

## Nucleophilic Displacements on Polyhalogenated Heterocyclic *N*-Methoxy Methyl Sulfates

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*N*-Methoxy methyl sulfates of 2,3,4,5- and 2,3,5,6-tetrachloropyridine, 3,4,5- and 3,4,6-trichloropyridazine, pentachloropyridine, and tetrachloropyridazine have been prepared. Their reactions with water and aqueous potassium cyanide have been investigated.

The preparation of substituted 2- or 4-cyanopyridines by nucleophilic substitution of cyanide ion on the appropriate *N*-methoxypyridinium methyl sulfate has been reported previously (1,2,3). The substituents present have included such groups as chloro, cyano, dibromo, dimethyl, and nitro.

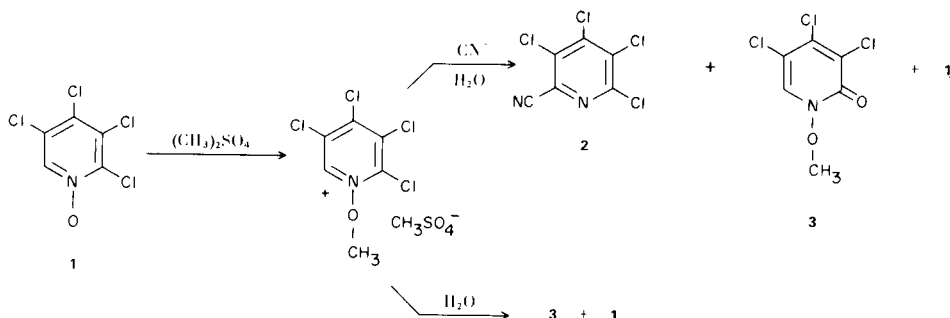
The purpose of this study was to investigate the effect on the reaction of nucleophiles with heterocyclic *N*-methoxy methyl sulfates as the number of chlorine atoms on the heterocyclic ring is increased. The compounds chosen for this study were 2,3,4,5- and 2,3,5,6-tetrachloropyridine *N*-oxides and a mixture of 3,4,6- and 3,5,6-pyridazine *N*-oxides. The preparation of these *N*-oxides was accomplished by treatment of the parent heterocyclic compound with 90% hydrogen peroxide in trifluoroacetic acid (4,5).

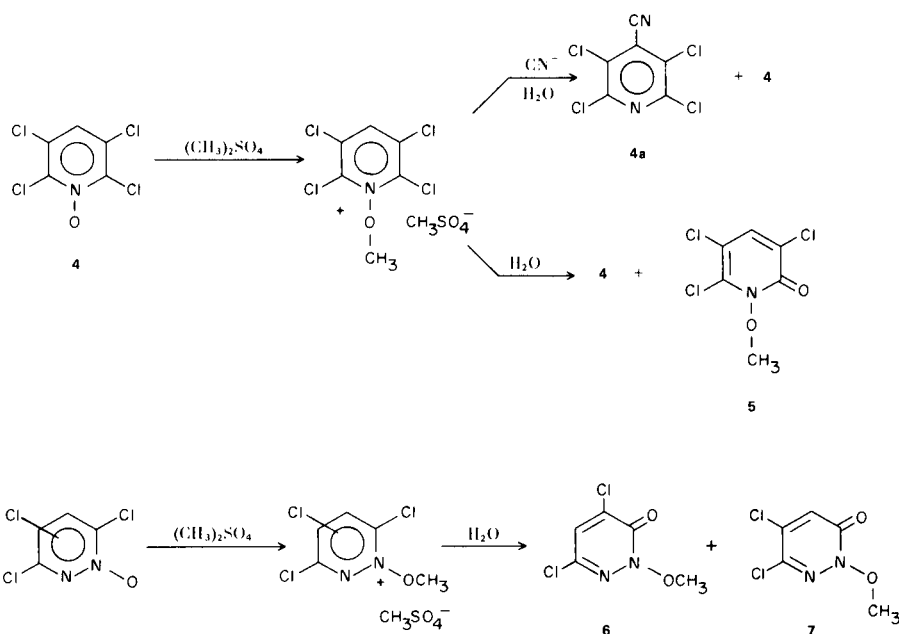
In contrast to the reported exothermic reaction of dimethyl sulfate with pyridine *N*-oxide, reaction with the various *N*-oxides employed in this study proceeded only with prolonged heating at 95 to 100°. Treatment of 2,3,4,5-tetrachloropyridine *N*-oxide (1) with dimethyl sulfate formed the corresponding *N*-methoxypyridinium methyl sulfate. Reaction of the latter material with an aqueous solution of potassium cyanide gave a mixture of

