# The Acid-Catalyzed Reaction of Diazomethane with Six-Membered Aromatic Nitrogen Heterocyclic Compounds[1]

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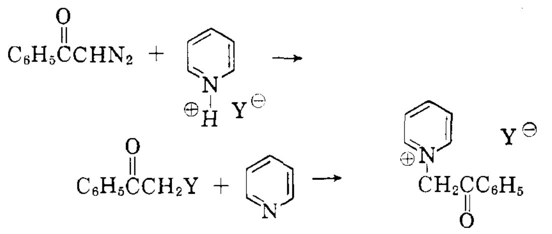
Pyridine, quinoline, and isoquinoline have been transformed into the corresponding *N*-methyl quaternary salts by a reaction with diazomethane catalyzed by the nonnucleophilic fluoboric acid.

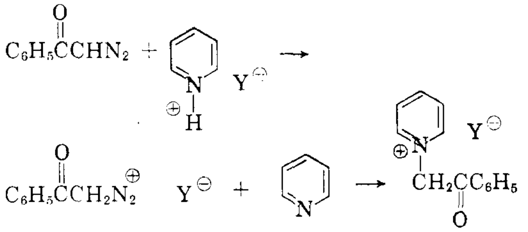
Although reactions of diazo compounds with five-membered aromatic heterocycles[2] have been investigated, reports of corresponding reactions with six-membered aromatic heterocycles are notably rare.[3] When polyfunctional compounds are employed in which the six-membered aromatic heterocycle is one of several reactive sites, usually it is *not* the heterocyclic ring which suffers reaction[4] but rather another functional group present within the molecule. The classical example of this is 2-pyridone which affords 2-methoxypyridine upon treatment with diazomethane.[5]

One of the more significant papers dealing with the reaction of diazo compounds with six-membered aromatic heterocycles is that of King and Miller[6] which deals with the reaction between diazoacetophenone and a variety of salts of pyridine, isoquinoline, and 3-methylisoquinoline. The products were the related *N*-phenacyl salts. However, in these cases the anion present is a potential nucleophile (halide, perchlorate, sulfate, phosphate, or tosylate ions) so that their data cannot permit a clear discrimination between two reaction schemes: (1) a two-step process involving the conversion of diazoacetophenone to a phenacyl halide or ester which then suffers attack by the nitrogen atom of the heterocyclic compound:



(1)

(2) direct attack of the heterocyclic compound on the protonated diazoacetophenone:



(2)

The two-step process (equation 1) receives support from the observations that pyridinium chloride and 2-picolinium chloride react with diazomethane to give quantitative yields of the free base together with methyl chloride.[7] Furthermore, it is not surprising that the systems studied by King and Miller afforded the quaternary salts since the phenacyl halide or ester would be expected to be much more susceptible to nucleophilic displacement than methyl chloride.[8]

To avoid the two-step process (equation 1) we used fluoborate salts of the heterocyclic compounds because the fluoborate anion cannot participate in the nucleophilic displacement of equation 1.

The formation of fluoborate salts of organic bases had been described previously.[9] Thus Ryss and Idel's neutralized pyridine with aqueous fluoboric acid and isolated a 60% yield of pyridinium fluoborate.[10] Müller[11] prepared several acyclic and cyclic aliphatic fluoborates by

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[2] G. M. Badger, B. J. Christie, H. J. Rodda, and J. M. Pryke, *J. Chem. Soc.*, 1179 (1958); J. Ratusky and F. Sorm, *Coll. Czech. Chem. Comm.*, **23**, 467 (1958); J. Novak and F. Sorm, *Coll. Czech. Chem. Comm.*, **23**, 1126 (1958).

[3] R. Daniels and O. L. Salerni, *Proc. Chem. Soc.*, 286 (1960).

[4] L. Capuano, *Chem. Ber.*, **92**, 2670 (1959); M. Los and W. H. Stafford, *J. Chem. Soc.*, 1680 (1959).

[5] H. Meyer, Monatsh., **26**, 1311 (1906); H. von Pechmann, *Ber.*, **28**, 1624 (1895); see also M. P. Cava and N. K. Bhattacharyya, *J. Org. Chem.*, **23**, 1614 (1958). It is noteworthy that 8-hydroxyquinoline and diazomethane yield *N*-methyl-8-quinolone together with a small amount of 8-methoxyquinoline [J. P. Phillips and R. W. Keown, *J. Am. Chem. Soc.*, **73**, 5483 (1951)].

