

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

5-Bromo-6-methoxy-8-aminoquinoline and its Transformation to 7-Bromo-6-methoxy-8-aminoquinoline¹

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The preparation of 5-bromo-6-methoxy-8-aminoquinoline is described. It was found that this substance is transformed into its isomer, 6-methoxy-7-bromo-8-aminoquinoline, by means of boiling hydrobromic acid. This transformation gives evidence for the positive character of the bromine atom in the 5-position of 5-bromo-6-methoxy-8-aminoquinoline.

The preparation of 5-chloro-6-methoxy-8-aminoquinoline has been described by Robinson and Tomlinson,² Misani and Bogert,³ and by Drake and his co-workers.⁴ The corresponding bromo compound has not been described although its preparation has been carried out by Elderfield, *et al.*⁵ 5-Bromo-6-methoxy-8-aminoquinoline is conveniently obtained by bromination of 6-methoxy-8-acetaminquinoline in acetic acid followed by hydrolysis of the bromination product. The same bromo compound can be prepared, but in low yield, by the reduction of 5-bromo-6-methoxy-8-nitroquinoline. This second method of preparation establishes the fact that bromination of 6-methoxy-8-acetaminquinoline leads to substitution in the 5-position of the quinoline nucleus.

The free base is a yellow crystalline compound (m.p. 153–154°) which can be conveniently crystallized from methanol or ethanol. The outstanding property of 5-bromo-6-methoxy-8-aminoquinoline is the stability of the bromine atom toward anionoid reagents and the lability of the bromine atom toward cationoid reagents. Accordingly, the free base was found to be stable when heated with methanolic ammonia at 100° and treatment with sodium methoxide in boiling methanol failed to effect any appreciable change. On the other hand, cold dilute hydriodic acid brings about the liberation of iodine and tar formation. If acetone is added prior to the addition of the hydriodic acid, it is possible to isolate 6-methoxy-8-aminoquinoline and the strong lachrymatory effect of a halo-acetone is evident.

The hydrolysis of 5-bromo-6-methoxy-8-acetaminquinoline with boiling aqueous hydrobromic acid (10%) results in the formation of the hydrobromide of the isomeric 7-bromo-6-methoxy-8-aminoquinoline in good yield. The same transformation but with greatly reduced yield can be achieved using concentrated hydrochloric acid. Comparable studies using the 5-chloro-6-methoxy-8-acetaminquinoline failed to furnish any evidence of a similar transformation.

The structure of the hitherto undescribed 7-bromo-6-methoxy-8-aminoquinoline is based on the following evidence. Proper analytical values for carbon, hydrogen, nitrogen and neutralization equivalent were obtained. Reduction with zinc and alkali yielded 6-methoxy-8-aminoquinoline; this fact and insolubility of the bromo compound in alkali shows that the methoxyl group remains intact.

Oxidation with alkaline potassium permanganate gave pyridine-2,3-dicarboxylic acid which was identified as its methyl ester. Furthermore, Berkenheim and Antik⁶ reported the isolation of 6-methoxy-7-bromoquinoline from a mixture with the 5-bromo compound. This mixture was obtained as a result of a Skraup reaction using 3-bromo-4-methoxyaniline. Our 7-bromo-6-methoxy-8-aminoquinoline was deaminated by treating the diazonium compound with hypophosphorous acid. A crystalline compound, which possessed the correct composition and which melted at the temperature reported by these investigators, was obtained.

5,7-Dibromo-6-methoxy-8-aminoquinoline was prepared by direct bromination in boiling acetic acid of either 5-bromo- or 7-bromo-6-methoxy-8-aminoquinoline. Oxidation of the dibromoquinoline produced pyridine-2,3-dicarboxylic acid which was characterized as its dimethyl ester. Consequently both of the bromine atoms are in the benzenoid ring. Reduction of the dibromo compound with zinc and alkali gave 6-methoxy-8-aminoquinoline, although in small yield.

The halogen atom in the 5-position appears to be positive in nature, in the case of both 5-bromo-6-methoxy-8-aminoquinoline and 5,7-dibromo-6-methoxy-8-aminoquinoline. Both of these compounds can act as brominating agents. The transformation of 5-bromo-6-methoxy-8-aminoquinoline into its 7-bromo isomer was carried out in boiling hydrobromic acid as described above, but with the addition of phenol. Bromophenols were isolated from the reaction mixture. Similar results were obtained in the case of 5,7-dibromo-6-methoxy-8-aminoquinoline. Apparently, the positive bromine in the 5-position of 5-bromo-6-methoxy-8-aminoquinoline in the presence of hydrobromic acid is capable of brominating a second molecule to give the 5,7-dibromo compound which likewise contains a positive bromine in the 5-position.

