

Studies on the Syntheses of Heterocyclic Compounds. Part CCCXVII. (I)  
The Benzyne Reaction of 3-Bromoquinoline with Alkyl Cyanides.

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In 1961, Kauffmann, *et al.* (3,4) reported that the reaction of 3-bromo-4-chloroquinoline and 3-bromo-2-chloroquinoline with furan in the presence of lithium amalgam afforded phenanthridine and acridine *via* the hetarynes, 2,3- and 3,4-dehydroquinoline. Assuming that the hetarynes would react with furan by a Diels-Alder reaction, Kauffmann, *et al.* (4) also examined the condensation of 3-haloquinolines (halogen = Cl, Br and I) with lithium piperidine in ether in the presence of piperidine. The result was that 3- and 4-piperidinoquinolines were obtained in 45-65% yield. Furthermore, we have reported that the benzyne reaction of halobenzene with cyanomethyl derivatives in liquid ammonia in the presence of sodium amide gave benzyl cyanide derivatives in good yield (5). We now wish to report the results of the benzyne reaction of 3-bromoquinoline with the alkyl cyanides, acetonitrile, propionitrile, and *n*-butyronitrile.

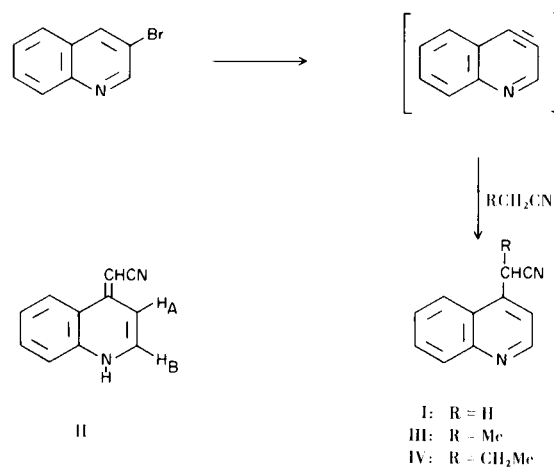
4-Cyanomethylquinoline (I) was prepared by reacting a mixture of 3-bromoquinoline and acetonitrile with sodium amide in liquid ammonia (5,6). The product had a melting point identical with that of an authentic sample (7). The ir and nmr spectra well supported the above compound to be 4-cyanomethylquinoline. The nmr data in dimethylsulfoxide was in good accord with Mordelli's results (8), which revealed the presence of the tautomeric compound II only in the above solvent. The nmr data are summarized in Tables I and II.

The reaction of 3-bromoquinoline with propionitrile gave 4-( $\alpha$ -cyanoethyl)quinoline (III) which was characterized as the hydrochloride. In the nmr spectrum, since the *ortho*-coupling between C<sub>2</sub>- and C<sub>3</sub>-protons in the quinoline nucleus showed, in general,  $4.0 \pm 0.2$  cps, and the coupling between C<sub>3</sub>- and C<sub>4</sub>-protons was  $8.0 \pm 0.4$  cps (9), the aromatic protons at 9.32 and 8.12 were assigned to C<sub>2</sub>- and C<sub>3</sub>-protons as shown in Table II. This fact was also proved by decoupling. Namely, on irradiation of the signal at 9.32, the doublet at 8.12 became a singlet, whereas, on decoupling of the signal at 8.12  $\tau$ , a doublet at 9.32  $\tau$  changed to a singlet.

The benzyne reaction of 3-bromoquinoline with butyronitrile also gave the expected 4-( $\alpha$ -cyanopropyl)quinoline (IV), which was also characterized as its hydrochloride. The nmr spectrum is summarized in Tables I and II.

Thus, this reaction provides a convenient synthetic method for 4-cyanoalkylquinolines (II).

SCHEME 1



EXPERIMENTAL

4-Cyanomethylquinoline (I).

To a stirred solution of 800 ml. of liquid ammonia and 4 g. of metallic sodium was added a small amount of ferric chloride in portions. After sodium amide had been formed, a mixture of 4 g. of acetonitrile and 10 g. of 3-bromoquinoline was added with stirring and the stirring was continued for a further 2 hours. The excess sodium amide was decomposed with addition of ammonium chloride and water, and extracted with chloroform. The chloroform extract was washed with 10% hydrochloric acid. The above aqueous layer and acidic washing were combined and basified with 20% sodium hydroxide and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 6 g. of a brown oil which was chromatographed on silicic acid using ether as an eluent to give pale yellow crystals. Recrystallization from benzene gave 1.2 g. (14.8%) (10) of pale yellow prisms, m.p. 144-145° (7). Infrared  $\nu$  max (potassium bromide)  $2230 \text{ cm}^{-1}$  (C $\equiv$ N).

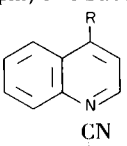
Anal. Calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.35; H, 4.79; N, 16.36.

