OXIDATION OF 2,4-DISUBSTITUTED PYRIMIDINES WITH ORGANIC PERACIDS

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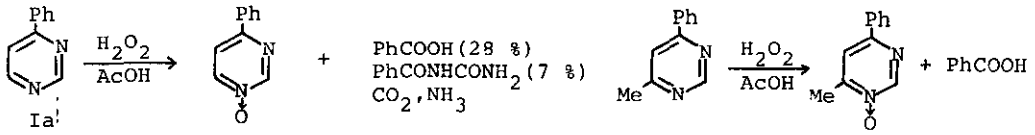
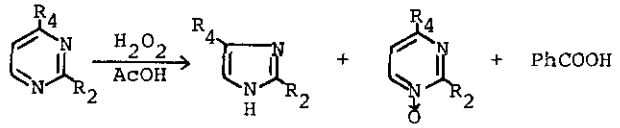
Abstract—— While 4,6-disubstituted(alkyl, aryl, alkoxyl) pyrimidines easily afforded the corresponding mono-N-oxides with hydrogen peroxide in glacial acetic acid, pyrimidine derivatives whose 6-position is free, are partly oxidatively degradated during N-oxidation reaction. The oxidation of the latter compounds under the above conditions gave 2,4-disubstituted imidazoles together with their mono-N-oxides. A likely mechanism of this ring-contraction and the improved conditions for the synthesis of the N-oxides are also described.

Previously, one of the present authors reported[1] that the N-oxidation of 4-phenylpyrimidine (Ia) and 4-methyl-6-phenylpyrimidine with hydrogen peroxide in glacial acetic acid gave their mono-N-oxides in 25 and 76 % yields, respectively. Since various kinds of fragmentary products were isolated during the N-oxidation of Ia, this clear contrast in the yields was explained by assuming the oxidative cleavage of pyrimidine ring at the N_1-C_6 bond. In order to establish the experimental procedure for the practical preparation of pyrimidine N-oxides with the free 6-position, we re-investigated the above N-oxidation reaction. The present paper describes an unexpected oxidative ring-contraction of pyrimidine derivatives to the correspoding imidazoles and also a successful N-oxidation of 6-substituted pyrimidines with m-chloroperbenzoic acid (m-CPBA).



As shown in Table I, treatment of several 2- and 4-phenylpyrimidines with hydrogen peroxide in glacial acetic acid afforded a considerable amount of phenylimidazoles[2] and benzoic acid besides the expected N-oxides. Typical example is as follows: a solution of 2-methyl-4-phenylpyrimidine (Ib; 0.85 g, 5 mmole) and 30 % hydrogen peroxide (1.13 g, 10 mmole) in glacial acetic acid (10 ml) was heated at 70° for 6 hr. After removal of acetic acid under reduced pressure, a residue was made alkaline by adding potassium carbonate. The resultant alkaline solution was extracted with chloroform. Then the aqueous layer was acidified with 20 % hydrochloric acid and extracted with etner. From the chloroform extract, 2-methyl-4-phenylimidazole (IIb), mp 158-160°,[3] and 2-methyl-4-phenylpyrimidine 1-oxide (IIIb),

mp 153-154°, were obtained by alumina column chromatography (ether and $CHCl_3$). From the ethereal extract, benzoic acid was isolated.



Ia-e IIa-e IIIa-e

Table I Yields (%) of Oxidation Products by H_2O_2-AcOH

Starting materials			Products			
	R_2	R_4	II	III	PhCOOH	recovery
Ia	H	Ph	11	24	18	15
Ib	Me	Ph	21	24	9	0
Ic	Ph	Ph	16	8	7	34
Id	Ph	H	6	5	2	23
Ie	Ph	Me	trace	9[a)]	6[b)]	25

a) Trace of 3-oxide was obtained.

b) Product was obtained as benzamide in theis case.

The position of an N-oxide group was determined to be position 1 by proton magnetic resonance spectroscopy in the presence of $Eu(fod)_3$ according to the previously reported procedure.[4)]

When pyrimidine derivatives with the free 6-position, shown in Table II, were treated with m-CPBA in chloroform, the corresponding N-oxides were obtained in satisfactory yields except for the cases of 4-methyl derivatives, in which the mixtures of 1- and 3-oxides were formed. The reactivities of 2-phenylpyrimidines were somewhat lower, and 2-methoxypyrimidines including 2,4-dimethoxypyrimidine resisted the N-oxidation, the starting materials being recovered, whereas 4-methoxypyrimidines afforded the 1-oxides in fairly good yields. No formation of imidazoles was ob-

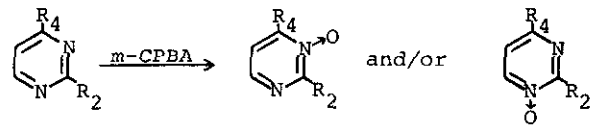


Table II Yields (%) of Pyrimidine N-Oxides by m-CPBA Oxidation

R_4 / R_2	H	Me		Ph	OMe
	1-oxide	1-oxide	3-oxide	1-oxide	1-oxide
H	48	12	30	64	44
Me	55	35	32	52	60
Ph	13 (54)[a)]	24 (35)	6	15 (42)	32 (44)
OMe	(49)	(46)		(48)	(41)