Buchner⁷ described the transformation of *p*-bromoaniline into aniline, and dibromoaniline when this compound was heated at 150–160° with an excess of concentrated hydrochloric acid. Likewise, Baltzly and Buck⁸ have reported the formation of considerable amounts of aniline and 2,4-dibromoaniline when *p*-bromoaniline was refluxed with hydrobromic acid (48%).

Experimental⁹

6-Methoxy-8-acetaminquinoline.—Colorless 6-methoxy-8-aminoquinoline (70 g.) was treated with acetic anhydride

(1) This work was made possible by a grant (R. G. 1187) from the U. S. Public Health Service.

(2) R. Robinson and M. L. Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(3) F. Misani and M. T. Bogert, *J. Org. Chem.*, **10**, 347 (1945).

(4) N. L. Drake, *et al.*, *THIS JOURNAL*, **68**, 1536 (1946).

(5) Private communication.

(6) A. M. Berkenheim and L. V. Antik, *J. Gen. Chem.* (U. S. S. R.), **11**, 537 (1941).

(7) E. Buchner, *Ber.*, **8**, 361 (1875).

(8) R. Baltzly and J. S. Buck, *THIS JOURNAL*, **63**, 1757 (1941).

(9) All melting points are uncorrected.

(50 ml.) and acetic acid (50 ml.). The mixture was shaken and allowed to stand for 30 minutes. Methanol (200 ml.) was then added and the solution was allowed to crystallize. An additional amount of product was recovered from the mother liquor; total yield 84 g. (96%, m.p. 126–127°).

5-Bromo-6-methoxy-8-acetaminoquinoline.—6-Methoxy-8-acetaminoquinoline (80 g.), dissolved in acetic acid (400 ml.), was brominated by the addition of a solution of bromine (60 g.) in acetic acid (150 ml.). The reaction mixture became semi-solid due to precipitation of the hydrobromide of the bromination product. Water (1500 ml.) was then added and the reaction mixture was allowed to stand for 30 minutes with frequent stirring. The product was removed by filtration, washed with water and then transferred to a beaker containing about two liters of water. Ammonia was added to slight alkalinity and the mixture allowed to stand for one-half hour. The precipitate was then collected, dried at about 80° and crystallized from ethanol; yield 98 g. (96%, m.p. 164–166°, after recryst. m.p. 167–168°).

5-Bromo-6-methoxy-8-aminoquinoline Hydrochloride.—5-Bromo-6-methoxy-8-acetaminoquinoline (50 g.) and boiling water (250 ml.), in a one-liter 3-neck flask fitted with a reflux condenser and stirrer, was treated with aqueous hydrochloric acid (250 ml., 18%). The reaction mixture was maintained at the boiling temperature for 45 minutes after the addition of the acid. Orange crystals separated from the hot reaction mixture. The solid product was separated from the cold reaction mixture and washed once with water and twice with alcohol; yield 46 g. (94%).

5-Bromo-6-methoxy-8-aminoquinoline.—The conversion of the hydrochloride to the free base offers difficulties unless certain precautions are observed. The free base must not be heated in the presence of its hydrochloride. The following procedure has been found to be satisfactory. The hydrochloride (32 g.) was added to water (1 l.) containing a slight excess of ammonia. The mixture was stirred vigorously. The free base was then collected, washed with water and dried. The product was then crystallized from ethanol containing Norite and several drops of aqueous ammonia; yield 24 g. (74%, pale yellow crystals, m.p. 153–154°).

Anal. Calcd. for $C_{10}H_9ON_2Br$: C, 47.5; H, 3.56; N, 11.07. Found: C, 47.8; H, 3.94; N, 10.94.