[6] L. C. King and F. M. Miller, *J. Am. Chem. Soc.*, **70**, 4154 (1948).

[7] R. Gompper, *Chem. Ber.*, **93**, 187 (1960).

[8] A. Streitwieser, *Chem. Revs.*, **56**, 573 (1956).

[9] H. E. Thompson, C. P. Swanson, and A. G. Norman, *Botan. Gaz.*, **107**, 476 (1946) [*Chem. Abstr.*, **41**, 3902 (1947)].

[10] I. C. Ryss and S. L. Idel's, *Zhur. Neorg. Khim.*, **2**, 2270 (1957). [*Chem. Abstr.*, **52**, 14603 (1958)]; see also M. F. Lappert, *J. Chem. Soc.*, 784 (1955).

[11] E. Müller, H. Huber-Emden, and W. Rundel, *Ann.*, **623**, 34 (1959).

neutralizing the appropriate amine with fluoboric acid in the presence of a methyl red indicator. When these procedures were repeated with pyridine, difficulties were encountered consistently because the crude fluoborates of the six-membered aromatic heterocycles are hygroscopic and difficult to purify. It was found that a higher yield of a purer and less hygroscopic product was obtained when a solution of fluoboric acid in dimethoxyethane was dried for an extended period with a large amount of Drierite. Addition of the heterocyclic bases to this dried solution gave the related fluoborates. In this way, pyridinium fluoborate, quinolinium fluoborate, and isoquinolinium fluoborate were prepared.

The reaction of these fluoborates with diazomethane was carried out by dissolving the salt in its free base and introducing gaseous diazomethane by means of a stream of dry nitrogen. The reaction product was isolated by removing excess diazomethane and free base and obtaining the *N*-methyl quaternary salt as its picrate. The picrates were identified by the correspondence of their infrared spectra and melting points with authentic samples.

These results are consistent with the reaction sequence shown in equation 2: a proton is transferred from the pyridinium ion to diazomethane and the methyl diazonium ion that is produced reacts with the free base to give the *N*-methyl compound and nitrogen gas. Alternatively, but less probably, the methyl diazonium ion can disproportionate to nitrogen and a methyl carbonium ion which attacks the free base to produce the *N*-methyl derivative.

## EXPERIMENTAL[12]

*Preparation of fluoborates.* A. *Pyridinium fluoborate.* Commercially available 48–50% aqueous fluoboric acid (22.2 g., 0.13 mole) was dissolved in 220 ml. of dimethoxyethane and dried with 220 g. of Drierite for 1 day. The filtered solution was treated with redistilled pyridine (5.0 g., 0.063 mole) under cooling. Precipitation of the product was completed by the addition of 300 ml. of anhydrous ether. The solid was filtered, washed with dry ether, and recrystallized from absolute ethanol and afforded 9.5 g. (90%) of pyridinium fluoborate, m.p. 220–222° (lit.,[10] m.p 217°).

*Anal.* Calcd. for $C_5H_6NBF_4$: N, 8.39. Found: N, 8.14, 8.69.

*B. Quinolinium fluoborate.* In a similar fashion 5 g. (0.039 mole) of redistilled quinoline was treated with 13.9 g. (0.08 mole) of dried commercial fluoboric acid in 140 ml. dimethoxyethane. Crystallization of the product did not occur even after the addition of large amounts of absolute ether and only an oily layer was present. The light yellow reaction mixture was concentrated *in vacuo* and the yellow viscous residue was dissolved in hot 1-propanol. The solid obtained on cooling was filtered, washed with absolute ether, and dried *in vacuo* over phosphorus pentoxide and yielded 7.80 g. (92%) of a yellow solid. Recrystallization from ethyl acetate–absolute alcohol gave a white hygroscopic solid, m.p. 94–96°.

*Anal.* Calcd. for $C_9H_8NBF_4$: N, 6.46. Found: N, 6.59.

