

## The Meisenheimer Reaction In The Isoquinoline Series

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The Meisenheimer reaction is the reaction of phosphorus oxychloride or sulfuryl chloride on *N*-oxides of pyridine or various polycyclic pyridine type heterocycles (1). We have been interested in this reaction in several series (2).

There are three reports in the literature concerning the Meisenheimer reaction using isoquinoline 2-oxide (3) and various substituted isoquinoline 2-oxides (4,5). In each instance, only one chloro isomer has been isolated from the reaction mixture. This same reaction with pyridine 1-oxide (6,7) quinoline 1-oxide (8) and 1,5-naphthyridine 1-oxide (2) yields a mixture of chloro isomers in each case. We wished to investigate the Meisenheimer reaction using isoquinoline 2-oxide and isolate all of the chloro isomers from the reaction mixture rather than just the major product and to determine the ratios in which these chloro isomers are formed.

Various techniques have been used for the Meisenheimer reaction including the use of phosphorus oxychloride or sulfuryl chloride with either the *N*-oxide or the *N*-oxide hydrochloride. However, these techniques have not been studied in relation to product ratios. We have used both reagents on isoquinoline 2-oxide and its hydrochloride and wish to report that a mixture of chloro isomers is indeed formed and that the ratio of products varies with the technique used.

The results of the four variations of the Meisenheimer reaction are shown in Table I. It can be seen that 1-chloro, 3-chloro and 4-chloroisoquinoline are formed in all four reactions. The major isomer of each reaction is 1-chloroisoquinoline, however, this can range from 60-80 percent of the products.

A comparison of the data from Table I for the two reagents, phosphorus oxychloride and sulfuryl chloride reveals that both 1- and 3-chloroisoquinoline constitute a greater percentage of the reaction products when phosphorus oxychloride is used with either isoquinoline 2-oxide or isoquinoline 2-oxide hydrochloride. When sulfuryl chloride is used, twice as much 4-chloroisoquinoline is formed from the reaction with isoquinoline 2-oxide when compared to the same reaction using phosphorus oxychloride. Almost three times as much 4-chloroisoquinoline

is formed from the hydrochloride when sulfuryl chloride is used instead of phosphorus oxychloride.

A comparison of the two substrates isoquinoline 2-oxide and its hydrochloride shows that 1-chloroisoquinoline is obtained in a slightly higher yield from the isoquinoline 2-oxide hydrochloride with either of the two reagents. It is noticeable that both reagents give less 3-chloroisoquinoline with the 2-oxide hydrochloride, as compared to the 2-oxide. With the 4-chloroisoquinoline isomer, no clear pattern can be seen. Sulfuryl chloride produces more 4-chloroisoquinoline when reacted with isoquinoline 2-oxide hydrochloride, but phosphorus oxychloride produces a greater yield of 4-chloroisoquinoline using isoquinoline 2-oxide.

Injection of each mixture into the gas chromatograph clearly showed five distinct peaks. Peak 1 had the same retention time as a sample of isoquinoline injected into the gas chromatograph under the same conditions. A sample of the isoquinoline 2-oxide injected under the same conditions as isoquinoline gave a similar retention time and a mixture of isoquinoline and the 2-oxide could not be separated into two distinct peaks. The infrared spectrum of the collected material was almost identical with isoquinoline. The composition of peak 2 was not determined.

The three remaining peaks, corresponded to the three chloroisoquinolines: peak 3, 4-chloroisoquinoline; peak 4, 1-chloroisoquinoline; and peak 5, 3-chloroisoquinoline. The mixture of isomers was separated on the preparative gas chromatograph and the individual peaks compared with the synthetic 4-, 1-, and 3-chloroisoquinolines. They are shown to be identical by NMR and infrared analyses along with the melting points of the picrates.

## EXPERIMENTAL

## Meisenheimer Reaction.

Seventeen g. of isoquinoline 2-oxide (9) or 20 g. of isoquinoline 2-oxide hydrochloride (1) was treated with 100 ml. of either sulfuryl chloride or phosphorus oxychloride in the cold, warmed to reflux and refluxed 2 hours. The reaction mixture was evaporated on a steam bath with an aspirator to give a residue which was treated with ice and water and made basic with ammonium hydrox-

TABLE I  
Meisenheimer Reaction Isomer Percentages

Compound	Reagent	% Crude	Peak 1 Isoquinoline	Peak 2	Peak 3 4-Chloro- isoquinoline	Peak 4 1-Chloro- isoquinoline	Peak 5 3-Chloro- isoquinoline
Isoquinoline 2-Oxide	POCl <sub>3</sub>	76	1.4 (a) 2.7 (b)	1.8 (a) 3.1 (b)	15.3 (a) 4.3 (b)	75.3 (a) 7.0 (b)	6.3 (a) 8.0 (b)
Isoquinoline 2-Oxide·HCl	POCl <sub>3</sub>	67	1.0 2.7	3.1 1.5	10.9 4.6	81.8 6.9	4.8 8.1
Isoquinoline 2-Oxide	SO <sub>2</sub> Cl <sub>2</sub>	81	1.4 2.7	3.2 1.6	30.7 4.3	62.9 7.3	3.4 8.2
Isoquinoline 2-Oxide·HCl	SO <sub>2</sub> Cl <sub>2</sub>	78	1.5 2.7	3.2 0.8	32.8 4.8	63.5 7.1	1.3 8.2

(a) These are percent of total crude. (b) These are retention times in minutes.

ide. Extraction with toluene and evaporation gave the crude mixtures. These are listed in Table I.

#### Chloroisoquinolines.

1-Chloroisoquinoline was prepared according to Haworth and Robinson (11) and melted at 37-38°. 3-Chloroisoquinoline was prepared from 1,3-dichloroisoquinoline (11) and melted at 46.5-47.5°. 4-Chloroisoquinoline was synthesized from 4-aminoisoquinoline by diazotization in concentrated hydrochloric acid and warming. It melted at 28-29° after recrystallization from ligroin (lit. (12) 27.5-29.5°).

The crude mixtures were analyzed on a Beckman G.C. 4 gas chromatograph fitted with a 6 ft. x 0.125 in. aluminum column filled with 15% Carbowax 20 M on Chromosorb W and the column temperature maintained at 220°. The percentages and retention times for each sample are recorded in Table I. The crude mixtures from the reactions with phosphorus oxychloride were separated on a F and M Model 5750 gas chromatograph fitted with a 20 ft. x 0.375 in. aluminum column filled with 20% Carbowax 20 M on Chromosorb W at a column temperature of 230° using a thermal conductivity detector. The three chloro isomer fractions were collected and compared with synthetic samples. The infrared spectra were taken with a Beckman IR-8 spectrometer using potassium bromide pellets. The nuclear magnetic resonance spectra were obtained with a Varian HA-60 spectrometer.

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