The Action of Hydrobromic Acid on 5-Bromo-6-methoxy-8-acetaminoquinoline.—The hydrobromides of 5-bromo-6-methoxy-8-aminoquinoline and of the isomeric 7-bromo-6-methoxy-8-aminoquinoline are, respectively, orange and yellow. Under certain conditions of treatment a mixture of these two hydrobromides is obtained. The following procedure was adopted for the preparation of 7-bromo-6-methoxy-8-aminoquinoline. To boiling aqueous hydrobromic acid (10%, 200 ml.) contained in a 3-neck flask equipped with a stirrer, 5-bromo-6-methoxy-8-acetaminoquinoline (15 g.) was added in small portions over a period of 90 minutes. After an additional 30 minutes of boiling, the reaction mixture was allowed to cool. The yellow needles were removed by filtration, washed with a small amount of water and then placed in a sodium bicarbonate solution for several hours. The free base obtained in this way was then washed thoroughly with water and finally crystallized from ethanol using Norite; yield 10.8 g. (84% theory, m.p. 111.5–112.8°, after recryst. 4 times from alc. m.p. 114–114.5°).

Anal. Calcd. for $C_{10}H_9ON_2Br$: C, 47.5; H, 3.56; N, 11.07. Found: C, 47.6; H, 3.64; N, 11.34.

6-Methoxy-7-bromo-8-acetaminoquinoline (m.p. 222–222.5°) was prepared by heating the free base for 30–60 minutes on the steam-bath with an excess of acetic anhydride. The reaction mixture was poured onto ice and the well washed solid was crystallized from alcohol.

Anal. Calcd. for $C_{12}H_{11}O_2N_2Br$: C, 48.8; H, 3.73; N, 9.49. Found: C, 48.7; H, 3.97; N, 9.31.

6-Methoxy-7-bromo-8-benzaminoquinoline (m.p. 200.5–201.5°) was prepared by means of the Schotten-Baumann reaction.

Anal. Calcd. for $C_{17}H_{13}O_2N_2Br$: C, 57.1; H, 3.64; N, 7.85. Found: C, 56.9; H, 3.99; N, 7.62.

Reduction of 5-Bromo-6-methoxy-8-nitroquinoline.—To a cold solution (10°) of stannous chloride (21 g.) in hydrobromic acid (40%, 50 ml.), a suspension of the nitroquinoline (5 g.) in hydrobromic acid (40%, 50 ml.) was added with

stirring. The reaction mixture was kept at 10° during the addition and for a period of one hour after the addition was complete. The ice-bath was then removed and stirring continued for one-half hour. A red precipitate formed. The reaction mixture, diluted with ice and water, was then made alkaline with sodium hydroxide. The precipitate was next extracted with ether. The ether soluble material was crystallized from alcohol; yield 1.4 g. (31%). The melting point (and mixed m.p.) of the 5-bromo-6-methoxy-8-aminoquinoline prepared in the above manner was identical with that obtained by bromination of 6-methoxy-8-acetaminoquinoline followed by hydrolysis. The melting points of the acetylated derivatives of the two samples obtained by the two different procedures were also identical.

Reduction of 5-Bromo-6-methoxy-8-aminoquinoline.—A mixture of 5-bromo-6-methoxy-8-aminoquinoline (1 g.), stannous chloride (4 g.) and concd. HCl (10 ml.) was allowed to stand for 20 hours at room temperature. The orange color of the hydrochloride slowly changed to a yellowish green. The insoluble product was removed by filtration, and then treated with aqueous sodium hydroxide. The alkaline mixture was next extracted with ether. The ether extract yielded an oil (0.5 g.). This oil was dissolved in methanol and some (0.15 g.) of the starting material separated out. The filtrate yielded an oil which crystallized. This crystalline product was acetylated to form 6-methoxy-8-acetaminoquinoline (m.p. 126–127°).

Reduction of 6-Methoxy-7-bromo-8-aminoquinoline.—The method of Kreis¹⁰ which utilizes zinc and alkali was found to be applicable. A mixture of 6-methoxy-7-bromo-8-aminoquinoline (2.0 g.), zinc dust (1.0 g.) and sodium hydroxide (2.0 g.) in aqueous ethanol (20 ml., 50%) was refluxed for two hours. The resulting mixture was cooled, and water was added. Ether extraction yielded an orange oil. This oil was treated with acetic anhydride and then poured over ice. The solid obtained by this treatment was crystallized from alcohol; yield 1.2 g. (86% theory, m.p. 125.8–126.5°).

