6-Chloro-8-Ethylquinoline and Some Derivatives

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2,6-Dichloro-8-ethylquinoline and 2,6-dichloro-8-ethyl-5-nitroquinoline, as obtained from the corresponding 1-methylquinolinium salts and 2-quinolones, hydrolyzed to 2-quinolinols. Nitration of 6-chloro-, 2,6-dichloro-, and 6-chloro-2-hydroxyderivatives of 8-ethylquinoline gave the corresponding 5-nitro compounds which were compared with authentic samples prepared by alternate routes. 6-Chloro-8-ethyl-5-nitroquinoline and 2,6-dichloro-8-ethyl-5-nitroquinoline were reduced to the amines; the amines were acetylated and benzoylated.

A SEARCH of the literature revealed no information concerning 6-chloro-8-ethylquinoline and hence the preparation of it and some of its derivatives was undertaken. A comparison of the properties of such compounds with those of 6-chloro-8-methylquinoline and its derivatives as reported by Irving, Greene, Peterson, and Capps (*3*) as well as with those of 6-bromo-8-ethylquinoline as reported by Beasley, Brown and Capps (*2*) appeared to be of interest.

6-Chloro-8-ethylquinoline was prepared from 2-amino-5-chloroethylbenzene by the modified Skraup method as reported by Altau and others (*1*). The 2-amino-5-chloroethylbenzene was obtained from the chlorination of 2-acetamidoethylbenzene, which in turn had been synthesized from ethylbenzene (*1*).

A solution of 6-chloro-8-ethylquinoline in sulfuric acid (sp. gr. 1.84) was added to a solution of fuming nitric acid (sp. gr. 1.5) in sulfuric acid (sp. gr. 1.84) at 0–5° prior to increasing the internal temperature to 60° and maintaining it for 30 minutes. The structure of the 6-chloro-8-ethyl-5-nitroquinoline, thus obtained, was established by comparing its properties with those of an authentic sample as synthesized by a Skraup ring-closure upon 2-acetamido-4-nitro-5-chloroethylbenzene (*1*).

6-Chloro-8-ethyl-1-methylquinolinium methyl sulfate resulted when 6-chloro-8-ethylquinoline was heated with dimethyl sulfate at 135°–140°. 6-Chloro-8-ethyl-1-methyl-2-quinolone was obtained by the oxidation of the methylquinolinium salt with alkaline ferricyanide solution at 60°–65°. A mixture of phosphorus oxychloride and phosphorus pentachloride reacted with the quinolone, when heated in an oil bath at 125°–130°, yielding 2,6-dichloro-8-ethylquinoline, which was then hydrolyzed by heating with sulfuric acid (52.5 ml.; sp. gr. 1.84)–water (35 ml.) solution.

6-Chloro-8-ethyl-2-hydroxyquinoline was nitrated with a mixture of sulfuric acid (sp. gr. 1.84) and nitric acid (sp. gr. 1.42) under relatively mild conditions yielding 6-chloro-8-ethyl-2-hydroxy-5-nitroquinoline. An authentic sample of 6-chloro-8-ethyl-2-hydroxy-5-nitroquinoline was prepared for comparison purposes from 6-chloro-8-ethyl-5-nitroquinoline *via* 6-chloro-8-ethyl-1-methyl-5-nitro-2-quinolone and 2,6-dichloro-8-ethyl-5-nitroquinoline. The 6-chloro-8-ethyl-1-methyl-5-nitro-2-quinolone was prepared according to modifications of conditions reported by Beasley, Brown, and Capps (*2*) for reacting 6-brome-8-ethyl-5-nitroquinoline with dimethyl sulfate and then oxidizing with alkaline hydrogen peroxide. Reaction of the 6-chloro-8-ethyl-1-methyl-5-nitro-2-quinolone with a mixture of phosphorus oxychloride and phosphorus pentachloride, while being heated in an oil bath at 125°–130°, gave some 2,6-dichloro-8-ethyl-5-nitroquinoline, which was hydrolyzed upon heating with sulfuric acid (50 ml.; sp. gr. 1.84)–water (25 ml.) solution to 6-chloro-8-ethyl-2-hydroxy-5-nitroquinoline.

A dinitro derivative of 6-chloro-8-ethyl-2-hydroxyquinoline formed, along with an unseparated mixture, upon nitration under more stringent conditions, while using a mixture of fuming nitric acid (sp. gr. 1.5) and sulfuric acid (sp. gr. 1.84). No attempt was made establish the structure of this dinitro derivative.

