A Reinvestigation of Known Bromination Reactions of Quinoline

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Much research has been directed toward studies on electrophilic substitution of quinoline and isoquinoline. However, many research results obtained in this field remain unexplained at the present time. In a slightly acidic to basic reaction medium the *N*-heterocyclic compound exists as the free base, and electrophilic attack occurs in the pyridinoid ring at positions which cannot be completely rationalized in terms of electron density calculations. In a strongly acidic reaction medium the *N*-heterocyclic compound exists as its conjugate acid and undergoes attack by certain electrophiles in the carbocyclic ring. The positions of substitution in the carbocyclic ring do appear to be those predicted by relative electron density calculations.

The conflicting results obtained by many of the earlier workers have been due to inadequate separation and identification of the isomeric products and lack of an accurate quantitative analysis of the reaction mixture. For example, the literature reveals that bromination of quinoline by the Derbyshire-Waters procedure appears to give the 5- and 8- substituted isomers in almost equal amounts (2). However, in our laboratories this procedure gave 5- and 3-bromoquinoline in 63 per cent and 37 per cent, respectively (3). This represents one of numberous examples of inaccurate product analysis.

When quinoline is brominated in the vapor phase over pumice at 300°, a 25 per cent yield of 3-bromoquinoline is obtained. At 500° the product is 2-bromoquinoline in 50-60 per cent yield (4). Edinger reported the preparation of 3-bromoquinoline by direct bromination of quinoline in the presence of a relatively large amount of sulfur (5). Presumably, sulfuryl bromide is the actual brominating agent. A more convenient method for the preparation of 3-bromoquinoline is that of Eisch, which consists of bromination in hot carbon tetrachloride with pyridine as a hydrogen bromide scavenger to give 3-bromoquinoline in 91 per cent yield (6). Eisch also reported the preparation of 4-bromoquinoline by the pyrolysis of 3-bromoquinoline hydrobromide at 300° (7). In glacial acetic acid, decomposition of the quinoline-bromine complex led predominantly to 3,6-dibromo- and 3,6,8-tribromoquinoline.

A recent study of the bromination of quinoline and isoquinoline has been reported by Kress and Costantino (8). They found that the addition of bromine to a slurry of quinoline or isoquinoline hydrochloride in nitrobenzene, heating for a 4-5 hour period, affords 3-bromoquinoline or 4-bromoisoquinoline as crystalline hydrobromide salts. The free bases were isolated after neutralization in 81 and 76 per cent yields, respectively.

Quinoline substituted with halogens in the benzenoid ring generally is prepared most easily by the various ring-closure methods such as the Skraup synthesis. As is generally true, the early work by which structures were assigned to some of these compounds is open to question and had led to much confusion. Recently, the Derbyshire-Waters procedure, employing concentrated sulfuric acid, silver sulfate, and bromine, has been used to obtain benzenoid brominated products of quinoline (2). De la Mare, Kiamuddin, and Ridd brominated quinoline in sulfuric acid and obtained 5- and 8-bromoquinoline and 5,8-dibromoquinoline as products. The "Swamping Catalyst" procedure, involving bromination in an excess of aluminum chloride, led to similar results (9).

Various brominated isomers of quinoline were needed for use as starting compounds leading to the synthesis of other substituted compounds which had desirable biological activity. For this reason, a systematic study of selected known bromination processes of quinoline was undertaken.

Results and Discussion

A. Authentic Brominated Quinolines and Isoquinolines.

2-Bromoquinoline was prepared by three different reactions utilizing, as starting materials, 2-aminoquinoline, 2-iodoquinoline, and 2-quinolone. The action of phosphorus pentabromide on 2-quinolone gave 2-bromoquinoline in a 90 per cent yield. The yields obtained with the other two starting materials were much less than 90 per cent, with a considerably more lengthy workup procedure being involved. Previous workers report that Sandmeyer reactions on 2-aminoquinoline give very low yields (10). An equilibrium exists between 2-aminoquinoline and tautomeric imino-form; however, spectrometric data has shown that the compound exists predominantly in the amino form. The low yields are most likely due to the difficulty involved