*C. Isoquinolinium fluoborate.* Similarly, a dried solution of 13.9 g. (0.08 mole) of 48–50% fluoboric acid and 5 g. (0.038 mole) of redistilled isoquinoline in 140 ml. dimethoxyethane was treated with absolute ether. The greyish solid was washed with absolute ether, dried *in vacuo* over phosphorus pentoxide, and afforded 8.05 g. (95%) of product. The solid was taken up in hot 2-propanol, treated with charcoal, and yielded a white, nonhygroscopic solid, m.p. 137–139°.

*Anal.* Calcd. for $C_9H_8NBF_4$: N, 6.46. Found: N, 6.14.

*Reaction of the fluoborates with diazomethane.* Solutions of diazomethane in *cis*-decalin were prepared by the method of Doering and Prinzbach[13] from nitrosomethylurea.[14]

A. *Pyridinium fluoborate* (5.6 g., 0.033 mole) was dissolved in 40 ml. of dry pyridine, cooled to 5°, and diazomethane (from 10.3 g., 0.1 mole of nitrosomethylurea) was introduced from a decalin solution by means of a slow stream or dry nitrogen. The end of the reaction was indicated by the appearance of a yellow color. Excess diazomethane and pyridine were removed *in vacuo*, and the last traces of pyridine were removed by azeotropic distillation with 1-butanol. The dark viscous residue was taken up in 40 ml. water and treated with a solution of 7.8 g. of picric acid in 340 ml. of water and boiled. Upon cooling, the solution afforded 10.4 g. (98% based on the amount of pyridinium fluoborate) of *N*-methylpyridinium picrate, m.p. 104–106°. Recrystallization from 2-propanol afforded a yellow solid, m.p. 115–117°, identical in melting point and infrared spectrum with authentic material.

*Anal.* Calcd. for $C_{12}H_{10}N_4O_7$: N, 17.39. Found: N, 17.50.

The authentic sample was prepared by refluxing 1 g. of 2,4,6-trinitroanisole with 5 ml. of pyridine and recrystallizing the yellow solid from 2-propanol.

B. *Quinolinium fluoborate* (3.00 g., 0.014 mole) was dissolved in 24 ml. of dry quinoline and treated as above with diazomethane prepared from 4.20 g. of nitrosomethylurea. After removing the volatile components *in vacuo*, the viscous residue was placed in a vacuum desiccator over concd. sulfuric acid. The residue was taken up in absolute ethanol, decolorized with charcoal, and treated with a saturated solution of 3.1 g. of picric acid in ethanol. The *N*-methylquinolinium picrate, 3.0 g. (58% based on the amount of quinolinium fluoborate), was recrystallized from water and afforded material melting at 159–160° undepressed on admixture with authentic material and with an identical infrared spectrum.

*Anal.* Calcd. for $C_{16}H_{12}N_4O_7$: N, 15.05. Found: N, 15.20.

Authentic *N*-methylquinolinium picrate was prepared by heating on a steam bath, 2.0 g. of 2,4,6-trinitroanisole with 3.0 ml. of quinoline. The yellow solid was recrystallized from water.

C. *Isoquinolinium fluoborate* (3.0 g., 0.014 mole) in 60 ml. of isoquinoline was treated as described above with diazomethane prepared from 6.5 g. of nitrosomethylurea. The reaction mixture was subjected to a steam distillation and the aqueous residue concentrated *in vacuo* and dried in a vacuum desiccator over concd. sulfuric acid. The residue was dissolved in 20 ml. of absolute ethanol, decolorized with charcoal, and treated with a saturated solution of 3.0 g. of picric acid in 50 ml. of ethanol. The solid, 3.85 g. (74%) was taken up in methanol and chromatographed on F-20 alumina (Alcoa) and afforded material melting at 168–170°, undepressed by authentic material and possessing an identical infrared spectrum.

*Anal.* Calcd. for $C_{16}H_{12}N_4O_7$: N, 15.05. Found: N, 14.80.

Authentic *N*-methylisoquinolinium picrate was prepared by heating on a steam bath, 2.0 g. of 2,4,6-trinitroanisole and 3.0 ml. of isoquinoline. The yellow solid was recrystallized from methanol.

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(12) All melting points are uncorrected.

(13) W. von E. Doering and H. Prinzbach, *Tetrahedron*, 6, 24 (1959).

(14) E. D. Amstutz and R. R. Myers, *Org. Synthesis*, **Coll. Vol. II**, 462 (1943).