The 2,6-dichloro-8-ethyl-5-nitroquinoline, as obtained from 6-chloro-8-ethyl-5-nitroquinoline, also served as a reference compound for indicating the position taken by the nitro group during the nitration of 2,6-dichloro-8-ethylquinoline with a mixture of sulfuric and fuming nitric acid.

6-Chloro-8-ethyl-5-nitroquinoline and 2,6-dichloro-8-ethyl-5-nitroquinoline were each reduced independently with hydrogen at 40 p.s.i. pressure, in the presence of Raney nickel catalyst, to the corresponding amine. 6-Chloro-8-ethyl-5-nitroquinoline was reduced also with a mixture of stannous chloride and hydrochloric acid to 5-amino-6-chloro-8-ethylquinoline.

Heating 5-amino-6-chloro-8-ethylquinoline and 5-amino-2,6-dichloro-8-ethylquinoline under refluxing conditions with a solution of acetic anhydride and glacial acetic acid gave the corresponding acetamido derivatives.

The benzoylation of 5-amino-6-chloro-8-ethylquinoline and 5-amino-2,6-dichloro-8-ethylquinoline under Schotten-Baumann conditions (*4*) yielded the corresponding benzamido derivatives.

EXPERIMENTAL

6-Chloro-8-ethylquinoline. This was prepared by a modified Skraup ring-closure upon 2-amino-5-chloroethylbenzene according to the procedure reported by Altau and others (*1*).

6-Chloro-8-ethylquinoline Picrate. 6-Chloro-8-ethylquinoline (1.0 g.) was dissolved in 95% ethanol (15 ml.) and saturated aqueous picric acid solution (150 ml.) was added. The mixture was heated to boiling for ten minutes and allowed to cool. A bright, yellow picrate separated upon cooling and was purified, after isolating, by crystallization from 95% ethanol; yield, 2.0 g. (89.7%); m.p. 161°–162°.

ANAL. Calcd. for $C_{17}H_{13}ClN_4O_7$: Cl, 8.43; N, 13.32. Found: Cl. 8.20; N, 13.49.

6-Chloro-8-ethyl-5-nitroquinoline. A solution of 6-chloro-8-ethylquinoline (30.0 g.) in sulfuric acid (40 ml.; sp. 1.84) was added dropwise, with stirring and at 0–5°, to a solution of fuming nitric acid (25 ml.; sp. gr. 1.50) in sulfuric acid (27 ml.; sp. gr. 1.84). After maintaining an internal temperature of 0–5° for an additional hour, the reaction mixture was allowed to warm to room temperature and finally heated for 30 minutes at 60°. The resulting solution was poured, after cooling, into cracked ice–water mixture (2000 ml.) before collecting the impure 6-chloro-8-ethyl-5-

nitroquinoline by filtration and washing it with water. Recrystallization from 95% ethanol gave long, yellow needles; yield, 39.4 g. (87.5%); m.p. 56–57°.

ANAL. Calcd. for $C_{11}H_9ClN_2O_2$: Cl, 14.99; N, 11.84. Found: Cl, 15.11; N, 11.84.

2-Acetamido-5-chloro-4-nitroethylbenzene was subjected to the conditions of a modified Skraup ring-closure according to conditions reported by Altau and others (*1*).

2,6-Dichloro-8-ethylquinoline. 6-Chloro-8-ethylquinoline (40.0 g.) and dimethyl sulfate (50 ml.) were heated together in an oil bath maintained at 135°–140° for 3 hours. Water (160 ml.) was added prior to extracting with diethyl ether. The aqueous solution was then mixed with a solution of potassium ferricyanide (214 g.) in water (1480 ml.) before increasing the internal temperature to 60°–65° and dropping in, with stirring, a solution of potassium hydroxide (480 ml.; 10% by weight). The internal temperature was maintained at 60°–65° for 2 additional hours before separating the oil that had formed and drying it in a vacuum desiccator over soda-lime. The aqueous phase was extracted with diethyl ether, and the ether extract was dried over anhydrous sodium sulfate. Some additional quinolone resulted when the ether was removed by distillation under reduced pressure.