TABLE I

Bromination Reactions of Quinoline

Reaction Number	Quinoline (Moles)	Base or Acid (0.1 Mole)	Solvent (100 ml.)	Reaction Temperature	Reaction Time (hours)
1	0.10	a	d	75	18
2	0.10	b	e	120	15
3	0.20	b	e	120	15
4	0.20		d	75	15
5	0.10	c	d	79	13
8	0.10		d	75	15
9	0.15		d	75	15
10	0.10		f	86	15
11	0.20		f	88	15
12	0.10	a	f	90	15
13	0.10		g	132	18
14	0.20		g	135	17
15	0.10	a	g	125	15

Reaction Number	Quinoline (Moles)	Ag_2SO_4 (Moles)	Solvent H_2SO_4 (ml.)	Reaction Time (hours)
16	0.25	0.06	50	3
17	0.10	0.05	50	5
18	0.10	0.10	50	5
19	0.10	0.10	50 + 20 H_2O	5

Reaction Number	Quinoline·HCl (Moles)	Bromine (Moles)	Solvent Nitrobenzene (ml.)	Reaction Temperature	Reaction Time (hours)
20	0.20	0.11	50	180	4.5

In each reaction 0.1 mole of bromine was used unless otherwise stated. a = pyridine; b = aluminum chloride; c = triethylenediamine; d = carbon tetrachloride; e = acetic acid; f = 1,2-dichloroethane; g = 1,2-dibromoethane.

TABLE II

Results of Bromination of Quinoline;
Isomer Yields are Given in Mole Per Cent

Reaction Number	Quinoline	2-Bromo-quinoline	3-Bromo-quinoline	5-Bromo-quinoline	6-Bromo-quinoline	7-Bromo-quinoline	8-Bromo-quinoline
1	38.79	T (a)	24.16	15.39	T	T	21.66
2	96.52		3.48	T			T
3	91.51		8.33	0.16			T
4	67.92		22.39	7.70	2.29		
5	100.00						
8	5.18		94.82				
9	21.65		78.35				
10	81.79		15.94	T	2.27		
11	53.20		46.18	0.62			
12	31.48		68.52				
13	100.00						
14	43.61		11.22			45.17	
15	100.00		T				
16	98.67			0.78			0.55
17	64.52	T		19.58	0.16	T	15.74
18	64.25	T		22.60	0.22	T	12.93
19	86.15	T		10.40	T	T	3.45
20	2.39		97.61				

(a) T = Trace

in decomposing the diazonium salt. Although 2-bromoquinoline has not been previously prepared by a halogen exchange reaction, the desired product was obtained starting with 2-iodoquinoline in a 48 per cent yield, but required a reaction period of forty-eight hours.

3-Bromoquinoline has been prepared by Eisch's procedure for direct bromination of quinoline in the presence of pyridine. The reaction was carried out over a ten-hour period and gave 3-bromoquinoline in a 24 per cent yield. The recent reaction of Kress and Costantino is much less time-consuming (4.5 hours) and gave 3-bromoquinoline in a 97 per cent yield.

Attempted preparation of 4-bromoquinoline by a procedure given by Eisch (7) failed to give any of the desired product. However, 4-bromoquinoline has been prepared by the action of phosphorus pentabromide on 4-hydroxyquinoline. 4-Bromoquinoline was not sufficiently stable to permit purification.

5-Bromoquinoline has been prepared by two reactions. 5-Aminoquinoline, using the Sandmeyer reaction, gave 5-bromoquinoline in a 65 per cent yield. 5-Bromoquinoline was also prepared by direct bromination of quinoline in aluminum chloride.

7-Bromoquinoline has been prepared by two reactions. 7-Aminoquinoline, using the Sandmeyer reaction, gave 7-bromoquinoline in a 50 per cent yield. This reaction, although giving the desired product in a fair yield and pure form, is somewhat limited since the 7-aminoquinoline must be prepared by a ring closure reaction similar to that discussed below. 7-Bromoquinoline was also prepared by a ring closure reaction which gave approximately equal amounts of 5- and 7-bromoquinoline.

8-Bromoquinoline has been prepared from 8-aminoquinoline by the Sandmeyer reaction. The desired product was obtained relatively pure in a yield of 65 per cent. 8-Bromoquinoline was also obtained by separation of a mixture of 5- and 8-bromoquinoline obtained using the "Swamping Catalyst" procedure.