4-( $\alpha$ -Cyanoethyl)quinoline (III).

To a stirred solution of 400 ml. of liquid ammonia were added 2.2 g. of metallic sodium and a small amount of ferric chloride in portions. After sodium amide had been formed, 2.6 g. of propionitrile and 5.0 g. of 3-bromoquinoline was added and

TABLE I

Chemical Shifts (ppm) of 4-Substituted Quinolines

R									
	Solvent (a)	CH <sub>2</sub>	-CH <sub>2</sub> CN (I) =CH	NH (b)	CH (c)	CH <sub>3</sub> (d)	CH (e)	-CH-CH <sub>2</sub> -CH <sub>3</sub> (IV) CH <sub>2</sub> (f)	CH <sub>3</sub> (g)
CDCl <sub>3</sub>		4.30	—	—	4.80	1.82	4.68	1.80	1.20
DMSO-d <sub>6</sub>		4.60	4.91 (h)	3.40	5.41	1.91	5.20	2.04	1.07
HCl salt		5.10 (i)	—	—	5.48	1.78 (j)	5.48	2.10	1.12 (j)

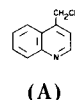
(a) Concentrations are in the range of 40-60 mg. in 0.4 ml. of solvent. (b) broad signal. (c) quartet,  $J = 7.0$  cps. (d) doublet,  $J = 7.0$  cps. (e) triplet,  $J = 7.0$  cps. (f) quintet,  $J = 7.0$  cps. (g) triplet,  $J = 7.0$  cps. (h) *ca.* 20-25%. (i) in deuterium oxide. (j) in dimethylsulfoxide-d<sub>6</sub>.

TABLE II

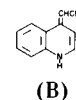
Chemical Shifts (ppm) and Coupling Constants (cps) of 4-Substituted Quinolines (Aromatic Protons)

Solvents (a)	R	CDCl <sub>3</sub>			DMSO-d <sub>6</sub>			HCl salt		
		H <sub>2</sub>	H <sub>3</sub>	J <sub>23</sub>	H <sub>2</sub>	H <sub>3</sub>	J <sub>23</sub>	H <sub>2</sub>	H <sub>3</sub>	J <sub>23</sub>
I	-CH <sub>2</sub> CN (b)	9.15	7.72	4.5	8.93	7.57	4.7	9.48	8.50	6.0 (e)
	=CHCN (c)	—	—	—	7.40-7.20	6.25	7.0	—	—	—
III	-CH-CH <sub>3</sub> (d)   C	9.20	7.75	4.5	9.18	7.86	4.5	9.32	8.12	4.5 (f)
IV	-CH-CH <sub>2</sub> CH <sub>3</sub> (d)   CN	9.08	7.75	4.5	8.90	7.50	4.5	9.35	8.13	4.5 (f)

(a) Concentrations are in the range of 40-60 mg. in 0.4 ml. of solvent. (b) Tautomer A, No tautomer form was observed. (c) in deuterium oxide. (f) in dimethylsulfoxide-d<sub>6</sub>.



(c) Tautomer B,



the reaction mixture was treated as usual to give 4 g. of a brown oil. Purification by silicic acid chromatography using chloroform as an eluant gave a pale yellow oil, whose hydrochloride was recrystallized from ethanol-ether to give 2.2 g. (50.3%) (10) of pale yellow needles, m.p. 246-248° dec. Infrared  $\nu$  max (potassium bromide) 2230 (C≡N) and 1630 cm<sup>-1</sup> (C=N<sup>+</sup>).

*Anal.* Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>·HCl: C, 65.90; H, 5.07; N, 12.81. Found: C, 65.80; H, 5.52; N, 12.73.

4-( $\alpha$ -Cyanopropyl)quinoline (IV).

To a stirred solution of 400 ml. of liquid ammonia were added 2.2 g. of metallic sodium and a small amount of ferric chloride. After the addition, a mixture of 2.3 g. of *n*-butyronitrile and 5.0 g. of 3-bromoquinoline was added in small portions with stirring during 3 hours. The reaction mixture was treated as usual to give 4.9 g. of a brown oil, which was chromatographed on silicic acid using chloroform as an eluant to give 1.5 g. of a

pale brown oil. Recrystallization of the hydrochloride from ethanol-ether gave 1.2 g. (25.4%) (10) of pale yellow needles, m.p. 208-210° dec. Infrared  $\nu$  max (potassium bromide) 2230 (C≡N) and 1635 cm<sup>-1</sup> (C=N<sup>+</sup>).

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>·HCl: N, 12.04. Found: N, 11.95.

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to Professor Tetsuji Kametani.

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(10) In these reactions, the starting materials were recovered and a tar was also formed.

(11) No 3-cyanoalkylquinolines were obtained because of the electron-attracting power of the nitrogen in the hetero system.

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