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Synthesis of some Halogenated Quinolines (1)

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Interest in the biological activity of certain halogenated derivatives of quinoline and isoquinoline prompted the preparation of other derivatives similar to those previously reported (1). In order to obtain halogenated quinoline moieties which had different water-oil solubility ratios, the compounds described in the experimental section were synthesized.

Halogenation of quinoline and isoquinoline using an excess of aluminum chloride proceeds with extreme ease and in good yield (1). Also of interest is the relatively simple pattern of orientation of the halo-atoms within these compounds. In all halogenation reactions of quinoline and isoquinoline conducted in molten aluminum chloride, products were obtained with halogen attached to the benzenoid ring. In no cases do we obtain products halogenated in the pyridinoid ring when excess aluminum chloride is used. Substitution in the benzenoid ring is attributed to a deactivation of the pyridinoid ring by complexation with aluminum chloride. Complexation with excess aluminum chloride produces a partial positive charge on the nitrogen atom which tends to repel the bromonium or chloronium ion. In addition to mutual repulsion of the like charges it is believed that the complex exerts certain steric effects which have the greatest effect on the pyridinoid ring. Indeed, one would expect the entire molecule to be deactivated by complexation; but, due to the very polar reaction medium (molten aluminum chloride which would be expected to provide excellent polarization of the halogen molecule thus producing a very active electrophile) any such deactivation is overcome since good yields of the halogenated products are obtained.

The orientation of halogen within the benzenoid ring is relatively simple. When no directing substituent is present, the halo atoms seek the positions of highest electron density which are 5- and 8- for the protonated forms of quinoline and isoquinoline (5). If a directing group is present, orientation of halogen within the benzenoid ring is further influenced by that group. For example, the 5,6-dihalo- compounds are exclusively produced by monohalogenation of the 6-halo which directs *ortho* bacause of no position capable of bond formation *para* to it. Halogenation of 6-ethylquinoline in excess aluminum chloride leads first to 5-halo-6-ethylquinoline and more strenuous conditions give 5,8-dihalo-6-ethylquinoline because of the introduction of *para* director (halogen) in position 5.

EXPERIMENTAL (6)

5,6-Dichloroquinoline.

6-Chloroquinoline (32 g., 0.2 mole, Columbia Organic Chemicals) was mixed with anhydrous aluminum chloride (80 g., 0.6 mole). Manual stirring was needed until the complex became molten which was at approximately 100°. Chlorine (14.2 g., 0.2 mole) was added to the violet complex at 100°. Two hours were required to add the chlorine and when no more hydrogen chloride was evolved the mixture was decomposed with ice. The resulting beige precipitate was collected by filtration and air-dried. Sublimation (65°/0.1mm.) followed by recrystallization from ethanol and water gave 5,6-dichloroquinoline (34 g., 85%) as white needles, m.p. 82-84° (lit. (7) m.p. 85°).

5,8-Dichloroquinoline.

Quinoline (36 g., 0.28 mole) was added to anhydrous aluminum chloride (112 g., 0.84 mole). During the formation of the complex considerable heat was evolved and caused the complex to become molten. By means of an oil bath the temperature of the molten complex was increased to 110°. Chlorine (39.8 g., 0.56 mole) was added to the stirred complex at this temperature during 6 hours. After the evolution of hydrogen chloride had ceased, the mixture was decomposed with ice and steam distilled with superheated steam. Because of the acidic medium lesser chlorinated products did not steam distill to contaminate the distillate. The distillate was cooled and the white solid collected by filtration. Recrystallization from cyclohexane gave 5,8-dichloroquinoline (40 g., 73%) as white needles, m.p. 96-97° (lit. (7) m.p. 97-98°).

5,6,8-Trichloroquinoline.

