# The Methylation of 8-Aminoquinoline

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Received July 14, 1975

The position of alkylation of amino azine heterocycles is an important and interesting problem in heterocyclic chemistry. The situation is complicated in that the position and nature of the amine function, as well as the alkylating agent and reaction conditions all affect the result. For example, 2-aminopyridine methylates on the ring nitrogen with methyl iodide (1); 2-dimethylaminopyridine reacts on the exocyclic nitrogen (2) while the analogous quinoline gives a mixture in which the ring methylated product is thermodynamically more stable (3). Recent work with 5-aminoquinoline has indicated that either site can react depending on the reagent (4).

In connection with this work, we have looked at the methylation of 8-aminoquinoline, where steric effects might be expected to hinder ring-nitrogen alkylation. 8-Amino-1-methylquinolinium iodide was reported in a study of the synthesis of quaternized quinolines as potential antileukemic drugs (5), but we believe that the methylation of 8-aminoquinoline with methyl iodide occurs on the amino nitrogen and the product isolated is the hydroiodide salt of 8-methylaminoquinoline. The ir spectrum indicated the presence of a secondary amine, the nmr spectrum contained no $N^+$-$CH_3$ peak, and treatment with base gave the free amine, identified spectroscopically and by its known picrate.

We have prepared the desired quinolinium salt by an indirect method involving methylation of 8-nitroquinoline and subsequent reduction (6) of the nitro group. The nmr spectrum of the product was in accord with it being the 8-amino-1-methylquinolinium salt.

For comparison purposes, an nmr spectrum was obtained of the product from reaction of 2-aminoquinoline with methyliodide. In this case it is clear that reaction occurs at the ring nitrogen in that a peak for the primary amino group was apparent. The relatively high field $N^+$-Me peak is consistent with the known effect of an amino substituent *ortho* to the quaternary centre (7).

## EXPERIMENTAL

8-Methylaminoquinoline.

8-Aminoquinoline (1.0 g.) and methyl iodide (1.9 g.) in ethanol (5 ml.) were refluxed for 9 hours. The orange crystals which formed on cooling were filtered and recrystallized from ethanol to give 8-methylaminoquinolinium iodide (0.8 g.), m.p. 192-193° [lit., (5) 196-198°]; nmr (DMSO): δ 3.1 ($NCH_3$), 7.25-8.05 (m, 4H), 8.7 (d, 1H), 9.1 (d, 1H); ir (nujol): 3300, 1620, 1580, 800, 765, 740 $cm^{-1}$.

*Anal.* Calcd. for $C_{10}H_{11}IN_2$: C, 42.0; H, 3.9; N, 9.8. Found: C, 41.85; H, 3.85; N, 9.9.

Treatment of an aqueous solution of this salt with alkali, followed by ether extraction, gave the free base as a yellow oil; nmr (carbon tetrachloride): δ 3.05 (d, $NCH_3$) 6.2 (broad s, NH), 6.5 (d, 1H), 6.9 (d, 1H), 7.1-7.5 (m, 2H), 8.0 (d, 1H), 8.6 (d, 1H). The orange picrate (prepared in methanol) had m.p. 184-185° [lit., (8) 185-186°].

1-Methyl-8-nitroquinolinium Perchlorate.

8-Nitroquinoline (2.0 g.) and dimethyl sulfate (3 ml.) were heated at 100° for 1 hour. The crude methosulfate separated from the cooled mixture on the addition of ether. This was washed by decantation with ether and dissolved in a small amount of ethanol. Addition of a few drops of perchloric acid caused instant precipitation of the product (2.8 g.), m.p. 209-210° (ethanol).

*Anal.* Calcd. for $C_{10}H_9ClN_2O_6$: C, 41.6; H, 3.15; N, 9.7. Found: C, 41.5; H, 3.1; N, 9.7.

8-Amino-1-methylquinolinium Perchlorate.

A solution of the 8-nitro salt (1.0 g.) in water (10 ml.) and glacial acetic acid (2 drops) was stirred with iron powder (1.3 g.) on a water-bath at 90° for 40 minutes. The hot mixture was filtered and orange needles separated from the filtrate on cooling. After recrystallization from ethanol the product (0.45 g.) had m.p. 159-160°; nmr (DMSO) δ 4.9 ($NCH_3$), 6.1 ($NH_2$), 7.3-8.1 (m, 4H), 8.9-9.3 (2 doublets, 2H).

*Anal.* Calcd. for $C_{10}H_{11}ClN_2O_4$: C, 46.6; H, 4.3; N, 10.8. Found: C, 46.2; H, 4.35; N, 10.8.

Exchange of the counterion by iodide, for direct comparison with the product from methylation of 8-aminoquinoline, was achieved by treating a warm ethanolic solution of the perchlorate salt with 55% aqueous hydrogen iodide solution. Crystals of 8-ammonio-1-methylquinolinium di-iodide separated on cooling which, when recrystallized from ethanol containing a few drops of triethylamine, gave 8-amino-1-methylquinolinium iodide, m.p. 165-166°. The nmr spectrum was identical with that of the perchlorate.

*Anal.* Calcd. for $C_{10}H_{11}IN_2$: C, 42.0; H, 3.9; N, 9.8. Found: C, 41.9; H, 3.9; N, 9.7.

2-Amino-1-methylquinolinium Iodide.

This compound, m.p. 244-245° [lit., (9) 247°] was prepared by reaction of 2-aminoquinoline with methyl iodide in ethanol;

nmr (DMSO) $\delta$ 2.85 ($NCH_3$), 6.15 (d, 1H), 6.35-7.1 (m, 4H), 7.3 (d, 1H), 8.0 (broad s, $NH_2$).

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