B. Bromination Reactions of Quinoline.

Table I summarizes the experimental conditions used in each bromination reaction. Table II gives results from gas chromatographic analysis of each reaction mixture.

Eisch Procedure (Reactions's 1-15, Tables I and II). Eisch (6) reports that the decomposition of a quinoline-bromine complex in carbon tetrachloride with pyridine as a hydrogen bromide scavenger has given 3-bromoquinoline as the only monobrominated product in a 82 per cent yield. Eisch employed infrared spectroscopy as a means of identification and indicates that characteristic bands prominent in the spectra of the other bromo isomers were absent. Many reactions were conducted employing slight variations reaction 1) has been carried out using the same conditions as Eisch giving 3- (24 per cent), 5- (15 per cent), 8- (22 per cent), and traces of 2-, 6-, and 7-bromoquinoline along with unreacted quinoline (39 per cent). 3-Bromoquinoline has been obtained in a 95 per cent yield when bromine was added to quinoline (1:1 molar ratio) in carbon tetrachloride (Table I, reaction 8). Another notable reaction (Table I, reaction 14), gave high yields of 7-bromoquinoline along with 3-bromoquinoline when bromine was added to quinoline (1:2 molar ratio) in 1,2-dibromoethane. Since this was an unusual occurrence, the analysis was repeated, giving similar results.

Derbyshire-Waters Procedure (Reaction's 16-19, Tables I and II). Bromine was added to a solution of quinoline in concentrated sulfuric acid containing silver sulfate; the mixture was shaken; and the reaction was essentially complete within five hours at room temperature. Kiamud-din, de la Mare, and Ridd (2) previously reported the reaction giving 5-bromo- (28 per cent), 8-bromo- (29 per cent), and 5,8-dibromoquinoline (43 per cent); the proportions of the products being determined by isotopic dilution.

We find that bromination of quinoline under the same conditions gives no dibrominated product and that the product distribution is quite dependent on the molar ratios of the reactants. A molar ratio of quinoline to silver sulfate (4.2:1) gave, although in low yields, 5-bromo- (59 per cent) (11) and 8-bromoquinoline (41 per cent). A 2:1 molar ratio of quinoline to silver sulfate gave, along with 5- (55 per cent) and 8- (44 per cent) substituted products, a small amount of 6-bromoquinoline (0.5 per cent), and traces of the 2- and 7- substituted products. A 1:1 molar ratio of quinoline to silver sulfate gave 5- (63 per cent), 8- (36 per cent), and 6-bromoquinoline (0.6 per cent) along with traces of 2- and 7- substituted products. Furthermore, when water (20 ml.) is added to the 1:1 molar ratio of reactants, the yield of 5-bromoquinoline is increased to 75 per cent, 8-bromoquinoline is decreased to 25 per cent, and trace amounts of the 2-, 6-, and 7- substituted products are also formed. These results indicate that the 5- substituted product is favored as the molar ratio of quinoline to silver sulfate approaches 1:1; and even more so upon the addition of water.

Kress-Costantino Procedure (Reaction 20, Tables I and II). A precedure recently described by Kress and Costantino has effectively given very selective bromination at the 3-position (8). To a slurry of quinoline hydrochloride in nitrobenzene at 180°, a 10 per cent molar excess of bromine was added and heating was continued for 4.5 hours. Appropriate workup has given 3-bromoquinoline (98 per cent) as the only brominated product along with unreacted quinoline (2 per cent). Kress and Costantino have reported 85 per cent yield of 3-bromoquinoline as having a purity of 97 per cent as determined by gas chromatographic

C. Spectroscopic Studies of Brominated Quinolines.

Infrared Spectra. Much of the previous work in this field has employed infrared spectra alone to identify the various halogenated isomers of quinoline and isoquinoline. Upon looking briefly at the spectra of these compounds as prepared, it was noticed that they were not well defined and varied with the method of preparation. It was concluded that impurities present, even though in small amounts, were responsible for the ill-defined spectra. Infrared spectra of the brominated isomers purified by collecting from the GC were sharp and well defined.