6-Chloroquinoline (8 g., 0.05 mole) was complexed with aluminum chloride (20 g., 0.15 mole) and heated to 125°. Chlorine (7.1 g., 0.1 mole) was added to the molten complex during two hours. Decomposition of the mixture with ice yielded a white precipitate which was collected by filtration, dried, and sublimed (100°/0.1 mm.). Recrystallization from acetone gave the title compound (10.4 g.) as white needles, m.p. 123-125°.

Anal. Calcd. for $C_9H_4Cl_3N$: Cl, 45.75. Found: Cl, 46.01.

The structure of this compound was ascertained by a comparison of its n.m.r. spectrum with that of 5,6,8-tribromoquinoline whose structure was established by alternate synthesis (1). Known bromo and chloro compounds of the same structure give very similar spectra. Only a slight shift in the position of the peaks due to the different shielding effects of bromine and chlorine is observed. The typical ABX spectrum for the three hydrogens in the heterocyclic ring, positions 2, 3, and 4, was observed for the title compound – H_2 (quartet), τ = 0.9 (center); H_3 (quartet), τ = 2.4 (center); H_4 (quartet), τ = 1.4 (center). This ABX pattern

is present in all of the haloquinolines reported in this paper which means that all halo atoms are contained in the benzenoid ring. The proton at position 7 appears as a sharp singlet, $\tau = 1.7$.

5,6-Dibromoquinoline.

6-Bromoquinoline (36 g., 0.17 mole, Eastman) and aluminum chloride (68 g., 0.51 mole) gave no evidence for complexation when mixed at room temperature. Upon heating the mixture to approximately 100°, it became molten. When a temperature of 120° was reached, gaseous bromine (28 g., 0.17 mole) was added over a period of two hours. After the evolution of hydrogen bromide had ceased the mixture was poured onto ice. The resulting beige precipitate was collected by filtration and air-dried. Sublimation (60°/0.1 mm.) followed by recrystallization from methanol and water gave 5,6-dibromoquinoline (40 g., 80%), m.p. 77-79° (lit. (7) m.p. 81°).

5-Bromo-6-chloroquinoline.

6-Chloroquinoline (16.3 g., 0.1 mole) was complexed with aluminum chloride (40 g., 0.3 mole) by heating the mixture to 100°. Gaseous bromide (16.0 g., 0.1 mole) was added to the molten complex during 1 hour. After evolution of hydrogen bromide had ceased the mixture was poured onto ice and the resulting precipitate collected by filtration. Sublimation (50°/0.1 mm.) followed by recrystallization from cyclohexane gave 5-bromo-6-chloroquinoline (21 g., 84%), m.p. 62-63°.

Anal. (8) Calcd. for C_9H_5BrClN: Cl, 29.24. Found: Cl, 29.44.

The n.m.r. spectrum of this compound was compared with those of 5,6-dichloro- and 5,6-dibromoquinoline and was identical with regard to types of peaks. For example, the ABX grouping for the protons of the heterocyclic ring was observed, and protons 7 and 8 appear as a quartet, $\tau = 2.1$ (center).

5,8-Dibromo-6-ethylquinoline.

6-Ethylquinoline (31.4 g., 0.2 mole) was added dropwise to anhydrous aluminum chloride (80 g., 0.6 mole). During the complexation enough heat was liberated to cause the mixture to be liquid; however, external heating was supplied to maintain a temperature of 100°. Gaseous bromine (72.0 g., 0.4 mole) was added to the molten complex over a period of four hours during which time the temperature was gradually increased from 100° to 125°. Upon decomposition of the mixture with ice a tarry product resulted. This product was extracted with pentane using a Soxhlet extractor. Evaporation of the pentane extracts left a cream colored solid which was slightly oily. Sublimation (40°/0.1 mm.) followed by a recrystallization from pentane gave 5,8-dibromo-6-ethylquinoline (38 g., 60%), m.p. 71-72°.

Anal. Calcd. for $C_{11}H_9Br_2N$: Br, 50.73. Found: Br, 50.79.