Oxidation of 6-Methoxy-7-bromo-8-aminoquinoline.—6-Methoxy-7-bromo-8-aminoquinoline (2.5 g.) was added to potassium permanganate (9.5 g.), sodium hydroxide (2.0 g.) and water (350 ml.). The mixture was stirred and boiled vigorously for two hours; an additional amount of permanganate (0.5 g.) was then added and boiling continued for two hours longer. A small amount of sodium bisulfite was added to remove the last traces of permanganate, and the reaction mixture was filtered. The filtrate was brought to a pH 4–5 and concentrated. A hot solution of copper acetate (6.0 g. in 100 ml. of water) and the mixture was heated for one hour. A light blue-green solid was obtained on cooling. This solid was suspended in water (50 ml.) and treated with hydrogen sulfide. After the copper sulfide was removed, the filtrate was evaporated and a yellow liquid that finally crystallized was obtained. Treatment of this product with diazomethane gave the methyl ester of pyridine-2,3-dicarboxylic acid (m.p. 54–55°, reported, *Ber.*, 27, 1787 (1894), 53–54°).

Deamination of 6-Methoxy-7-bromo-8-aminoquinoline.—The aminoquinoline (2.5 g.) was treated at 0–3° with sulfuric acid (1.0 g.) and water (50 ml.). Sodium nitrite (0.8 g.) dissolved in water (10 ml.) was then added slowly. Hypophosphorous acid (50%, 15 g.), together with ice (15 g.), was added and the reaction mixture placed in a refrigerator for two days. The third day the reaction mixture was allowed to come to room temperature. The mixture was then made alkaline with sodium carbonate and the precipitate was collected. Repeated crystallization from alcohol-water mixtures gave colorless needles (m.p. 110.5–111.5°); yield approx. 30%.

Anal. Calcd. for $C_{10}H_9ON_2Br$: C, 50.4; H, 3.36; N, 5.88. Found: C, 50.5; H, 3.55; N, 6.05.

5,7-Dibromo-6-methoxy-8-aminoquinoline.—Bromine (3.2 g.) in acetic acid (50 ml.) was added to 5-bromo-6-methoxy-8-aminoquinoline (or 7-bromo-6-methoxy-8-aminoquinoline) (5.0 g.). An orange precipitate formed immediately. The mixture was boiled for five minutes and then allowed to cool. A small amount of sodium bisulfite was added to remove unused bromine. Ammonia was then added slowly (cooling) until an excess was present. The precipitate was collected, washed with water and crystallized from alcohol; yield 5.3 g. (m.p. 87–88.5°).

(10) Kreis, *Ann.*, **286**, 377 (1895).

Anal. Calcd. for $C_{10}H_8ON_2Br$: C, 36.2; H, 2.43. Found: C, 36.6; H, 2.69.

The acetyl derivative (m.p. 135–136.5°) was obtained by treatment with acetic anhydride.

The Action of Hydrobromic Acid on 5,7-Dibromo-6-methoxy-8-aminoquinoline in the Presence of Phenol.—5,7-Dibromo-6-methoxy-8-aminoquinoline (1.2 g.) and phenol (ca. 0.3 g.) were placed in a flask with hydrobromic acid (20%, 70 ml.) and heated under reflux for 1.5 hours. The reaction mixture was cooled and the orange solid was removed by filtration. (The filtrate contained the phenolic substances.) The orange solid was treated with alkali to convert the hydrobromide to the free base, which was washed with water and crystallized from ethanol. 6-Methoxy-7-bromo-8-aminoquinoline (0.4 g., m.p. 113–114°) was obtained.

The filtrate containing the phenolic substances was extracted with ether. The ether extract gave a small amount of an oil, which was dissolved in sodium hydroxide and treated with 2,4-dinitrochlorobenzene. *o*-Bromophenyl 2,4-dinitrophenyl ether (m.p. 84–85.5°) was obtained.

The Transformation of 5-Bromo-6-methoxy-8-aminoquinoline into 6-Methoxy-7-bromo-8-aminoquinoline in the Presence of Phenol.—A solution of phenol (4.7 g.) in hy-

drobromic acid (10%, 200 ml.) was placed in a 3-neck flask fitted with stirrer and reflux condenser. The solution was heated to boiling and then 5-bromo-6-methoxy-8-aminoquinoline (15 g.) was added in small portions over a period of 1.75 hours. The solution became deep red. After the addition of the quinoline was complete, refluxing was continued for another one-half hour. During this time, a large quantity of yellow needles separated. The mixture was then cooled and filtered. (The filtrate contained the phenolic substances.) These yellow needles were treated with sodium hydroxide (10%, 270 ml.) to produce the free base. (Additional phenolic material can be recovered from the alkaline filtrate.) Repeated crystallization of the free base from alcohol yielded 6-methoxy-7-bromo-8-aminoquinoline (m.p. 112–114°, 4.1 g., 32% theory).