Using the C-H out-of-plane bending region of the spectrum (950-650 cm^{-1}), it seems at first to be possible to identify each of the isomers. The position of these group frequencies should be related to the substitution on the ring. Actually, the frequency of absorbance in this region is a function of the number of adjacent hydrogens on the ring. 7-Bromoquinoline would be expected to have the same spectrum as 6-bromoquinoline, and 8-bromoquinoline the same as 5-bromoquinoline. By the same, it is not meant identical, for in the space of forty wave numbers, it would be impossible to assign a three adjacent hydrogen peak to either 5-bromoquinoline or 8-bromoquinoline.

Upon looking for another region to use as a fingerprint, we noticed the skeletal in-plane ring vibration region (1600-1550 cm^{-1}) where a sharp contrast is observed between each isomer. The tracings of absorbance in this region for the various bromoquinoline isomers are illustrated in Figure 1.

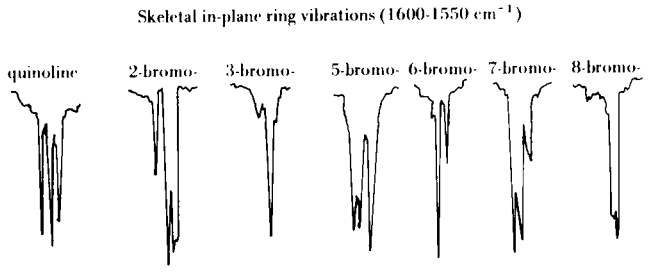

Figure 1. Tracings of the absorbance spectra in the skeletal in-plane ring vibration region for the bromoquinoline isomers.

EXPERIMENTAL (12)

A. Preparation of Monobromoquinoline Isomers.

Preparation of 2-Bromoquinoline.

a. 2-Aminoquinoline (1.0 g.) in concentrated (48 per cent) hydrobromic acid (3 ml.) and water (3 ml.) was diazotized at 0° with sodium nitrite (0.5 g.) in water (3 ml.). The resulting diazonium solution was slowly added to a solution of cuprous bromide (13) (1.2 g.) in hydrobromic acid (10 ml.) at 75°. After standing overnight at room temperature, the solution was basified with aqueous sodium hydroxide and filtered. The filtered precipitate after drying was sublimed (48°/0.20 mm) which gave 0.78 g. of white crystals melting over the range of 121-132°. The product mixture upon analysis by gas chromatography proved to be 2-bromoquinoline (39 per cent) and 2-aminoquinoline (61 per cent) corresponding to an overall 21 per cent yield of 2-bromoquinoline.

b. 2-Bromoquinoline was also prepared by a halogen exchange reaction. The procedure reported for the preparation of 2-fluoroquinoline (14) was followed with many necessary alterations.

2-Iodoquinoline (0.5 g.), anhydrous potassium bromide (0.95 g.) (1:4 molar ratio, respectively) and sulfolane (tetramethylene sulfone) (4.0 g.) were mixed, and the temperature raised to and maintained at 105° with vigorous stirring for 48 hours. The reaction mixture was steam-distilled and the distillate extracted with diethyl ether. After removal of the solvent, the crude product was sublimed (36°/2.0 mm) which gave 0.17 g. (48 per cent) of white crystals melting over the range of 41-47°. The crystals upon analysis by gas chromatography proved to be 2-bromoquinoline (98 per cent) and 2-iodoquinoline (2 per cent).

c. 2-Bromoquinoline was also prepared as follows: 2-quinolone (carbostyril) (7.25 g., 0.05 mole) and phosphorus pentabromide (15) (21.5 g., 0.05 mole) were mixed at 75° in a flask equipped with mechanical stirrer and reflux condenser. After 15 minutes, the temperature was raised to 120° and heating continued for 30 minutes. Upon cooling, the mixture was poured onto cracked ice, made basic with concentrated sodium hydroxide and extracted with diethyl ether. After removal of the solvent, the crude product was sublimed (35°/0.25 mm) which gave 4.8 g. (90 per cent) of 2-bromoquinoline, m.p. 48-49° (lit. (4) m.p. 48.4-48.8°, lit. (2) m.p. 49°).

Preparation of 3-Bromoquinoline (6).

