8-Chloro–6-Ethylquinoline and Some Derivatives

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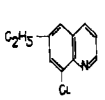
Hydrolysis of 2,8-dichloro-6-ethylquinoline and 2,8-dichloro-6-ethyl-5-nitroquinoline, as prepared from the corresponding 2-quinolones, gave 2-quinolinols. The 2-quinolones resulted from the oxidation of 1-methylquinolinium salts in basic media. Nitration of 8-chloro-, 2,8-dichloro-, and 8-chloro-2-hydroxy- derivatives of 6-ethylquinoline yielded the corresponding 5-nitro compounds that were compared with authentic samples as obtained by alternate routes. The amine resulting from the reduction of 8-chloro-6-ethyl-5-nitroquinoline was acetylated and benzoylated.

SOME NEW REACTIONS of 8-chloro–6-ethylquinoline (I) are recorded. Various derivatives (II) were prepared as well as the picrate of I.



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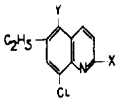

II

	X	Y		X	Y
a	H	NO_2	*e*	Cl	NO_2
b	Cl	H	*f*	H	NH_2
c	OH	H	*g*	H	NHAc
d	OH	NO_2	*h*	H	NHBz

Essentially the same reaction sequences were used in forming these derivatives as reported for the preparation of derivatives of 8-bromo–6-ethylquinoline.

Picrate of I. A saturated aqueous solution of picric acid (75 ml.) was added to a solution of I (0.5 gram) in 95% ethanol (7.5 ml.) prior to heating mixture to boiling. The solid that formed upon cooling was collected by filtration and recrystallized from 95% ethanol; bright yellow crystals, m.p. 160.5° to 161.5° C.

Anal. Calcd. for $C_{17}H_{13}ClN_4O_7$: Cl, 8.43; N, 13.32. Found: Cl, 8.48; N, 13.47.

Nitroquinolines (II *a*, *d* and *e*). Cold solutions of I (10.8 grams) and II *b* (5 grams) in sulfuric acid (12.5 ml. and 12.5 ml.; sp. gr. 1.84) were added dropwise with stirring, independently, at 0° C. to solutions of nitric acid (9 ml. and 3.5 ml.; sp. gr. 1.42) in sulfuric acid (12.5 ml. and 5.4 ml.; sp. gr. 1.84), respectively. These solutions were kept overnight before heating to 70° C. for 5 minutes. After cooling, they were poured (with stirring) into cracked ice and water mixtures (400 ml. and 175 ml.) causing the formation of solids that were collected, washed with water, and recrystallized from ethanol-water solution and 95% ethanol, respectively; yellow needles (12.5 grams; 89.9%), m.p. 81° to 82° C. and pale yellow needles (4.7 grams; 80.5%), m.p. 170° to 171° C.

A cold solution of nitric acid (0.5 ml.; sp. gr. 1.42) in sulfuric acid (1 ml.; sp. gr. 1.84) was added dropwise at 0° C., with stirring, to a solution of II *c* (1 gram) in sulfuric acid (2 ml.; sp. gr. 1.84). After remaining for 0.5 hour in cooling bath and 1.5 hours at ambient temperature the resulting mixture was poured into ice and water (50 ml.). Crude II *d* was collected, washed with water, and recrystallized from 95% ethanol; short, pale yellow needles, 1.2 grams (98%); m.p. 219° to 220° C.

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: Cl, 14.99; N, 11.84. Found: Cl, 14.87; N, 11.99.

Calcd. for $C_{11}H_9ClN_2O_3$: Cl, 14.03; N, 11.09. Found: Cl, 13.91; N, 11.08.

Calcd. for $C_{11}H_8Cl_2N_2O_2$: Cl, 26.16; N, 10.33. Found: Cl, 26.04; N, 10.35.

2-Chloroquinolines (II *b*, *e*). QUATERNIZATIONS. Compound I (20 grams) and compound II *a* (5 grams) were mixed with methyl sulfate (25 ml. and 15 ml.) prior to heating independently in oil baths maintained at 130° C. for 3 hours. Water (80 ml. and 25 ml.) was added, after cooling, before extracting with ethyl ether.

OXIDATIONS TO QUINOLONES. The aqueous solution from quaternization of compound I was mixed with potassium ferricyanide (107 grams) in water (740 ml.) prior to increasing temperature to 60° C. and dropping in (55° to 60° C.) with stirring, a solution of potassium hydroxide (10% by weight; 240 ml.). Mechanical stirring was continued and the temperature retained at 55° to 60° C. for an additional 1.5 hours before separating the red-brown oil, which was washed with water and dried over soda lime under reduced pressure; partial crystallization as long needles occurred; crude quinolone weighed 21.6 grams.