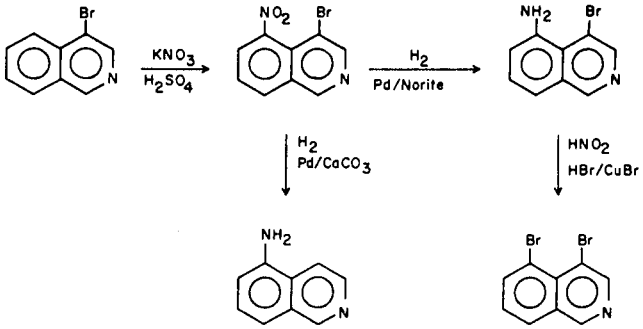
This compound had an n.m.r. spectrum in which the aromatic protons gave signals similar to those for 5,6,8-trichloro- and tribromoquinoline. The protons of the ethyl grouping cause little interference.

4,5-Dibromoisoquinoline.

4-Bromoisoquinoline (31 g., 0.15 mole) was complexed with aluminum chloride (40 g., 0.3 mole) at 90°. Bromine (16 g., 0.1 mole) in the gaseous phase was added to the stirred complex. During the addition of bromine the temperature was increased to approximately 120°. After addition of bromine, approximately three hours was utilized, the mixture was heated and stirred for an additional hour to insure completeness of reaction. The reaction mixture was decomposed with cracked ice and the resulting precipitate was dissolved in methanol and treated twice with Norite. Recrystallization afforded 4,5-dibromoisoquinoline (31 g., 72%) as white needles, m.p. 112-113°.

Anal. Calcd. for $C_9H_5Br_2N$: Br, 55.69. Found: Br, 55.70.

Identification of this compound was based on its synthesis by an alternate route and is shown in the scheme below:



Nitration of 4-bromoisoquinoline using the procedure of Osburn, *et al.* (9), afforded 4-bromo-5-nitroisoquinoline. That the nitro group did indeed assume position 5 was ascertained by simultaneous dehalogenation and reduction to 5-aminoisoquinoline (10). A Parr hydrogenator was employed for the reduction with 5% palladium on calcium carbonate as catalyst, ammonium acetate as buffer, and acetic acid (glacial) as solvent. Melting points, mixed melting point, and infrared spectra were identical for the reduction product and known 5-aminoisoquinoline.

4-Bromo-5-nitroisoquinoline was reduced to 4-bromo-5-aminoisoquinoline in good yield without hydrogenolysis in a Parr hydrogenator using 5% palladium on charcoal with glacial acetic acid as solvent. The catalyst was filtered and the resulting filtrate made basic with sodium hydroxide. The dark precipitate was filtered, air-dried, and sublimed (100°, 0.1 mm.) yielding 4-bromo-5-aminoisoquinoline as yellow crystals, m.p. 115°.

Anal. Calcd. for $C_9H_7BrN_2$: Br, 35.82; N, 12.55. Found: Br, 35.90; N, 12.52.

4-Bromo-5-aminoisoquinoline was converted to 4,5-dibromoisoquinoline via the Sandmeyer reaction.

Infrared spectra, melting points, and mixed melting point of 4,5-dibromoisoquinoline prepared by this unequivocal method were identical with those of the same compound prepared by direct bromination of 4-bromoisoquinoline.

Anal. Calcd. for $C_9H_5Br_2N$: Br, 55.69. Found: Br, 55.74.

4,5,8-Tribromoisoquinoline.

4-Bromoisoquinoline (21 g., 0.1 mole) was mixed with anhydrous aluminum chloride (40 g., 0.3 mole) and heated to 120°. During three hours gaseous bromine (32 g., 0.2 mole) was added to the molten complex. When the evolution of hydrogen bromide gas had stopped, the mixture was poured onto ice and the resulting precipitate collected by filtration. Sublimation (150°/0.1 mm.) followed by recrystallization from methyl ethyl ketone gave 4,5,8-tribromoisoquinoline (31 g.) as white needles, m.p. 165°.

Anal. Calcd. for $C_9H_4Br_3N$: Br, 65.52. Found: Br, 65.55.