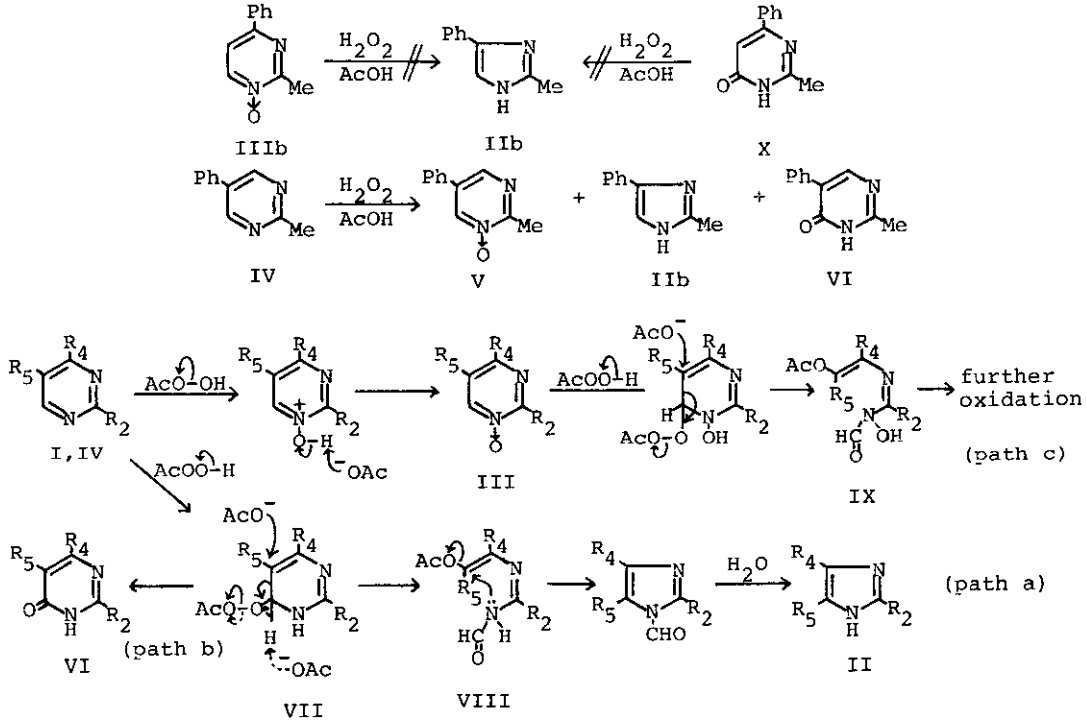
a) The figure in parentheses denote recovery yields.

served in the all reactions.

In order to obtain experimental evidence concerning the pathway to the imidazoles, the following reactions were carried out. An attempted further oxidation of IIIb with hydrogen peroxide in acetic acid did not give IIb, but IIIb was partially destroyed to give benzoic acid. When 2-methyl-5-phenylpyrimidine (IV) was treated under the same conditions, IIb, 2-methyl-5-phenyl-4-pyrimidinone (VI), and 2-methyl-5-phenylpyrimidine 1-oxide (V) were obtained in 12, 22, and 15 % yields, respectively. 2-Methyl-6-phenyl-4-pyrimidinone (X) was completely stable to further oxidation under the same conditions, although 4-pyrimidinones were not always isolated by N-oxidation of pyrimidines.

These findings demonstrated that the carbon atom at 6-(or 4-)position of pyrimidine ring was extruded during the ring-transformation from pyrimidines to imidazoles, and that pyrimidine N-oxides and 4-pyrimidinones were not the intermediates to imidazoles.

On the basis of the above experiments, the pathway of this ring-transformation and the formation of other products is tentatively illustrated as below.



There are so many papers[6] reported side reactions relating to the N-oxidation of N-heteroaromatics giving carbon-oxidized products, that it is reasonable to assume the addition of peracetic acid to the C_6-N_1 bond. If acetoxyl ion attacks the 5-position of the resultant intermediate (VII), the bond fission between C_5 and C_6 gives rise to an open-chain compound (VIII), which subsequently recyclizes to give imidazoles (path a). When acetoxyl ion abstracts the proton at the 6-position of VII, cleavage of an O-O bond (dotted arrow) results in the formation of 4-pyrimidinone (VI) with loss of acetic acid (path b). As a matter of course, per-

acetic acid attacks a ring nitrogen atom competitively to give the mono-N-oxides (III) (path c). Considering low π-electron density of pyrimidine N-oxide, it is assumable that the oxidative ring-opening reaction of III by the addition of peracetic acid to the C_6-N_1 bond of III gives an open-chain intermediate (IX). However this intermediate (IX) could not recyclize to give imidazoles, because of the presence of an oxygen atom on the nitrogen atom. Consequently, IX was further oxidized to give a lot of fragmentary products.

There are several papers[7-11] dealing with N-oxidation of simply substituted pyrimidines with hydrogen peroxide in acetic acid. For example, 4-methylpyrimidine,[7-9] 5-methylpyrimidine,[8] 5-bromopyrimidine,[10] and pyrimidine itself[5,8,9,11] were reported to give mono-N-oxides in low yields. Although no comment on the formation of imidazole derivatives was given in these papers, the ring cleavage from position 6 is conceivable as a cause of the low yields of these N-oxides.

Prior to the present work, the ring-transformation of pyrimidines into imidazoles under oxidative conditions has not been known, while thermal decomposition of 4-azido-6-methyl-2-methylthiopyrimidine,[12] reaction of potassium amide with 4-chloro-5-methyl-2-phenylpyrimidine,[13] and photolysis of 4,6-dimethyl-[14] and 5-methoxy-pyrimidine 1-oxide[15] were reported to give the corresponding imidazoles.

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