Finely ground potassium iodide was added, with stirring, to half of the aqueous solution from quaternizing II *a*. The resulting orange solid was collected, pressed dry between folds of paper (filter), and suspended in 95% ethanol (19 ml.). After warming to 60° C., a solution of potassium hydroxide (1.6 grams in 6.3 ml. of water) was added dropwise (60° to 65° C.) and the temperature maintained for 0.5 hour. Later (3 hours) the gummy semisolid which had formed was separated and dissolved in boiling 95% ethanol (35 ml.), given a decolorizing carbon treatment and allowed to cool. Bright yellow needles (0.161 gram) formed (melting range 134° to 137° C.). The filtrate was cooled in an ice bath causing more solid to form which was shown, after recrystallization, to be chiefly II *a*.

QUINOLONES TO CHLOROQUINOLINES. Some crude quinolone (9.8 grams) from compound I was dissolved in phosphoryl chloride (18.8 ml.; −10° C.) and phosphorus pentachloride (9.8 grams) was added prior to slowly increasing temperature of heating bath to 165° C. and maintaining for 2.5 hours while reaction mixture refluxed. The reaction mixture, after cooling to room temperature, was poured into a mixture of ice and water (800 ml.) containing hydrochloric acid (25 ml.; sp. gr. 1.19). The oil that first separated solidified on standing and after several recrystallizations from acetone-water mixture, fine, pale yellow needles resulted; yield 5.8 grams (57.5%), m.p. 92° to 93° C.

Anal. Calcd. for $C_{11}H_9Cl_2N$: Cl, 31.36; N, 6.20. Found: Cl, 31.32; N, 6.31.

The crude quinolone from II *a* (0.161 gram) was added to phosphoryl chloride (0.8 ml. which had been cooled in ice and salt bath). Phosphorus pentachloride (0.20 gram) was added and the mixture heated in an oil bath (under reflux conditions) at 120° to 130° C. for 2 hours. After cooling to room temperature, the mixture was poured into ice and water (5 ml.); and the solid that formed was collected by filtration, washed with water, and crystallized from 95% ethanol; thick, pale yellow needles; yield 0.098 gram (61.1%), m.p. 170° to 171° C. These crystals did not depress the melting range of II *e* as obtained by the nitration of II *b*.

Conversion of 2-Chloroquinolines into 2-Quinolinols. II *b* and II *e* (5.3 grams and 2.5 grams) were mixed with solutions of sulfuric acid (20 ml. and 25 ml.; sp. gr. 1.84) in water (12.5 ml. and 12.5 ml.) and refluxed for 4.5 and 0.33 hours, respectively. The resulting mixtures were poured, after cooling to room temperature, into cracked ice-water mixtures (200 ml. and 250 ml.). The solids resulting were collected by filtration, washed with water, and crystallized from acetone and 95% ethanol, respectively. Long, colorless needles of II *c* (4.6 grams, 94.6%; m.p. 161° to 162° C.) and pale yellow needles of II *d* (2.1 grams, 88%; m.p. 219° to 220° C.) formed. II *d* thus obtained did not depress the melting range of II *d* from the nitration of II *c*.

Anal. Calcd. for $C_{11}H_{10}ClNO$: Cl, 17.07; N, 6.75. Found: Cl, 16.99; N, 6.75.

Reduction of II *a* to II *f*. II *a* (5 grams in a minimum amount of absolute ethanol) was reduced with hydrogen (Raney nickel; 35 p.s.i.g.; 2 hours). After removal of catalyst, and after removal of ethanol under reduced pressure, the residual amine was dissolved in ethyl ether. Dry hydrogen chloride was passed into the ether solution (dried previously over sodium hydroxide pellets) causing precipitation of red amine hydrochloride. The amine was liberated from its hydrochloride by grinding in sodium hydroxide-water solution. Crystallization from ethanol-water solution gave fine, pale yellow needles; 2.3 grams, 53%; m.p. 69° to 70° C.

Anal. Calcd. for $C_{11}H_{11}ClN_2$: Cl, 17.16; N, 13.56. Found: Cl, 17.07; N, 13.42.

Acetylation and Benzoylation of II*f*. II *f* (0.5 gram and 0.5 gram) was acetylated and benzolated and benzoylated according to conditions previously reported for preparation of such derivatives of 8-bromo-6-ethylquinoline; yields: 0.3 gram of II *g* (50%), m.p. 183° to 185° C.; 0.52 gram of II *h* (69.4%), m.p. 221° to 222° C.

