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8-Bromo–6-Ethylquinoline and Some Derivatives

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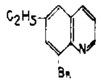
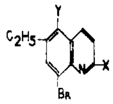
Hydrolysis of 8-bromo-2-chloro-6-ethylquinoline, as obtained by the oxidation of 8-bromo-6-ethyl-1-methylquinolinium salt to 8-bromo-6-ethyl-2-quinolone and treatment with phosphorus pentachloridephosphoryl chloride mixture, gave 8-bromo-6-ethyl-2-quinolinol. Nitration of 8-bromo-, 8-bromo-2-chloro-, and 8-bromo-2hydroxyderivatives of 6-ethylquinoline resulted in the formation of the 5-nitro compounds which were compared with authentic samples prepared by alternate routes. Oxidation of 8-bromo-6-ethyl-1-methyl-5-nitroquinolinium iodide, as obtained from 8-bromo-6-ethyl-5-nitroquinoline, gave 8-bromo-6-ethyl-1-methyl-5-nitro-2-quinolone that was converted by phosphorus pentachloride-phosphoryl chloride mixture into 8-bromo-2-chloro-6-ethyl-5-nitroquinoline; this product hydrolyzed to 8-bromo-6-ethyl-5-nitro-2-quinolinol. Amines resulting from the reduction of 8-bromo-6-ethyl-5-nitroquinoline and 8-bromo-2-chloro-6-ethyl-5-nitroquinoline were acetylated and benzoylated.

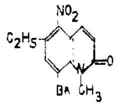
SOME NEW derivatives of 8-bromo–6-ethylquinoline (I) are recorded. Various derivatives (II) were prepared.



I



II



III

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

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 phosphoryl chloride and phosphorus pentachloride. 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, d,* and *e*). Cold solutions of nitric acid (24.5 ml., 0.57 ml., and 0.8 ml.; sp. gr. 1.42) in sulfuric acid (35 ml., 0.8 ml., and 1.2 ml.; sp. gr. 1.84) were added dropwise with stirring independently at 0° C. or less to solutions of I (35.0 grams), II *b* (0.8 gram), and II *c* (1.2 grams) in sulfuric acid (35 ml., 1.2 ml., and 0.8 ml.; respectively; sp. gr. 1.84). These solutions were kept overnight at 25° C. before heating to 70° C. for 5 minutes. After cooling, these solutions were poured into cracked ice and water mixtures causing the formation of solids that were collected, washed with water, and crystallized from 95% ethanol after applying decolorizing carbon treatments; yield is 29.0 grams (70%) of pale-yellow almost colorless needles (II *a*; m.p. 89° to 90° C.), 0.35 gram (II *e*; m.p. 168° to 169.5° C.), and 1.2 grams (85%) (II *d*; m.p. 198° to 199° C.). Attempts to oxidize II *a* to the corresponding COOH acid with potassium dichromate–sulfuric acid mixture failed.

Anal. Calcd. for $C_{11}H_8ClBrN_2O_2$: (Cl + Br), 36.56; N, 8.88. Found: (Cl + Br), 36.33; N, 8.59.

Calcd. for $C_{11}H_9BrN_2O_3$: Br, 26.90; N, 9.43. Found: Br, 27.13; N, 9.15.

2-Chloroquinolines (II *b, e*). QUATERNIZATIONS. Compound I (9.5 grams) and methyl sulfate (14.3 ml.) were heated together in an oil bath maintained at 125° C. for 2 hours. Water (50 ml.) was added before extracting with ethyl ether three times (25-15-10 ml.).

Compound II *a* (20.0 grams) and methyl sulfate (30 ml.) were heated together in an oil bath maintained at 120° C. for 2 hours. Water (90 ml.) was added, after cooling, followed by two extractions with ethyl ether (50-30 ml.).

