Peroxydichloromaleic Acid. A New Reagent for N-Oxidation of Heterocyclic Compounds

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Peroxydichloromaleic acid has been utilized for the conversion of various nitrogen-containing heterocycles into their N-oxides. It appears to be advantageous for the N-oxidation of some substituted heterocycles which are difficult to oxidize. Thus, 2-halogenoquinolines\(^1\), 2,5-dichloropyrazines\(^2\), chloropyrimidines\(^3\), substituted 1,2,4-triazines\(^4,5\), 9-chloro-tetrahydroacridine\(^6\), and various substituted benzothiazoles\(^7\) were
converted into corresponding N-oxides with this reagent. Recently, we have published an improved procedure for the N-oxidation of 3,6-dichloropyridazine, which leads with the use of this reagent to the desired 1-oxide in about 50% yield.

We report here that solutions of the previously unknown peroxydichloromalic acid (1), prepared from dichloromalic anhydride and 90% hydrogen peroxide in an inert polar solvent, provide a very convenient and occasionally superior reagent for the N-oxidation of various chloropyridazines (2a-2g) into corresponding 1-oxides (3a-3g).

![Chemical structures](image)

**SYNTHESIS**

bath and under stirring 90°C, hydrogen peroxide (6.00 g, 0.159 mol) was added. After stirring at 0°C for 2 h, the appropriate chloropyridazin (0.080 to 0.120 mol) was added and the mixture stirred for further 15 min. The reaction mixture was left to stand at 7°C for 48 to 96 h and the progress of N-oxidation was followed by T.L.C. on silica gel using chloroform/methanol (9:1) as eluent. At the end of the reaction the precipitated dichloromalic acid was filtered off, washed with methylene chloride (50 ml) and the filtrate was shaken twice with an aqueous solution of sodium carbonate (100 ml of 10% solution), once with sodium bisulfite solution (50 ml of 5% solution), once with water, and dried over magnesium sulfate. The solvent was evaporated in vacuo and the crude product recrystallized from benzene or a mixture n-hexane/benzene.

Received: June 25, 1973


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**Table. N-Oxidation of Chloropyridazines (2) into Corresponding 1-Oxides (3)**

<table>
<thead>
<tr>
<th>Compound 2</th>
<th>Reaction Time (hr)</th>
<th>m.p.*</th>
<th>Compound 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sub&gt;1&lt;/sub&gt; R&lt;sub&gt;2&lt;/sub&gt; R&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R&lt;sub&gt;4&lt;/sub&gt;</td>
<td></td>
<td>Yield (%)</td>
</tr>
<tr>
<td>a</td>
<td>Cl</td>
<td>H</td>
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<td>Cl&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>g</td>
<td>OCl&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

* Melting points were determined on a Kofler melting point apparatus and are uncorrected.
* Refer to the recrystallised products.
* C<sub>2</sub>H<sub>2</sub>Cl<sub>2</sub>N<sub>2</sub>O: calcd. C 37.33 H 3.13 N 14.52 (193.0) found C 37.56 H 3.38 N 14.22
* R.<sub>1</sub>R.<sub>2</sub>R.<sub>3</sub>R.<sub>4</sub> (KBr): v<sub>max</sub> = 1395, 1350, 1180 cm<sup>−1</sup>.

In all cases, the yields of 3 are better than 75%. Previously it has been possible to effect these N-oxidations using peroxyacetic<sup>13</sup>, peroxybenzoic<sup>14</sup>, monoperophthalic<sup>11</sup> or peroxytrifluoracetic<sup>12</sup> acid in some cases with very low yield and chromatographic separation of the desired N-oxides was necessary. The experimental results are presented in the Table along with the physical constants of the products obtained, which are in all cases identical to those found in the literature. The reactions were carried out by adding 2 to a solution of 1 in methylene chloride held at the appropriate temperature. As the N-oxidation proceeds, dichloromalic acid precipitates from the solution and may be removed by filtration when the reaction is complete. The products were then isolated and purified by conventional methods.

Throughout this communication dichloromalic anhydride of Fluka technical quality was used.

**N-Oxidation of Chloropyridazines with Peroxydichloromalic Acid. General Procedure:**

A solution of dichloromalic anhydride (33.4 g, 0.20 mol) in methylene chloride (400 ml) was cooled in an ice-water cooling