Acid Catalyzed Alcoholysis of 4,7-Dichloroquinoline (1)

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The nucleophilic displacement of "activated" halogen atoms from nitrogen heterocycles has long constituted an area of intensive synthetic and mechanistic study (2,3,4). Although it has been well established that nucleophilic attack on basic halo-heterocyclics is most often facilitated by acid-catalysis (5,6), presumably proceeding *via* the *N*-protonated iminium ion, the condensation of such hetero systems with alcohols has invariably involved the alkoxides (7,8). We have found no literature reports of alcoholic displacement in acidic medium.

Autocatalysis has been demonstrated for some reactions in which the nucleophilic atom of the displacing reagent is bound to a hydrogen which is eliminated as a proton during the condensation stage (5). Thus, with a few highly reactive chloro-*N*-heteroaromatics, alcohols alone effect an autocatalytic displacement of the halogen (9,10). We have established that 4,7-dichloroquinoline is not sufficiently reactive toward alcohols to undergo uncatalyzed alcoholysis, but in the presence of as little as 5% hydrochloric acid excellent conversions to the 4-alkoxyquinolines result.

Methanol, ethanol and 1-propanol containing hydrogen chloride gave the corresponding ethers in 86, 84 and 66% yields. 2-Propanol reacted to only a slight extent, presumably the reflection of a steric consideration, and resulted in a less than 12% conversion to the *i*-propoxy compound. This acid-catalyzed halogen displacement should be of merit in heterocyclic systems containing base-sensitive pendant functions.

EXPERIMENTAL (11)

7-Chloro-4-methoxyquinoline.

A solution of 4,7-dichloroquinoline (1.0 g., 5.0 mmoles) in 40 ml. of methanolic hydrogen chloride (0.5*N*) was refluxed for 24 hours and evaporated to dryness under reduced pressure. The white solid residue was dissolved in water, dried (magnesium sulfate), and concentrated *in vacuo* to yield 7-chloro-4-methoxyquinoline as white needles, m.p. 132-137°, yield 0.83 g. (86%). Two recrystallizations from ethanol raised the m.p. to 140-142°, lit m.p. 142-144° (12).

7-Chloro-4-ethoxyquinoline.

By the above procedure, 4,7-dichloroquinoline (1,0 g., 5.0 mmoles) was treated with ethanol containing 0.25 mmoles of hydrogen chloride to yield 0.87 g. (84%) of the product, m.p. 85-95°. Two recrystallizations from hexane reised the m.p. to 99-101°, lit m.p. 101-103.5° (13).

7-Chloro-4-*n*-propoxyquinoline.

The reaction of 3.0 g. (15 mmoles) of 4,7-dichloroquinoline with 60 ml. of anhydrous 1-propanol-hydrogen chloride (0.5*N*) produced 2.19 g. (66%) of crude 7-chloro-4-*n*-propoxyquinoline, m.p. 63-75°. Recrystallization from *n*-hexane gave analytical material, m.p. 77-79°.

Anal. Calcd. for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.45; Cl, 15.99. Found: C, 65.28; H, 5.65; Cl, 15.75.

Reaction of 4,7-Dichloroquinoline with 2-Propanol.

4,7-Dichloroquinoline and 2-propanol-hydrogen chloride were reacted as described for 7-chloro-4-ethoxyquinoline. Evaporation of solvent after 24 hour reflux produced a solid which was dissolved in a mixture of ether and water. The ether layer was dried and concentrated to return 88% of unreacted 4,7-dichloroquinoline. The aqueous layer was made basic with 10% sodium hydroxide and extracted thoroughly with ether. The dried ether extract was concentrated *in vacuo* to yield a pale yellow oil (approximately 10% based on starting quinoline) which displayed proton resonances characteristic of the 7-chloro-4-*i*-propoxyquinoline; unity integral septet at δ 4.72 ppm and six-proton doublet at 1.45 ppm in addition to aromatic resonances from 6.6 to 8.8 ppm. A pure sample could not be obtained.

When solutions of 4,7-dichloroquinoline in these alcohols without added hydrogen chloride were refluxed for 24 hours, complete recovery of unreacted quinoline resulted.

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