A quinoline-bromine complex was prepared by slowly adding a solution of bromine (32 g., 0.2 mole) in carbon tetrachloride (150 ml.) with stirring to quinoline (25.8 g., 0.2 mole) at room temperature. The resulting orange precipitate was filtered and dried in a vacuum desiccator.

A stirred orange slurry of the above complex was heated at reflux for one hour. Thereafter, a solution of pyridine (15.8 g., 0.2 mole) in carbon tetrachloride (50 ml.) was added slowly to the refluxing mixture over a period of 3 hours. After refluxing for 10 hours, filtration of the cooled suspension, removal of the solvent from the filtrate and fractional distillation (109-114°/2.0 mm) through a 10 inch Vigreux column gave 14 g. (34 per cent) of 3-bromoquinoline.

Attempted Preparation of 4-Bromoquinoline.

a. Phosphorus pentabromide (43 g., 0.1 mole) was slowly added with stirring to 4-quinolone trihydrate (Aldrich Chemical Co., Inc.) (4.0 g., 0.02 mole) at room temperature. Large amounts of hydrogen bromide gas were given off as the water of hydration was removed. Heat was applied with stirring at 120° for 3 hours. The mixture was poured onto cracked ice and chloroform (400 ml.) was added so as to extract the free amine as soon as released and reduce the possibility of decomposition. With vigorous stirring the solution was neutralized with aqueous sodium hydroxide. The layers were separated and the chloroform removed under vacuum leaving a white residue (3.4 g., m.p. 25-29°). Decomposition occurred on attempted sublimation of part of the crude product. Attempted analysis by gas chromatography also led to decomposition, yielding what appeared to be hydrogen bromide, quinoline, and a dibromo-compound identified as 3,4-dibromoquinoline on the basis of melting point and infrared data.

b. Preparation of 4-bromoquinoline was also attempted by pyrolysis of 3-bromoquinoline hydrobromide as reported by Eisch

(7). Hydrogen bromide gas, produced by adding dilute sulfuric acid to sodium bromide, was bubbled into an ice-cooled Erlenmeyer flask containing 3-bromoquinoline (15 g.) in anhydrous diethyl ether (150 ml.). After 30 minutes or until no more precipitate formed, the white precipitate was filtered and washed with fresh anhydrous diethyl ether. Upon drying in a vacuum desiccator, 20.6 g. (99 per cent) of 3-bromoquinoline hydrobromide was obtained.

3-Bromoquinoline hydrobromide (18 g., 0.06 mole) was placed in a 250 ml. flask equipped with a nitrogen inlet and outlet. A water-cooled condenser plugged with glass wool served as the outlet. The system was flushed with nitrogen and the nitrogen flow adjusted so a slow continuous flow was obtained. The system was heated with stirring at 300° for 3 hours. After cooling, the solid substance formed from the reaction was dissolved in water and the solution made basic with aqueous sodium hydroxide. Extraction with diethyl ether and removal of the solvent gave 7.6 g. of an orange oil. Gas chromatographic analysis revealed four components which were collected and identified by infrared spectra as: quinoline (53 per cent), 3-bromoquinoline (31 per cent), 6-bromoquinoline (9 per cent) and 5-bromoquinoline (7 per cent).

Preparation of 5-Bromoquinoline.

a. 5-Aminoquinoline (1.0 g.) in concentrated (48 per cent) hydrobromic acid (3 ml.) and water (3 ml.) was diazotized at 0° with sodium nitrite (0.5 g.) in water (3 ml.). The resulting diazonium solution was slowly added to a stirred solution of cuprous bromide (1.2 g.) in hydrobromic acid (10 ml.) at 75°. After eight hours at room temperature the solution was basified and filtered. The filtrate was extracted with diethyl ether and the residue left after removal of the solvent combined with the above precipitate and sublimed (40°/3.5 mm) which gave 0.88 g. (65 per cent) of 5-bromoquinoline, m.p. 50-51° (lit. (16) m.p. 47-48°).

b. Quinoline was brominated in the presence of excess anhydrous aluminum chloride according to reported procedures (9). The products from this reaction were quinoline, 5-bromoquinoline, 8-bromoquinoline, and 5,8-dibromoquinoline.

