

## A Facile Displacement of Nitro by Halogen in a Quinoline System

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During the course of another investigation (1), we prepared the nitroquinolinecarboxylic acid **2** and converted it with boron trifluoride-methanol into the methyl ester **3** (Figure 1).

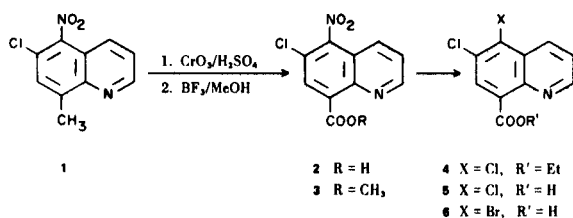
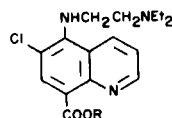


Figure 1

We have now found that attempted preparation of the ethyl ester of **2** by treatment first with boiling thionyl chloride and then with ethanol gave the dichloro ester **4** instead of the expected chloronitro ester. Hydrolysis of this ester gave the dichloro acid **5** which could also be obtained by passing dry hydrogen chloride into a dimethylformamide solution of **2** at 115-120°. Similarly, when **2** in dimethylformamide was treated with dry hydrogen bromide at 120-125° for a slightly longer period, an excellent yield of **6** was obtained. The acid **2** formed an unstable hydrochloride salt which dissociated to the free base and hydrogen chloride in methanol or water. When heated quickly to 180-220°, the salt was converted to **5** but the yield and quality were inferior to the above preparation. That the carboxyl function of **2** was essential for the reaction was demonstrated by experiments in which **1** was recovered unchanged after treatment with boiling thionyl chloride or hydrogen chloride in hot dimethylformamide.

In an attempt to prepare **7**, an intermediate of our previous work, we heated **3** and **4** with diethylaminoethylamine. In neither case could any of the desired product be obtained.



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Although nucleophilic displacements in benzenoid systems are relatively common, in heteroaromatic systems, these reactions usually occur at "activated" positions in the heterocyclic ring (2). Displacement of the aromatic nitro group by fluorine (3,4) or chlorine or bromine (5-8) is relatively rare and, with the latter elements, is usually associated with activating groups having large  $\sigma^-$  values (9). In the present case, the facile displacement of the nitro group may arise as a consequence of the participation of the heterocyclic ring nitrogen atom (10) or the relief of steric crowding about positions 4,5 and 6 in the transition state (11) (Figure 2). It is interesting to note that nucleophilic reactions on 3-chloro-4-nitrobenzoic acid and its ethyl ester proceed unexceptionally with displacement of halogen (12).

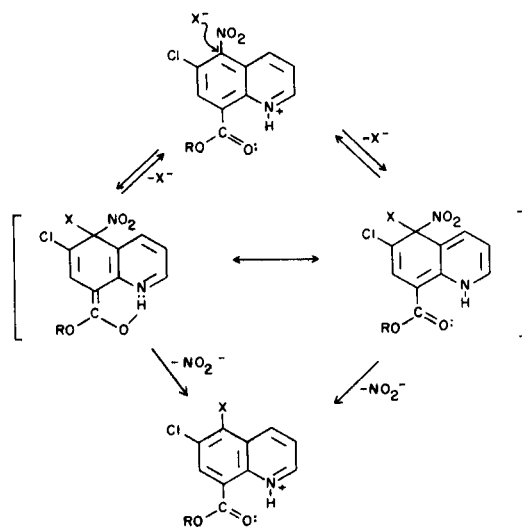


Figure 2

## EXPERIMENTAL

All melting points are uncorrected and were determined on a Mel-Temp apparatus. Mass spectra were obtained on a Jeolco JMS-O1SC High-resolution double-focusing mass spectrometer. Elemental analyses were performed by Instranal Laboratories, Rensselaer, N. Y.

## Ethyl 5,6-Dichloro-8-quinolinecarboxylate (4).

A solution of 12.5 g. (0.0496 mole) of 6-chloro-5-nitro-8-quinolinecarboxylic acid (1) in 50 ml of thionyl chloride was refluxed for 30 minutes. The excess thionyl chloride was removed under vacuum and the solid residue was boiled for 15 minutes with 50 ml. of absolute ethanol. The solvent was stripped and the residue was partitioned between chloroform and 10% potassium carbonate. From the organic solution was recovered 13.5 g. of oil which was crystallized from alcohol and then hexane (charcoal) to give 10.9 g. (81% yield) of white plates m.p. 76.5-77°.

*Anal.* Calcd. for  $C_{12}H_9Cl_2NO_2$ : N, 5.19; Cl, 26.25;  $M^+$ , 269. Found: N, 5.41; Cl, 25.94;  $M^+$ , 269 (2Cl).

## 5,6-Dichloro-8-quinolinecarboxylic Acid (5).

A solution of 40 g. (0.158 mole) of 6-chloro-5-nitro-8-quinoline carboxylic acid in 150 ml. of DMF was heated to 80-85° in an oil bath and a rapid stream of dry hydrogen chloride gas was introduced. The temperature rose to 115-120° and a solid precipitated. After 15 minutes, the solution was cooled and poured into 750 ml. of iced water. The solid was filtered off, washed with water and pressed dry. After drying at 90-100° for 4 hours, the solid was recrystallized with charcoaling from benzene to give 26.6 g. (69.5% yield) of white blades, m.p. 221-223°.

*Anal.* Calcd. for  $C_{10}H_5Cl_2NO_2$ : N, 5.79; Cl, 29.29;  $M^+$ , 241. Found: N, 5.80; Cl, 29.08;  $M^+$  -CO<sub>2</sub>, 197 (2Cl).

## 5-Bromo-6-chloro-8-quinolinecarboxylic Acid (6).

A solution of 6.0 g. (0.0237 mole) of 6-chloro-5-nitro-8-quinolinecarboxylic acid in 75 ml. of DMF was heated at 100-105° in an oil bath and a stream of dry hydrogen bromide was introduced below the surface. There was a small temperature rise to 110-115°. The oil bath temperature was raised to 120-125° and heating was

continued for a total of 40 minutes. The cooled solution was poured into iced water and the product was washed with water. After being sucked dry on the filter, the crude product consisted of 6.6 g. (97% crude yield) of off-white solid m.p. 246-250°. This was crystallized from toluene to give 6.0 g. (88% yield) of glistening white plates, m.p. 249-251°.

*Anal.* Calcd. for  $C_{10}H_5BrClNO_2$ : C, 41.92; H, 1.76; N, 4.89;  $M^+$ , 285. Found: C, 41.86; H, 1.76; N, 4.67;  $M^+$  -CO<sub>2</sub>, 241 (1Br, 1 Cl).

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- (11) For further examples see ref. 5 and probably examples XI, XII, and XV of ref. 3.
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