Identification of 4,5,8-tribromoisoquinoline was accomplished using n.m.r. techniques. The bromine atom remains attached to position 4 in the heterocyclic ring as is evidenced by singlets at $\tau = 0.65$ for H_1 and $\tau = 1.3$ for H_3. Presence of a quartet $\tau = 2.2$ (center) for H_6 and H_7 indicates that substitution occurred in positions 5- and 8-. This is expected since 4,5-dibromoisoquinoline forms on monobromination of 4-bromoisoquinoline and the second halogen would be directed *para* to the first halogen.

5-Bromo-3-methylisoquinoline.

5-Amino-3-methylisoquinoline (1.0 g.) was dissolved in concentrated hydrobromic acid (48%, 3 ml.) and water (3 ml.). This solution was diazotized at 0° with sodium nitrite (0.5 g.) dissolved

in water (3 ml.). The resulting diazonium solution was slowly added to a freshly prepared solution of cuprous bromide (1.2 g.) in hydrobromic acid (10 ml.) at 75°. The mixture was allowed to stand at room temperature for 24 hours after which time the solution was made basic with sodium hydroxide and filtered. The precipitate was sublimed (35°/0.75 mm.) to give 5-bromo-3-methylisoquinoline (0.8 g., 57%), m.p. 40-42°.

Anal. Calcd. for $C_{10}H_8BrN$: Br, 35.98. Found: Br, 35.81.

5-Chloro-3-methylisoquinoline.

The procedure for the preparation of this compound was identical to that for the bromo compound except for substitution of hydrochloric acid for hydrobromic acid and sodium chloride for sodium bromide. 5-Chloro-3-methylisoquinoline, m.p. 55-57°, was obtained in 76% yield.

Anal. Calcd. for $C_{10}H_8ClN$: Cl, 19.96. Found: Cl, 19.99.

5-Iodo-3-methylisoquinoline.

The diazotization procedure used was the same as that used for the bromo and chloro compounds. The diazonium solution was added to a solution of potassium iodide in water at 95°. After the usual workup, 5-iodo-3-methylisoquinoline, m.p. 80-82° was obtained in 44% yield.

Anal. Calcd. for $C_{10}H_8IN$: I, 47.16. Found: I, 47.41.

5-Halo-3-methylisoquinoline.

The identity of the 5-halo-3-methylisoquinolines was established by reduction of the 5-nitro-3-methyl derivative followed by the Sandmeyer reaction.

5-Nitro-3-methylisoquinoline was identified in the same manner as previously described by Popp and Brill (11). This procedure involves oxidation of the methyl group with selenium dioxide to the aldehyde, followed by oxidation of the aldehyde with hydrogen peroxide to the acid, and finally decarboxylation of the acid to give 5-nitroisoquinoline.

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REFERENCES

(1) Related paper. M. Gordon and D. E. Pearson, *J. Org. Chem.*, 29, 329 (1964).

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(3) Undergraduate PRF fellows.

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

(6) We are indebted to Dr. D. L. Tuleen, Vanderbilt University for obtaining and interpreting the n.m.r. spectra. The spectra were obtained using a Varian A-60 Nuclear Magnetic Resonance Spectrometer. Methylene chloride was used as solvent. Chemical shifts are expressed as shielding values, τ. Infrared spectra were recorded on a P. E. Model 137 and Beckmann IR 10 spectrophotometers. All melting points are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tennessee and Prof. Howell R. Clark, Murray State University. See reference 1 for the details of the method used in introducing chlorine and bromine into the reaction mixtures.

(7) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1953.

(8) The values calculated for C_9H_5BrClN: Cl, 29.24. Found: Cl, 29.44 represent total halogen calculated as chlorine.

(9) A. R. Osburn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).

(10) R. A. Robinson, *J. Am. Chem. Soc.*, 69, 1944 (1947).

(11) F. D. Popp and E. Brill, *J. Org. Chem.*, 26, 956 (1961).

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