The crude quinolone (39.2 g.), phosphorus oxychloride (75 ml.), and phosphorus pentachloride (39 g.) were heated together in an oil bath maintained at 130°–135° for 3 hours. After cooling, the mixture was poured into ice and water (3000 ml.) containing hydrochloric acid (100 ml.). The solid that formed was collected by filtration, washed with water and crystallized from acetone-water solution with the aid of cooling in an ice-salt bath; colorless (white) needles; yield, 19.5 g. (41.2%); m.p. 58–60°.

ANAL. Calcd. for $C_{11}H_9Cl_2N$: Cl, 31.36; N, 6.20. Found: Cl, 31.26; N, 6.20.

6-Chloro-8-ethyl-2-hydroxyquinoline. 2,6-Dichloro-8-ethylquinoline (5.0 g.), sulfuric acid (52.5 ml.; sp. gr. 1.84) and water (35 ml.) were heated together in an oil bath maintained at 175°–180° for 4½ hours. After cooling, the mixture was poured into cracked ice and water (800 ml.). The resulting solid was separated by filtration, washed with water, and crystallized from 95% ethanol; colorless (white) crystals; yield, 4.0 g. (87.4%); m.p. 221–3°.

ANAL. Calcd. for $C_{11}H_{10}ClNO$: Cl, 17.07; N, 6.75. Found: Cl, 16.80; N, 6.74.

6-Chloro-8-ethyl-2-hydroxy-5-nitroquinoline. 2,6-Dichloro-8-ethyl-5-nitroquinoline. (5.0 g.), sulfuric acid (50 ml.; sp. gr. 1.84) and water (25 ml.) were heated under reflux conditions for 20 minutes. After cooling and pouring into cracked ice-water mixture (500 ml.), the solid that formed was collected by filtration and washed with water. Crystallization from 95% ethanol gave needles; yield, 4.0 g. (86%); m.p. 260–2°.

ANAL. Calcd. for $C_{11}H_9ClN_2O_3$: Cl, 14.03; N, 11.09. Found: Cl, 13.92; N, 10.90.

A solution of nitric acid (0.5 ml.; sp. gr. 1.42) in sulfuric acid (0.5 ml.; sp. gr. 1.84) was added dropwise at 0° to a solution of 6-chloro-8-ethyl-2-hydroxyquinoline (0.5 g.) in sulfuric acid (1 ml.; sp. gr. 1.84). After keeping in the ice bath for an additional 30 minutes and then at ambient temperature for 2 hours, the resulting solution was poured into cracked ice and water (100 ml.). The crude 6-chloro-8-ethyl-2-hydroxy-5-nitroquinoline was purified, after collecting and washing with water, by crystallizations from 95% ethanol combined with decolorizing carbon treatments; yield, 0.33 g.; m.p. 260–2°.

6-Chloro-8-ethyl-2-hydroxy-(?)-dinitroquinoline. A solution of 6-chloro-8-ethyl-2-hydroxyquinoline (2.0 g.) in sulfuric acid (5 ml.; sp. gr. 1.84) was added dropwise, with stirring, to a solution of fuming nitric acid (1.6 ml.; sp. gr. 1.5) in sulfuric acid (1.6 ml.; sp. gr. 1.84) at 0°–5°. The 0°–5° internal temperature was maintained for 30 additional minutes prior to slowly heating to 65°, cooling, and pouring into ice-water mixture (200 ml.). The solid that formed was collected by filtration, washed with water and crystallized from glacial acetic acid; yield, 1.0 g.; melted with discoloration near 268°. An unseparated mixture of nitrated compounds (1.26 g.) was also isolated.

ANAL. Calcd. for $C_{11}H_8ClN_3O_5$: Cl, 11.91; N, 14.11. Found: Cl, 11.86; N, 13.92.

2,6-Dichloro-8-ethyl-5-nitroquinoline. 6-Chloro-8-ethyl-5-nitroquinoline (10.0 g.) was converted into crude 6-chloro-8-ethyl-1-methyl-5-nitro-2-quinolone (6.6 g.; 58.5%) under essentially the same conditions as reported by Beasley, Brown, and Capps (*2*) for changing 6-bromo-8-ethyl-5-nitroquinoline into 6-bromo-8-ethyl-1-methyl-5-nitro-2-quniolone. The oxidation was effected at 60–5° rather than 55°–60°, however.