products from which tetrachloropicolinonitrile (2) could be isolated. There was also obtained, in addition to the starting material, a compound identified as 1-methoxy-3,4,5-trichloropyrid-2(1*H*)one (3). In the absence of cyanide ion, the compound 3 was the only product obtained from the reaction of the methoxypyridinium salt and water. The structure of this product was assigned on the basis of its infrared and mass spectral data. The presence of an ion at *m/e* 141 (C<sub>3</sub>Cl<sub>3</sub>) strongly suggests the 2-oxo grouping in preference to the isomeric 4-orientation.

The reaction product obtained from 1-methoxy-2,3,5,6-tetrachloropyridinium methyl sulfate and an aqueous cyanide solution was tetrachloroisonicotinonitrile (4a) in addition to starting material (4). When the salt was treated with water, 1-methoxy-3,5,6-trichloropyrid-2(1*H*)one (5) was formed as evidenced by infrared spectral analysis, although the compound could not be isolated in the pure state.

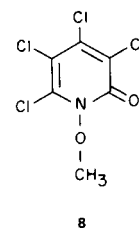
When a mixture of 3,4,6- and 3,5,6-trichloropyridazine 1-oxide with dimethyl sulfate was followed by reaction with an aqueous solution of potassium cyanide, it produced a mixture of the isomeric products, 6 and/or 7. None of the expected 3,5,6-trichloro-4-pyridazinecarbonitrile was





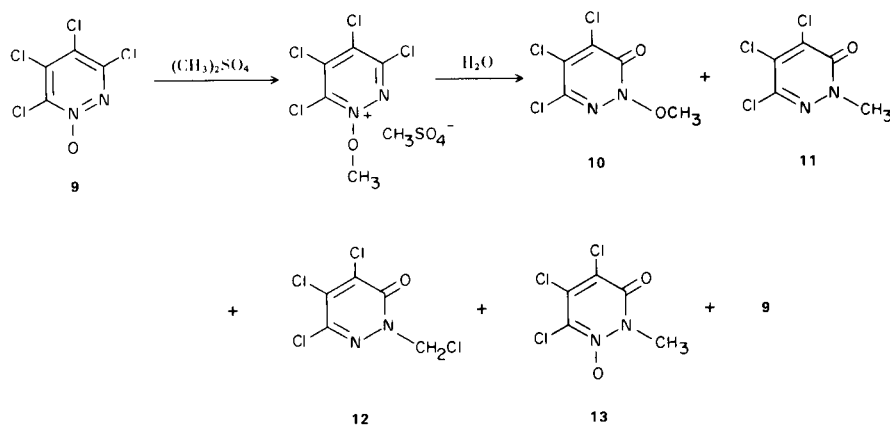
found to be present. The presence of an ion at  $m/e$  107 ( $\text{C}_3\text{HCl}_2$ ) in the mass spectrum confirms the 3-oxo grouping in contrast to the 5-oxo product.

The interaction of the previously mentioned 1-methoxypyridinium methyl sulfates with water suggested the examination of the corresponding pentachloropyridine and tetrachloropyridazine salts. Conversion of pentachloropyridine *N*-oxide to the corresponding methoxypyridinium salt, followed by reaction with water, produced a mixture of pentachloropyridine *N*-oxide and a material identified as 1-methoxy-3,4,5,6-tetrachloropyrid-2(1*H*)one (8). The assignment is based on its infrared and mass spectra. The presence of an ion at  $m/e$  141 establishes the 2-oxo structure. These findings are in agreement with the recently reported results of Roberts and Suschitzky (5,6) who found substitution reactions of pentachloropyridine 1-oxide with amines