The phenol containing filtrate was extracted with ether. This ether extract possesses the characteristic odor of halogenated phenols. Two derivatives were prepared from this phenolic fraction, *o*-bromophenyl 2,4-dinitrophenyl ether (m.p. 84–85°) and *p*-bromophenoxyacetic acid (m.p. 154–55°). A mixture of *o*- and *p*-bromophenol was therefore produced in this experiment.

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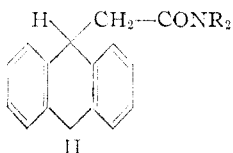
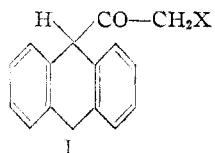
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Reaction of α -Haloketones with Bases

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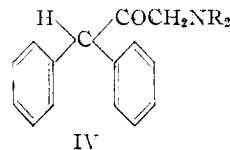
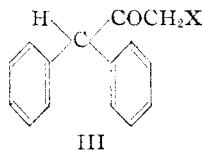
It was found that when benzhydryl chloromethyl or bromomethyl ketone was allowed to react with diethylamine only the displacement product was obtained. When the base was alcoholic sodium methoxide, however, rearrangement to methyl 3,3-diphenylpropionate occurred. The reaction of the corresponding 4,4'-dinitrobenzhydryl chloromethyl ketone with sodium methoxide yielded only the cleavage product, 4,4'-dinitrodiphenylmethane. Desyl chloride under the same conditions was transformed into benzoin methyl ether and not the oxirane as previous workers had reported.

In the course of a recent investigation dealing with the preparation of aryl aminomethyl ketones, May and Mosettig² studied the reaction of secondary amines with various aryl halomethyl ketones. When the aryl group was 9,10-dihydro-9-anthryl (I), it was found that in addition to the expected



displacement product, an amide was isolated and it was shown to be N,N-dialkyl 9,10-dihydro-9-anthrylacetylamide (II). Such a rearrangement of a α -haloketone in the presence of base is well-known^{3,4} and, indeed, the rearrangement of benzyl chloromethyl ketone in alkali is quite analogous.^{5,6} There is nevertheless one noticeable difference. The rearrangement of the dihydroanthryl compound was initiated by a weak organic base whereas all other rearrangements were brought about by much stronger organic or inorganic bases. Loftfield⁴ has recently pointed out that such a result is consistent with his theory in which the ease of removal of the hydrogen atom on the α -carbon not holding the halogen (the α' -hydrogen) greatly

influences the course of the reaction. Thus, in the dihydroanthryl case, since the α' -hydrogen atom is activated by two phenyl groups, the rate of its removal is increased and consequently the rearrangement proceeds readily. In line with the foregoing theory, a study of the reaction of the structurally similar benzhydryl halomethyl ketones (III) with amines and alkoxide which had been performed at an earlier date in this Laboratory, is of interest.



When either benzhydryl chloromethyl or bromomethyl ketone (III) was allowed to react with diethylamine in ether under the conditions of May and Mosettig² only the displacement product, 1,1-diphenyl-3-diethylamino-2-propanone (IV), was formed. It was found, as would be expected by previous work on analogous compounds,^{5,6} that rearrangement did occur when the halomethyl ketones were allowed to react in either methanol or ether with sodium methoxide and methyl 3,3-diphenylpropionate (V) was obtained.

In order to study the effect of substituents upon the ease of removal of the α' -hydrogen atom and upon the rearrangement reaction 4,4'-dimethoxybenzhydryl and 4,4'-dinitrobenzhydryl chloromethyl ketone (VI) were prepared. When the dimethoxy compound was allowed to react in

(1) Allied Chemical and Dye Corporation Fellow, 1949–1950.

(2) E. L. May and E. Mosettig, *THIS JOURNAL*, **70**, 1077 (1948).

(3) R. Jacquier, *Bull. soc. chim. France*, D-35 (1950).

(4) R. B. Loftfield, *THIS JOURNAL*, **73**, 4707 (1951).

(5) G. Richard, *Compt. rend.*, **197**, 1432 (1933).

(6) W. D. McPhee and E. Klingsberg, *THIS JOURNAL*, **66**, 1132 (1944).