A mixture of crude 6-chloro-8-ethyl-1-methyl-5-nitro-2-quinolone (6.6 g.), phosphorus oxychloride (12 ml.), and phosphorus pentachloride (5.0 g.) was heated in an oil bath maintained at 125°–130° for 3 hours. The resulting mixture was poured, after cooling, into cracked ice and water (600 ml.). Filtration was used to separate the solid that formed prior to washing with water and crystallizing from 95% ethanol; yield, 2.2 g.; pale-yellow needles, m.p. 130–1°.

ANAL. Calcd. for $C_{11}H_8Cl_2N_2O_2$: Cl, 26.16; N, 10.33. Found: Cl, 26.16; N, 10.30.

A solution of 2,6-dichloro-8-ethylquinoline (18.4 g.) in sulfuric acid (40 ml.; sp. gr. 1.84) was added dropwise, with stirring, to a solution of fuming nitric acid (11.7 ml.; sp. gr. 1.5) in sulfuric acid (11.7 ml.; sp. gr. 1.84) while maintaining an internal temperature of 0°–5°. The cooling bath was removed after maintaining the internal temperature at 0°–5° for an additional thirty minutes. When the internal temperature had increased spontaneously to that of the room, it was slowly increased to 60° by applying heat. The resulting solution was then poured into cracked ice-water mixture (1500 ml.), prior to collecting the solid by filtration and washing it with water. Pale yellow needles formed upon crystallizing from 95% ethanol; yield, 20.2 g. (90.1%); m.p. 130–2°.

5-Amino-6-chloro-8-ethylquinoline. A solution of 6-chloro-8-ethyl-5-nitroquinoline (5.0 g.) in absolute ethanol was subjected to hydrogenation at 35 p.s.i., with shaking, after having added Raney nickel catalyst. When hydrogen uptake ceased, the catalyst was removed by filtration, and the alcohol was removed by distillation under reduced pressure. The residue was dissolved in diethyl ether and the resulting solution dried over anhydrous sodium sulfate. Dry hydrogen chloride gas was then passed into the dried ether solution causing the precipitation of the orange-red amine hydrochloride; yield, 5 g.

A solution of $SnCl_2 \times 2H_2O$ (18.0 g.) contained in hydrochloric acid (35.5 ml.; sp. gr. 1.19) was added dropwise, with stirring, to a solution of 6-chloro-8-ethyl-5-nitroquinoline (8.0 g.) in 95% ethanol (50 ml.) at 50°. After keeping the mixture just below the boiling temperature for one hour, a solution of 20% aqueous sodium hydroxide was added until the system was almost neutral. Neutralization was completed by adding ammonium hydroxide while maintaining the system near its boiling temperature. The resulting solid was separated by filtration while the system was still hot, and the solid residue was extracted several times with boiling ethanol. Hydrochloric acid was added to acidify the filtrate after combining it with the alcoholic extracts. The amine hydrochloride formed upon concentrating the resulting solution by distillation under reduced pressure; yield, 8.0 g.

Addition of ammonium hydroxide (conc.) to 5-amino-6-chloro-8-ethylquinoline hydrochloride (2.0 g.) liberated the amine, which was separated by filtration, washed with water and crystallized from ethanol-water solution. Pale yellow needles were deposited upon cooling overnight; yield, 1.4 g.;

m.p. 37–9°.

ANAL. Calcd. for $C_{11}H_{11}ClN_2$: Cl, 17.15; N, 13.56. Found: Cl, 17.25; N, 13.39.

5-Amino-2,6-dichloro-8-ethylquinoline. A solution of 2,6-dichloro-8-ethyl-5-nitroquinoline (5.0 g.) in absolute ethanol was subjected to hydrogenation at 40 p.s.i., with shaking, after having added Raney nickel catalyst. When hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate saturated with dry hydrogen chloride gas. A feathery-like, white solid amine hydrochloride formed; yield, 4.3 g.

5-Amino-2,6-dichloro-8-ethylquinoline hydrochloride (2.0 g.) yielded 5-amino-2,6-dichloro-8-ethylquinoline upon treatment with concentrated ammonium hydroxide; yield, 1.5 g.; m.p. 123–5°.

ANAL. Calcd. for $C_{11}H_{10}Cl_2N_2$: Cl, 29.41; N, 11.62. Found: Cl, 29.41; N, 11.71.

5-Acetamido-6-chloro-8-ethylquinoline and 5-Acetamido-2,6-dichloro-8-ethylquinoline. 5-Amino-6-chloro-8-ethylquinoline and 5-amino-2,6-dichloro-8-ethylquinoline were acetylated under essentially the same conditions as reported by Beasley, Brown, and Capps (*2*) for the acetylation of 5-amino-6-bromo-8-ethylquinoline. Melting points of 54–6° and 286° with decomposition were obtained, respectively.