Anal. Calcd. for $C_{13}H_{14}ClN_2O$: Cl, 14.20; N, 11.22. Found: Cl, 14.21; N, 11.21.

Calcd. for $C_{18}H_{15}ClN_2O$: Cl, 11.41; N, 9.01. Found: Cl, 11.38; N, 8.89.

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6-Bromo–8-Ethylquinoline and Some Derivatives

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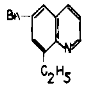
Hydrolysis of 6-bromo-2-chloro-8-ethylquinoline and 6-bromo-2-chloro-8-ethyl-5-nitroquinoline, as prepared by the action of a mixture of phosphorus pentachloride and phosphoryl chloride on the corresponding 2-quinolones, gave 2-quinolinols. The 2-quinolones resulted from the oxidation of the 1-methylquinolinum salts in basic media. Nitration of 6-bromo-, 6-bromo-2-chloro-, and 6-bromo-2-hydroxy- derivatives of 8-ethylquinoline yielded the corresponding 5-nitro compounds that were compared with authentic samples prepared by alternate routes. Amines resulting from the reduction of the nitro compounds were acetylated and benzoylated.

SOME NEW REACTIONS of 6-bromo–8-ethylquinoline (I) are recorded. Various derivatives (II) were prepared.



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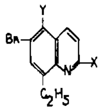

II

		Y		X	Y
a	H	NO_2	*h*	OH	NH_2
b	Cl	H	*i*	H	NHAc
c	OH	H	*j*	Cl	NHAc
d	OH	NO_2	*k*	OH	NHAc
e	Cl	NO_2	*l*	H	NHBz
f	H	NH_2	*m*	Cl	NHBz
g	Cl	NH_2	*n*	OH	NHBz

The 2-chloro compounds (II *b*, *e*) were made (from I, II *a*) by quaternizing the quinoline compound with methyl sulfate, oxidizing with alkaline ferricyanide or with alkaline peroxide, and finally treating with a mixture of phosphorus pentachloride and phosphoryl chloride. Acid hydrolysis of the 2-chloro compounds yielded the 2-quinolinols (II *c*, *d*). Other reactions used were conventional: reduction of nitro to amino and acylation or aroylation of amino to amido.

Nitroquinolines (II *a*, e and *d*). Cold solutions of fuming nitric acid (35 ml. and 1.5 ml.; sp. gr. 1.5) and sulfuric acid (40 ml. and 1.5 ml.; sp. gr. 1.84) were added dropwise with stirring independently to cold solutions of I (68.9 grams) and II *b* (0.4 gram) in sulfuric acid (80 ml. and 1.5 ml.; sp. gr. 1.84) at temperatures below 5° C. and 0° C., respectively. These solutions were then kept overnight at 25° C. before heating to 75° and 65° C. for 30 and 5 minutes. After cooling, these solutions were then poured into cracked ice and water mixtures causing the formation of solids that were collected and washed with water prior to purifying; yields were 78 grams (92%) from 95% ethanol, m.p. 87° to 88° C. and 0.46 gram from acetone-water, m.p. 131.5° to 132° C. A mixture of II *e* by this procedure with II *e* derived from II *a* also melted at 131.5° to 132° C.

A cold solution of nitric acid (4.1 ml.; sp. gr. 1.42) in sulfuric acid (8 ml.; sp. gr. 1.84) was added dropwise with stirring to a cold solution of II *c* (1.6 grams) in sulfuric acid (8 ml.; sp. gr. 1.84) below 0° C. The cooling bath was removed 1 hour later; and after warming to room temperature and pouring the solution into water and ice mixture, the resulting solid was collected, washed with water, and crystallized from 95% ethanol; fine, dense, yellow needles liquified at 245° C., with decomposition.

Anal. Calcd. for $C_{11}H_9BrN_2O_3$: (Br + Cl), 26.90; N, 9.43. Found: (Br + Cl), 26.99; N, 9.63.

2-Chloroquinolines (II *b*, *e*). QUATERNIZATIONS. Compound I (44.2 grams) and methyl sulfate (80 ml.) were heated together in an oil bath maintained at 120° to 125° C. for 2 hours. Water (160 ml.) was added the next day prior to extracting with ethyl ether (3 portions).

Compound II *a* (15 grams) and methyl sulfate (70 ml.) were heated together in an oil bath maintained at 135° to 140° C. for 2.5 hours. Water (85 ml.) was added after cooling, followed by extraction with ethyl ether (3 × 40 ml.).