Purification of 6-Bromoquinoline.

6-Bromoquinoline was commercially available (Eastman Organic Chemicals, Rochester, N.Y.), thus, did not have to be prepared in the laboratory. However, gas chromatographic analysis revealed two minor impurities. Preparatory gas chromatography was employed to isolate the pure 6-bromoquinoline.

Preparation of 7-Bromoquinoline.

a. A mixture of 5- and 7-bromoquinoline was prepared by a modified Skraup reaction (16). Glycerol (18.4 g., 0.2 mole), *m*-bromoaniline (17.2 g., 0.1 mole) and nitrobenzene (12.3 g., 0.1 mole) were placed in a 250 ml. three-neck, round-bottom flask. Sulfuric acid (65 ml., 75 per cent) was added dropwise with stirring for a 15-minute period. Time was allowed for the exothermic reaction to subside and the mixture heated to reflux for 4 hours. The reaction mixture was steam distilled to remove any unreacted nitrobenzene followed by treatment with sodium nitrite (15.0 g.) and refluxing to decompose any unaltered *m*-bromoaniline. The mixture was made basic with concentrated aqueous sodium hydroxide and steam-distilled until one liter of distillate was collected. Extraction of the distillate with diethyl ether and removal of the solvent gave a brown oil which was vacuum distilled. Two fractions were collected: the first being quinoline and the second (9.9 g.) a mixture of 5- and 7-bromoquinoline. The second fraction was shown by gas chromatographic analysis to contain 5-bromoquinoline (43 per cent) and 7-bromoquinoline (57 per cent). The 7-bromoquinoline as collected from the gas chromatograph was colorless crystals, m.p. 37° (lit. (2) m.p. 36°, lit. (16) m.p. 35°).

b. Preparation of 7-bromoquinoline.

7-Aminoquinoline (1.0 g.) in concentrated (48 per cent) hydrobromic acid (3 ml.) and water (3 ml.) was diazotized at 0° with sodium nitrite (0.5 g.) in water (3 ml.). This diazonium solution was slowly added to a stirred solution of cuprous bromide (1.2 g.) in hydrobromic acid (10 ml.) at 75°. After two hours at room temperature, the solution was basified and extracted with diethyl ether. After removal of the solvent, the crude product was sublimed (20°/2.0 mm) which gave 0.73 g. (50 per cent) of 7-bromoquinoline as colorless crystals, m.p. 33-35° (lit. (16) m.p. 36°).

Preparation of 8-Bromoquinoline.

8-Aminoquinoline (3.0 g.) in concentrated (48 per cent) hydrobromic acid (10 ml.) and water (10 ml.) was diazotized at 0° with sodium nitrite (1.5 g.) in water (10 ml.). The diazonium solution was added slowly to a stirred solution of cuprous bromide (3.6 g.) in hydrobromic acid (20 ml.) at 75°. After 12 hours at room temperature, the solution was basified and extracted with carbon tetrachloride. Upon removal of the carbon tetrachloride, the crude product, as a brown oil, was vacuum distilled (162-168°/20 mm) which gave 2.8 g. (65 per cent) of 8-bromoquinoline, a colorless oil.

B. Bromination Reactions of Quinoline.

Reactions numbered 1-15, Table I, are different variations of the Eisch procedure. The procedure consists of forming a quinoline-bromine complex by slowly adding bromine to a solution of quinoline in carbon tetrachloride. This complex was decomposed in various reaction media at the reflux temperature of the reaction mixture over a period of 13-18 hours. The reaction mixture was cooled, basified, and the free bases extracted with an organic solvent.

Reactions numbered 16-19, Table I, are different variations of the Derbyshire-Waters procedure. Quinoline and silver sulfate were dissolved in sulfuric acid and stirred with bromine for 3-5 hours, when most of the bromine had usually disappeared. The solution was filtered and any free bromine removed by addition of sodium sulfite. The filtrate was then basified and the free bases extracted with diethyl ether.

Reaction number 20, Table I, is a recent bromination procedure described by Kress and Costantino. To a slurry of quinoline hydrochloride salt in nitrobenzene at 180° was added a 10 per cent molar excess of bromine over 30 minutes. Heating and stirring were continued for 4.5 hours. The mixture was cooled and 3 volumes of benzene were added. The resulting slurry was filtered, washed with benzene and dried. The salt was dissolved in water, basified and the free bases extracted with diethyl ether.