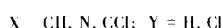
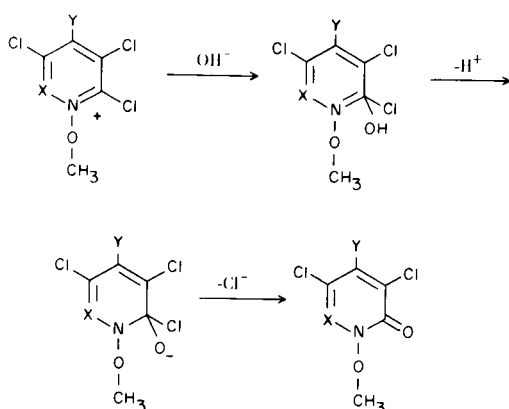
occurred in the 2- and 6-position. No 2,4- or 2,4,6-substituted products were found. Liveris and Miller (7) have also found enhanced ease of nucleophilic substitution in the 2-positions of pyridine *N*-oxides as compared to substitution in the 4-position.

Tetrachloropyridazine *N*-oxide (9) and dimethyl sulfate provide the corresponding salt which, when treated with water, reacts vigorously to form the four different products as shown below:



Identification of the reaction products was carried out by collecting each of the components from repeated glc separations and analyzing them by mass spectrometric and infrared techniques. Under the conditions of glc analysis, tetrachloropyridazine *N*-oxide undergoes thermal deoxygenation to a slight degree. This has been shown by trapping pure tetrachloropyridazine *N*-oxide and resubmitting it to the glc, thereupon observing tetrachloropyridazine. Similar results have been found for the penta- and tetrachloropyridine *N*-oxides studied. A portion of compound **11** is formed by thermal deoxygenation of **13** in the gas chromatograph. That **13** was also present in the crude reaction product was confirmed by nmr analysis. The structure of **12** was confirmed by authentic synthesis (see Experimental).

While no mechanism studies have been carried out, a possible pathway by which products of the type, **3**, **5**, **6**, **7**, **8**, and **10**, are formed is shown below in generalized form:



The second step, loss of a proton, need not occur as a separate step but may be synchronous with the loss of chloride ion. An alternative mechanism involving nucleophilic attack by water itself is equally likely. The omnipresence of starting *N*-oxide in each of the cases studied can be attributed to incomplete or reversible reaction between the dimethyl sulfate and each of the respective *N*-oxides.

The yields obtained in any of these reactions are 40 to 70%. However, in many instances, the mixtures of products necessitate separation by column chromatography and the yield of any one product is generally low.

#### EXPERIMENTAL

Elemental analyses were performed on a Perkin Elmer Model 240 Elemental Analyzer; mass spectral analyses were conducted on Atlas Model CH-4. Vapor phase chromatographic analyses

were carried out on an Aerograph Autoprep Model A-700 equipped with a 5-foot x 4-inch stainless steel column packed with diethyleneglycol succinate (5%) on chromosorb P (60-80), unless otherwise stated. All melting points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 257 spectrophotometer.

#### Preparation of Tetrachloropyridazine 1-Oxide.

To a stirred solution of 15.0 g. of tetrachloropyridazine in 100 ml. trifluoroacetic acid was added slowly a solution of 5.0 g. of 90% hydrogen peroxide in 50 ml. of trifluoroacetic acid. When the addition was complete, the reaction mixture was heated to reflux for 15 minutes, cooled, and poured over ice. The resultant white solid was removed by filtration and dried *in vacuo* to provide 14.0 g. (87%) tetrachloropyridazine *N*-oxide having m.p. 133°. A recent report lists a melting point of 124° (13).

*Anal.* Calcd. for C<sub>4</sub>Cl<sub>4</sub>N<sub>2</sub>O: C, 20.5; N, 12.0. Found: C, 20.7; N, 11.9.

#### Preparation of 3,4(and 5),6-Trichloropyridazine 1-Oxide.

To a stirred solution of 4.2 g. of 3,4,6-trichloropyridazine in 50 ml. of trifluoroacetic acid was added slowly 1.0 g. of 90% hydrogen peroxide in 25 ml. of trifluoroacetic acid. After the addition was complete, the reaction mixture was maintained at reflux for 12 minutes, cooled, and poured over ice. No precipitate formed and the solution was extracted three times with chloroform. The organic phase was separated, dried over anhydrous magnesium sulfate, and evaporated to provide 3.5 g. of a pale, yellow solid, having m.p. 90 to 110°.

