A New Method of Preparing *N*-Oxides from Polyhalogenated *N*-Heteroaromatic Compounds

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Summary Polyhalogen-substituted *N*-heterocycles are converted into *N*-oxides in high yield by oxidation in a mixture of sulphuric acid, hydrogen peroxide, and acetic or trifluoroacetic acid.

AROMATIC *N*-heterocycles in which the basicity of the ring nitrogen is severely reduced by the presence of electron-withdrawing substituents such as halogens are often resistant to *N*-oxidation by the usual reagents such as peracetic or *m*-chloroperbenzoic acid.[1] Oxidation in these cases is sometimes effected with trifluoroperacetic acid. Thus 2,6-dichloropyridine[2] or 2,6-dibromopyridine,[3] which are not affected by perbenzoic or peracetic acid, can be oxidised in fair yield with a solution of 30% hydrogen peroxide and trifluoroacetic acid. By contrast, polyhalogeno-*N*-heterocycles are difficult to oxidise even with this reagent. For instance, pentachloropyridine 1-oxide[4,5] could be obtained in only 20% yield with trifluoroacetic acid and 90% hydrogen peroxide. Similarly, *N*-oxidation of pentabromopyridine[6] under the same conditions gave the 1-oxide in only 5% yield.

As part of an extensive study of the synthesis and reactions of polyhalogenated *N*-oxides derived from *N*-heteroaromatics, we investigated the action of a number of oxidising agents[7] on the readily available pentachloropyridine. We found that pentachloropyridine 1-oxide was produced in high yield (> 80%) by a mixture of an organic peracid and concentrated sulphuric acid. For the best results, the substrate is dissolved in a mixture of sulphuric and acetic acid and hydrogen peroxide varying in strength from 30—90% is added slowly with stirring at or below 0° and the mixture is then allowed to reach room temperature.

N-*Oxidation of polyhalogeno*-N-*heteroaromatics with a mixture of a peracid and sulphuric acid*

N-Heteroaromatic compound	Reagent[b]	Reaction conditions	Yield (%)[c] of *N*-oxide
Pentachloropyridine ..	A	20° (48 h)	85
2,3,5,6-Tetrachloropyridine	A	20° (48 h)	80
2,6-Dichloropyridine ..	A	90° (18 h)	65
2,3,5,6-Tetrachloro-4-nitropyridine[a]	B	20° (24 h)	67
2,3,5,6-Tetrachloro-4-methylpyridine[a]	A	60° (18 h)	70
Pentabromopyridine ..	B	65° (18 h)	85
Tetrachloropyrazine[a] ..	B	20° (18 h)	56 (4·5)
Tetrachloropyridazine[a] ..	B	20° (18 h)	50

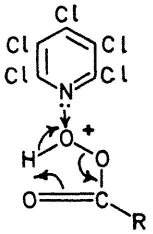
[a] This compound gives a new *N*-oxide. Correct elemental analyses and expected spectral data have been obtained for all *N*-oxides.

[b] Reagent A; acetic acid, concentrated sulphuric acid, and 90% H_2O_2. Reagent B; trifluoroacetic acid, concentrated sulphuric acid, and 90% H_2O_2.

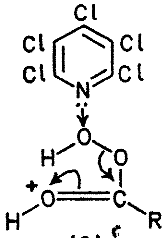
[c] Figure in brackets indicates the percentage yield of di-*N*-oxide.

This reagent system has proved successful for the *N*-oxidation of a number of weakly basic *N*-heteroaromatic compounds. Apart from making new *N*-oxides available, the method in most cases utilises acetic acid where previously trifluoroacetic had to be used (*e.g.* in the oxidation of 2,6-dichloropyridine).

N-Oxidation with peracids is recognised to be due to nucleophilic attack by the amine nitrogen on the electrophilic peroxidic oxygen.[1] The success of a mixture of peracid and sulphuric acid in oxidising weakly basic nitrogen compounds is probably brought about by enhancement of the electrophilicity of the peroxidic oxygen through protonation of the acid. This must ease the transfer of $(OH)^+$ to the nucleophile as shown in (**1**) or (**2**) and compensates for the low nucleophilicity of the hetero-nitrogen. The use of polyphosphoric acid instead of sulphuric acid usually gave inferior results with our compounds although a mixture of polyphosphoric acid and hydrogen peroxide has been reported to be effective in the *N*-oxidation of the weakly basic azolopyridazines.[8] A mixture of polyphosphoric and peracetic acid was, however, effective in the *N*-oxidation of 4-methoxytetrachloropyridine (80% yield) which in the presence of sulphuric acid suffered hydrolysis and gave the corresponding 4-hydroxy-*N*-oxide.



(1)



(2)

We thank the University of Salford for a Fellowship (to G.E.C.), Dr. J. A. H. McBride for samples of tetrachloropyrazine and tetrachloropyridazine, and Laporte (Warrington), for gifts of hydrogen peroxide.

(*Received, November 6th,* 1970; *Com.* 1926).

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