibromoquinoline, m.p. 127–129° (mixture melting point with authentic sample undepressed).

Secondly, the reaction products from the brominations conducted in glacial acetic acid were isolated by pouring the reaction mixture into water and adding the necessary sodium bisulfite and ammonium hydroxide. The system was extracted with ether to remove ether-soluble bases and the residual water suspension was filtered to collect ether-insoluble products. The ether extract yielded recovered quinoline, traces of 3-bromoquinoline and 3,6,8-tribromoquinoline, and modest amounts of 3,6-dibromoquinoline. The ether-insoluble residue consisted largely of 3,6,8-tribromoquinoline in the unbuffered acetic acid run. Upon recrystallization from 95% ethanol the latter compound was obtained as glistening needles, m.p. 170.5–171.5 (admixed with authentic 3,6,8-tribromoquinoline the product melted undepressed). However, in the ether-insoluble residue from the acetic acid–sodium acetate run new products accompanied the tribromo compound. The product was digested with hot ethanol to remove the tribromoquinoline, whereupon the 5.4 g. residue melted over the range, 160–200°. Repeated recrystallizations of this residue from nitrobenzene, pyridine, and finally isopropyl alcohol gave apparently homogeneous needles, m.p. 255–257°. The elementary analysis of 63.2% bromine and 4.3% nitrogen did not agree well with any envisaged product. As this product displayed prominent absorptions at 3100 and 1665 cm.$^{-1}$, it was felt to be a tribromocarbostyril contaminated with 3,6,8-tribromoquinoline.[26]

The ether extract of either acetic acid run was dried, freed of solvent, and fractionally distilled under reduced pressure to obtain unreacted quinoline (and some 3-bromo isomer). The distillation residue, according to its infrared spectrum, contained 3,6-dibromo, 3,6,8-tribromo-, and possibly 3,8-dibromoquinolines. The 3,6-dibromo- and 3,6,8-tribromoquinolines could be isolated by fractional crystallization from ethanol.

*f. Preparative decomposition of* I *in the presence of pyridine.* A stirred orange slurry of the complex I [prepared by mixing 129 g. (1.0 mole) of quinoline and 160 g. (1.0 mole) of bromine in 1 l. of carbon tetrachloride] was heated at reflux for 1 hr. Thereafter, a solution of 79 g. (1.0 mole) of anhydrous pyridine in 50 ml. of carbon tetrachloride was added slowly to the refluxing mixture over a period of 3 hr. During the terminal 18-hr. reflux period the original orange suspension became tan-colored. Filtration of the cooled suspension, removal of solvent from the filtrate, and fractional distillation through a 10-in. packed column at 11 mm. gave the following fractions: 1) 123–125°, 3.2 g., $n^{25}$D 1.6412; 2) 136–142°, 68 g., $n^{25}$D 1.6572; 3) 142–143°, 98 g., $n^{25}$D 1.6628; and 4) 143–148°, 13 g., $n^{25}$D 1.6632. Solution of the 8.0 g. distillation residue in warm petroleum ether (b.p. 30–60°) and cooling yielded 3.9 g. of 3,6-dibromoquinoline, m.p. 123–127°. From ethanol colorless needles, m.p. 127–129°, were obtained (mixture melting point with authentic 3,6-dibromoquinoline undepressed). By its characteristic infrared spectral bands the balance of the distillation residue (4 g.) was shown to contain 3-bromoquinoline, together with smaller amounts of 3,6- and 3,8-dibromoquinolines and 3,6,8-tribromoquinoline.

To remove the small amount of quinoline in distillation fraction 2 (infrared band at 810 cm.$^{-1}$), it was warmed with a solution of 20 g. of D-tartaric acid in 500 ml. of water and the resulting biphasic system was filtered by gravity. Solution of the residual oil on the filter paper in ether, drying, and re-

(26) *Cf.* H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, 79, 5479 (1957), for infrared data concerning such cyclic amides of the phenanthridine system.

moval of solvent left 60 g. of 3-bromoquinoline, $n^{25}D$ 1.6608. Treatment of the tartaric acid extract with sodium hydroxide and isolation of the liberated base by ether extraction afforded 5.8 g. of quinoline, $n^{25}D$ 1.6260.

Treatment of the tan-colored precipitate filtered from the original carbon tetrachloride solution with sodium hydroxide and usual work-up yielded 3.4 g. of quinoline, b.p. 110–113° (13 mm.) after a large forerun of pyridine).