*Anal.* Calcd. for C<sub>4</sub>HCl<sub>3</sub>N<sub>2</sub>O: C, 24.09; H, 0.5; N, 14.01. Found: C, 24.3; H, 0.5; N, 14.3.

In a similar manner, pentachloropyridine *N*-oxide (m.p. 176 to 177°; lit. (8) 175 to 176°) and 2,3,5,6-tetrachloropyridine *N*-oxide (m.p. 221 to 223°; lit. (9) 212 to 215°) were prepared.

Reactions of 1-Methoxy-2,3,4,5-tetrachloropyridinium Methyl Sulfate and 1-Methoxy-2,3,5,6-tetrachloropyridinium Methyl Sulfate.

A mixture of 4.6 g. of 2,3,4,5-tetrachloropyridine 1-oxide and 2.5 g. of dimethyl sulfate was heated on a steam bath for 8 hours, during which time the flask was rotated several times to effect mixing. The resultant solid was divided into two equal batches, one treated with water and the other, with a 4 *M* aqueous solution of potassium cyanide. The reaction mixtures were filtered and the solids dried (ca. 1 to 1.5 g. in each case) and analyzed by glc at 200°. The products of the reaction with water were found to be 2,3,4,5-tetrachloropyridine (ca. 5%), 2,3,4,5-tetrachloropyridine 1-oxide (ca. 40%), and 1-methoxy-3,4,5-trichloropyrid-2-one (ca. 55%). The latter was identified by its infrared and mass spectra.

The dried solids from the reaction of the pyridinium salt with water were placed on a column of Alcoa F-20 alumina (activity grade III) and eluted with hexane. Evaporation of the hexane eluate provided a trace of 2,3,4,5-tetrachloropyridine. When the eluent was changed to 10% ether-hexane, 1.0 g. of 1-methoxy-3,4,5-trichloropyrid-2-one was obtained having m.p. 163 to 164°,  $\nu$  CO 1669 (potassium bromide) and an ion at *m/e* 141 (C<sub>3</sub>Cl<sub>3</sub>). The presence of the C<sub>3</sub>Cl<sub>3</sub> peak confirms the 2-oxo structure.

*Anal.* Calcd. for C<sub>6</sub>H<sub>4</sub>Cl<sub>3</sub>NO<sub>2</sub>: C, 31.5; H, 1.8; N, 6.1. Found: C, 31.8; H, 1.8; N, 6.0.

The products of the aqueous cyanide reaction were identical to those obtained above, in addition to tetrachloropyridine (ca. 5%). The last compound was trapped as it was eluted from the glc. It was identified by its melting point (151 to 152°; lit. (10) 148 to 150°) and by comparison of its infrared spectrum with

that of an authentic sample.

When a reaction identical to that above was carried out using 1-methoxy-2,3,5,6-tetrachloropyridinium methyl sulfate, treatment with water gave only 2,3,5,6-tetrachloropyridine and its *N*-oxide. Reaction with a 4 *M* aqueous solution of potassium cyanide gave the above materials in addition to tetrachloroisonicotinonitrile. The nitrile was identified by its melting point (136 to 138°, Lit. (11) 138°) and comparison of its infrared spectrum with that of an authentic sample.

Reactions of 1-Methoxy-3,4,5 (and 3,4,6)-trichloropyridazinium Methyl Sulfate.

A mixture of 9.0 g. of 3,4,5 (and 3,4,6)-trichloropyridazine 1-oxide and 5.5 ml. of dimethyl sulfate was heated at 100° for 4 hours. The mixture was cooled and treated with 4 *M* aqueous potassium cyanide. A solid formed and was removed by filtration. Analysis by glc (5' = 5%; SE-30, 160°) demonstrated the presence of only one peak. The crude solid (4 g.) was recrystallized from ethanol to give 1.0 g. of a material (possibly a mixture of isomers) having m.p. 101 to 104°. An additional 3 g. was obtained by evaporation of the mother liquor. The material was identified as 2-methoxy-4,6 (and/or 5,6)-dichloropyridazin-3(2*H*)one by means of its infrared and mass spectra in conjunction with elemental analysis. The compound has  $\nu$  CO 1680 (potassium bromide) and an ion at *m/e* 107 (C<sub>3</sub>HCl<sub>2</sub>), the latter being indicative that the structure is that of the 3-oxo compound.