All infrared spectra were obtained on a Perkin-Elmer, Model 137 Spectrophotometer. Spectra of all samples were obtained in the neat form. Even though many of the compounds are solids at room temperature, their low melting points permitted all to be run as liquids between heated potassium bromide plates.

All nmr spectra were obtained on a Varian A-60A and a JEOL (Japan Electron Optics Laboratories), 100 MH_Z nuclear magnetic resonance instrument. The spectra of the samples were well defined and characteristic of substituted quinolines. Copies can be made available to interested persons.

All mass spectra were obtained on a Varian, Model CH-7, single focusing mass spectrometer. The samples were injected by means of a direct insertion probe and were sufficiently volatile at 75° (5 x

10^{-6} torr) to produce good spectra. All spectra were obtained using an ionization voltage of 70 eV, resolution of 1200, and a filament current of 1000 μA. Publication of a detailed study of the mass spectra is planned.

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(3) The percentages given are an average representing four reactions employing the Derbyshire-Waters procedure.

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(11) The percentages given exclude the amount of unreacted quinoline and are based on the total brominated products as 100 per cent.

(12) Melting points were performed on a Thomas Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tennessee. The liquid phase used was a silicone QF-1 coated onto Chromosorb G, aw, DMCS, 60/70 mesh support and packed into a 10 ft. x 0.093 in. (1/8 in. o.d.) aluminum tube. There was no pretreatment of the support; it was used as received (Johns-Manville Corp.). Of the five different liquid loadings tested (ranging from 5-20 per cent), the optimum loading was 10 per cent. Several other liquid phases, as well as support materials, were examined and found to be ineffective for the separation of the bromoquinolines. These included SE-30, OV-225, and Apeizon L for the liquid phases while Chromosorb W, regular; Chromosorb V, DMCS; Chromosorb G, DMCS; and Chromosorb T were the other supports tested. Helium was used as a carrier gas for all analyses. The column temperature was 163°; the injector port temperature was 210°; the detector temperature was 225°. Sample size was 0.06 μl; the carrier gas flow rate was 14.4 ml./minute. An effluent splitter located at the column flame base junction effectively let 48 per cent (6.6 ml./minute) of the effluent by-pass the detector leaving the 51 per cent (7.8 ml./minute) to enter the hydrogen flame. The recorder used was a Honeywell 1.0 millivolt full scale, Model 1630, connected to an Infotronics Digital Integrator, Model CRS-104. The GC was a dual channel Varian Aerograph, Model 1520, equipped with flame-ionization dectectors.

(13) In each of the reactions in which cuprous bromide was used (Sandmeyer), it was necessary to prepare it immediately before using. It was prepared by dissolving cupric sulfate pentahydrate (2.25 g.) and sodium bromide monohydrate (1.32 g.) in water (8 ml.) and adding to this hot solution a solution of sodium bisulfite (0.6 g.) in water (6 ml.) during 5 minutes. The white precipitate of cuprous bromide which formed was separated by decantation of the supernatant liquid. To prevent oxidation, the precipitate was washed twice with 5 ml. portions of water and dissolved in concentrated (48 per cent) hydrobromic acid (10 ml.) for use in the diazotization reaction.

(14) J. Hamer, W. J. Link, and T. L. Vigo, *Rec. Trav. Chim.*, 81, 1058 (1962).

(15) In each of the reactions in which phosphorus pentabromide was used, it was necessary to prepare it immediately before using. In each case finely divided phosphorus pentabromide was prepared by slowly adding the theoretical amount of bromine to a cold, vigorously stirred suspension of red phosphorus powder in carbon tetrachloride. The carbon tetrachloride was removed by decantation and the phosphorus pentabromide washed twice with fresh carbon tetrachloride. Removal of the carbon tetrachloride in a vacuum desiccator gave phosphorus pentabromide in yields of 94 per cent and higher.

(16) L. Bradford, T. J. Elliot, and F. M. Rowe, *J. Chem. Soc.*, 437 (1947).