The total yield of 3-bromoquinoline was 171 g. (82%). As 12 g. of quinoline was recovered, the yield based upon unrecovered quinoline was 91%. The yield of isolated 3,6-dibromoquinoline was 1.5%. By careful infrared examination of the isolated bromoquinoline and comparison with the reference spectra of the seven authentic bromoquinolines, only bands characteristic of the 3-bromo isomer were found. Characteristic bands prominent in the spectra of the other bromo isomers were absent.

To obtain a limit of certainty for this conclusion, an aliquot of the combined fractions 3 and 4 was fractionally distilled through a 1 × 50 cm. column packed with glass helices. The successive fractions [b.p. 84–86° (0.5 mm.)] and the residue were examined by infrared spectroscopy. The spectra of all fractions were completely free of bands other than those attributable to the 3-isomer. Only the residue displayed weak new bands at 810, 828, and 964 cm.$^{-1}$. The band at 828 cm.$^{-1}$ could signify traces of 6-bromoquinoline or 3,6-dibromoquinoline. As this band was found only in the spectrum of the residue and as the 3-bromo and 6-bromo isomers have almost identical boiling points at 760 mm. (276° *vs.* 278°), the 828 cm.$^{-1}$ band was more likely due to the higher boiling 3,6-dibromoquinoline.

The bands at 810 and 964 cm.$^{-1}$ were ascribable to traces of 8-bromo- or 3,8-dibromoquinolines. (Bands in the 950–970 cm.$^{-1}$ region indicate vicinal trisubstituted benzenes or pyridines.). Again, however, the fact that 3,8-dibromoquinoline was isolated in certain brominations lends some support for the view that these bands indicate traces of 3,8-dibromoquinoline.

Even assuming fractionation to be ineffectual in separating and allowing infrared detection of any 6-bromoquinoline present, one could not have had more than 1% of undetected 6-bromoquinoline. This follows from the observation that a synthetic mixture of authentic 3- and 6-bromoquinolines containing 1% by weight of the 6-bromo isomer still had a readily discernible 6-bromo infrared band at 832 cm.$^{-1}$.

A bromination procedure identical with the above method was carried out, except that reagents were scrupulously dried and purified and the reaction was conducted with the complete exclusion of light and moisture. Moreover, the reaction was run under a nitrogen atmosphere. Upon usual work-up 160 g. (77%) of 3-bromoquinoline, 10 g. of quinoline, and 10 g. of distillation residue were obtained. The yield based on unrecovered quinoline was 83%.

*Bromination of bromoquinolines.* (*a*) *3-Bromoquinoline.* Refluxing a solution of 20.8 g. (0.10 mole) of 3-bromoquinoline and 8.0 g. (0.050 mole) of bromine in 150 ml. of carbon tetrachloride for 96 hr. gave upon usual work-up 20.1 g., $n^{22}D$ 1.6657 of unchanged starting material. Infrared examination showed no new bands.

Heating a mixture of 0.10 mole each of 3-bromoquinoline, bromine, and pyridine in 100 ml. of carbon tetrachloride for 24 hr. and usual work-up gave 20.5 g. of an oil, whose infrared spectrum was that of 3-bromoquinoline with very weak bands at 810 and 832 cm.$^{-1}$. These bands seem to indicate a minute content of 3,6-dibromoquinoline.

(*b*) *6-Bromoquinoline.* An orange slurry of 5.16 g. (0.025 mole) of 6-bromoquinoline, 4.0 g. (0.025 mole) of bromine, and 2.0 g. (0.025 mole) of pyridine in 50 ml. of carbon tetrachloride turned pale yellow and deposited a brown gum upon refluxing for 45 min. Filtration of the mixture and removal of the solvent from the filtrate left an oil. Solution in warm 95% ethanol and cooling provided 4.5 g. (62%) of 3,6-dibromoquinoline, m.p. 120–125°. Recrystallization from ethanol gave colorless needles, m.p. 127–128.5°. Infrared bands at 828(s), 915(s), 950(s), 1073(m), and 1085(m) cm.$^{-1}$ were characteristic.

(*c*) *8-Bromoquinoline.* In a similar fashion 0.010 mole of 8-bromoquinoline was brominated to yield 2.0 g. (70%) of 3,8-dibromoquinoline, m.p. 97–101°. Recrystallizations from petroleum ether (b.p. 30–60°) yielded flat needles, m.p. 102–104°. Significant infrared bands occurred at 762(s), 810(m), 888(m), 952(m), 964(m), and 1080 (m) cm.$^{-1}$.

From the original reaction precipitate a small amount of 3,6,8-tribromoquinoline, m.p. 169–171°, was isolated. Principal infrared bands occurred at 675(s), 815(m), 905(s), 965(s), and 1080(m) cm.$^{-1}$.

ANN ARBOR, MICH.