*Anal.* Calcd. for C<sub>5</sub>H<sub>4</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 30.8; H, 2.1; N, 14.4  
Found: C, 30.5; H, 2.0; N, 14.1.

Reaction of 1-Methoxy-3,4,5,6-tetrachloropyridazinium Methyl Sulfate with Water.

A mixture of 4.7 g. of tetrachloropyridazine 1-oxide and 2.5 g. of dimethyl sulfate was heated on a steam bath for 6 hours, during which time a homogeneous melt formed. The mixture was allowed to cool, then diluted with 15 ml. of ice water (exothermic). The mixture was stirred at 10° for 1 hour; the precipitate which formed was removed by filtration. The dried solid (4.0 g.) was dissolved in chloroform and submitted to glc analysis at 200° on the column described above. Six peaks were observed; each was trapped and submitted to ir and mass spectral analysis. The mass spectra of compounds **10-13** all contain a peak at *m/e* 141 (C<sub>3</sub>Cl<sub>3</sub>) which confirms their structures as those of the 3-oxo compounds. The materials in order of their elution were identified as tetrachloropyridazine (*ca.* 1%); 4,5,6-trichloro-2-methylpyridazin-3(2*H*)one (**11**, 4%, m.p. 99°); 4,5,6-trichloro-2-methoxy-pyridazin-3(2*H*)one (**10**, 57%, m.p. 104 to 106°); 4,5,6-trichloro-2-chloromethylpyridazin-3(2*H*)one (**12**, 4%, m.p. 97 to 99°; lit. (12) 98 to 100°); tetrachloropyridazine 1-oxide (35%); and 4,5,6-trichloro-2-methylpyridazin-3(2*H*)one 1-oxide (**13**, *ca.* 1%, m.p. 184°). The latter compound, upon reinjection in the glc, gave a mixture of **11** and **13**. This loss of oxygen indicates that **13** is not the 5-oxo isomer of **10**. Nuclear magnetic resonance analysis of the crude reaction product indicated the presence of protons attributable to -OCH<sub>3</sub>, -CH<sub>2</sub>Cl, and N-CH<sub>3</sub>. The N-CH<sub>3</sub> was confirmed as being due to **11** by nmr analysis of a small sample isolated from glc, thus confirming its presence as a reaction product and not merely an artifact derived from **13** in the glc analysis.

The structure of **12** was confirmed by comparison of its melting point and infrared spectrum with those of an authentic sample (**12**). The infrared spectra of compounds **10-13** contain carbonyl absorption at  $\nu$  CO 1690 cm<sup>-1</sup>, 1680 cm<sup>-1</sup>, 1690 cm<sup>-1</sup> (all carbon disulfide) and 1670 cm<sup>-1</sup> (potassium bromide), respectively.

Reaction of 1-Methoxy-2,3,4,5,6-pentachloropyridinium Methyl Sulfate with Water.

A mixture of 4.5 g. of pentachloropyridine 1-oxide and 2.5 g. of dimethyl sulfate was heated for 6 hours on a steam bath. The reaction mixture was cooled and treated with 100 ml. ice water and stirred for 1 hour. The resultant solid was removed by filtration and dried to provide 3.4 g. of product. The material was dissolved in a minimum amount of chloroform and placed on a column of alumina (Alcoa F-20, activity grade III). Elution with hexane provided, after evaporation of the solvent, 1.8 g. of pentachloropyridine. When the eluent was changed to 5% ether-hexane, 1.4 g. of a mixture of pentachloropyridine *N*-oxide and an unknown material resulted. Continued elution with 5% ether-hexane removed an additional 0.2 g. of the unknown material. The latter product (m.p. 143 to 144°) was identified as 1-methoxy-3,4,5,6-tetrachloropyrid-2(1*H*)one by its infrared and mass spectra.

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