OXIDATIONS TO QUINOLONES. The aqueous solution from quaternization of I was mixed with potassium ferricyanide (46 grams) in water (375 ml.) followed by benzene (50 ml.) prior to increasing temperature to 60° C. and dropping in, with stirring, a solution of potassium hydroxide (17 grams) in water (50 ml.). Mechanical stirring was continued and the temperature retained at 60° C. for an additional hour before allowing it to decrease spontaneously to 40° C. The benzene-rich layer was separated, dried over anhydrous sodium sulfate, and distilled under reduced pressure; crude quinolone (8.0 grams) remained in the residue.

Finely ground potassium iodide (15 grams) was added with stirring to the aqueous solution from the quaternization of II *a*. The resulting solid was collected by filtration, suspended in boiling 95% ethanol (150 ml.), and then potassium hydroxide (13 grams) dissolved in water (50 ml.) was added dropwise with stirring. The internal temperature was adjusted to 55° to 60° C. before dropping in hydrogen peroxide (120 ml.; 30%) and keeping at 55° to 60° C. for 0.5 additional hour. After standing overnight, the crude quinolone was collected by filtration, washed with 50% ethanol-water solution and dried at 60° C. Recrystallization from methanol gave fine, long, yellow needles; yield 13.0 grams (59%), m.p. 152° to 153° C.

Anal. Calcd. for $C_{12}H_{11}BrN_2O_3$: Br, 25.69; N, 9.00. Found: Br, 25.74; N, 8.75.

QUINOLONES TO CHLOROQUINOLINES. The crude quinolone fractions from compound I and compound III (10.0 grams derived from compound II *a*) were independently dissolved in phosphoryl chloride (17 ml.; −10° C. and 17.3 ml.; 0° C.) and phosphorus pentachloride (8.0 grams and 7.6 grams) was introduced prior to heating in an oil bath (145° C. and 125° to 130° C.) for 3 hours under reflux, respectively. After cooling, each of the mixtures was poured into cracked ice and water (350 ml. and 400 ml.) and the resulting solids were washed with water after separation. Water was added to a previously decolorized (carbon treatment) solution of compound II *b* in acetone yielding pale-yellow crystals (2.5 grams; 31%; m.p. 89° to 91° C.); compound II *e* crystallized from acetone (after treating with carbon) as a fine, dense solid with greenish luster (8.8 grams; 87%; m.p. 168° to 169° C.). II *e* as obtained from III did not depress melting range of II *e* as obtained from II *b*.

Anal. Calcd. for $C_{11}H_9ClBrN$: (Cl + Br), 42.64; N, 5.18. Found: (Cl + Br), 42.51; N, 5.02.

Calcd. for $C_{11}H_8ClBrN_2O_2$: (Cl + Br), 35.56; N, 8.88. Found: (Cl + Br), 36.33; N, 8.59.

Conversion of 2-Chloroquinolines into 2-Quinolinols. II *b* and II *e* (2.5 grams and 1.4 grams) were mixed with solutions of sulfuric acid (10 ml. and 7.5 ml.; sp. gr. 1.84) in water (7.5 ml. and 7.5 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 (400 and 100 ml.). The solids resulting were collected by filtration, washed with water, and crystallized, after giving decolorizing carbon treatments, from acetone and ethanol respectively. Fine, colorless needles of II *c* (1.9 grams; 82%; m.p. 156° to 157° C.) and long, yellow needles of II *d* (almost theoretical yield; m.p. 197° to 198° C.) formed. The II *d* thus formed compared favorably with that obtained by the nitration of II *c*.

Anal. Calcd. for $C_{11}H_{10}BrNO$: N, 5.56. Found: N, 5.31. Calcd. for $C_{11}H_9BrN_2O_3$: Br, 26.90; N, 9.43. Found: Br, 27.13; N, 9.15.