ANAL. Calcd. for $C_{13}H_{14}ClN_2O$: Cl, 14.20; N, 11.22. Found: Cl, 14.38; N, 11.34.

ANAL. Calcd. for $C_{13}H_{13}Cl_2N_2O$: Cl, 25.04; N, 9.89. Found: Cl, 24.95; N, 9.77.

5-Benzamido-6-chloro-8-ethylquinoline. A mixture of 5-amino-6-chloro-8-ethylquinoline hydrochloride (2.0 g.), benzoyl chloride (10 ml.) and aqueous sodium hydroxide (20 ml.; 5%) was shaken vigorously. Additional aqueous sodium hydroxide was added occasionally to keep the system alkaline. When the odor of benzoyl chloride could no longer be detected, the resulting solid was separated by filtration, washed with water, and finally recrystallized twice from hot 95% ethanol; yield, 1.35 g. (61%) of white solid; m.p. 242–4°.

ANAL. Calcd. for $C_{18}H_{15}ClN_2O$: Cl, 11.41; N, 9.01. Found: Cl, 11.35; N, 9.02.

5-Benzamido-2,6-dichloro-8-ethylquinoline. A mixture of 5-amino-2,6-dichloro-8-ethylquinoline (0.254 g.), benzoyl chloride (1 ml.) and aqueous sodium hydroxide (25 ml.; 5%) was shaken vigorously. Additional aqueous sodium hydroxide was added occaisonally to keep the system alkaline. When the odor of benzoyl chloride could no longer be detected, the resulting solid was separated by filtration, washed with water and finally crystallized from ethanol and water solution; yield, 0.275 g. (75%) of feathery-like, white crystals; m.p. 202–3°.

ANAL. Calcd. for $C_{18}H_{14}Cl_2N_2O$: Cl, 20.54; N, 8.12. Found: Cl, 20.41; N, 8.14.

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Some Derivatives of Ethylbenzene

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2-Acetamido and 4-acetamidoethylbenzene yielded the corresponding 5-halo and 3-halo derivatives when brominated and when chlorinated. Nitration of the corresponding haloamines gave 4-nitro and 2-nitro derivatives that were acetylated. 2,4-Diacetamido-5-bromoethylbenzene was prepared from both 2-acetamido-5-bromo-4-nitroethylbenzene and 4-acetamido-5-bromo-2-nitroethylbenzene. Oxidation of 2,5-dibromoethylbenzene, 2,5-dichloroethylbenzene, 3,4-dichloroethylbenzene, and 3-chloro-4-nitroethylbenzene as derived from 2-amino-5-bromo-, 2-amino-5-chloro-, 4-amino-3-chloro-, and 2-amino-5-chloro-4-nitroethylbenzenes gave the corresponding benzoic acid derivatives. 2-Amino-4-nitro- and 2-amino-5-nitroethylbenzene, from the nitration of 2-acetamidoethylbenzene, were converted into 2-ethyl-4-nitro- and 2-ethyl-5-nitrobenzonitrile, which were hydrolyzed to the corresponding benzoic acids. Modified Skraup ring closures on the properly substituted aminoethylbenzenes were accomplished with retention of all substituents to yield 8-bromo-, 8-bromo-5-nitro-, 8-chloro-, and 8-chloro-5-nitro- derivatives of 6-ethylquinoline. 6-Bromo-, 6-bromo-5-nitro-, 6-chloro-, 6-chloro-5-nitro-, 5-nitro-, and 6-nitro- derivatives of 8-ethylquinoline were also obtained in a similar manner. Methods of preparing authentic samples of benzene derivatives used in making structural comparisons were recorded. 4-Benzamido-3-bromoethylbenzene was also prepared.

MANY DERIVATIVES of ethylbenzene required for the synthesis of certain substituted quinolines are not described in the chemical literature, and studies were needed to verify the structures assigned to these intermediates. The results of some of these investigations are described.

A modification of the recommendations of Cline and Reid (*4*) was used for the nitration of ethylbenzene, the conditions being more severe than those commonly used for the nitration of toluene. Quantities of unreacted ethylbenzene ranging from 12 to 22% were usually recovered and about equal amounts of ortho and para isomers were isolated, the ortho isomer predominating during certain