Reduction of Nitroquinolines to Aminoquinolines. A solution of stannous chloride ($SnCl_2 \cdot 2H_2O$; 9.0 grams) contained in hydrochloric acid (16.5 ml.; sp. gr. 1.19) was cautiously added at 60° C. to a solution of II *a* (4.0 grams) in 95% ethanol (25 ml.). After keeping the mixture just below its boiling point for 1 hour, a warm solution of sodium hydroxide (20% by weight) was carefully added until the system was almost neutral toward litmus. Neutralization was completed by adding ammonia water while maintaining near the boiling temperature. Filtration followed immediately, and the residue was extracted several times with boiling ethanol. The original filtrate was combined with the alcoholic extracts and concentrated by distillation under reduced pressure, after acidifying with sulfuric acid.

A green oil separated at the bottom of the container upon neutralization of the residue by adding sodium hydroxide (20% by weight) followed by ammonia water. The oil that solidified upon cooling was separated and extracted with boiling heptane leaving a red oil. Small yellow needles separated from the heptane; yield 1.3 grams (38%); m.p. 99° to 101° C.

Anal. Calcd. for $C_{11}H_{11}BrN_2$: Br, 31.88; N, 11.16. Found: Br, 31.57; N, 11.24.

II *e* (5.0 grams) dissolved in acetone was reduced at 50° C. with hydrogen (40 p.s.i.g.) in presence of Raney nickel. The amine hydrochloride precipitated after filtering away the catalyst and saturating the filtrate with dry hydrogen chloride. After filtering, the filtrate was concentrated by distillation under reduced pressure and an additional amount of the amine hydrochloride crystallized; total recovery, 4.6 grams (90.5%).

Ammonia was added to the amine hydrochloride to liberate the amine which was then dissolved in 95% ethanol (warm). Upon diluting with water and cooling, long, slender, yellow needles formed; m.p. 120° to 121° C. with decomposition.

Anal. Calcd. for $C_{11}H_{10}ClBrN_2$: N, 9.81. Found: 9.82.

Acetylation of Aminoquinolines. The aminoquinolines II *f* (0.316 gram) in 3 ml. glacial acetic acid plus 0.3 ml. of acetic anhydride) and II *g* (1.2 grams in 5 ml. glacial acetic acid plus 2.5 ml. acetic anhydride were heated to refluxing temperature of solvent mixture for 0.5 hour prior to pouring with stirring into cracked ice-water mixtures (25 ml. and 50 ml.). The solids that formed were collected by filtration, washed with water, dissolved in boiling 95% ethanol and subjected to decolorizing carbon treatments. II *h* formed as fine, colorless (white) crystals upon diluting the alcoholic solution to cloud point with water and cooling; yield 0.17 gram (46%), m.p. 206° to 207° C. II *i* precipitated from 95% alcoholic solution upon cooling as fine, white crystals; yield 0.3 gram (22%), m.p. 270° to 271° C. with decomposition.

Anal. Calcd. for $C_{13}H_{13}BrN_2O$: N, 8.55. Found: N, 8.34.

Benzoylation of Aminoquinolines. II *f* (0.295 gram) and II *g* (0.8 gram) were mixed independently with benzoyl chloride (0.4 ml. and 2.5 ml.) and aqueous sodium hydroxide solution (4 ml.; 10% and 10 ml.; 10%) prior to shaking until the oil that first formed solidified. The resulting solids were separated by filtration, washed with water, dissolved in boiling 95% ethanol, and subjected to decolorizing carbon treatments. It was necessary to dilute the alcoholic solution of II *j* with water prior to cooling in order to obtain small, colorless (white) needles; yield 0.280 gram (67%), m.p. 220° to 221° C. II *k* crystallized from the 95% ethanol as small, slightly colored needles; yield 0.5 gram (46%), m.p. 207° to 208° C.

Anal. Calcd. for $C_{18}H_{15}BrN_2O$: Br, 22.50; N, 7.89. Found: Br, 22.32; N, 7.97.

Calcd. for $C_{18}H_{14}ClBrN_2O$: (Cl + Br), 29.60; N, 7.19. Found: (Cl + Br), 29.66; N, 6.89.

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